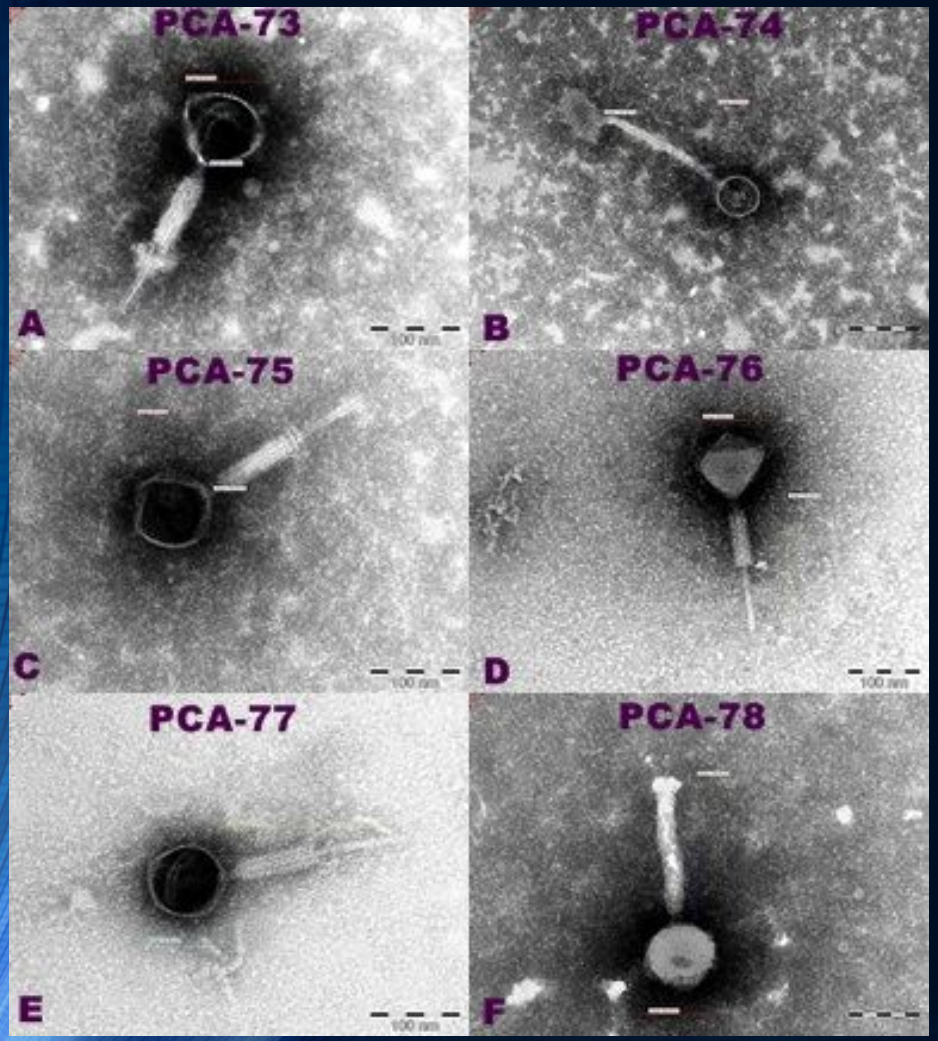
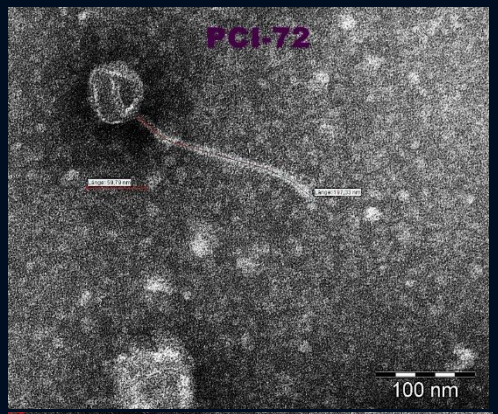
Faszination Bakteriophagen

Der Feind meines Feindes ist mein Freund

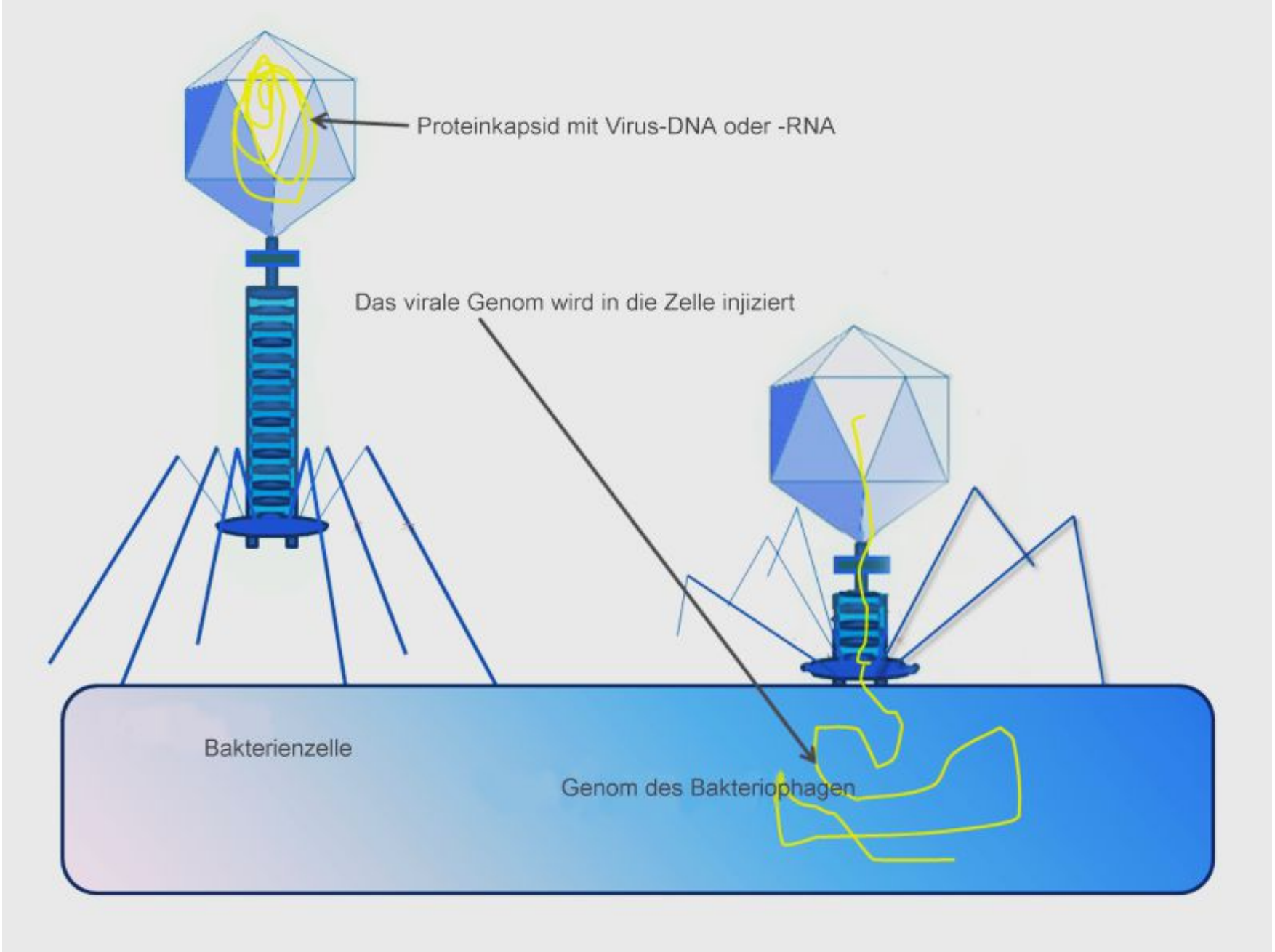
PD Dr. Wolfgang Beyer
Universität Hohenheim
homepage: uniho-beyer.de

Bakteriophagen aus *Bacillus anthracis*
Feldisolate aus Wildtieren





Aufnahmen:
C. Rohmer
und Dr. V. Akimkin
(CVUAS)
Juli 2016



Graham Colm - Englische Wikipedia.
http://en.wikipedia.org/wiki/File:Phage_injecting_its_genome_into_bacterial_cell.png

Wussten Sie schon...?

M. Youle et al., "Scratching the surface of biology's dark matter," *Viruses: Essential Agents of Life*, ed. Günther Witzany (Springer Netherlands), 61-81, 2012.

Bacteriophages are the most ubiquitous "organisms" on Earth (>10^{30}).

1000.000.000.000.000.000.000.000.000.000(0)

We encounter billions of phages daily in what we breathe, eat, drink, and bath in - shedding an equally large number as we live our lives.

Phages powerfully affect genetic change in soils, vegetation, and oceans, regulating nutrient cycling, evolution, and even climate change on a global scale.

Wussten Sie schon...?

Viruses and bacteria are in a constant evolutionary arms race, modifying their genetics in a madcap attempt to infect or evade infection. Scientists estimate that 2.5 x 10^{25} viral genomes are replicated every second, and those genomes are packaged and transferred to the next suitable cell.

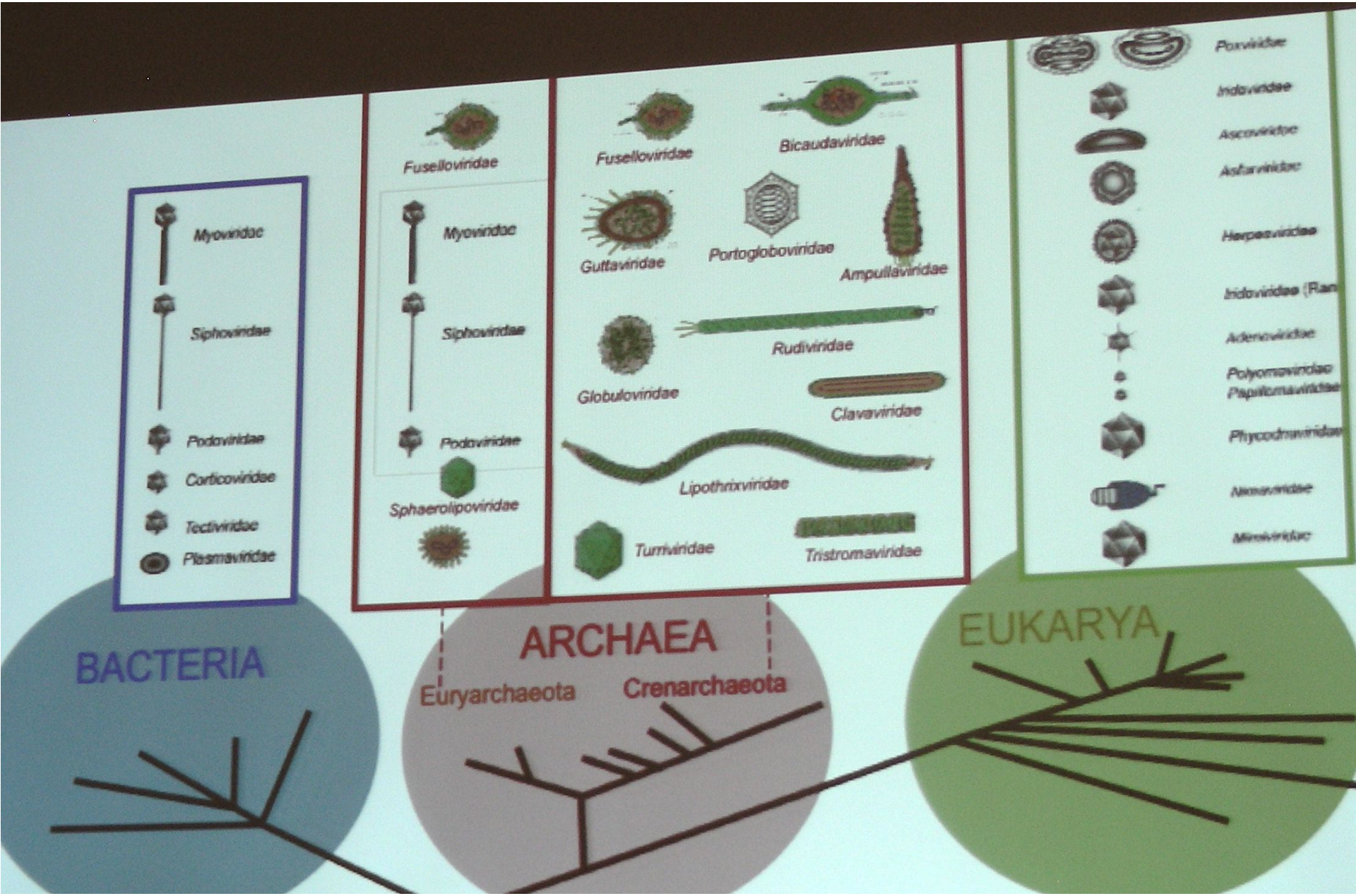
Researchers believe that there is at least one "mistake" every 1,000 genomes replicated. It means that 2.5 x 10^{22} altered viruses are made every second.

M. Youle et al., "Scratching the surface of biology's dark matter," *Viruses: Essential Agents of Life*, ed. Günther Witzany (Springer Netherlands), 61-81, 2012.

