Sind alternative Strategien zur Behandlung von multiresistenten Erregern (MRE) nicht nur theoretisch möglich, sondern auch klinisch realisierbar ?

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Apokryphes Zitat

Dr. William H. Stewart (US Surgeon General 1965 – 1969):

- It is time to close the book on infectious diseases, and declare the war against pestilence won.

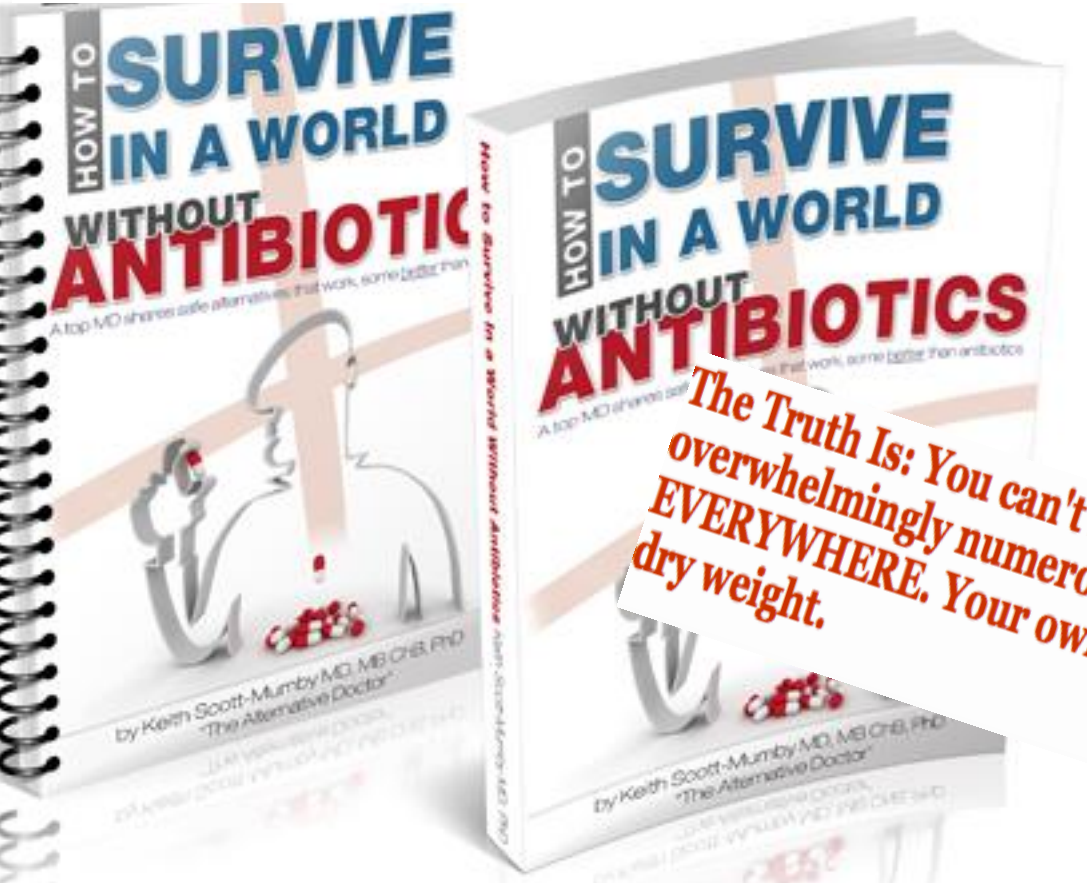
(The office of the Public Health Service Historian. Frequently asked questions. 7 December 2004.
Available at: *http://lhncbc.nlm.nih.gov/apdb/phsHistory/faqs.html*.

ABER

- He never made any such statement: Numerous other verfiable sources, however, confirm that other people in academia adopted this belief. (Spellberg B, Taylor-Blake B: On the exoneration of Dr. William H. Stewart: debunkering an urban legend. Infectious Diseases of poverty 2013, **2**:3. *Available at:* *http://www.idpjournal.com/content/2/1/3*)

The "Golden Age" Of Antibiotics Is Over!

Deadly new organisms, resistant to all known antibiotics, are emerging all over the planet and gaining ground FAST...



The Truth Is: You can't hold back bacteria. They are too overwhelmingly numerous and powerful. Bacteria are EVERYWHERE. Your own body, incredibly, is 10% bacteria by dry weight.

Drug companies snub antibiotics as pipeline threatens to run dry

(Tom Clarke, Nature 2003; 425: 225)

Die Pipeline ist gut gefüllt

Investigational antimicrobial agents (Pucci MJ, Bush K, CMR 2013; 26: 792-821) :

In der *klinischen Entwicklung* befindliche Präparate
(Stand Herbst 2012 + Frühjahr 2013):

- 11 Chinolone, 9 ß-Lactame, 8 Anti-Tuberkulostatika,
  4 anti- *C. difficile* Präparate, 5 Präparate gegen Gram-+,
  14 Proteinsynthese-Inhibitoren = 51 gesamt

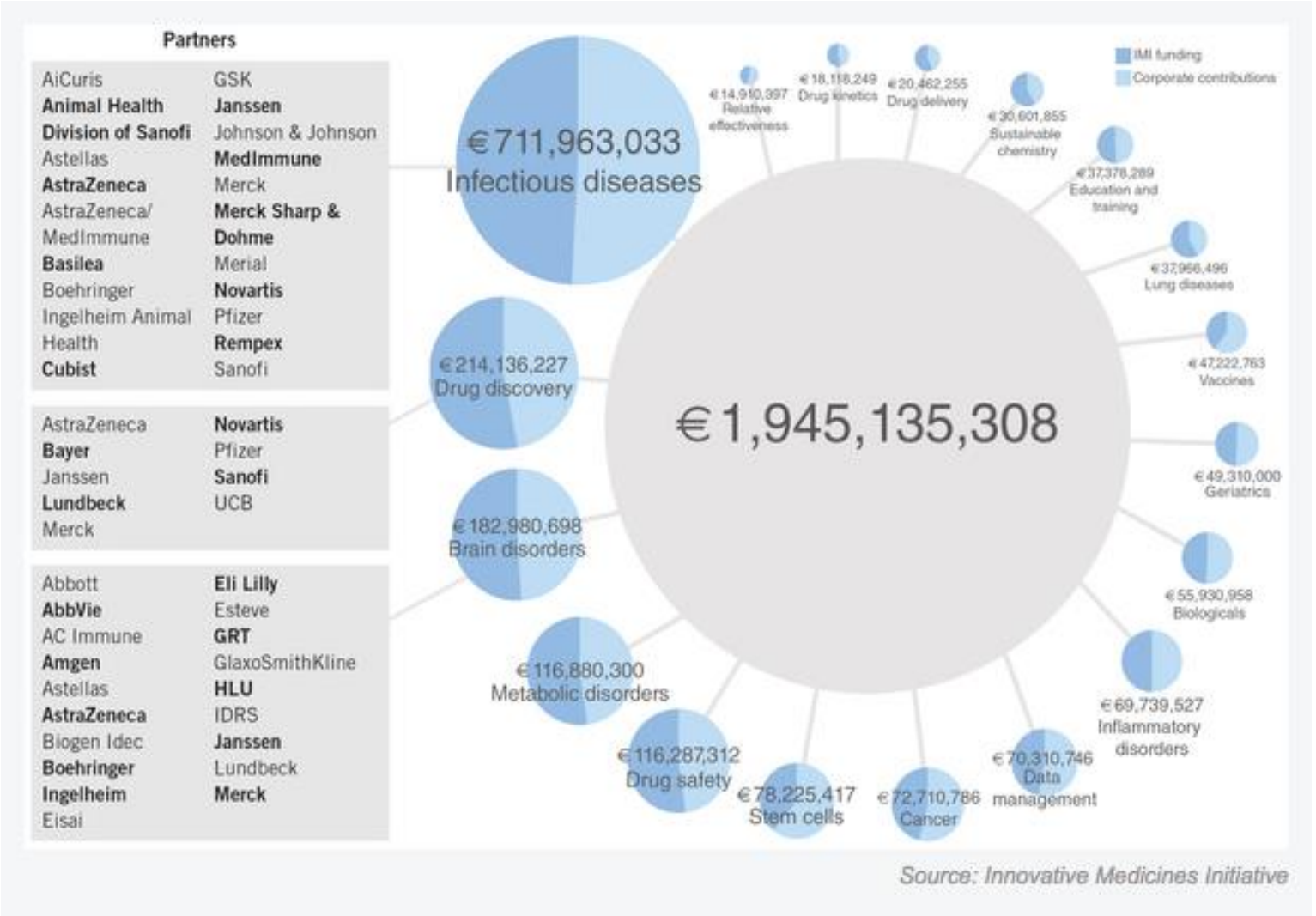
Speculative strategies for new antibacterials: all roads should not lead to Rome. (Shapiro S, J Antibiotics 2013; 66: 371-386)

- ....decline in the breadth of chemical space for new antibacterial molecules and a failure to exploit the plethora of cellular processes potentially targetable by novel classes of antibacterial molecules. This Review focuses on some streategies relating to antibacterial chemotherapy, *paths less trodden*.

  >20 Strukturen

The EU Innovative Medicines Initiative

(Nature Medicine 2014; 20: 5; doi:10.1038/nm0114-5)

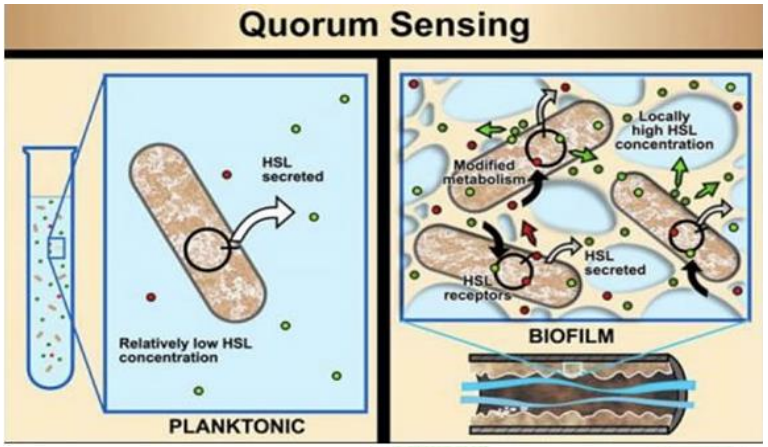


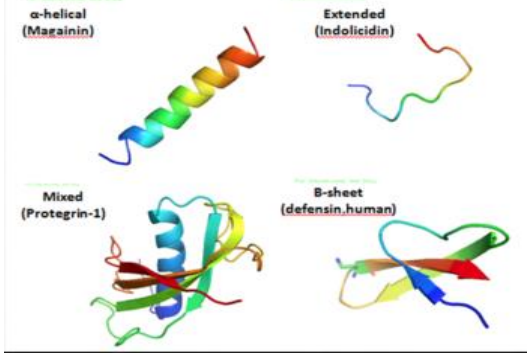
The EU Innovative Medicines Initiative

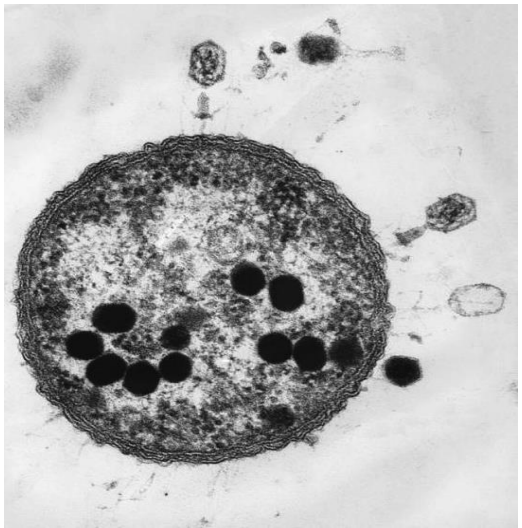
(Nature Medicine 2014; 20: 5; doi:10.1038/nm0114-5)

- The Innovative Medicines Initiative (IMI) launched in 2008 as part of a massive European push to foster public-private partnerships in biomedicine. Over its six years of existence, the € 2 billion ($2.7 billion) joint venture between the EU and the European Federation of Pharmaceutical Industries and Associations has collaborated with 43 companies and worked with scientists from 31 participating countries. Nine IMI-backed medicinal products have gone into a total of 90 clinical trials. Close to 600 peer-reviewed research papers have come out of the effort.
- Now, the IMI is coming to the end of its first phase. Last month, the Brussels-based institution announced its eleventh and final call for proposals within the initial budget allocation. The next phase of the initiative—what's known as IMI 2—is hoped to launch this spring and last another ten years. Here, *Nature Medicine* takes a look at where the IMI's money has been allocated to date and highlight the industry partners who have supplied funds in three areas.