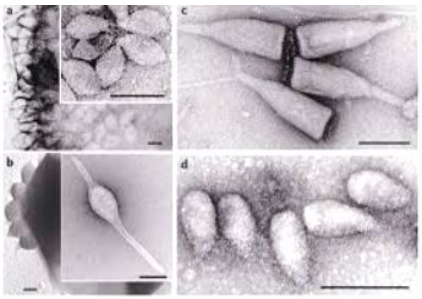
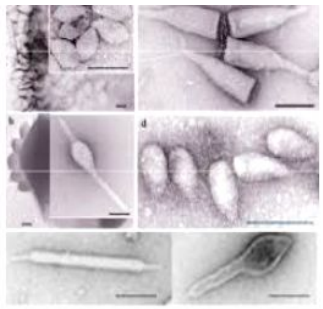
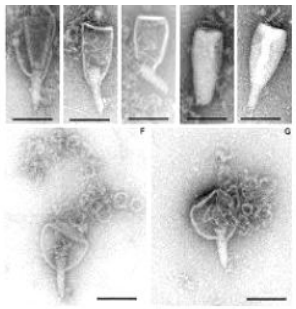
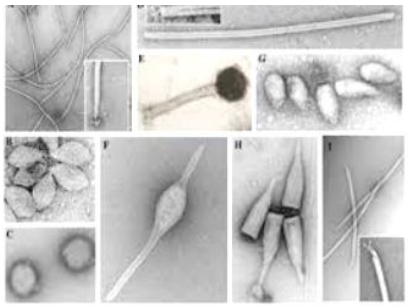
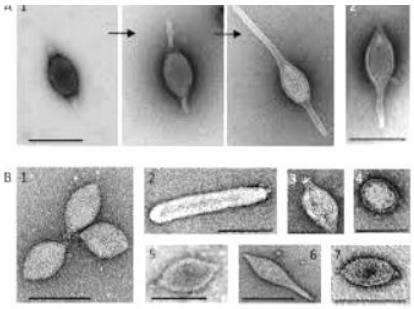
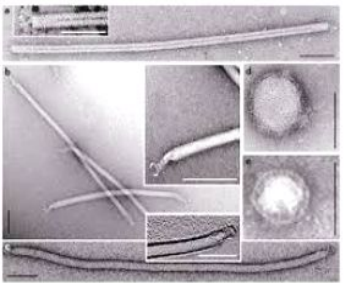
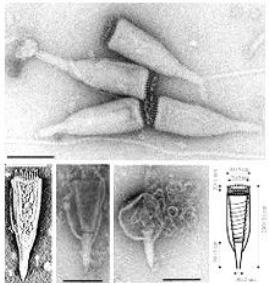
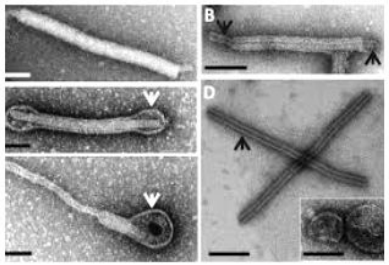
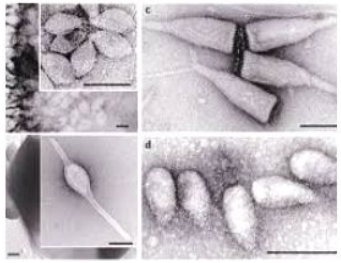
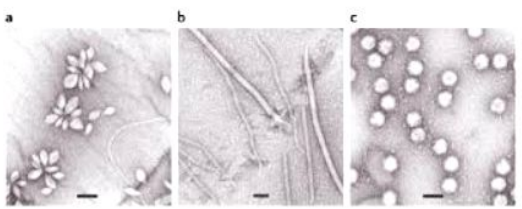
Klassifizierung und Diversität von Bakteriophagen

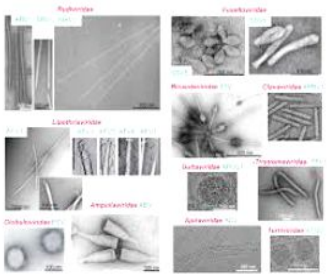
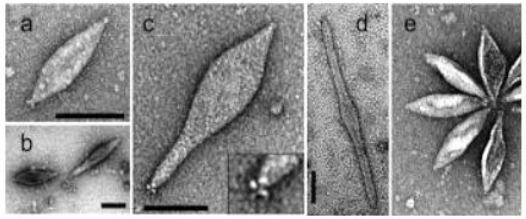
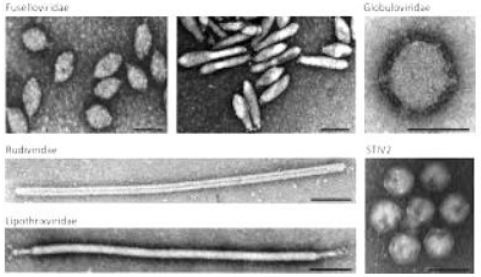
PD Dr. Wolfgang Beyer
Universität Hohenheim
homepage: uniho-beyer.de

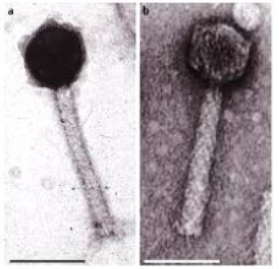
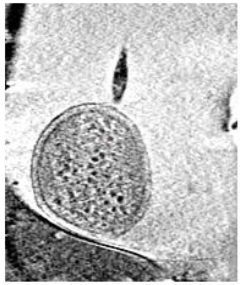
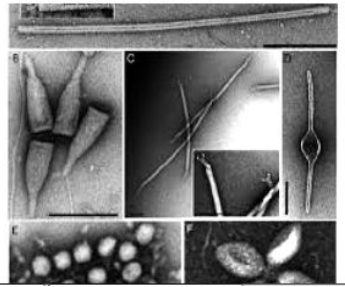
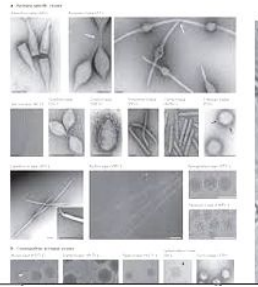
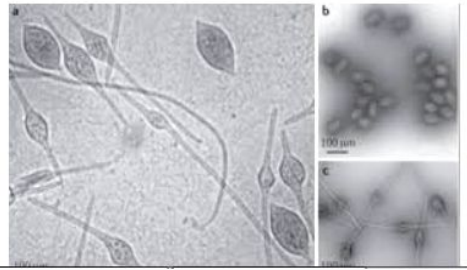
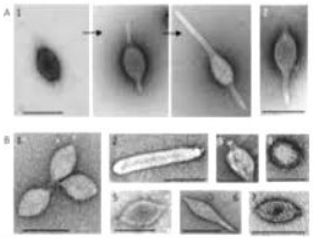
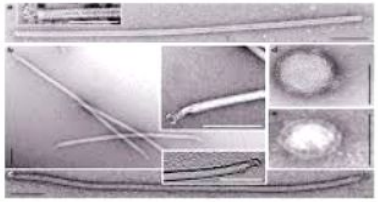
Wussten Sie schon...?

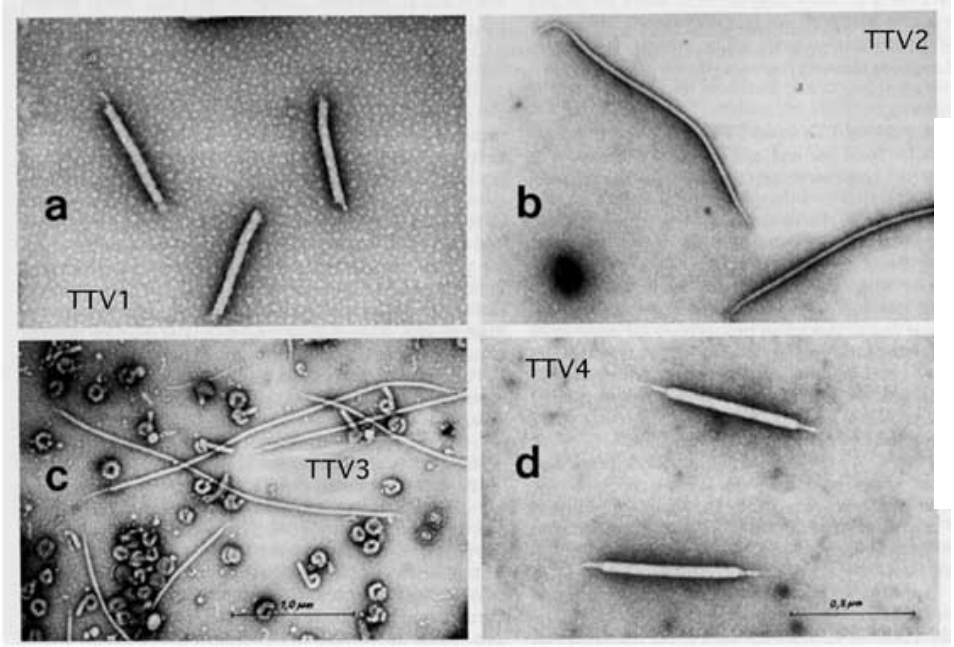


Phagen: Die Formenvielfalt ist schier grenzenlos...



Habitats of hyperthermophilic Archaea: An acidic iron-rich geothermal spring, another *Sulfolobus* habitat

•Habitats of hyperthermophilic Archaea: Sulfur-rich hot spring, a habitat containing dense populations of *Sulfolobus*.
•The acidity in solfataras and sulfur springs comes from the oxidation of H_2S and S0 to H_2SO_4 by Sulfolobus and related prokaryotes

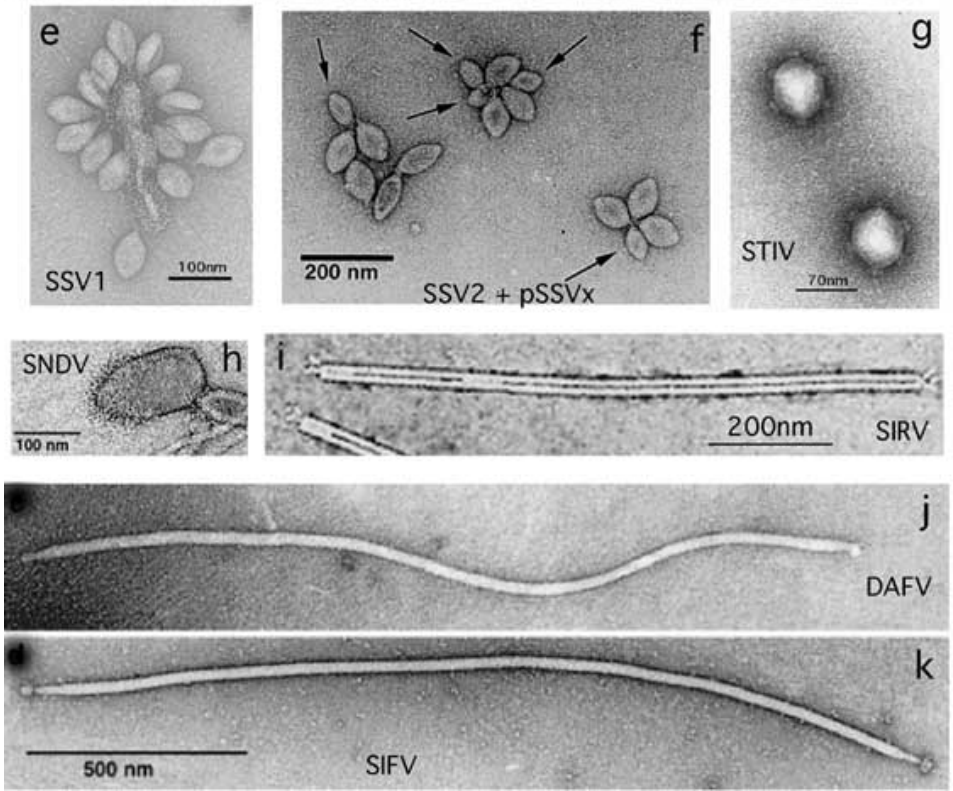


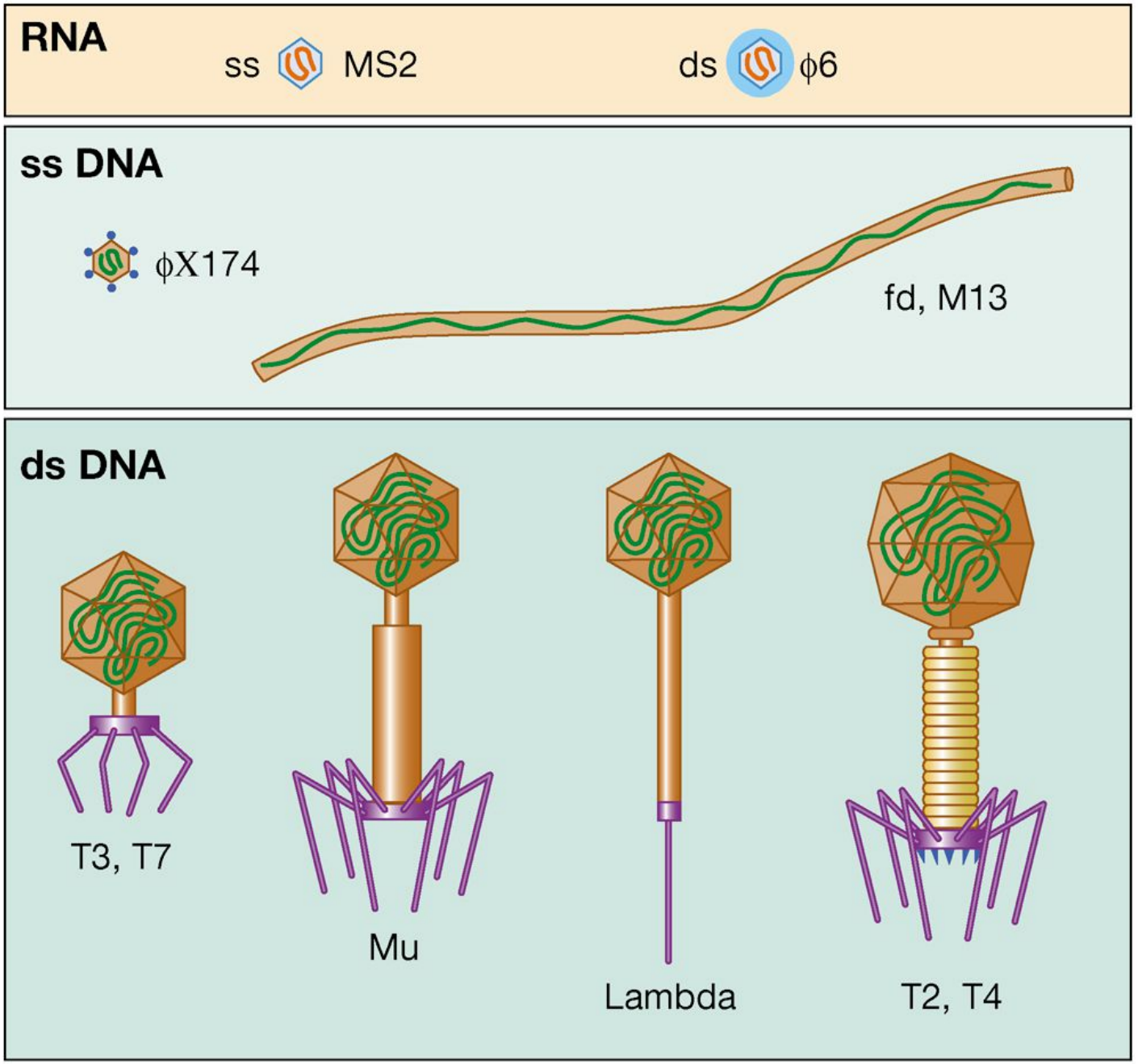
Figure 31-3: Viruses of the *Crenarchaeota*: Transmission electron micrographs of viruses from crenarchaeal hosts, all negative stain.

TheBacteriophages.org

Habitats of hyperthermophilic Archaea: A typical boiling spring of neutral pH in Yellowstone Park; Imperial Geyser

Figure 31-4: Viruses and VLPs from hot springs in Yellowstone National Park, USA. Bars, 200 nm (100 nm in insets).

Klassifizierung und Diversität von Bakteriophagen

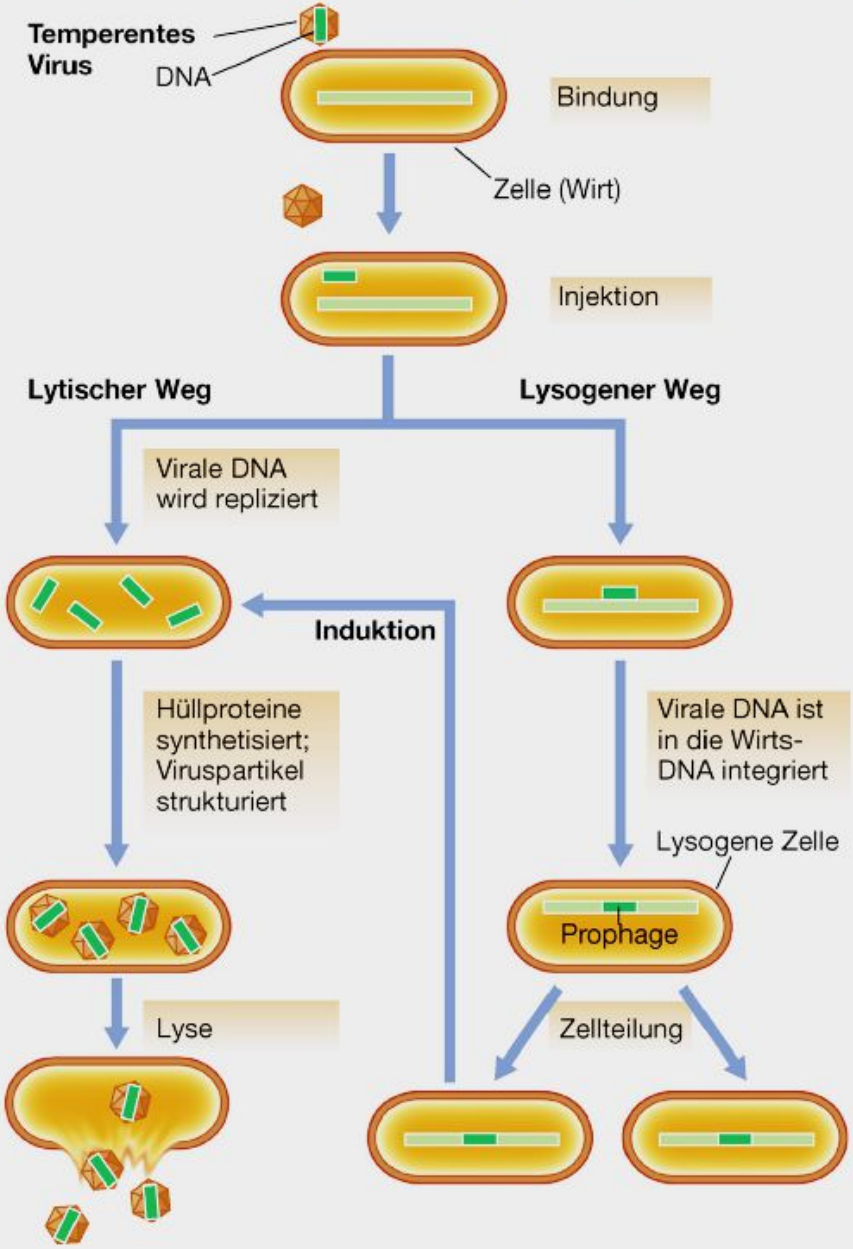


Lytisch, Lysogen oder Pseudolysogen?

Wer steuert hier Wen?

PD Dr. Wolfgang Beyer
Universität Hohenheim
homepage: uniho-beyer.de

Lysogene Phageninfektion



- Virulente Phagen:
  nur lytische Vermehrung
  (T-Phagen, MS2)

- Temperente Phagen:
  alternative Strategien
  lytisch oder lsogen (λ)

- Prophage:
  - Latente Form des Phagen
  - Integriert im Chromosom des Wirtes
  - Vererbt mit dem Wirtsgenom
  - vermittelt Immunität gegen weitere Infektionen

nature International weekly journal of science

NATURE | NEWS

Do you speak virus? Phages caught sending chemical messages

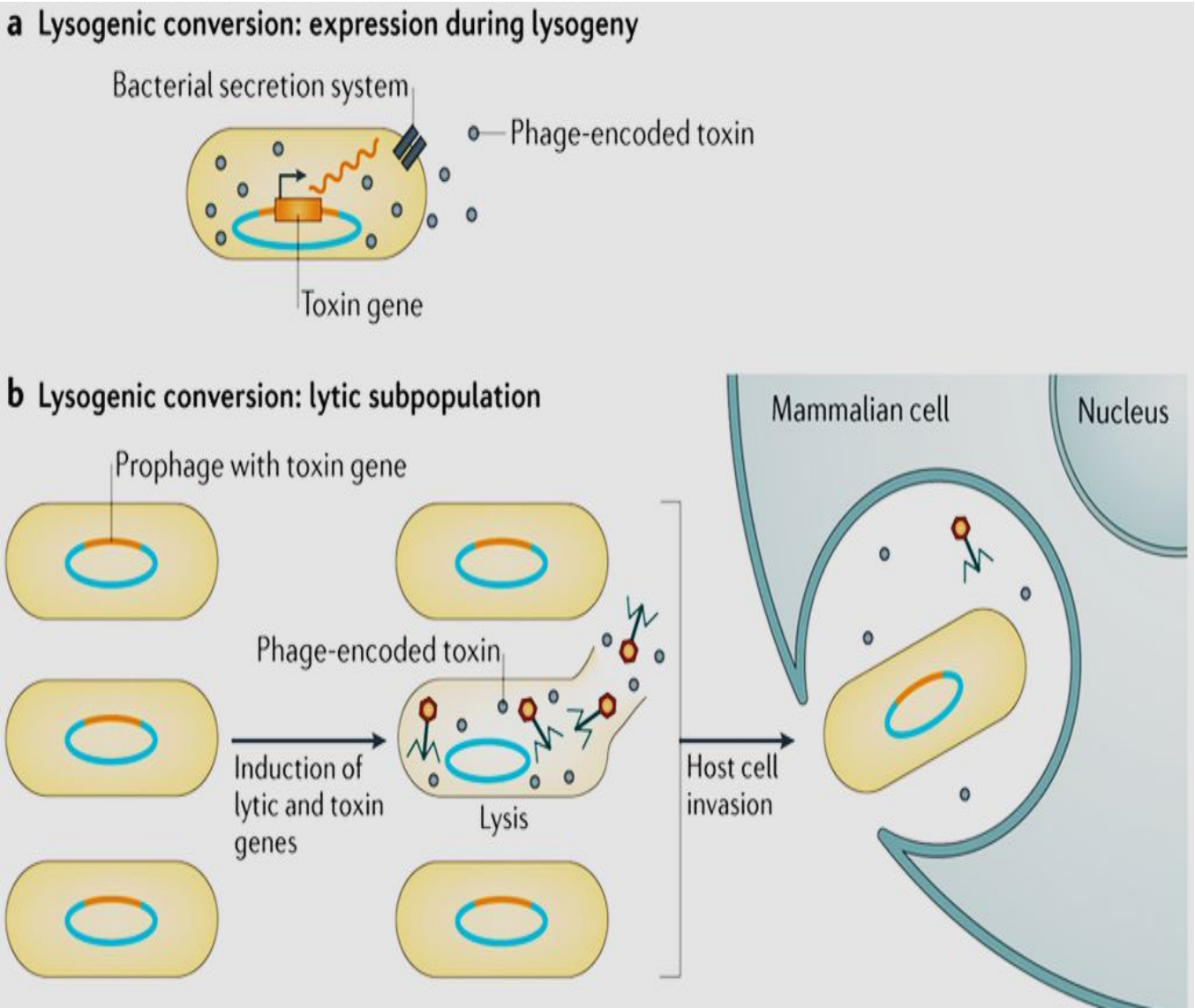
A virus that infects bacteria listens to messages from its relatives when deciding how to attack its hosts.

Ewen Callaway

18 January 2017

Bacterium–phage lysogenic interactions.

NATURE REVIEWS | **MICROBIOLOGY** VOLUME 13 | OCTOBER 2015



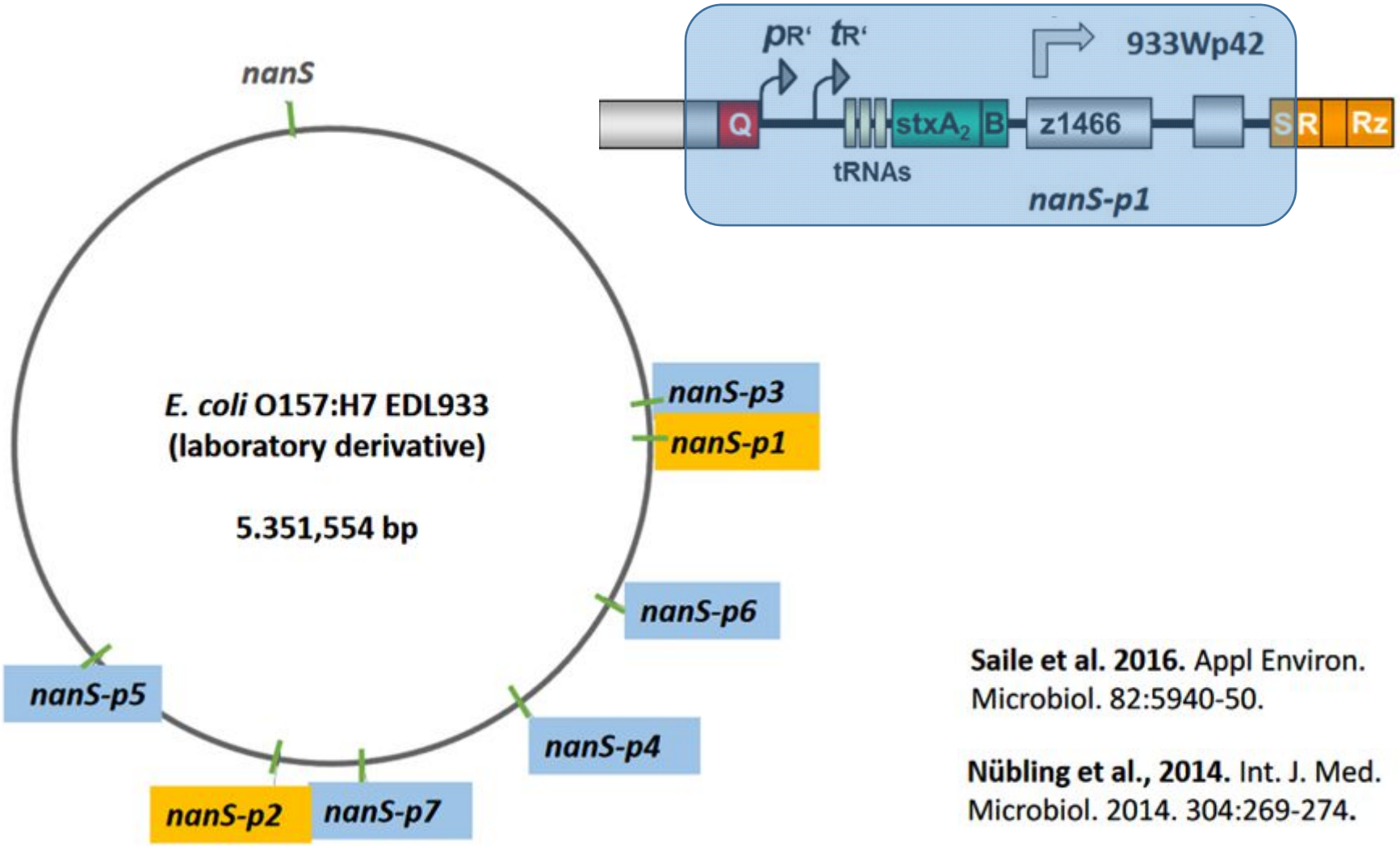
Lysogenic conversion and active lysogeny are two lysogenic processes whereby bacteria and phages cooperate.

a | Virulence factors are expressed from lysogenic prophages during bacterial infection of mammalian cells and secreted by bacterial secretion systems.

b | Alternatively, phage-encoded virulence factors are expressed only in those cells in a subpopulation that switch to the lytic life cycle.