Alternativen – so oder so ?







Eat leeks in March and wild garlic in May, and all the year after the physicians may play.
Traditional Welsh rhyme

An apple a day keeps the doctor away. Traditional American rhyme

(Martin KW, Ernst E, JAC 2003; 51: 241-246; Cowan KW, CMR 1999; 12: 564-582)

Antimicrobial peptides: Old molecules with new ideas

(Nakatsuji T, Gallo RL., J Invest Dermatol 2012; 132: 887-895)

- Fleming beobachtete die antibakterielle Wirkung des Nasalsekretes von einem erkältetem Patienten

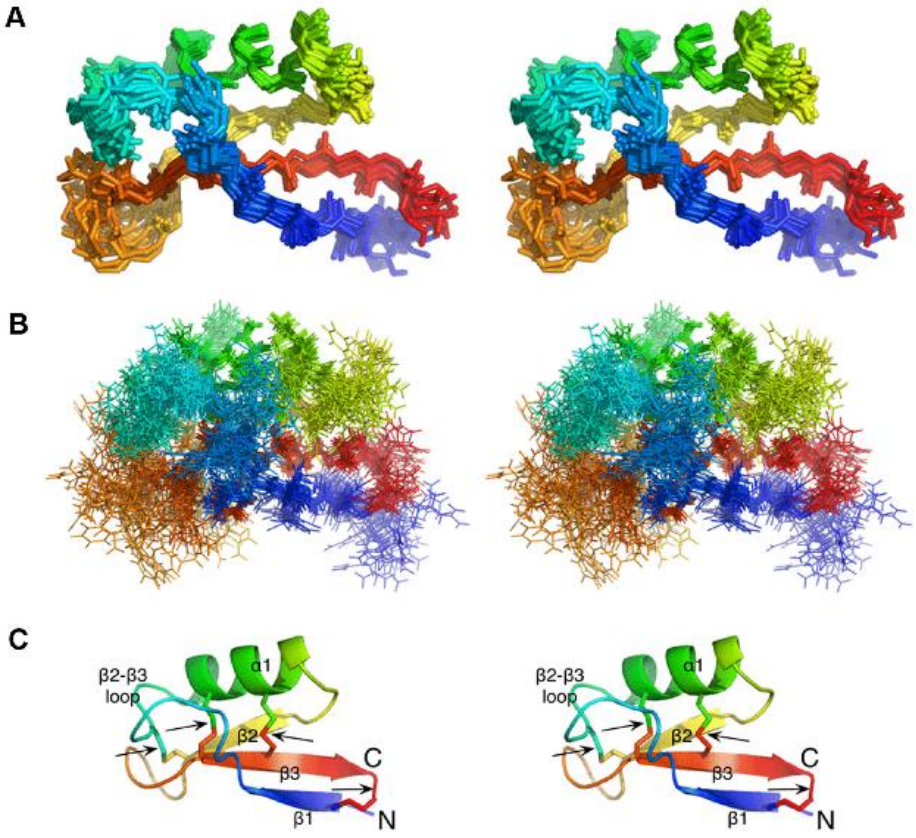
  Lsozym

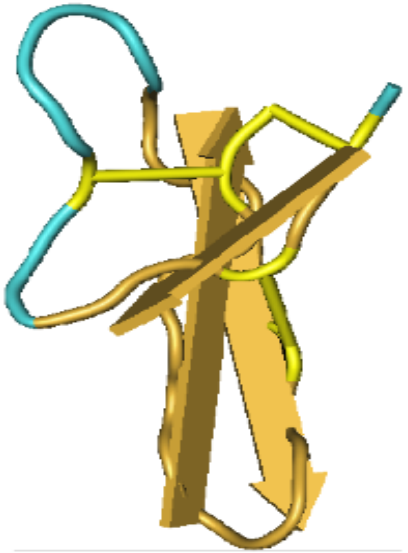
  (Fleming A. On a remarkable bacteriolytic element found in tissues and secretions. Proc R Soc London B 1922; 70: 11-17)

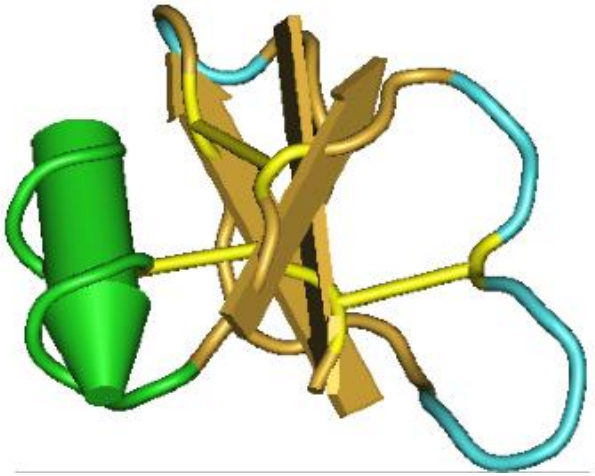
- Seitdem wurden mehr als 2.336 antimikrobielle Peptide isoliert

  (Antimicrobial Peptide Database http://aps.unmc.edu/AP/main.php)

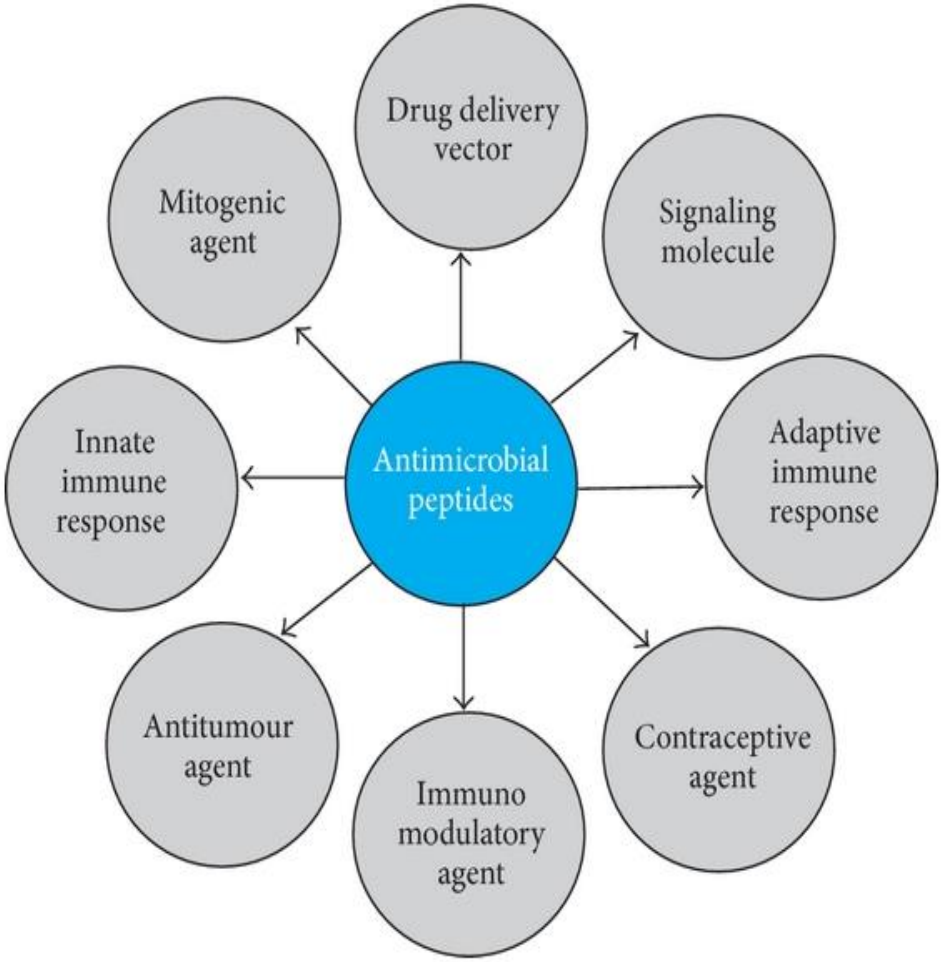
Defensine: Medicago trunculata Defensin 4 (links), α-Defensin (rechts oben), ß-Defensin (rechts unten)







Pushpanathan M. et al., Antimicrobial Peptides: Versatile Biological Properties (International Journal of Peptides, vol. 2013, Article ID 675391, 15 pages, 2013. doi:10.1155/2013/675391)



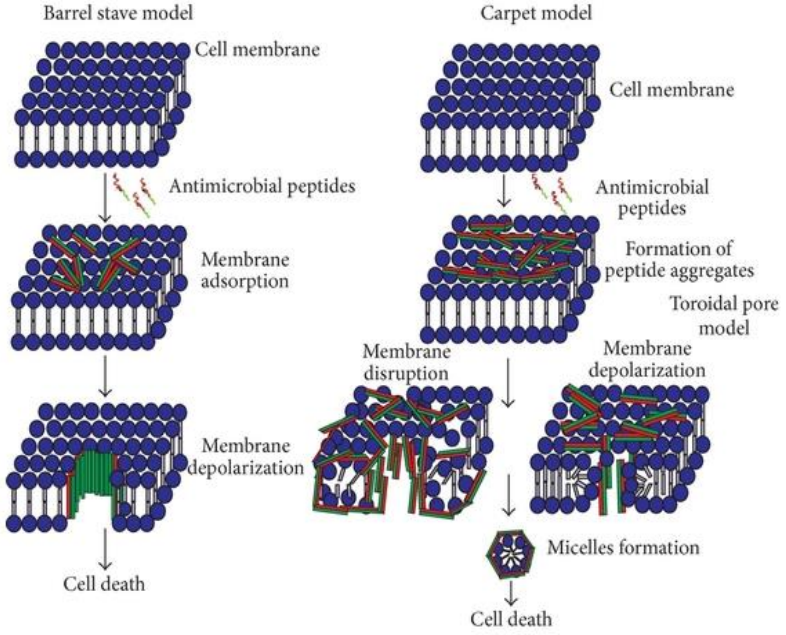
Pushpanathan M. et al., Antimicrobial Peptides: Versatile Biological Properties (International Journal of Peptides, vol. 2013, Article ID 675391, 15 pages, 2013. doi:10.1155/2013/675391)

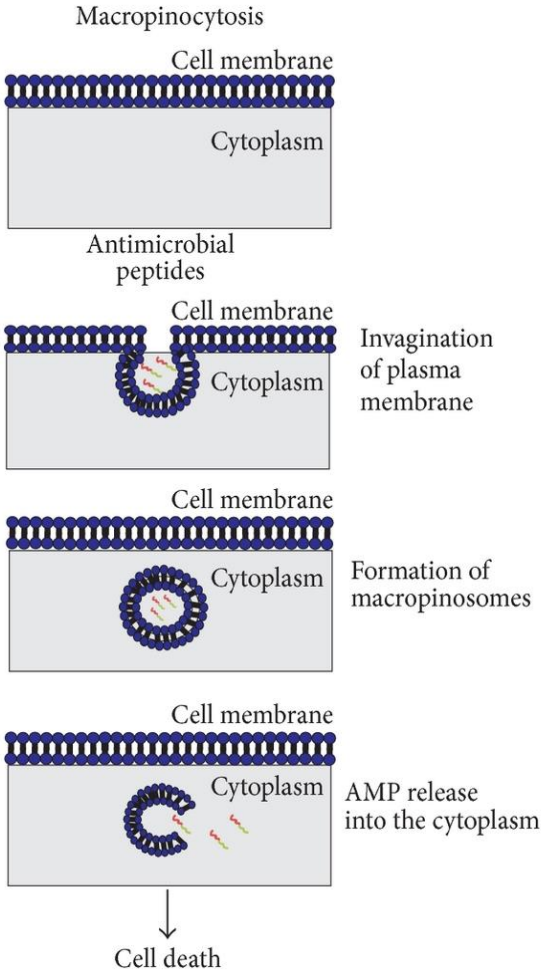
Source of AMPs	AMPs
Insect	Cecropin A, Sarotoxin IA, ponericin G2, ceratotoxin, stomoxyn, spinigerenin, thanatin, heliomicin, Alo3, sapecin, defensin A, smD1, gallerimycin, termicin, royalisin, drosomycin, drosocin, metchnikowin, apidaecin IA, abaecin, formaecin, lebocin, pyrrhocoricin, melittin, attacins, coleoptericin,diptericin,
Amphibians	Japonicin-1 & 2, nigrocin 1 & 2, brevinin-20a, temporin-1Od, tigerin-1, pseudin-2, maximin-1, distinctin
Echinoderms	Strongylocins, centrocins, betathymosins, filamin A
Crustaceans	Callinectin, astacidin 2, armadillidin, homarin, scygonadin, penaeidin, crustin, hyastatin, arasin, stylicin, hemocyanin derived peptides
Plants	Thionins, plant defensins, lipid transfer proteins
Mammals	Defensin, histatin, LL-37, indolicidin, protegrin, lactoferricin
Bacteria	Iturin, bacillomycin, syringomycin, syringostatins, syringotoxins, nikkomycins
Fungi	Echinocandins, aculeacins, mulundocandins, FK463, aureobasidin, leucinostatins, helioferins
Fishes	Pardaxins, misgurin, pleurocidins, parasin, oncorhyncin II and III, chrysophsin and HFIAP

Pushpanathan M. et al., Antimicrobial Peptides: Versatile Biological Properties (International Journal of Peptides, vol. 2013, Article ID 675391, 15 pages, 2013. doi:10.1155/2013/675391)

Class of AMP	Structural features	Representative peptides	Structure
Cationic peptides	Peptides forming α-helical structures	Cecropins	α-Helix
	Single disulphide bridge	Thanatin	β-Sheet
	Two disulphide bridge	Tachyplesin II	β-Sheet
	Three disulphide bridge	Penaeidins	β-Sheet
	More than three disulphide bridge	Drosomycin	$\alpha\,\beta$-Structure
	Proline-rich peptide	Pyrrhocoricin	$\alpha\,\beta$-Structure
	Glycine-rich peptide	Diptericins	—
	Histidine-rich peptide	Histatin	Rich in H
	Tryptophan-rich peptide	Indolicidin	Extended
Noncationic peptides	Neuropeptide derived molecules	Secretolytin	α-Helix
	Aspartic acid rich peptides	Dermcidin	—
	Aromatic dipeptides	*N*-Alanyl-5-s-glutathionyl-3,4 Dihydroxy-phenylalanine and *p*-hydroxy cinnamaldehyde	—
	Oxygen binding proteins	Lactoferricin	β-Turn

Pushpanathan M. et al., Antimicrobial Peptides: Versatile Biological Properties (International Journal of Peptides, vol. 2013, Article ID 675391, 15 pages, 2013. doi:10.1155/2013/675391)Proposed mechanisms of action: Energy independent (left), and energy dependent (right)

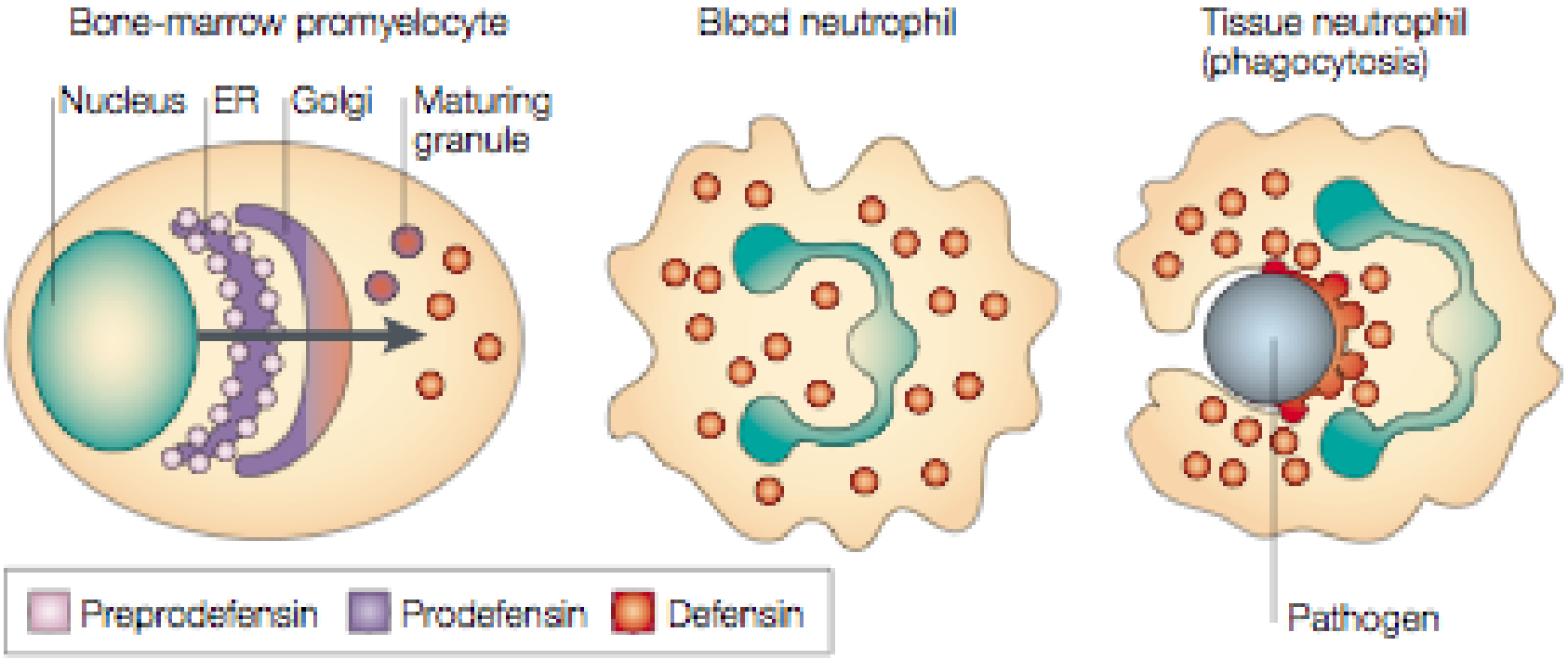




Defensins: antimicrobial peptides of innate immunity

(Ganz T. Nature Rev Immunol 2003; 3: 710-720)

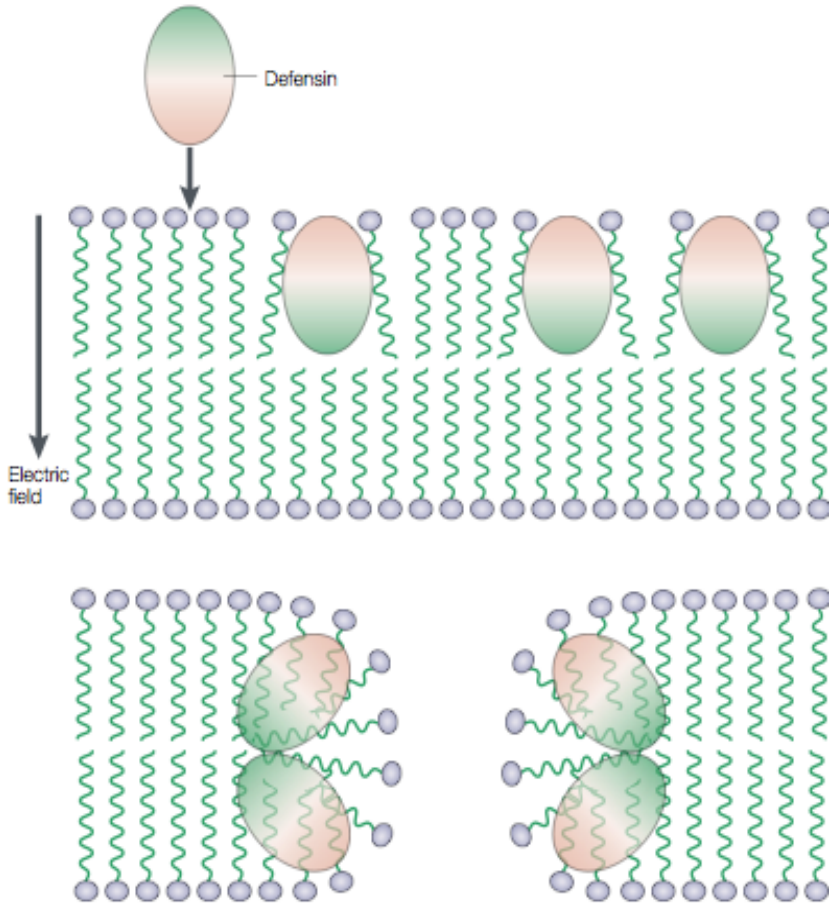
Human neutrophil peptide alpha-defensin synthesis and release onto microorganisms:

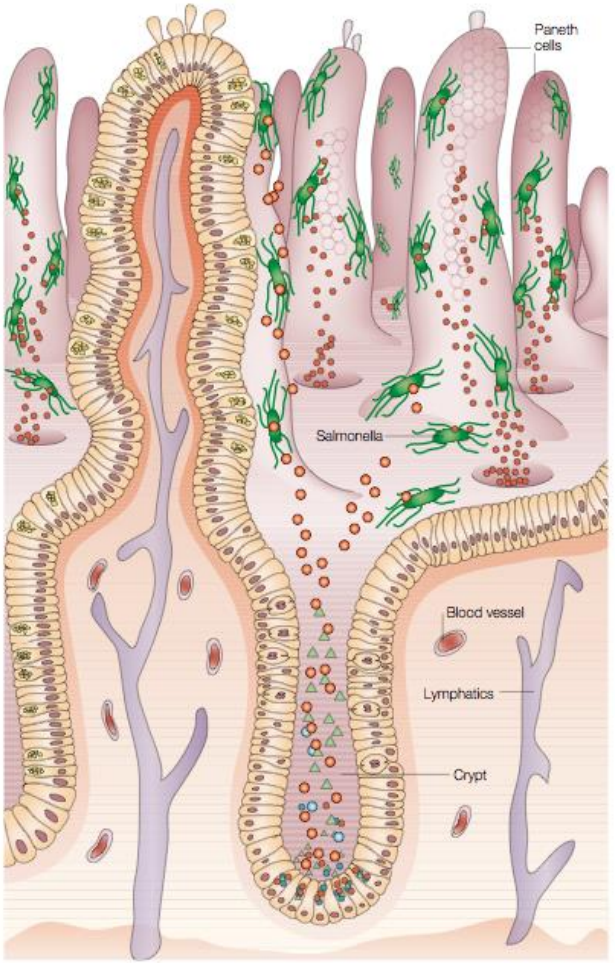


Defensins: antimicrobial peptides of innate immunity

(Ganz T. Nature Rev Immunol 2003; 3: 710-720)