Lysogenie: Phagen kontrollieren die Physiologie ihres Wirts

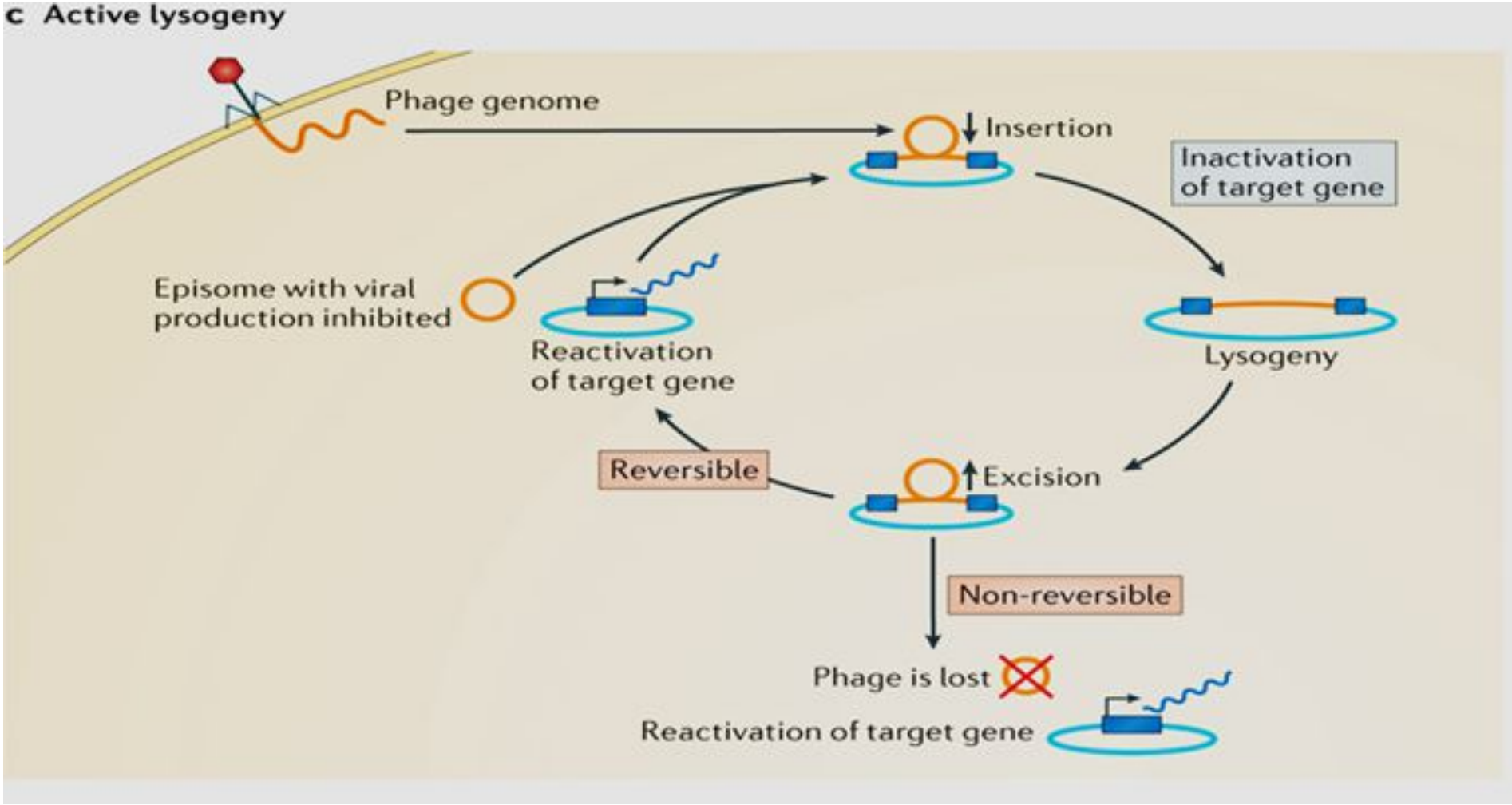
nanS: 5-N-acetyl-9-O-acetyl-Neuraminsäure-Esterase in EHEC



Saile et al. 2016. Appl Environ. Microbiol. 82:5940-50.

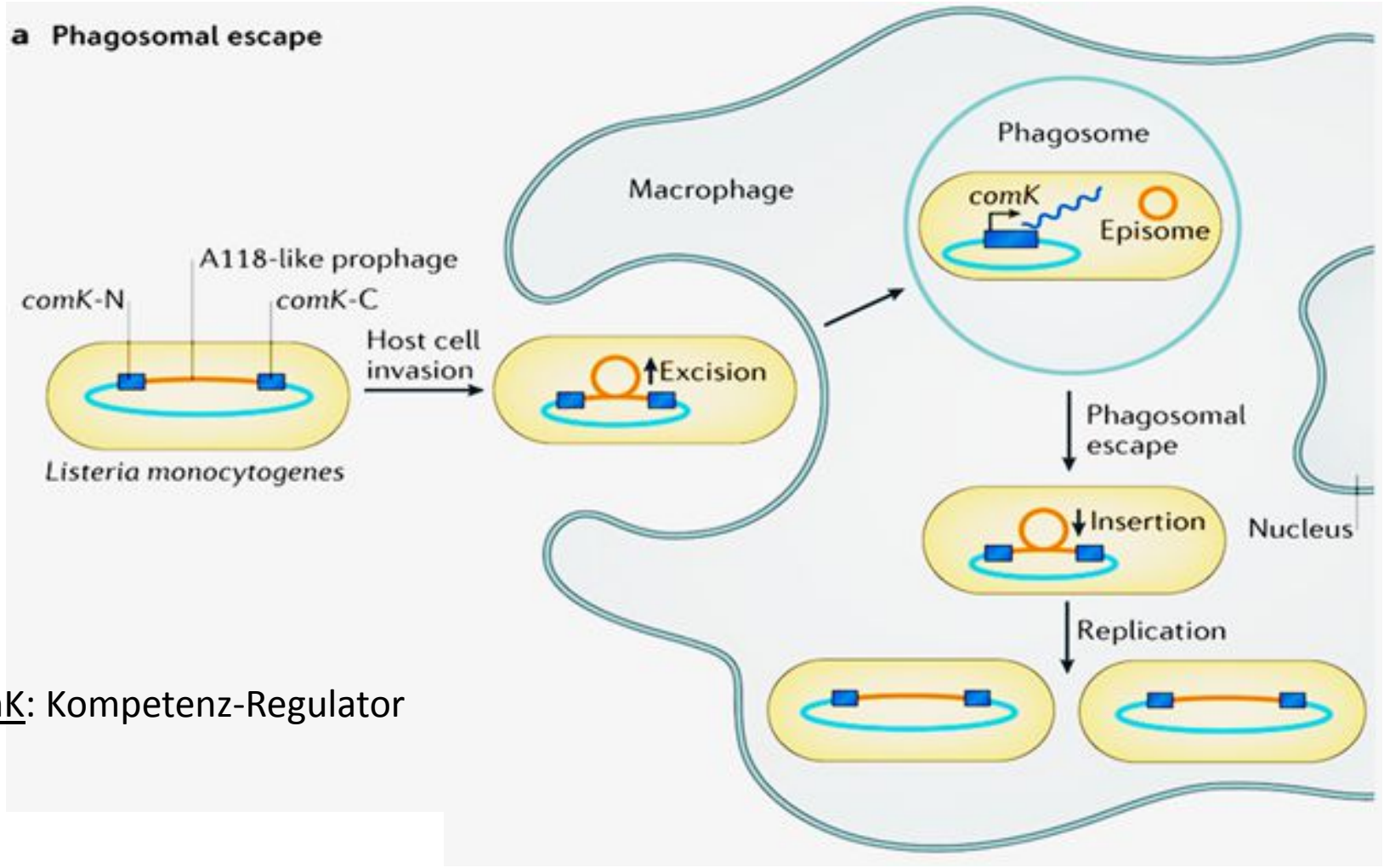
Nübling et al., 2014. Int. J. Med. Microbiol. 2014. 304:269-274.

Aktive Lysogenie: Phagen kontrollieren die Physiologie ihres Wirts



Active Lysogenie beschreibt eine Bakterium-Phagen Interaktion, bei der ein integrierter Prophage als regulatorischer Schalter für die Expression von Wirtsgenen dient.

Aktive Lysogenie: Phagen kontrollieren die Physiologie ihres Wirts



comK: Kompetenz-Regulator

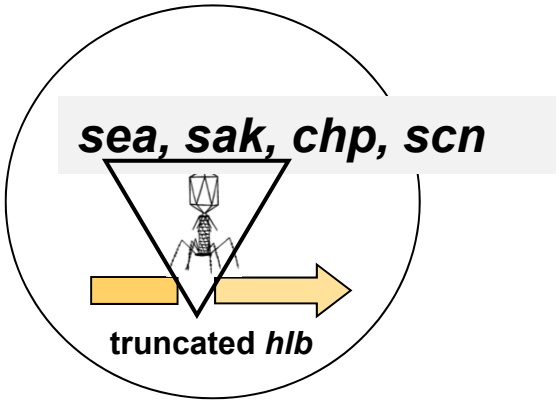
Reversible active Lysogenie reguliert kritische Prozesse in Bakterien.

Regulation des Entweichens von *Listeria monocytogenes* aus dem Phagosom von Makrophagen.

Phage conversion during infection

by: Prof. Christiane Wolz
Interfakultäres Institut für Mikrobiologie und Infektionsmedizin Tübingen

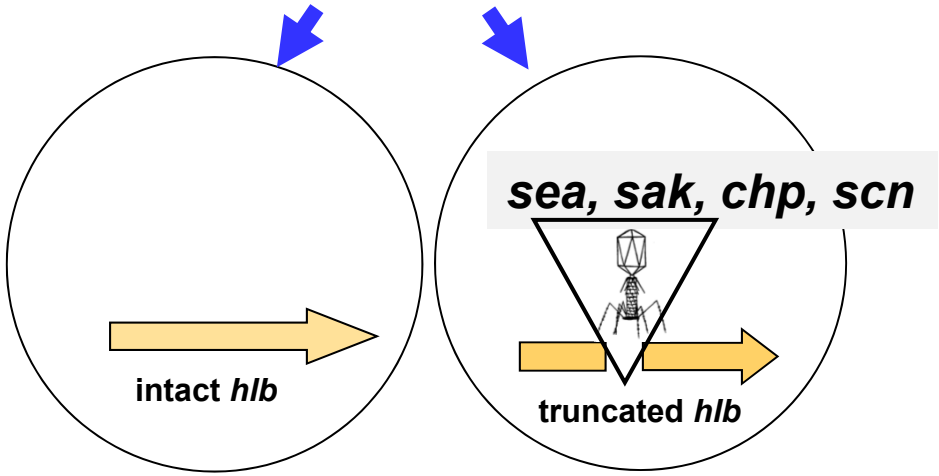
Colonization



Immune suppression

Infection

Splitting of the population



Cytotoxicity

Immune suppression

- **During Infection significant more Hlb-positive Isolates**
- **Often Co-culture of Hlb + and Hlb - isolates**