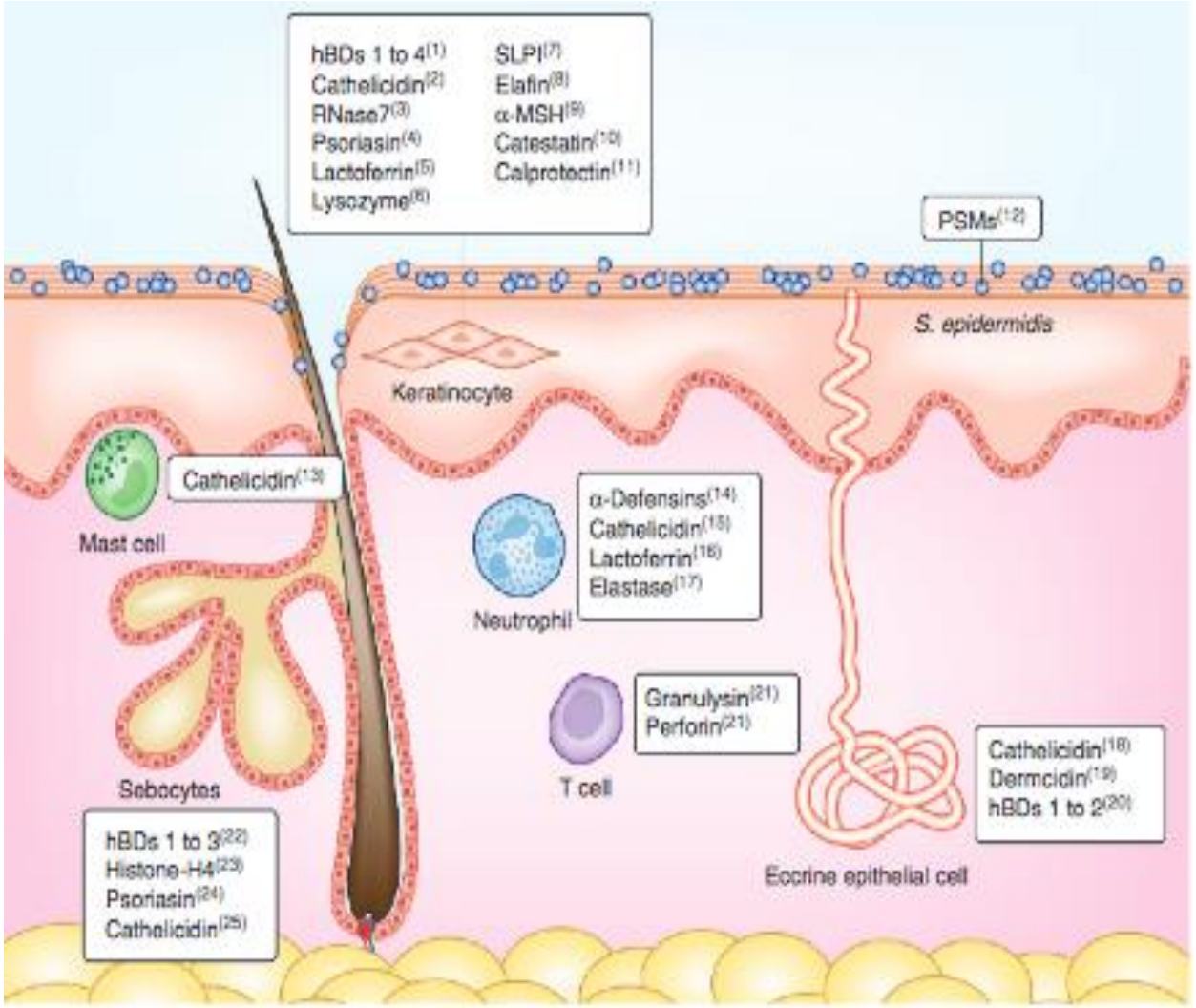
The carpet-wormhole model of action of defensins (left), and killing of Salmonella by human defensins secreted by Paneth cells (right)





The layered antimicrobial peptides of the human skin

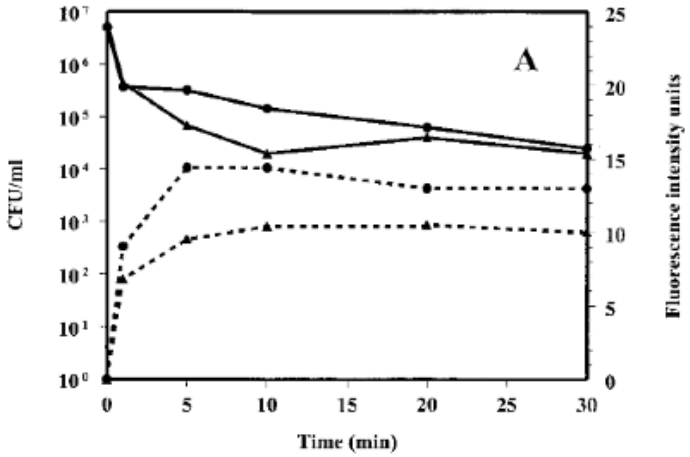
(Nakatsuji T, Gallo RL, J Invest Dermatol 2012; 132: 887-895)

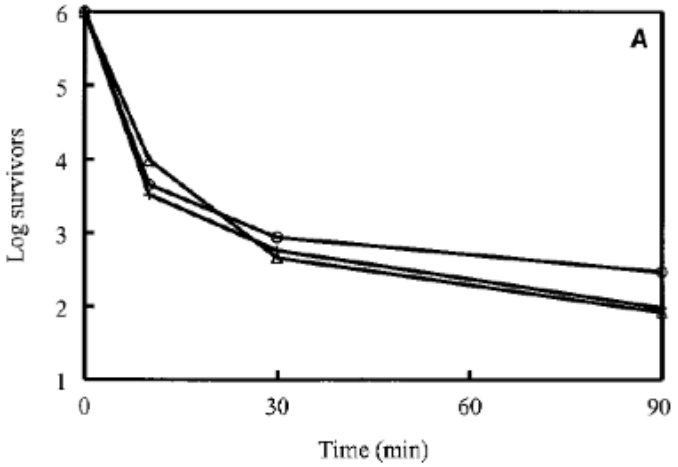


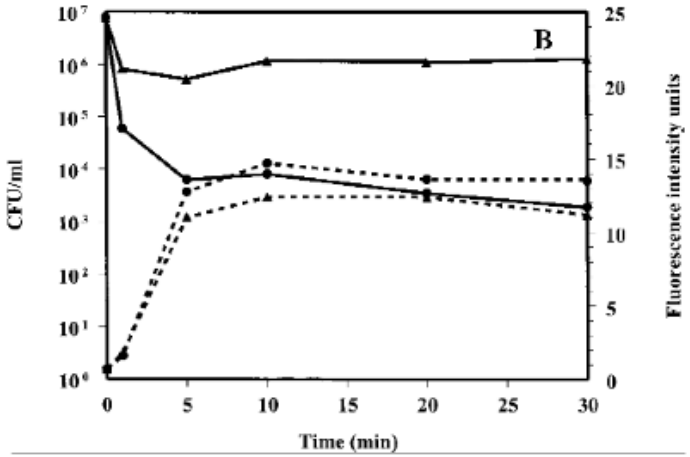
Zaslow M.: Magainins, a class of antimicrobial peptides from Xenopus skin (left, PNAS 1987; 84:5449-5453); Observations on the remarkable and mysterious wound-healing process of the bottlenose dolphin (right, J Invest Dermatol 2011; 131: 2503-2505)

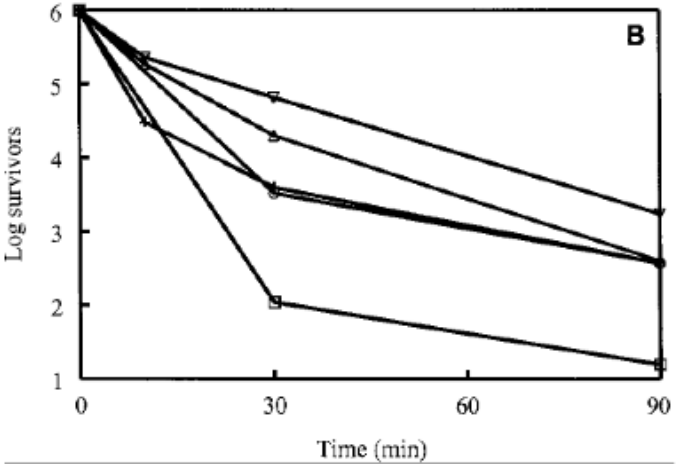
Antibacterial action of structurally diverse cationic peptides on Gram-positive bacteria (Friedrich CL et al., AAC 2000; 44: 2086-2092)

(permeabilization of the cytoplasmic membrane of *S. aureus* (dashed lines) and viable counts (solid lines) in the presence of 8mg CP26/mL or 2mg CP29/mL, left A, and indolicidin or CPHCN, left B; antibacterial action against *S. aureus*, right A, or *S. epidermidis*, right B)









Topical versus Systemic Antimicrobial Therapy for Treating Infected Diabetic Foot Ulcers: A Randomized, Controlled, Double-Blinded, Multicenter Trial of Pexiganan Cream. (Diabetic Foot Global Conference 2008, Los Angeles, March 13 to 15, Lipsky BA)

Pexiganan (1%) phase III clinical trial results as topical therapy for the treatment of infected diabetic foot ulcers: overall clinical outcome (cure or improved)

Evaluation point	Pexiganan	%	Ofloxacin	%	95% CI
End of therapy	363/418	87	377/417	90	-7.87,0.74
Follow-up	320/406	79	338/403	84	-10.41,0.31

Phase 3 Registration Trial In Mildly Infected Diabetic Foot Ulcers With Locilex

http://www.science20.com/news_articles/phase3 registration trial mildly infected diabetic foot ulcers locilex-100113

- Dipexium Pharmaceuticals, LLC today announced that it has has reached an agreement with the U.S. Food and Drug Administration on a Special Protocol Assessment for an upcoming Phase 3 registration trial in mild infections of diabetic foot ulcers with Locilex (pexiganan acetate cream 1%).
- Study DPX-305 will be a randomized, double-blind, multi-center, superiority, placebo-controlled Phase 3 Study of Pexiganan Cream 1% (Locilex(TM)) applied twice daily for 14 days to treat adult patients with mild infections of diabetic foot ulcers in the United States. Study DPX-305 will involve approximately 180 patients and the primary efficacy endpoint is resolution of infection in the medical judgment of each treating physician.