➔ **Phage inducing condition and selection**

Goerke et al., Mol Microbiol, 2006, 1673
aus: Chr. Wolz, Vortrag 2017

Phagen in der Humantherapie

PD Dr. Wolfgang Beyer
Universität Hohenheim
homepage: uniho-beyer.de

Frederick Twort
1877-1950

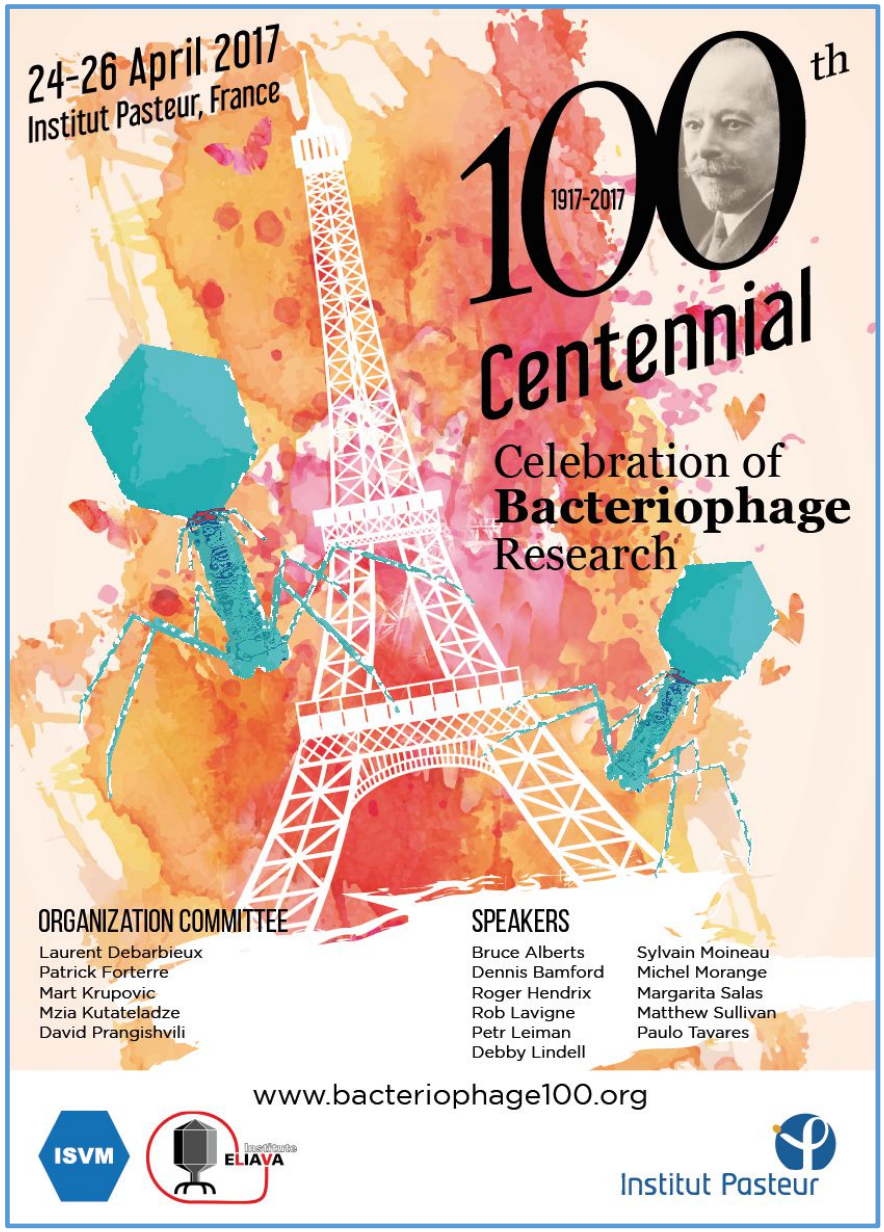
Felix d'Herelle
1873-1949

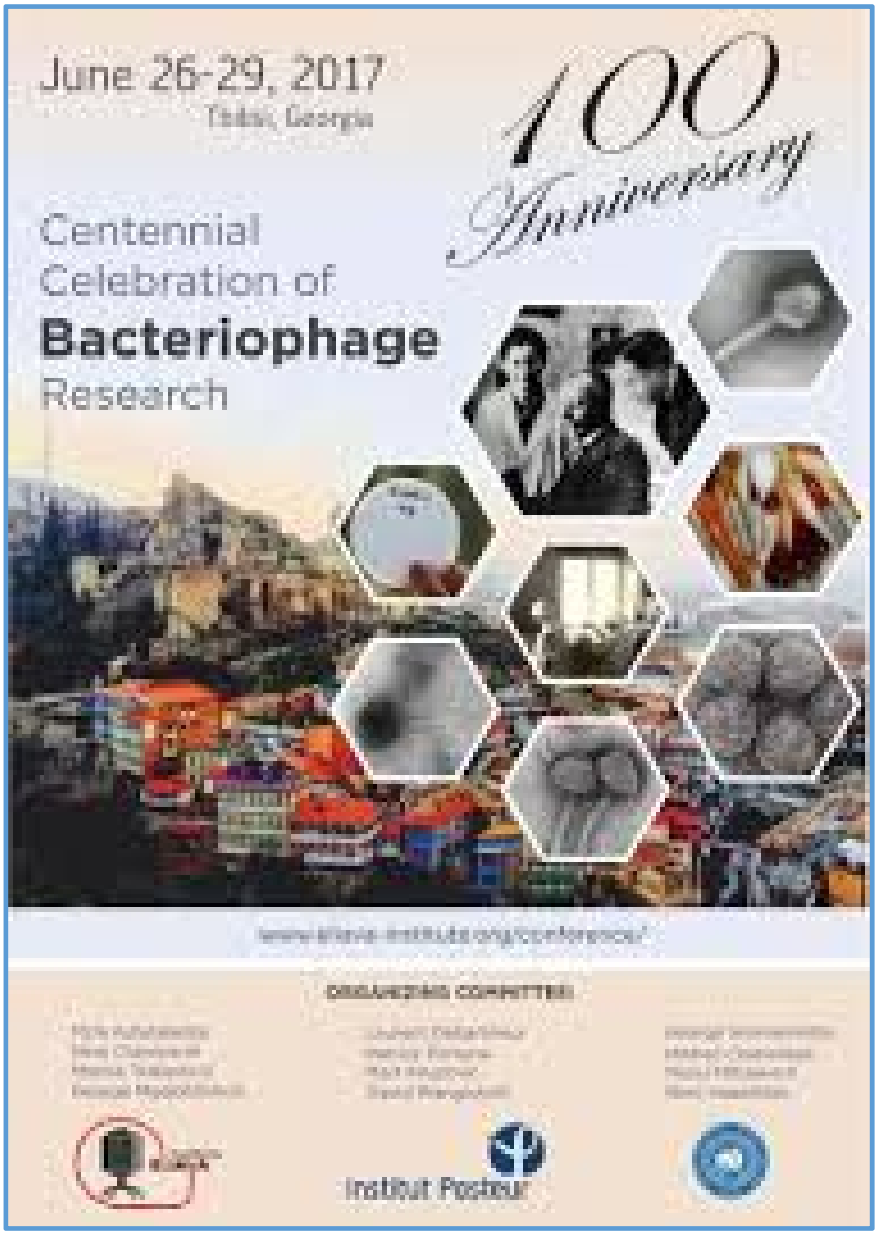
Frederick W. Twort beschrieb 1915 ein „*ultra-microscopic virus*“, das als „*transparent material*“ Bakterien zerstören konnte, sich ohne diese aber nicht vermehren ließ und darüber hinaus in Infektions-versuchen mit Labortieren keinerlei Pathogenität aufwies [1]. 1917 nannte Felix d'Herelle diese Bakterienkiller Bakteriophagen – Bakterienesser - und nutzte sie bereits, als Therapeutikum gegen Dysenterie auslösende Bakterien [2].

1. Twort FW (1915) An investigation on the nature of ultra-microscopic viruses. Lancet ii:1241-1243
2. D'Herelle F (1917) Sur un microbe invisible antagoniste des bacilles dysentériques. CR Hebd Seances Acad Sci D165,11:373-375.

Dr Graham Beards - en:Image:Phage.jpg

100 Jahre Bakteriophagen – Forschung und Anwendung





Early History of Phage Therapy

1919 – The first clinical trial – Hospital des Enfants-Malades,
Felix D'Herelle, Paris, France

1921 – The first publication on phage therapy: Richard Bruynoghe and Joseph Maisin, Essais de therapeutique au moyen du bakcteriophage.
C.R. Soc.Biol. 85:1120-1121

1927 – The first mass application of phages, Campbell Hospital, Calcutta, India, Felix D'Herelle


Institute
ELIAVA
George Eliava Institute of Bacteriophages,
Microbiology and Virology

George Eliava Institute of Bacteriophages, Microbiology and Virology

Kurze Geschichte...

1916 – Pasteur-Station in Tiflis wird zum Zentrallabor für Bakteriologie (CBL)

1918 – George Eliava wird Direktor des CBL

1923 – Institut für Bakteriologie gegründet von G. Eliava

1930/1931 – Felix D'Herelle arbeitet am Institut in Tbilisi

1937 – G. Eliava ermordet

Behandlungsspektrum für Phagentherapie am Eliava-Institut

Acute and Chronic Infections

- Acne
- Bladder Infections
- Bronchiectasis
- bronchitis
- **Burns (infected)**
- Colitis
- **Cystic Fibrosis (co-infections)**
- Dysbiosis / Pathogenic Intestinal Flora
- **Ear Infections (Otitis Media)**
- Gingivitis
- Intestinal Infections
- Laryngitis
- **Lung Infections**
- Nose / Throat Infections
- Prostatitis and Associated Sexual Problems
- Infected Prosthesis
- Chronic Sinusitis (Rhinosinusitis)
- Rosacea
- Skin Boils / Abscess / Lesions
- Tracheitis
- **Urinary Tract Infections (UTI) and Cystitis**
- vaginitis

Infections Where Circulation is Poor

Such conditions include, but are not limited to, the following:

- Bed Sores
- **Chronic / Non-healing / Infected Wounds**
- **Diabetic Foot**
- Osteomyelitis
- Tropic Ulcers

Infections with Bacteria Resistant to Standard or Advanced Antibiotics

Such cases can include:

- *Staphylococcus spp.* (more than one species) including Methicillin Resistant *Staphylococcus aureus* **(MRSA)** and Community Acquired *Staphylococcus aureus* (**CA-MRSA)**.
- Streptococcus spp.
- Enterococcus spp.
- E. coli
- Proteus spp.
- *Pseudomonas aeruginosa*
- *Salmonella* spp.
- *Shigella* spp.

Phagenprodukte aus dem Eliava-Institut

STAPHYLOCOCCUS
Staphylococcus aureus

FERSISI
Staphylococcus (2x) and Streptococcus (3x)

SES
Staphylococcus (2x), Streptococcus (4x), EPEC

PYO
Staphylococcus aureus, Streptococcus spp., Proteus (2x), E. coli and P. aeruginosa

ENCO
Shigella (2x), Salmonella (7), EPEC, Staphylococcus

INTESTI
Staphylococcus, Enterococcus, Proteus (2), Shigella (3), Salmonella (6), EPEC, Pseudomonas aeruginosa

Bacteriophages versus Antibiotics

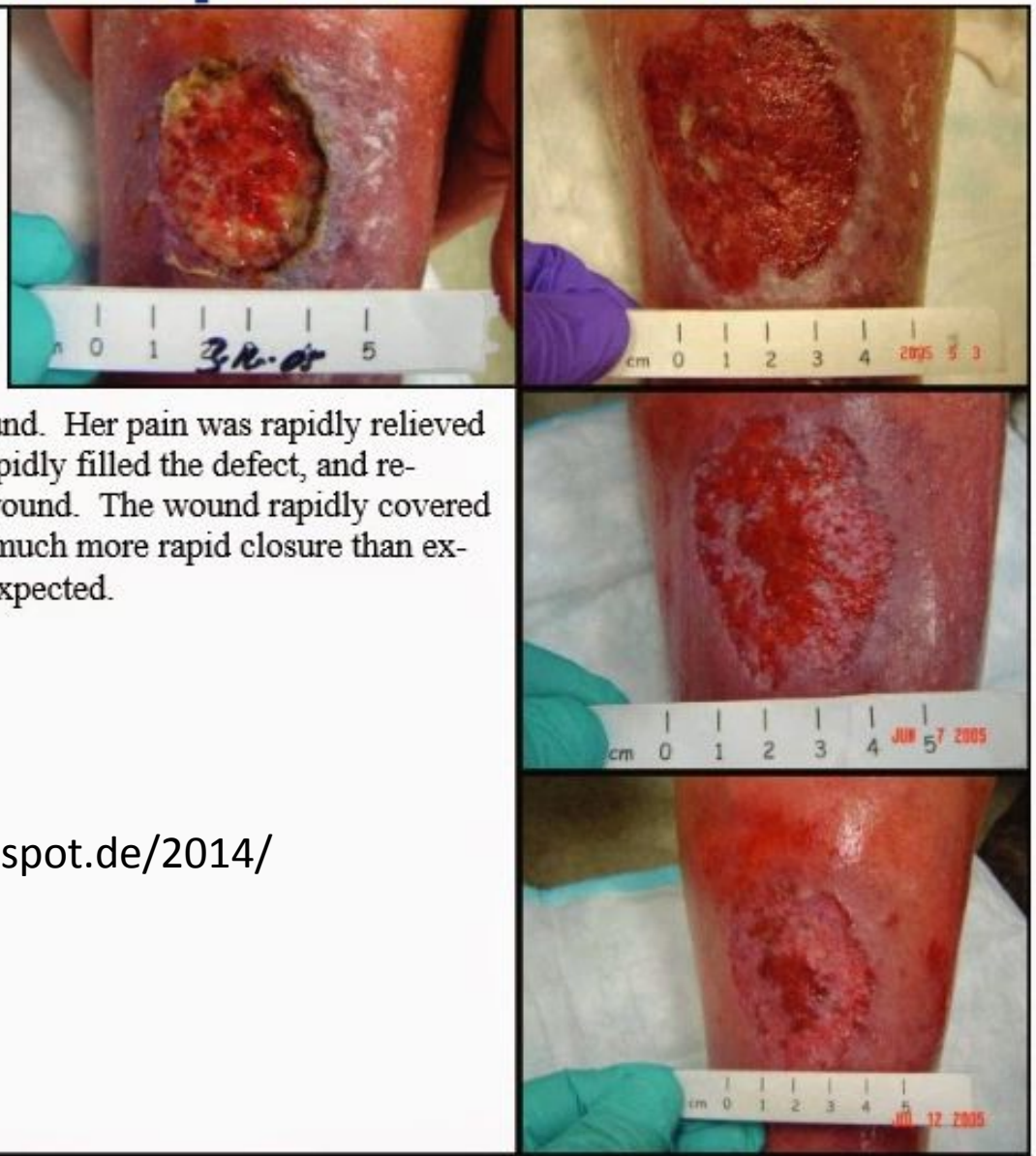
Bacteriophages	Antibiotics
Very specific (i.e., usually affect only the targeted bacterial species); therefore, dysbiosis and chances of developing secondary infections are avoided.	Antibiotics **target both pathogenic** microorganisms **and normal microflora**. This affects the microbial balance in the patient, which may lead to serious secondary infections.
Replicate at the site of infection and are thus available where they are most needed.	They are metabolized and eliminated from the body and **do not necessarily concentrate at the site of infection**.
No serious side effects have been described.	**Multiple side effects**, including intestinal disorders, allergies, and secondary infections (e.g., yeast infections) have been reported.
Phage-resistant bacteria remain susceptible to other phages having a similar target range.	**Resistance to antibiotics is not limited to targeted bacteria**.
Selecting new phages (e.g., against phage-resistant bacteria) is a relatively rapid process that **can frequently be accomplished in days or weeks**.	Developing a new antibiotic (e.g., against antibiotic-resistant bacteria) is a time-consuming process and **may take several years**.

Phage Therapy of Chronic Wounds With Associated Epithelial Islands

Case History

NAME: R.T.
ACCT: 10171

A.H. is a very pleasant 53-year-old white female with a very painful venous leg ulcer for over a year. The patient was treated with phage cocktail in March and showed very rapid closure of the wound. Her pain was rapidly relieved over a 24- to 48-hour period. Granulation tissue rapidly filled the defect, and re-epithelization began out in the mid portion of the wound. The wound rapidly covered with epithelium, healing within 12 weeks. This is much more rapid closure than expected, and the pattern of re-epithelization was unexpected.



http://sellanophagetherapy.blogspot.de/2014/

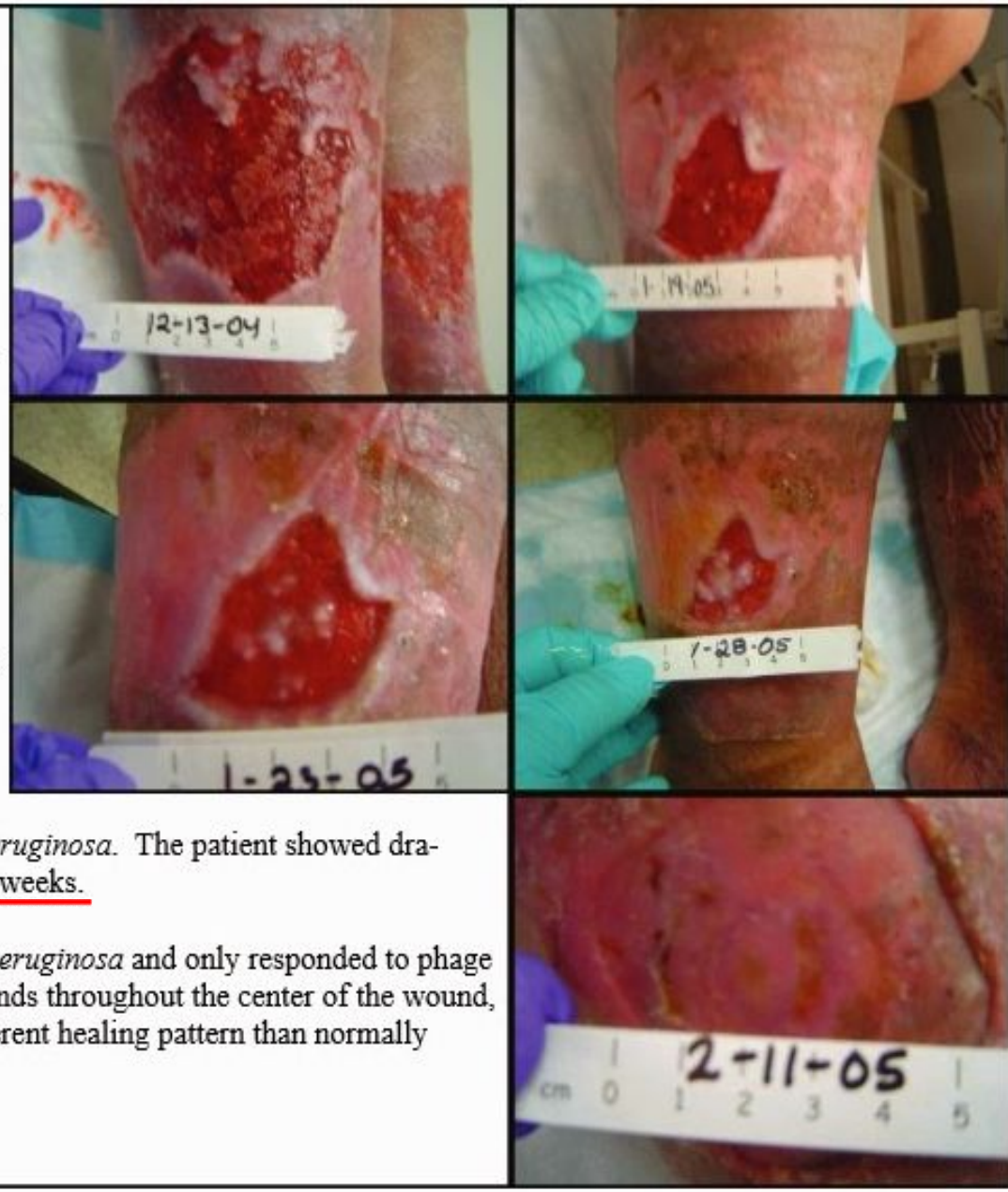
CASE HISTORY:

NAME: R.B.
ACCT: 4146

The patient is a very pleasant 60-year-old white male with lymphedema in the bilateral lower extremities, uncontrolled noninsulin dependent diabetes mellitus and nonhealing wounds on his lower extremities for many years. The patient's first visit to our clinic was 06-26-2002 with a very painful highly exudative wound. He failed to respond to comprehensive wound management.

The patient was readmitted in May of 2004 with dramatic increase in pain. The wounds were much deeper and more exudative. The patient had multidrug resistant *P. Aeruginosa* bacteria intermediately sensitive to Amikacin and resistant to all other antibiotics. He was depressed, and ended up losing his job. The patient was started on biofilm based wound management along with bacteriophage therapy with specific phages against *P. Aeruginosa*. The patient showed dramatic improvement in his wounds over the course of six weeks.

Teaching Point: The patient has multi drug resistant *P. Aeruginosa* and only responded to phage therapy. Of interest, his wound developed epithelial islands throughout the center of the wound, which coalesced and filled the wound in, which is a different healing pattern than normally seen.

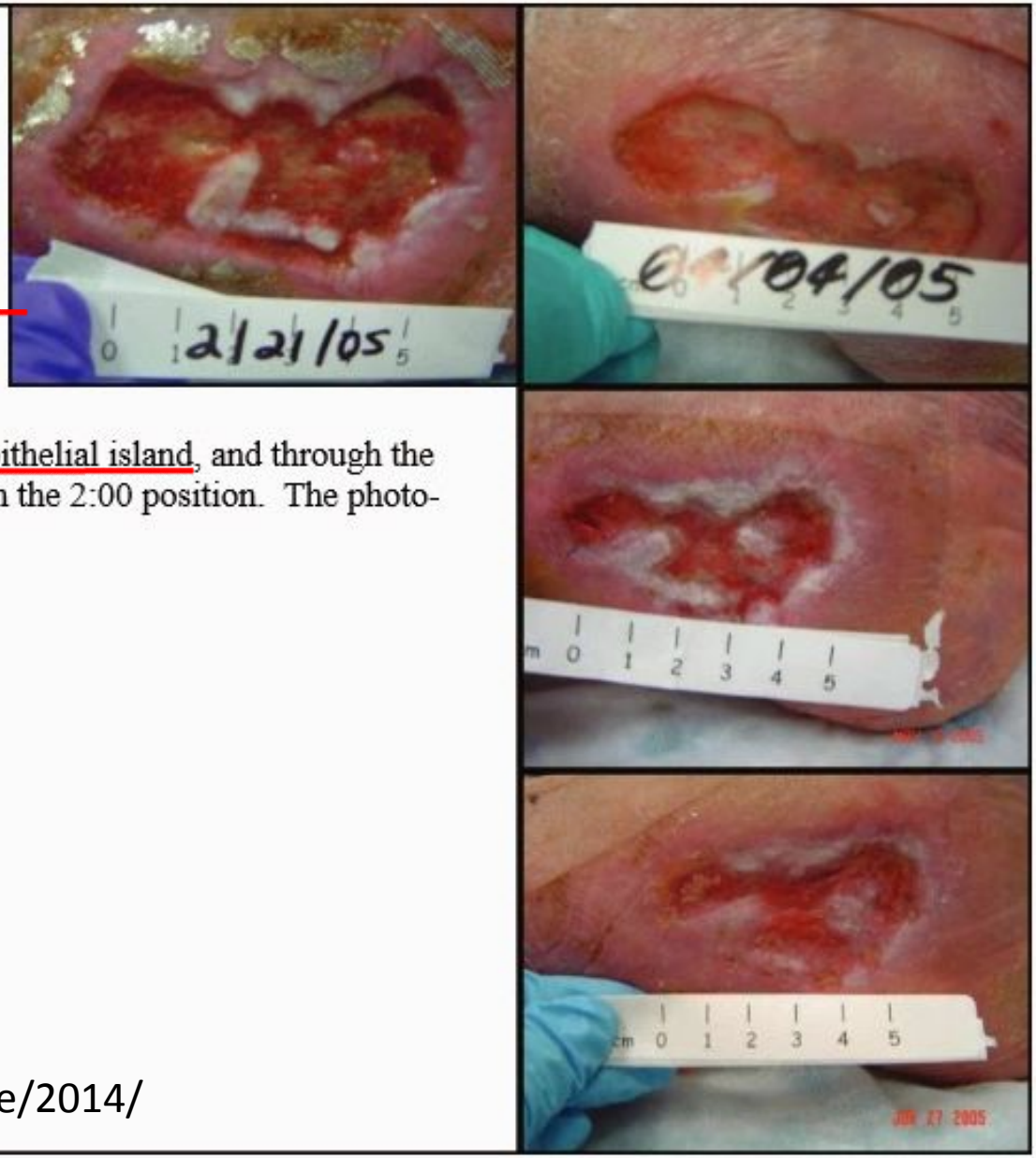


http://sellanophagetherapy.blogspot.de/2014/

Case History

NAME: A.H.
ACCT: 2965

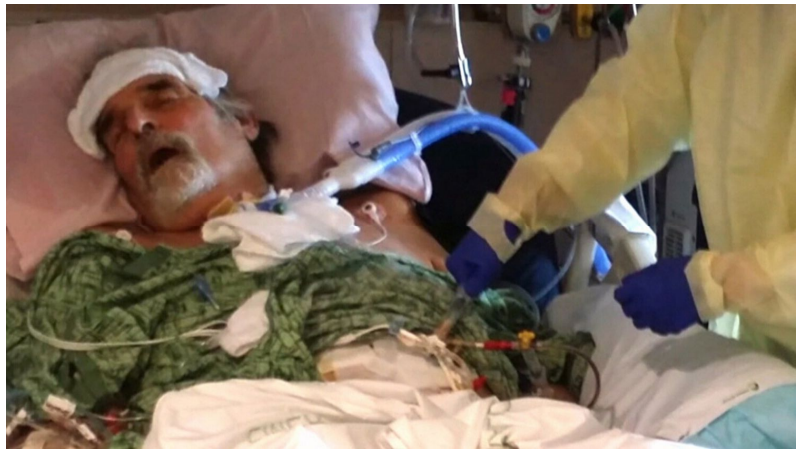
A.H. is a very pleasant 73-year-old white male with a long history of recurrent venous leg ulcers. The area of this venous leg ulcer is very sclerotic from 30 years of recurrent wounds. The patient had application of phage cocktail the first week in February. Within three weeks the patient has an epithelial island, and through the course of his healing he developed another island in the 2:00 position. The photographs document the development of the island.



http://sellanophagetherapy.blogspot.de/2014/

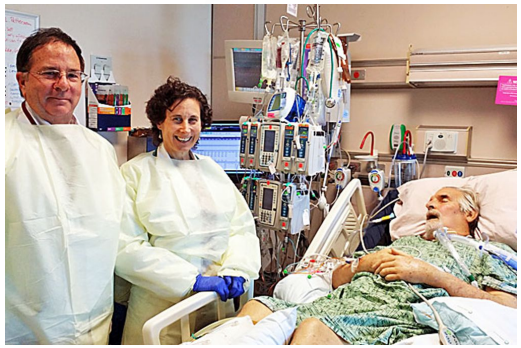
The Story of Mr. P: Patient with Deadly Infection

- 68-year-old male
- Contracted abdominal MDR *Acinetobacter baumannii* infection while traveling
- Received multiple courses of antibiotics over 4-month period
  - Vancomycin, meropenem, colistin, tigecycline, azithromycin, and rifampin
- Critically ill; in a coma for several weeks



The Story of Mr. P: Preparing Personalized Phage Therapy

- Multi-disciplinary team including UCSD, Texas A&M, SDSU, U.S. Navy, and AmpliPhi
- Bacterial isolates screened against phage library
- Personalized phage formulations provided within 10 days
- Phage administered IP and IV, under Emergency IND allowed by FDA



The Story of Mr. P: Successful Outcome

- Patient emerged from coma 4 days after initial phage administration
- 5 days after initial phage dose, bacteria became sensitive to antibiotics
- Continued phage administration (for selective pressure) and antibiotics
- Patient experienced durable microbiological cure
- Released from the hospital and doing well

PhagoBurn

3.85 million €
EC funding!