Klinischer Erfolg einer Brilacidin (PMX-30063, ein Defensin Mimetikum der Firma PolyMedix - Cellceutics) Behandlung von akuten bakteriellen Hautinfektionen, Phase II

Nebenwirkungen: 5,6 – 9,5% in der PMX-Gruppe vs. 10,9% in der Daptomycin-Gruppe sowie 65 – 87% Taubheit + „Kribbeln“ in der PMX-Gruppe
(aus: Tillotson GS, Theriault N, F1000 Prime Reports 2013, 5:51; doi:10.12703/P5-S1)

Table 1. Clinical response of brilacidin (PMX-30063) and daptomycin in acute bacterial skin and skin structure infections: a Phase II study

Clinical response	Low dose N = 52	Medium dose N = 54	High dose N = 54	Daptomycin N = 55
Day 3	94.4%	90.7%	81.5%	90.6%
Day 7	87.0%	92.6%	83.3%	96.2%
Sustained response				
Day 10	90.2%	91.8%	95.5%	97.9%
Day 28	95.7%	89.6%	95.6%	98.0%

POL 7080, ein *P. aeruginosa* spezifisches Peptidomimetikum

Wissenschaftler der Universität Zürich und der Firma Polyphor (nunmehr Roche) haben unter Verwendung der neuartigen PEM (protein epitope mimetic) –Technologie, die auf der Erkennung von oberflächen-exponierten Sekundärstrukturen wie z.B. „ß-hairpins“ und α–Helices beruht, das Protegrin I Epitop-Mimetikum POL 7080 entwickelt. Protegrin 1 wurde aus Leukozyten der Schweine isoliert und desintegriert bakterielle Membranen. POL 7080, hingegen, interagiert mit dem Protein LptD, das an der Biogenese der äusserem Membran von *P. aeruginosa* beteiligt ist.

$MIC_{50/90}$ für *P. aeruginosa, P. stutzeri, P. luteola, P. alcaligenes, P. mendocina* = 0.12/0.25 mg/L ; inaktiv gegenüber anderen Spezies.

3h i.v.-Infusion

z.Zt. in der Phase II, VAP

(Olbrecht D. et al., Drug Discov. Today 2012; 9, e63-e69;
Srinivas N. et al., Science 2010; 327: 1010-1013)

Front. Immunol., 03 July 2013 | doi: 10.3389/fimmu.2013.00143

The human cathelicidin antimicrobial peptide LL-37 as a potential treatment for polymicrobial infected wounds

Allen J. Duplantier[1] and Monique L. van Hoek[1,2]*

1 National Center for Biodefense and Infectious Diseases, George Mason University, Manassas, VA, USA
2 School of Systems Biology, George Mason University, Manassas, VA, USA

Diabetic patients often have ulcers on their lower-limbs that are infected by multiple biofilm-forming genera of bacteria, and the elimination of the biofilm has proven highly successful in resolving such wounds in patients. To that end, antimicrobial peptides have shown potential as a new anti-biofilm approach. The single human cathelicidin peptide LL-37 has been shown to have antimicrobial and anti-biofilm activity against multiple Gram-positive and Gram-negative human pathogens, and have wound-healing effects on the host. The combination of the anti-biofilm effect and wound-healing properties of LL-37 may make it highly effective in resolving polymicrobially infected wounds when topically applied. Such a peptide or its derivatives could be a platform from which to develop new therapeutic strategies to treat biofilm-mediated infections of wounds. This review summarizes known mechanisms that regulate the endogenous levels of LL-37 and discusses the anti-biofilm, antibacterial, and immunological effects of deficient vs. excessive concentrations of LL-37 within the wound environment. Here, we review recent advances in understanding the therapeutic potential of this peptide and other clinically advanced peptides as a potential topical treatment for polymicrobial infected wounds.

Cationic antimicrobielle Peptide – pro‘s und con‘s

Pro

- Schnelle anti-mikrobielle Wirkung
- Struktur abhängiges anti-mikrobielles Spektrum
- Pleiotrope Wirkungen
  - Anti-mikrobiell
  - Anti-inflammatorisch
  - Immunmodulatorisch
  - Wundheilung

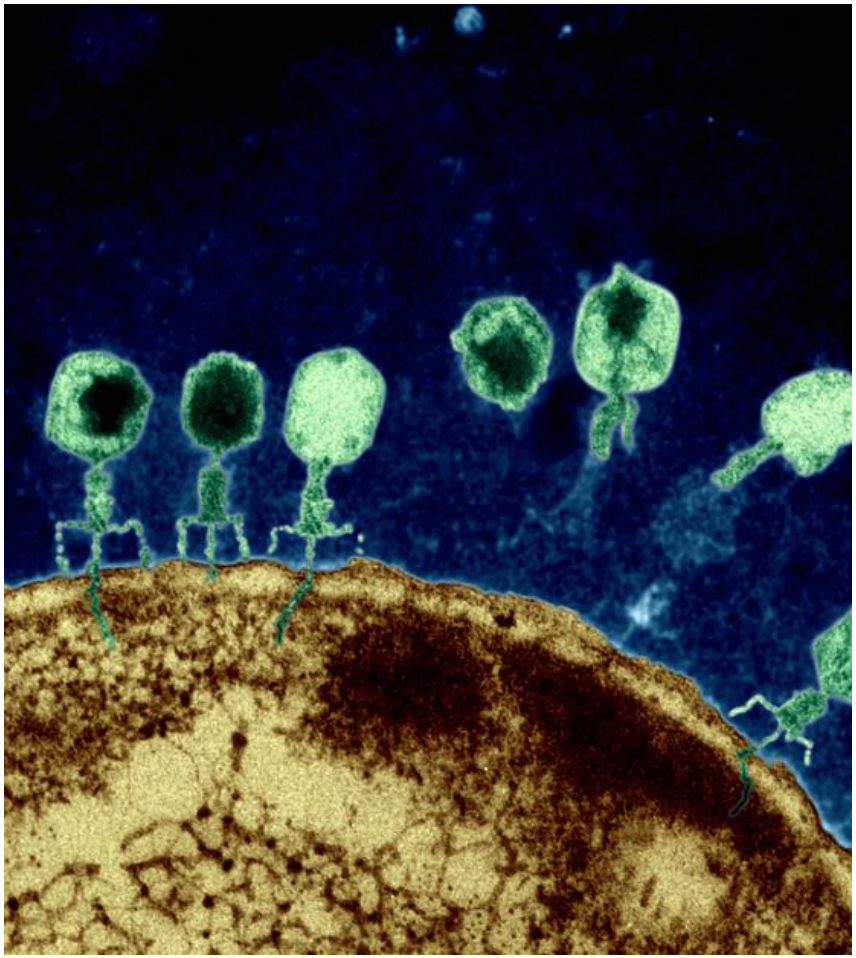
Con

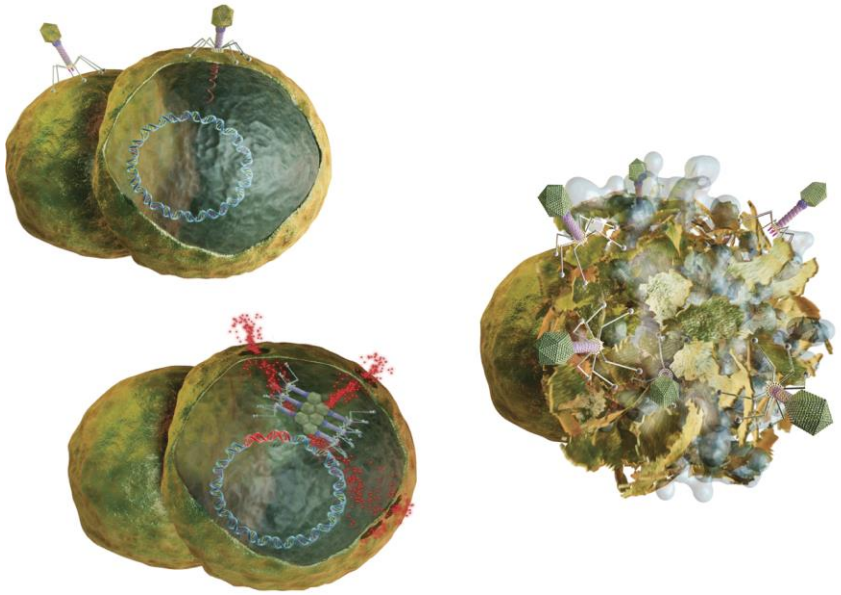
- Hohe Produktionskosten aufgrund der komplexen Struktur
- Hömolyse aufgrund der membran-aktiven Wirkung
- Instabilität, Proteolyse, somit kurze Halbwertzeit
- Hohe Proteinbindung

Aktuelle Entwicklungen/Lösungen:

Innovative Screeningstrategien mit dem Ziel
Resistenz gegen Proteolyse
Keine hämolytische Aktivität
Kosteneffektive Expressionssysteme

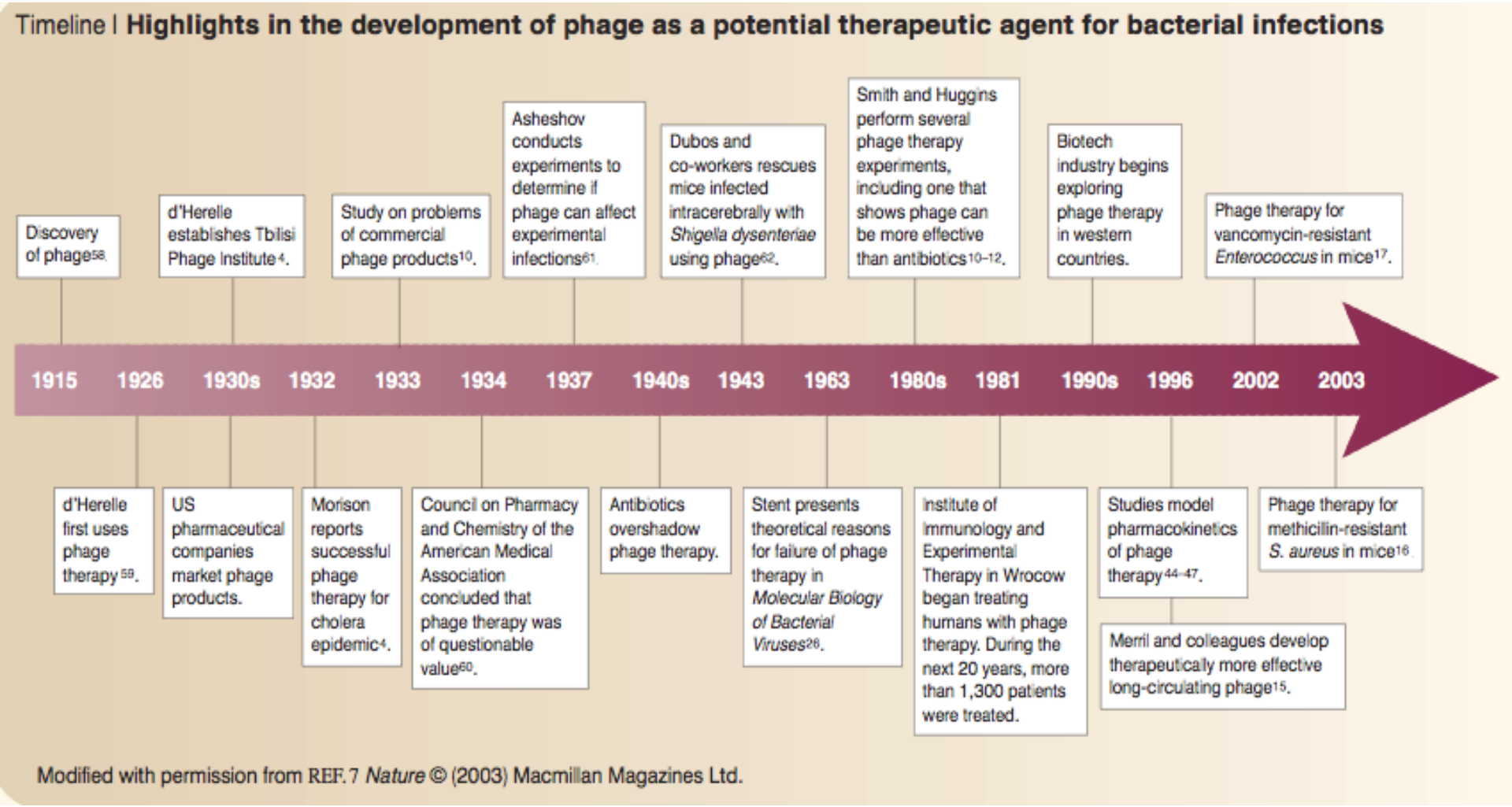
Bacteriophages battle superbugs





Population and evolutionary dynamics of phage therapy

(Levin BR, Bull JJ, Nature Rev Microbiol 2004; 2: 166-173; Abbildung aus Merril CR, et al., Nature Rev Drug Discov 2003; 2: 489-497)



Eliava Institute of Bacteriophage, Microbiology and Virology
Tbilisi, Georgia

Dr. Elena Makashvili (links), Prof. Felix D'Herelle (mitte), Prof. George Eliava (rechts)

- More than 15 effective bacteriophage preparations were elaborated and produced commercially at the Institute. For example, IBMV was used for prophylaxis and treatment throughout the former Soviet Union, in the Public Health network and in military forces. Throughout the 1970s to1980s, phage preparations such as Pyophage, Intestyphage, Pyoceaneus bacteriophages, Intravenous Staphylococcus bacteriophage, Dysenterial bacteriophage were recognized at national and international exhibitions and became brands know worldwide.