News

- Press release : Phagoburn clinical trial has now been launched officially. Click on "All News" for more information. ----------
- Publication : A scientific article written by Phagoburn partners was published in Annals of Burn & Fire Disasters in Spring 2015. Click on "All News" for more information. ----------
- Phage therapy dossier : A series of articles were published in "Enquêtes de santé" (French) in March 2015. Click on "All News" for more information. ----------

All news

Phagoburn is a European Research & Development (R&D) project funded by the European Commission under the 7th Framework Programme for Research and Development. The project was launched on June 1st 2013 and will last 36 months.

It aims at evaluating phage therapy for the treatment of burn wounds infected with bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. This evaluation is currently running through the implementation of a phase I-II clinical trial.

In addition, results obtained within Phagoburn will contribute to provide basis for an optimisation of current regulatory guidelines in phage therapy.

A world first! Phagoburn clinical trial is now running

Read the press release

Bakteriophagen als Arzneimittel im Kampf gegen Infektionen

Forschungsverbund startet mit dem Ziel, Bakteriophagen als zugelassenes Arzneimittel zu etablieren

»Phage4Cure«

Target: *Pseudomonas aeruginosa*

Ziel: Phagentherapie in CF-Patienten

- **Fraunhofer-Institut für Toxikologie und Experimentelle Medizin ITEM**
- **Leibniz-Institut DSMZ-GmbH**
- **Charité – Universitätsmedizin Berlin**
- **Charité Research Organisation GmbH**

Gefördert durch BMBF über drei Jahre mit knapp vier Millionen Euro.

Phagen in der Veterinärmedizin

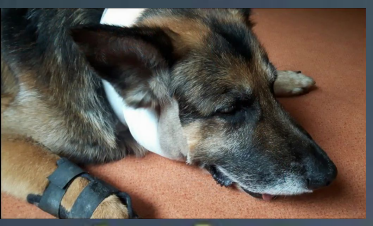
PD Dr. Wolfgang Beyer
Universität Hohenheim
homepage: uniho-beyer.de

Leibniz-Institut DSMZ
9. November 2016

Phagentherapie bewahrt Nashorn im Tiergarten Nürnberg vor dem Einschläfern

dsmz.de

Der 28-jährige Nashornbulle Ropen hatte sich eine schwere und trotz Behandlung nicht verheilende Entzündung am Fuß zugezogen. Erst die in Vergessenheit geratene Phagentherapie brachte die Wende. DSMZ-Phagen-Expertin Dr. Christine Rohde konnte einen Phagencocktail bereitstellen, dessen Wirkung die Erwartungen übertraf.



Lebensretter PHAGEN -

Patient
Schäferhund mit Mittelohrentzündung

- **9 Monate Behandlung mit Antibiotika**
- **OP mit kompletter Exzision des Innenohrs – Taubheit**
- **3 Tierärzte befragt, BU erst bei 3. Konsultation –**
  MDR *P. aeruginosa*
- **Gefahr des Durchbruchs, Vorschlag: erneute OP oder Euthanasie**

Ein Weg aus der Antibiotika-Resistenz

https://www.youtube.com/watch?v=h5vVxWtJer4

Ein Video von Franca Pott

Mögliche Folgen der OP:

- Keimbeseitigung nicht garantiert – Rückfall wahrscheinlich
- Gefahr einer zusätzlichen Infektion
- Gefahr der Nervenverletzung mit Folge „schiefe Schnauze“

Behandlung: 5x 2 Spülungen pro Tag mit Phagensuspension

Ein Weg aus der Antibiotika-Resistenz

https://www.youtube.com/watch?v=h5vVxWtJer4

Ein Video von Franca Pott

Anmelden

Berliner Morgenpost

Suche

Home Berlin Bezirke Interaktiv Politik Wirtschaft Sport Panorama Kultur **Wissen** Reise Lifestyle Abo Specials Service

In den Nachrichten: Olympische Winterspiele | Flughafen BER | Unter 20 Euro | WhatsApp-Service | Alle Themen

Home – Wissen – Bakterienkiller gegen Keime im Stall

HANNOVER

Bakterienkiller gegen Keime im Stall

Tierärzte erproben den Einsatz sogenannter Phagen in der Massentierhaltung – als natürliche Alternative zu Antibiotika

15.06.2017, 03:01 Uhr **Johannes Kaufmann**

Reduction of *Campylobacter* load in broiler chickens by the use of phage application

1st German Phage Symposium
Universität Hohenheim

S. Kittler[a], S. Fischer[b], G. Glünder[b]
Institut für Lebensmittelqualität und –sicherheit[a]
Klinik für Geflügel[b]
Stiftung Tierärztliche Hochschule Hannover

Ergebnisse der Labor- und Feldexperimente

Fischer et al. 2013 Impact of a Single Phage and a Phage Cocktail Application in Broilers on Reduction of *Campylobacter jejuni* and Development of Resistances p. e78543, PLos ONE, vol. 8


AEM
Journals.ASM.org

Effect of Bacteriophage Application on *Campylobacter jejuni* Loads in Commercial Broiler Flocks

Sophie Kittler,[a] Samuel Fischer,[b] Amir Abdulmawjood,[a] Gerhard Glünder,[b] Günter Klein[a]

Institute for Food Quality and Food Safety, University of Veterinary Medicine Hannover, Hannover, Germany[a]; Clinic for Poultry, University of Veterinary Medicine Hannover, Hannover, Germany[b]

Labor - Vorversuche

- Min. Reduktion $\log_{10}$ 2.5 mit 2 verschiedenen *Campylobacter*-Feldisolaten

Feldversuche

- **Signifikante Reduktion in 2 Versuchen** ($P<0.05$) bis 4 Tage nach Behandlung
- Entstehung resistenter Biotypen mit reduziertem Potential zur Kolonisierung (Versuch 3)

- **Zur Verbesserung der Reproduzierbarkeit:**
  - **Optimierung der Behandlungszeit**
  - **Stammspezifische Phagencocktails**
  - **Optimierung der Phagendosis**

Niedersächsisches Landesamt
für Verbraucherschutz und
Lebensmittelsicherheit

Technische
Universität
Braunschweig

Bacteriophage application in honeybees infected with *Paenibacillus larvae*

1st German Phage Symposium

9. – 10. October 2017

University of Hohenheim

Hannes Beims
LAVES – Inst. f. Bienenkunde Celle

Phagen in der Lebensmittelkette

PD Dr. Wolfgang Beyer
Universität Hohenheim
homepage: uniho-beyer.de

PhageGuard

THE POWER OF NATURE

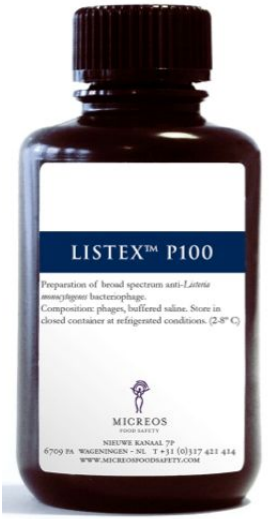
MICREOS

Main Office
Micreos Food Safety B.V.
Nieuwe Kanaal 7p
6709 PA Wageningen
The Netherlands
Tel: +31 (0)888 007 151
info@micreos.com

Bacteriophages for biocontrol of Listeria and Salmonella in foods

Steven Hagens
October 11th, Hohenheim

PhageGuard Listex & PhageGuard S



- Safe
  - Strictly lytic
  - Harmless to plants, animals and humans
  - No food safety issues
  - Chance of resistance development is minimal in food processing environments
- Effective
  - 1 – 3 log reduction
  - Specific against Listeria spp (PhageGuard Listex) and Salmonella spp (PhageGuard S)
- Processing aid status
  - Phages work instantly - no ongoing function in the end product
- Regulatory Status
  - FDA GRAS status for PhageGuard Listex & PhageGuard S
  - USDA- 7120 approval
  - Canada: letter of no objection for Listex, PhageGuard S pending
  - FSANZ (Australia & New Zealand) Listed approved as processing aid, PhageGuard S pending
  - EFSA concluded no human safety concern
  - Netherlands: processing aid on all foods

PhageGuard

Regularien

PD Dr. Wolfgang Beyer
Universität Hohenheim
homepage: uniho-beyer.de

Workshops on “Phages as tools for therapy, prophylaxis and diagnostics”, October 2015, Tbilisi, Georgia.

Biotechnology Journal
www.biotechnology-journal.com

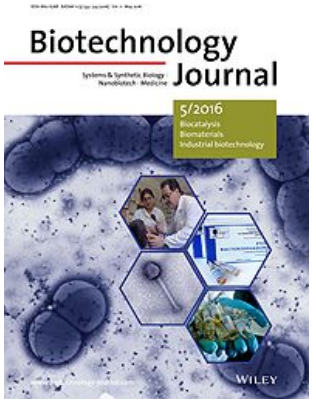
Biotechnol. J. 2016, 11, 595–600

DOI 10.1002/biot.201600023

Silk route to the acceptance and re-implementation of bacteriophage therapy

Expert round table on acceptance and re-implementation of bacteriophage therapy.

Supporting information available online



Minimal quality and safety requirements for phage therapy products

Top four root causes for delay in acceptation and application of phage therapy from scientific, legal, practical, financial, and educational points of view

Biotechnology Journal published by Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Biotechnol. J. 2016, 11 DOI 10.1002/biot.201600023

Silk route to the acceptance and re-implementation of bacteriophage therapy

Biotechnology Journal published by Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Biotechnol. J. 2016, 11 DOI 10.1002/biot.201600023

	Essential
Phages	Free of potentially damaging genetic determinants (e.g. encoding for integrase, toxins and antibiotic-resistance)
	Activity against target strains as well as a broad host range at pathogen species level
	Lytic only, non-transducing
Production host bacterial strains	Non-virulent, non-toxin producing strain
Production process	Animal component free culture media and additives
Final products	Non-pyrogenic
	Sterile
	Endotoxin levels within accepted levels for specific endotoxin definition

J Antimicrob Chemother 2016; **71**: 2071–2074
doi:10.1093/jac/dkw083 Advance Access publication 10 April 2016

Journal of Antimicrobial Chemotherapy

Bacteriophage therapy: a regulatory perspective

Eric Pelfrene[1]*, Elsa Willebrand[1], Ana Cavaleiro Sanches[2], Zigmars Sebris[3] and Marco Cavaleri[1]

[1]Office of Anti-infectives and Vaccines, Human Medicines Evaluation Division, European Medicines Agency, London, UK; [2]Quality Office, Human Medicines Evaluation Division, European Medicines Agency, London, UK; [3]Regulatory Affairs Office, Human Medicines Research and Development Support Division, European Medicines Agency, London, UK

*Corresponding author. Tel: +44-20-3660-8593; Fax: +44-20-3660-5515; E-mail: eric.pelfrene@ema.europa.eu

Despite the recognized problem of antibiotic multidrug resistance, very few antibacterial agents with new mechanisms of action are under development. Bacteriophage therapy could offer one alternative strategy to mitigate this challenge. Although widely used throughout the 20th century in Eastern Europe and the former Soviet Union, this potential therapy has not yet been investigated according to rigorous scientific standards.

This paper reports on a … meeting held at the EMA, which outlined the **existing regulatory frame-work to which such therapy should adhere** and reviewed the current obstacles and shortcomings in scientific development for bacteriophage therapy.

European Food Safety Authority

The EFSA Journal (2009) 1076, 1-26

SCIENTIFIC OPINION

The use and mode of action of bacteriophages in food production[1]

Scientific Opinion of the Panel on Biological Hazards

(Question No EFSA-Q-2008-400)

Endorsed by the BIOHAZ Panel for public consultation 22 January 2009

Public consultation 30 January – 6 March 2009[2]

Adopted on 22 April 2009

Forschung zu definierten Kombinationen aus

Phage-Pathogen-Lebensmittel

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 7 July 2016

doi: 10.2903/j.efsa.2016.4565

Evaluation of the safety and efficacy of Listex™ P100 for reduction of pathogens on different ready-to-eat (RTE) food products

EFSA Panel on Biological Hazards (BIOHAZ)

- **P_{100} is not considered to pose a risk to human health**
- **More studies on the efficacy of ListexTM P_{100} in naturally contaminated RTE foods should be undertaken**

FINAL REPORT
Systematic and critical review on the potential use of bacteriophage on foods
FS102079, March 2016, Campden BRI

Campden BRI
food and drink innovation

Guidance Quality Control and Quality Assurance criteria for stocks of host bacteria used in the bacteriophage production process sourced from Pirnay et al. 2015

Guidance Quality Control and Quality Assurance criteria for bacteriophage seed stocks used in the bacteriophage production process sourced from Pirnay et al. 2015

Deutscher Bundestag Drucksache 18/**12075**

18. Wahlperiode 25.04.2017

Beschlussempfehlung und Bericht

des Ausschusses für Bildung, Forschung und Technikfolgenabschätzung (18. Ausschuss)

zu dem Antrag der Fraktionen der CDU/CSU und SPD
– Drucksache 18/10972 –

Pharmazeutische Forschung gegen Infektionskrankheiten stärken – Nationale Wirkstoffoffensive starten

Nach Erhebungen des Europäischen Parlaments sterben gegenwärtig 25 000 Bürger pro Jahr in Europa, weil Antibiotika gegen resistent gewordene Erreger nicht mehr richtig wirken. Es steht zu befürchten, dass bei einer ungehemmten Weiterverbreitung von Resistenzen bis zu 10 Millionen Todesfälle im Jahr durch nicht behandelte Infektionen in Zukunft möglich wären.