Effekt einer topischen oder sub-cutanen Applikation von „Phagen“ bei Patienten mit chronischen dermalen S. aureus Infektionen

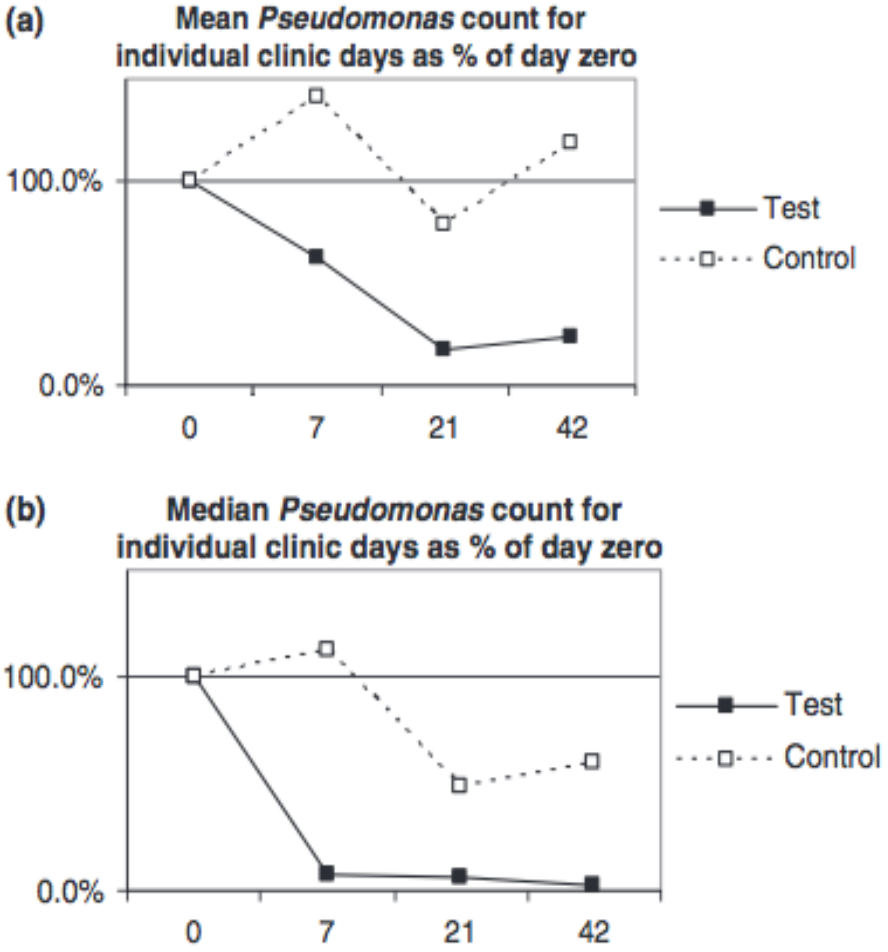
(Shvelidze Dissertion 1970; zitiert aus Chanishvili N „Ex-soviet develpoments in the Eliava Institute of Bacteriophage, Microbiology and Virology, a world premier institute in bacteriophage research“)

Groups	Diagnosis	Number of patients	Type of therapy	Duration of treatment (min-max)	Complete cure (%)	Improvement (%)	Temporary effect (%)	No effect (%)	Re-infection (%)
Exp. Gr 1	Furuncu-losis	62	Phage	3-10 days	97.7	3.3	-	0	4.8
Control 1	Furuncu-losis	62	Anti-biotics	3 months 16 years	0	53.3	20.9	25.8	100
Exp. Gr 2	Carbun cu-losis	54	Phage	5-10 days	66.7	20.0	-	13.3	11.1
Control 2	Carbun cu-losis	54	Anti-biotics	2 months 15 years	0	7.4	92.6	0	100

A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic resistant *Pseudomonas aeruginosa*: a preliminary report of efficacy.

(Wright A et al., Clin Otolaryngol 2009; 34: 349-357)

- Test material contained 100 000 plaque-forming units of each of six bacteriophages (BC-BP-01 to BC-BP-06) containing 2.4 ng protein and 0.06 ng DNA suspended in 10% glycerol in phosphate-buffered saline.
- Placebo material consisted only of glycerol-PBS diluent.



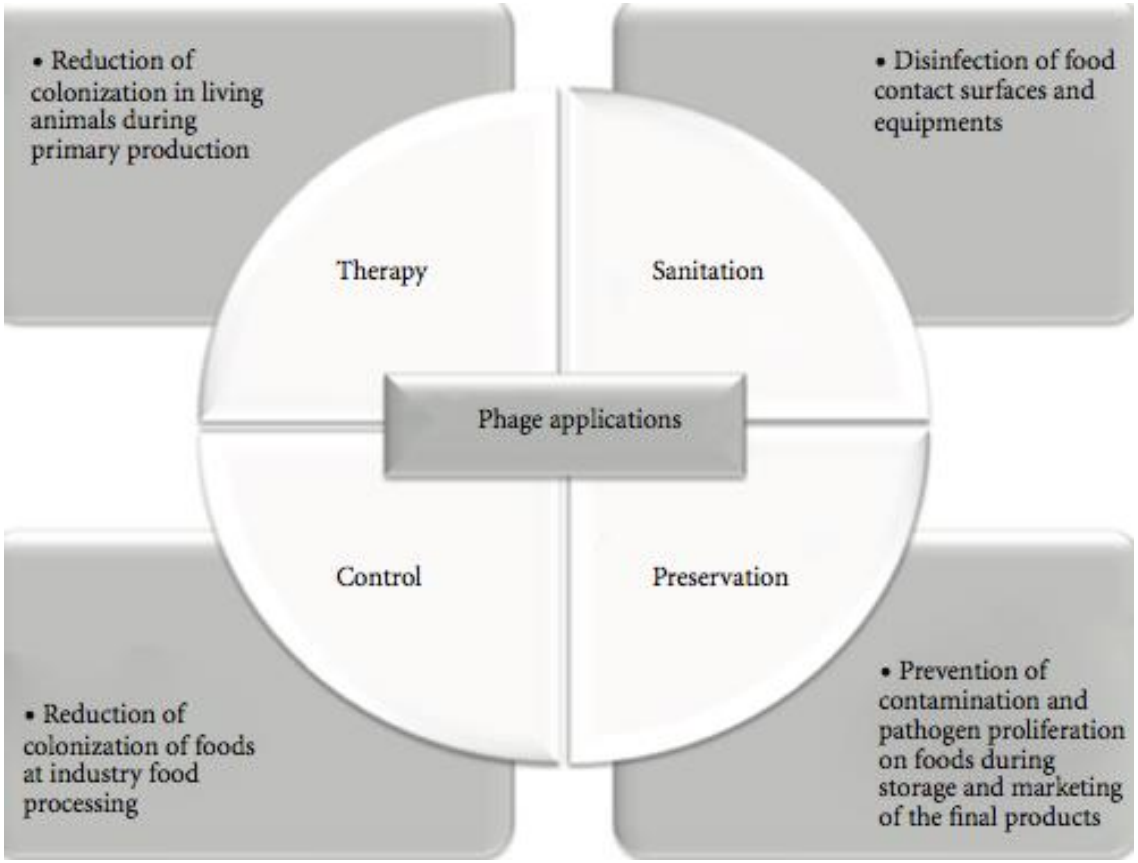
Weitere Studien

- Bacteriophage therapy of venous leg ulcers in humans: results of a phase I safety trial. (Rhoads DD et al., Journal of Wound Care,2009; 18: 237 – 243)
- Human Volunteers Receiving Escherichia coli Phage T4 Orally: a Safety Test of Phage Therapy. (Bruttin A, Brüssow H, AAC 2005; 49: 2874–2878)
- Quality-Controlled Small-Scale Production of a Well-Defined Bacteriophage Cocktail for Use in Human Clinical Trials. (Merabishvili M, et al. (2009) PLoS ONE 4(3): e4944. doi:10.1371/journal.pone.0004944) :

  This cocktail, consisting of P. aeruginosa phages 14/1 (Myoviridae) andPNM (Podoviridae) and S. aureus phage ISP (Myoviridae) was produced and purified of endotoxin. The bacteriophage cocktail is currently *being evaluated in a pilot clinical st*udy cleared by a leading Medical Ethical Committee

Anwendung von Phagenpräparationen in der Lebensmittelindustrie

(Greer GG, Bacteriophage control of foodborne bacteria, J Food Protection, 2005; 68: 1102–111)



Anwendung von Phagenpräparationen in der Lebensmittelindustrie

1. **Phage Biotech Ltd** is among a handful of pioneers in the field of Phage Therapy – Targeted Bacterial Eradication – Nature's way

   Founded in 2000, Phage Biotech Ltd unique expertise is in development of Phage Bactericides in Health; Food Safety; Veterinary; Agriculture, Aquaculture and Fermentation

   Our mission is to replace antibiotics and disinfectants where these no longer work, are inapplicable or becoming the problem itself

2. **3 August 2012** Approval Report – Application A1045

   Bacteriophage Preparation P100 as Processing Aid

   Food Standards Australia New Zealand (FSANZ) has assessed an application made by Micreos B.V. (previously EBI Food Safety) to permit the use of a bacteriophage (*Listeria* phage) preparation Listex™ P100 as a processing aid.

3. Krishna Khairnar, Mahendra P Raut, Rajshree H Chandekar, Swapnil G Sanmukh and Waman N Paunikar

   Novel bacteriophage therapy for controlling metallo-beta-lactamase producing Pseudomonas aeruginosa infection in Catfish.

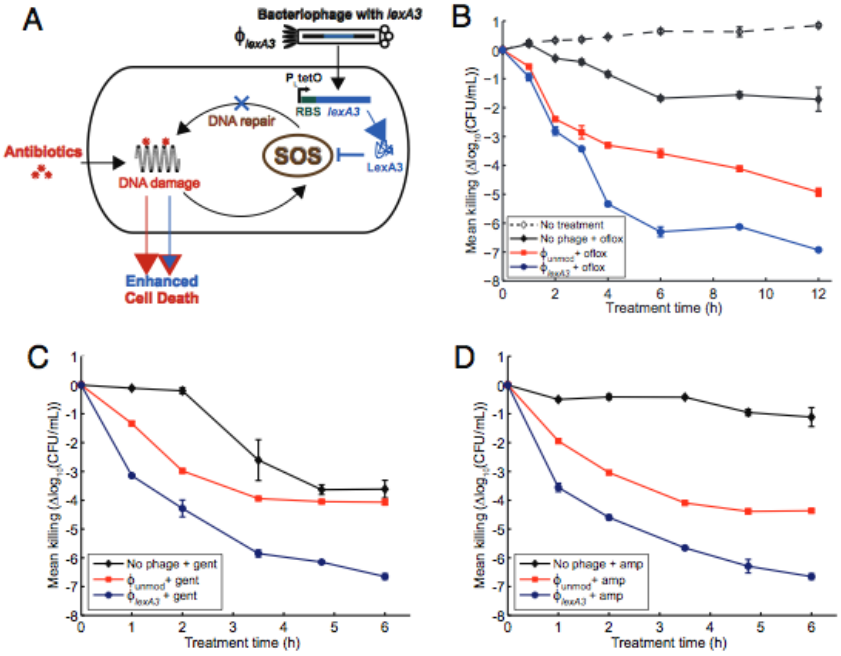
   BMC Veterinary Research 2013, 9:264, http://www.biomedcentral.com/1746-6148/9/264

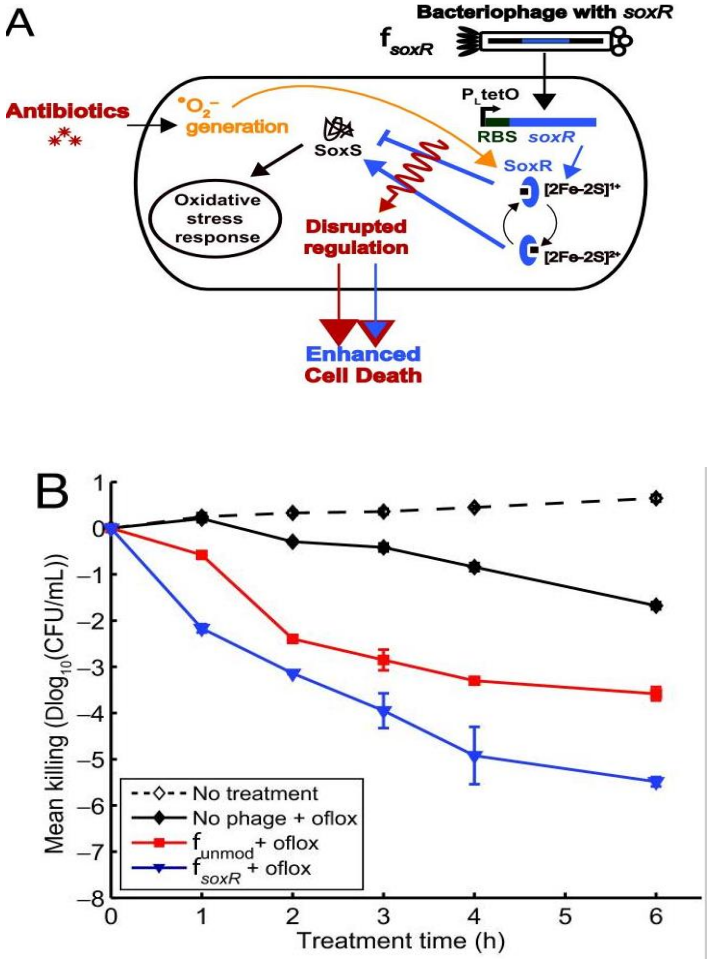
Kommerziell erhältliche Phagenpräparationen

- ListShield™: Intralytics
- EcoShield™: Intralytics
- SalmoShield™: Intralytics
- Listex™: Micreos Food Safety, USDA approval, GRAS;
- AgriPhage: Omnilytics, EPA approval
- Phage against *Salmonella* (PLSV-1™) and *Clostridium perfringens* (INT-401™) in poultry licensed products: Intralytics;
- BioPhage-PA: Biocontrol (UK) , Clinical Phase 2 finished
- Custom designed phage therapies in Poland, Georgia, Russia

Engineered bacteriophage targeting gene networks as adjuvants for antibiotic therapy

(Lu TK, Collins JJ, PNAS 2009;106:4629-4634)





Leibniz-Institut DSMZ

FP7-HEALTH-2013-INNOVATION-2

1. DSMZ website:

25.11.13 PLANETOPIA - Das Wissensmagazin mit Markus Appelmann:

Ein Mittel gegen multiresistente Keime? Viren aus Klärschlamm sollen Killer-Keime abtöten

Und hier für alle, die den Planetopia-Beitag "Ein Mittel gegen multiresistente Keime“ verpasst haben - der Link zum Video:

http://www.planetopia.de/nc/magazin/news-details/datum/2013/11/25/ein-mittel-gegen-multiresistente-keime-viren-aus-klaerschlamm-sollen-killer-keime-abtoeten.html

2. European commission:

Specific Programme “Cooperation” – Theme "Health“

Call identifier: FP7-HEALTH-2013-INNOVATION-2

Proposal No: 601942-2

Acronym: PARADIGM

Indicative budget: EUR 140 million from the 2013 budget

Leibniz-Institut DSMZ

- One of DSMZ's key aspects are medically relevant bacteria, also in the context of *DZIF* consortium (Deutsches Zentrum für Infektionsforschung, German Centre for Infection Research).
- The most obvious application of lytic phages is in the medical area: MRSA and ESBL producing bacteria
- In collaboration with the Eliava Institute IBMV, Tbilisi, Georgia, the DSMZ has finished a phage project to fight against MRSA.
- Another actual phage research focus at the DSMZ aims at bacteria of the order Burkholderiales that play a role in the biofilms of patients' lungs suffering from COPD or CF

Phagentherapie – pro‘s und con‘s

Pro

- Phagen vermehren sich in einer dichten Bakterienpopulation, so dass bereits eine niedrige Phagen-Dosis effektiv ist
- Daher sollten Phagen in der Behandlung chronischer Infektionen besonders effektiv sein – *cave*: Mucus + Biofilm.
- Single-hit Kinetik
- Geringe/keine Beeinflussung des humanen Mikrobioms + der Umwelt

Aktuelle Entwicklungen/Lösungen

- Verabreichung eines Phagencocktails = Multiphagen-Therapie
- Nutzung spezifischer Phagenprodukte wie z.B. Protein A_2 oder Phagen-Lysine, die mit der bakteriellen Zellwandbiosynthese/-integrität interferieren.
- Topische Applikation
- Phagen mit Wirkung auf Gen-Netzwerke (z.B. SOS response) als Adjuvantien zur Antibiotika-Therapie

Con

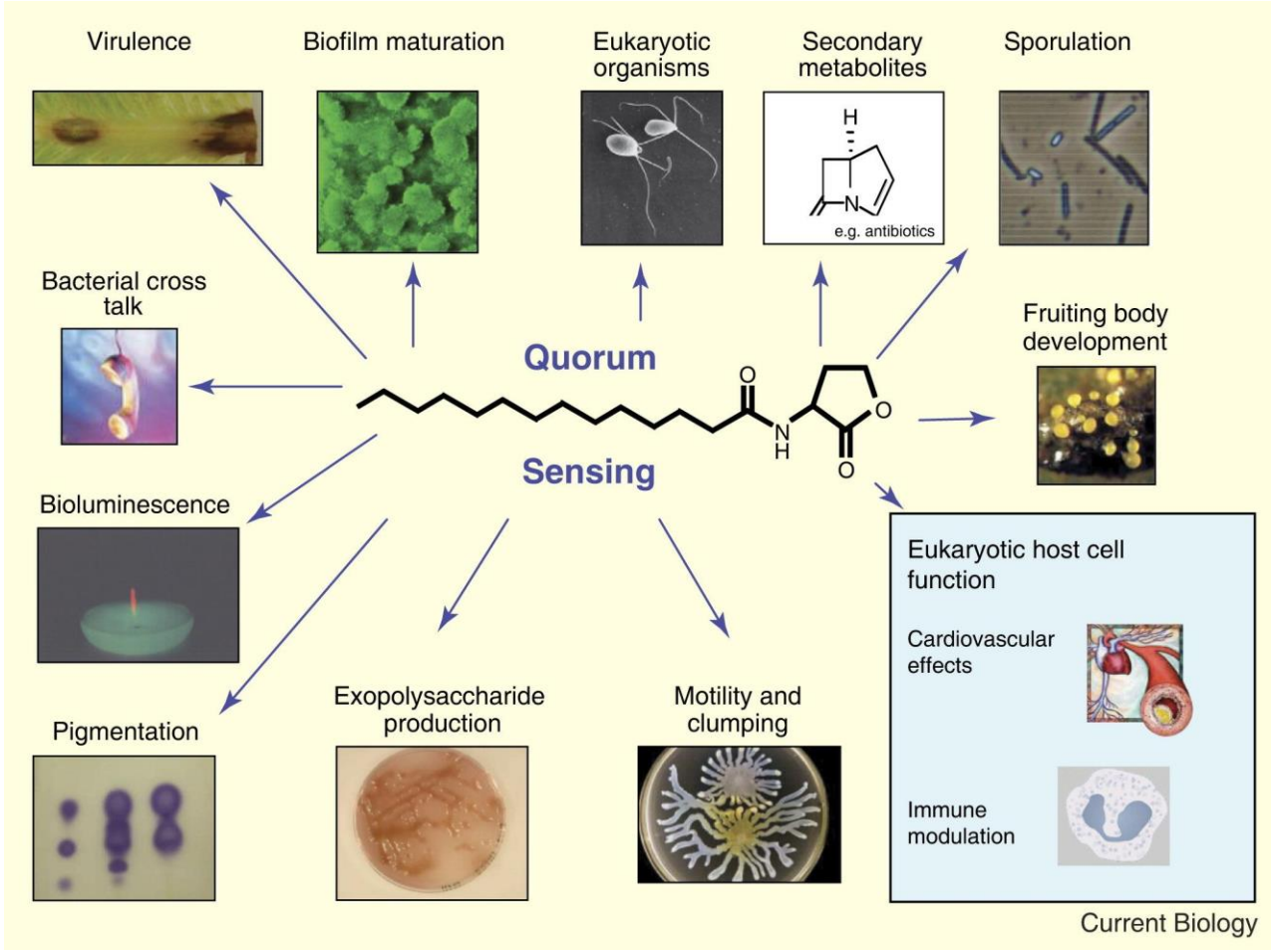
- Bildung von Antikörpern
- Verunreinigungen mit Endo- + Exotoxin
- Wirkungsweise *in vivo* unklar
- Langsam wachsende/ruhende Bakterien Bakterien sind refraktär
- Spezies- und sogar Stamm-spezifisches Wirkspektrum
- schnelle Elimination durch das retikuloendotheliale System
- Komplexe Populationsdynamik, abhängig von der Phagenreplikations-geschwindigkeit vs. Elimination + Bakteriendichte vs. Generationszeit
- Resistenzentwicklung: Verlust des Rezeptors; mucoide Kolonieform; Restriktionsendonucleasen degradieren Phagengenom

Reviews zum Thema Phagentherapie

- Keen EC: Phage therapy: concept to cure. Frontiers in Microbiology 2012; doi: 10.3389/fmicb.2012.00238
- Sulakvelidze A et al.: Bacteriophage therapy. AAC 2001; 45: 649-659
- Brüssow H: What is needed for phage therapy to become a reality in Western medicine? Virology. http://dx.doi.org/10.1016/j.virol.2012.09.015
- Loc-Carillo C, Abedon ST: Pros and cons of phage therapy. Bacteriophage 2011; 1: 111-114
- Levin BR, Bull JJ: Population and evolutionary dynamics of phage therapy. Nature Rev Microbiol 2004; 2: 166-173
- Lu TK, Koeris MS: The next generation of bacteriophage therapy. Curr Opin Microbiol 2011; 14: 524-531

Quorum sensing

(Diggle SP et al., Current Biology 2007; 17: R907-R910)



Rutherford ST, Bassler BL: Bacterial quorum sensing: its role in virulence and possibilities for its control.