DEFENSIE
LA DÉFENSE

VOORRANG AAN VREDE
PRIORITÉ À LA PAIX

Art. 37 of the Declaration of Helsinki

Compassionate Use („Anwendung aus Mitgefühl“)

“In the treatment of a patient, ***where proven*** *prophylactic, diagnostic and* ***therapeutic methods do not exist or have been ineffective****, the physician, with informed consent from the patient, must be free to use* ***unproven or new*** *prophylactic, diagnostic and* ***therapeutic measures, if in the physician’s judgment it offers hope of saving life, re-establishing health or alleviating suffering****”*

- Sporadically used (8 cases)
  - Osteomyelitis (2)
  - Pneumonia (1)
  - Respiratory tract infection (1)
  - Chronic sinusitis (1)
  - Sepsis (1)
  - Burn wounds (1)
  - Bedsores (1)
- On average one request/week

.be

Current bacteriophage collection of the L. Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences

Lp.	Bacteriophage host ranges	Number of phages
1.	*Staphylococcus aureus, epidermidis, haemolyticus* (including MSSA, MRSA, MRCNS)	9
2.	*Enterococcus faecalis, faecium* (including HLAR, HLGR, VRE)	102
3.	*Escherichia coli* (including ESBL+)	303
4.	*Klebsiella pneumoniae, oxytoca* (including ESBL+)	110
5.	*Enterobacter cloacae, aerogenes, sakazakii* (including ESBL+)	49
6.	*Shigella flexneri, sonnei*	39
7.	*Citrobacter freundii, koseri*	32
8.	*Pseudomonas aeruginosa, fluorescens*	55
9.	*Salmonella enteritidis, typhimurium*	47
10.	*Stenotrophomonas maltophilia* (including ESBL+)	21
11.	*Serratia marcescens, liquefaciens* (including ESBL+)	15
12.	*Proteus mirabilis, vulgaris* (including ESBL+)	26
13.	*Morganella morganii* (including ESBL+)	16
14.	*Acinetobacter baumannii, lwoffii*	6
15.	*Burkholderia cepacia*	2
	TOTAL	**832**

Weber-Dąbrowska et al. 2017 (unpublished data)

>300 Patienten behandelt, seit 2008

Eine mögliche Lösung:

The “Belgian Magistral Phage Medicine Strategy”

Viruses 2018, 10, 64; doi:10.3390/v10020064

Formula magistralis

Pharmazeutische Zubereitung in einer Apotheke nach ärztlicher Vorschrift

defined as “any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient” (Article 3 of Directive 2001/83).

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use.

On 26 October 2016, it was formally agreed that natural phages whose derivative finished products are

- **not fully compliant with the requirements relating to medicinal products for human use (Directive 2001/83),**
- **and for which there is no monograph in an official pharmacopoeia,**

can be processed by a pharmacist as active pharmaceutical ingredients (APIs) in magistral preparations, providing compliance to a number of logical provisions:

- **Phages should be delivered in the form of a magistral preparation to a specific (nominal) patient.**
- **Magistral preparations should always be delivered under the direct responsibility of a medical doctor and a pharmacist.**
- **The relevant characteristics and qualities of the phage APIs should be defined in an internal monograph (prepared by the supplier).**
- **Before the pharmacist can use the unlicensed material, he/she must ascertain—based on certificates of analysis issued by a Belgian Approved Laboratory—that the raw materials conform to the provisions of the internal monograph.**
- **Even if not legally required, it is recommended that the supplier submits the monograph for assessment by the FAMHP (Federal Agency for Medicines and Health Products)**

Standard Prozedur für die Anwendung eines “Unauthorized active ingredient” in einem “Magistralen Präparat”

- **Arzt**
- **individueller, informierter Patient,**
- **Produzent der “aktiven Substanzen” gemäß interner Monographie**
- **zugelassenes Bestätigungslabor (Referenzlabor),**
- **Apotheker,**

plus ggf.

- **Zulassungsbehörde (FAMHP in Belgien) (BfArM / PEI / BVL?)**

Aus: Viruses 2018, 10, 64; doi:10.3390/v10020064

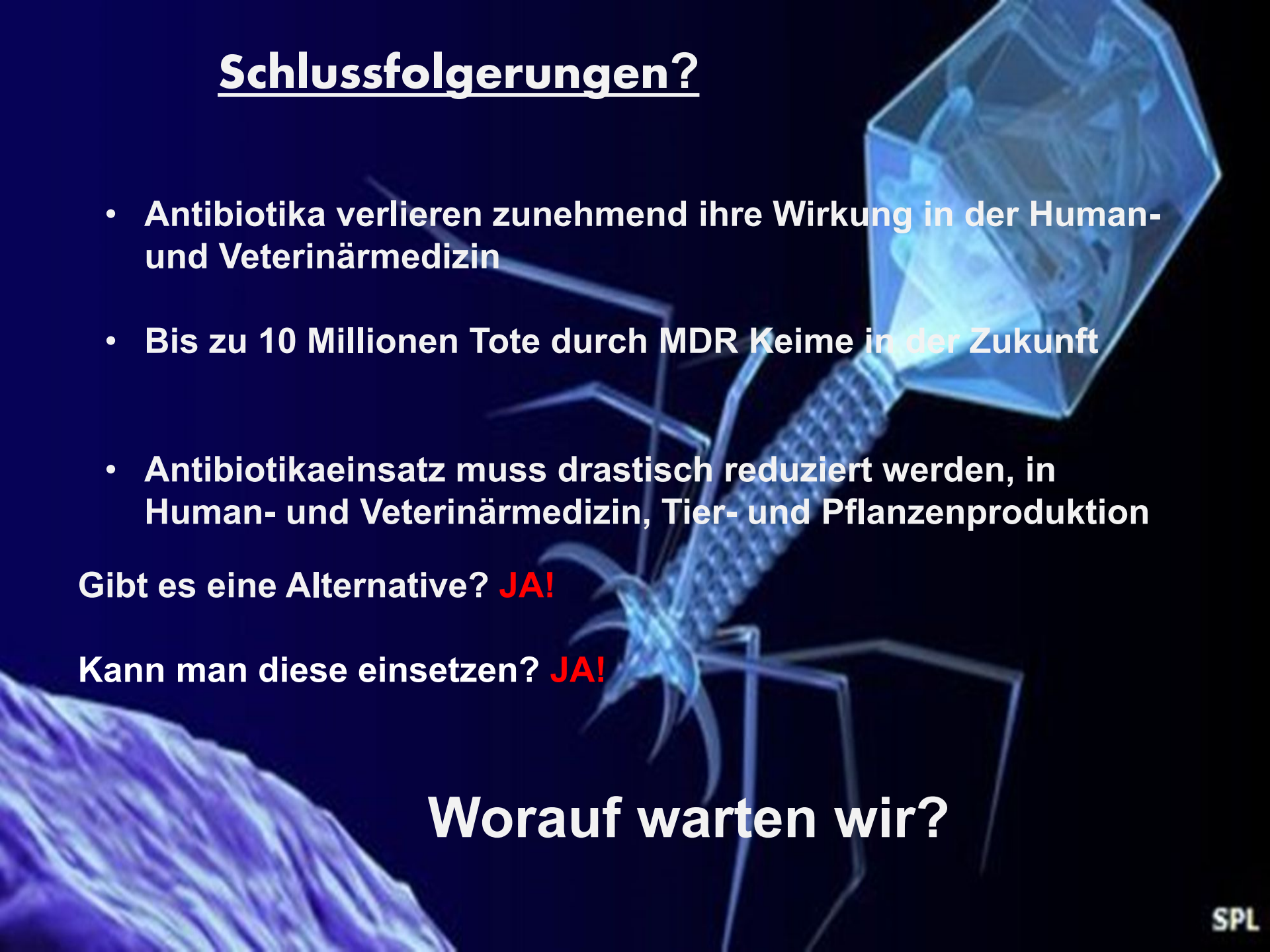
Schlussfolgerungen?

- Antibiotika verlieren zunehmend ihre Wirkung in der Human- und Veterinärmedizin
- Bis zu 10 Millionen Tote durch MDR Keime in der Zukunft
- Antibiotikaeinsatz muss drastisch reduziert werden, in Human- und Veterinärmedizin, Tier- und Pflanzenproduktion

Gibt es eine Alternative? JA!

Kann man diese einsetzen? JA!

Worauf warten wir?



1st German Phage Symposium

Program and Abstract Book

09 – 11 October 2017

1ST GERMAN PHAGE SYMPOSIUM

Viruses **2018**, *10*(4), 158; doi:10.3390/v10040158

Open Access | Conference Report

1st German Phage Symposium—Conference Report

Irene Huber [1] ✉, Katerina Potapova [1] ✉, Andreas Kuhn [1,2] ✉, Herbert Schmidt [1,3] ✉, Jörg Hinrichs [1,3] ✉, Christine Rohde [4] ✉ and Wolfgang Beyer [1,5,*] ✉

Professor Martin Witzenrath, Charité Berlin

Professor Martin Witzenrath, Charité Berlin, 10 October 2017, Stuttgart
Photo: University of Hohenheim, Photographer: Kaan Arduc

Dr Mzia Kutateladze, Eliava Institute, Tbilisi, Keynote Lecture

Dr Mzia Kutateladze, Eliava Institute, Tbilisi, Georgia, Keynote Lecture, 10 October 2017, Stuttgart
Photo: University of Hohenheim, Photographer: Kaan Arduc

Professor Andrzej Górski, Ludwik Hirszfeld Institute, Wrocław

Professor Andrzej Górski, Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, 10 October 2017, Stuttgart
Photo: University of Hohenheim, Photographer: Kaan Arduc

Dr Thomas Rose, Queen Astrid Military Hospital, Att. P.H.A.G.E., Brussels

Dr Thomas Rose, Queen Astrid Military Hospital, Att. P.H.A.G.E., Brussels, 10 October 2017, Stuttgart
Photo: University of Hohenheim, Photographer: Kaan Arduc

Dr Brigitte Brake (BfArM, Bonn) and Dr Isabelle Bekeredjian-Ding (PEI)

Dr Brigitte Brake (BfArM) and Dr Isabelle Bekeredjian-Ding (PEI) (Panel Discussion "Quo vadis, deutsche Bakteriophagenforschung?", 11 October 2017, Stuttgart)
Photo: University of Hohenheim, Photographer: Joachim E. Röttgers

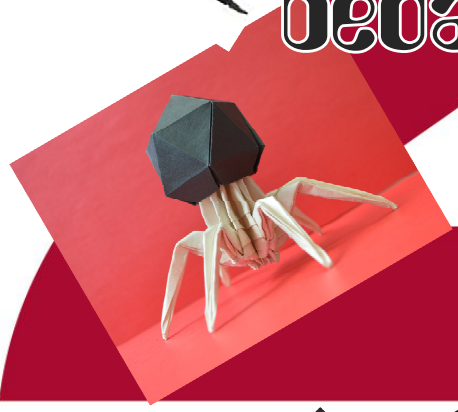
Dr Christine Rohde, Leibniz Institute – DSMZ Braunschweig

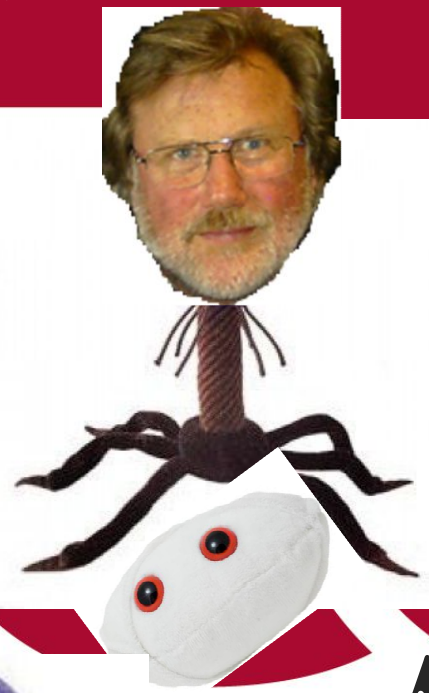
Dr Christine Rohde, DSMZ Braunschweig (Panel Discussion "Quo vadis, deutsche Bakteriophagenforschung?", 11 October 2017, Stuttgart)
Photo: University of Hohenheim, Photographer: Joachim E. Röttgers

200 JAHRE 1818 2018
UNIVERSITÄT HOHENHEIM

Wir

bedanken





1818

uns

JAHRE

für

Aufmerksamkeit

die

HOLLENHEIM