(Cold Spring Harb Perspect Med 2012; doi 10.1101/cshperspect.a012427)

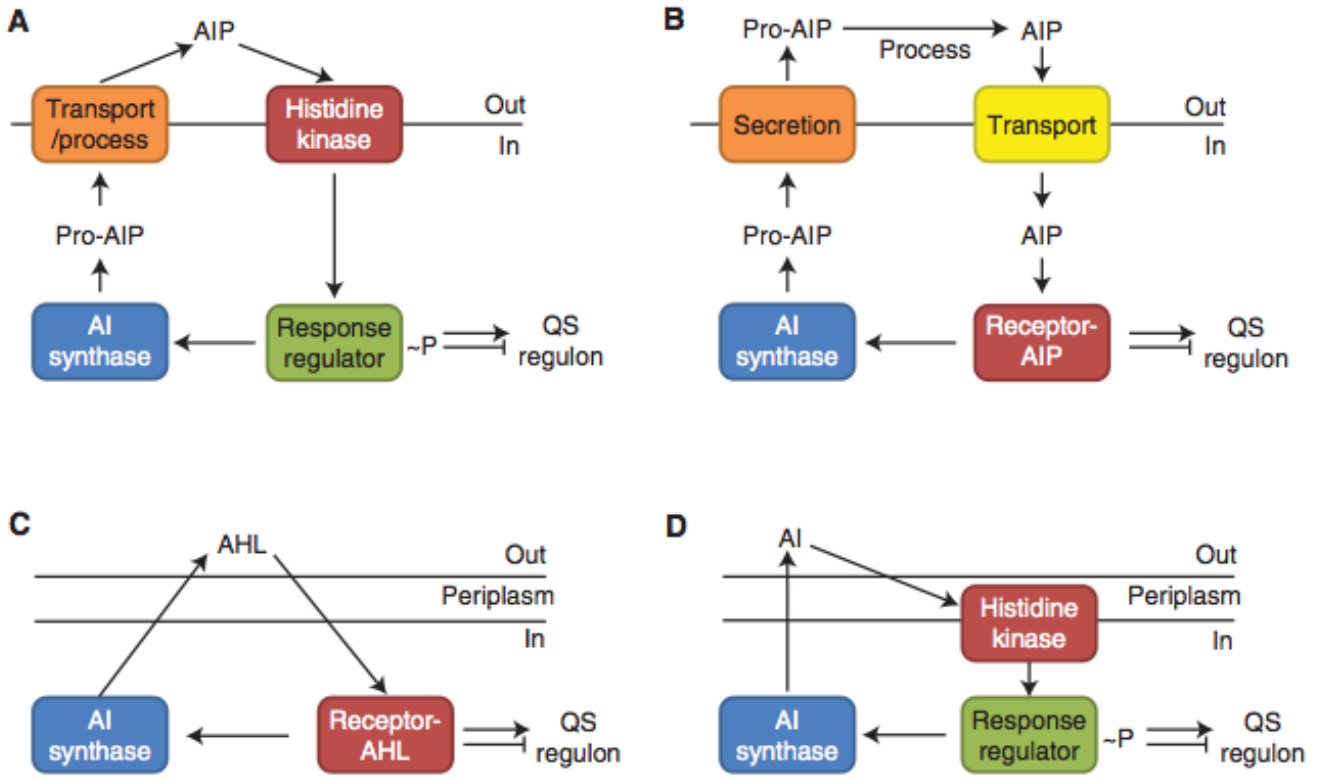


Figure 1. Canonical bacterial quorum-sensing (QS) circuits. Autoinducing peptide (AIP) QS in Gram-positive bacteria by (*A*) two-component signaling, or (*B*) an AIP-binding transcription factor. Small molecule QS in Gram-negative bacteria by (*C*) a LuxI/LuxR-type system, or (*D*) two-component signaling.

Komplexizität der Signalsysteme

(aus Schuster M, Greenberg EP, Regulatory networks in pathogenic bacteria...; In: Virulence mechanisms of bacterial pathogens. 4th ed., Brogden KA et al. (Eds), ASM Press, Washington DC, 2007, Kapitel 6, pp 75-88)

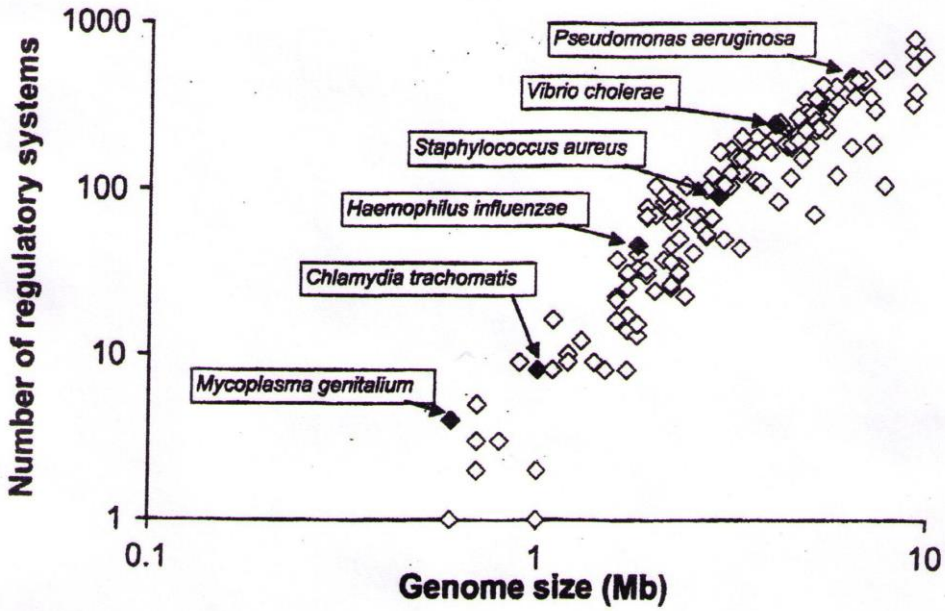


FIGURE 1 Signaling complexity is related to genome size. Shown are the numbers of signaling systems (one- and two-component systems) corresponding to 150 sequenced genomes as a function of genome size

New antipathogenic drugs

Natural quorum-sensing inhibitors (QSIs)

QSI compound(s)	*Source*	*Quorum-sensing system affected*
Agrocinopine B	Crown gall cells of host plants	Tra system of A tumefaciens
Furanone	D pulchra	Swr system of S liquefaciens and other Gram-negative bacteria
Canavanine	M sativa	Sin/ExpR system of S meliloti
Norepinephrine, epinephrine	Human hormones	AI-3 system of EHEC
Penicillic acid, Patulin	Penicillium spp.	Las and Rhl systems of P aeruginosa
4-NPO *	Garlic	„virulence genes“ in P aeruginosa LuxR QS system in E coli

(4-NPO = 4-nitro-pyridine-N-oxide)*

Antibakterielle Substanzen als Signalmoleküle

Antibacterials as signalling molecules ?

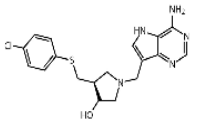
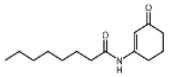
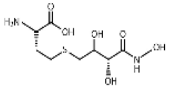
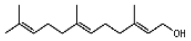
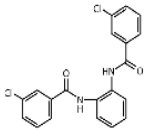
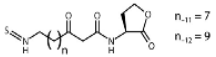
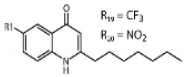
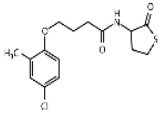
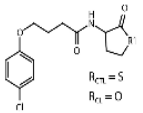
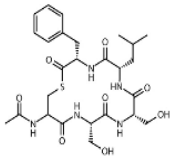
Julian Davies:

- Antibacterials (sub MICs) with distinct modes of action modulate transcription in E coli, P aeruginosa, S typhimurium *(Goh et al., PNAS 2002; 99: 17026 – 17030)*
- „Most microbial metabolites modulate gene transcription at low concentrations, and
- this is proposed to be the primary effect of the compounds in the maintenance of microbial communities in the environment“

(Yim et al., Phil Trans R Soc (B) 2007; 362: 1195 – 1200)

Quorum-sensing Inhibitoren

(LaSarre B, Federle MJ, MMBR 2013; 77: 73-111)

Category	Inhibitor	Structure	Target(s)
Synthase inhibitors			
Synthetic	*p*ClPhT–DADMe–ImmA		MTAN
	JA-C8		TofI (LuxI family, *B. glumae*)
	Compound 10		LuxS
Natural source	Farnesol		PqsA
Receptor inhibitors			
Synthetic	TP-5		LasR
	Itc-11, -12		LasR (covalent)
	Compounds 19 and 20		PqsR
	4606-4237		LuxN, CviR
	CTL, CL		CviR
	trAIP-II		AgrC

Quorum-sensing Inhibitoren

- **Patent application title: SMALL MOLECULE ANTAGONISTS OF BACTERIAL QUORUM-SENSING RECEPTORS**
- **Inventors: Bonnie L. Bassler (Princeton, NJ, US) Lee R. Swem (Lawrenceville, NJ, US) Scott M. Ulrich (Ithaca, NY, US) Colleen T. O'Loughlin (Princeton, NJ, US)**
  IPC8 Class: AA01N4308FI
  USPC Class: 514472
  Class name: The hetero ring is five-membered nitrogen containing the nitrogen bonded directly to the hetero ring
  Publication date: 2014-01-23
  Patent application number: 20140024707

Quorum-sensing Inhibition – pro‘s und con‘s

pro

- QS Spezies Spezifität ermöglicht engspektrige/gezielte Therapie
- Adjuvans zur AB-Therapie
- Erregermodulation sollte keinen Selektionsdruck ausüben, somit wird allg. postuliert, dass
- (Keine)/geringe Resistenzentwicklung stattfindet – cave: adaptive Prozesse beobachtet (Defroidt T et al., PLoS Pathog 6(7):e 1000989. doi 10.1371/journal.ppat.1000989)

Con

- QS extrem vielfältig
  - Kombinatorisches QS in Bakterien bislang sehr wenig untersucht
  - Interaktion mit dem Wirt in seiner Komplexizität nicht verstanden ➔Toxizität ?
  - Wirt-spezifischer Abbau von QS-Signalen
- QS spezifisch für Infektlokalisation
- QS Spezies-spezifisch
- QS Inhibition = Modulation des Bakterium
- sub-inhibitorische Konzentrationen antibakterieller Substanzen wie Makrolide, Chinolone, Aminoglycoside, ß-Laktame = QS Inhibitoren

Reviews zum Thema Quorum-sensing

- Davis J: Are antibiotics naturally antibiotics? J Ind Microbiol Biotechnol 2006; 33: 496-499
- Yim G et al.: Antibiotics as signalling molecules. Phil Trans R Soc B 2007; 362: 1195-1200
- Williams P et al.: Look who‘s talking: communication and quorum sensing in the bacterial world. Phil Trans R Soc B 2007; 362: 1119-1134
- Bassler B: How bacteria talk to each other: regulation of gene expression by quorum sensing. Curr Opin Microbiol 1999; 2: 582-587
- Waters MNC, Bassler BL: Quorum-sensing: cell-to-cell communication in bacteria. Ann Rev Cell Dev Biol 2005; 21: 319-346
- Bauer WD et al.: Eukaryotes deal with bacterial quorum sensing. ASM New 2005; 71: 129-135
- Williams P: Quorum sensing, communication and cross-kingdom signalling in the bacterial world. Microniology 2007; 153: 3923-3938
- Hirakawa H, Tomita H: Interference of bactrial cell-to-cell communication: a new concept of antimicrobial chemotherapy breaks antibiotic resistance. Frontiers Microbiol 2013; doi: 10.3389/fmicb.2013.00114

Conclusion