香港中文大學
The Chinese University of Hong Kong

New strategies for combating multidrug-resistant bacteria

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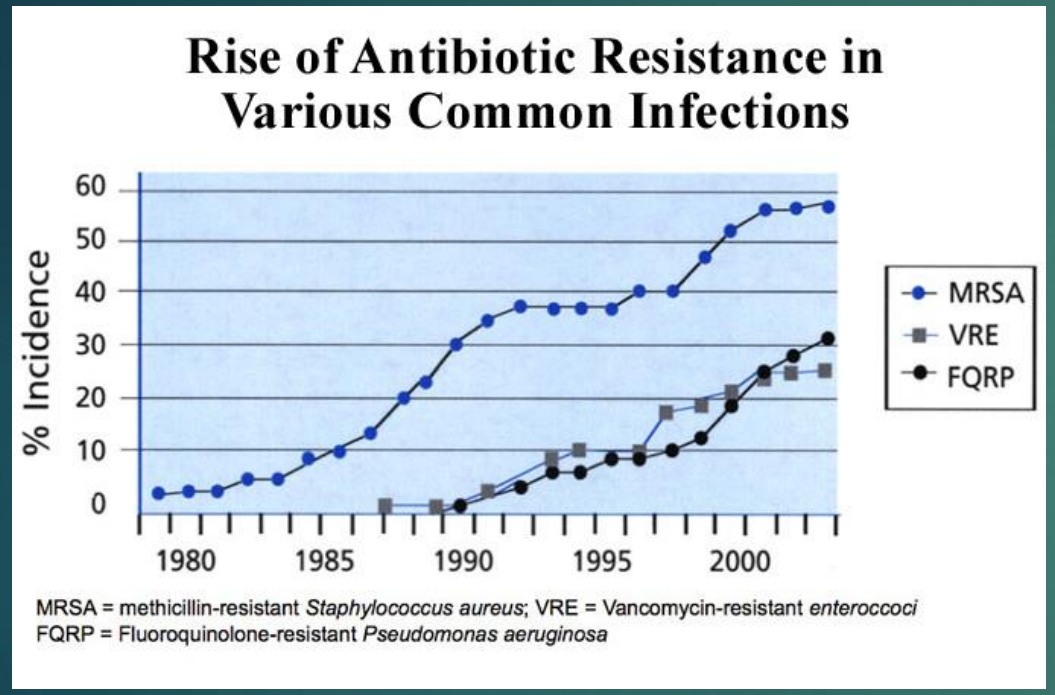
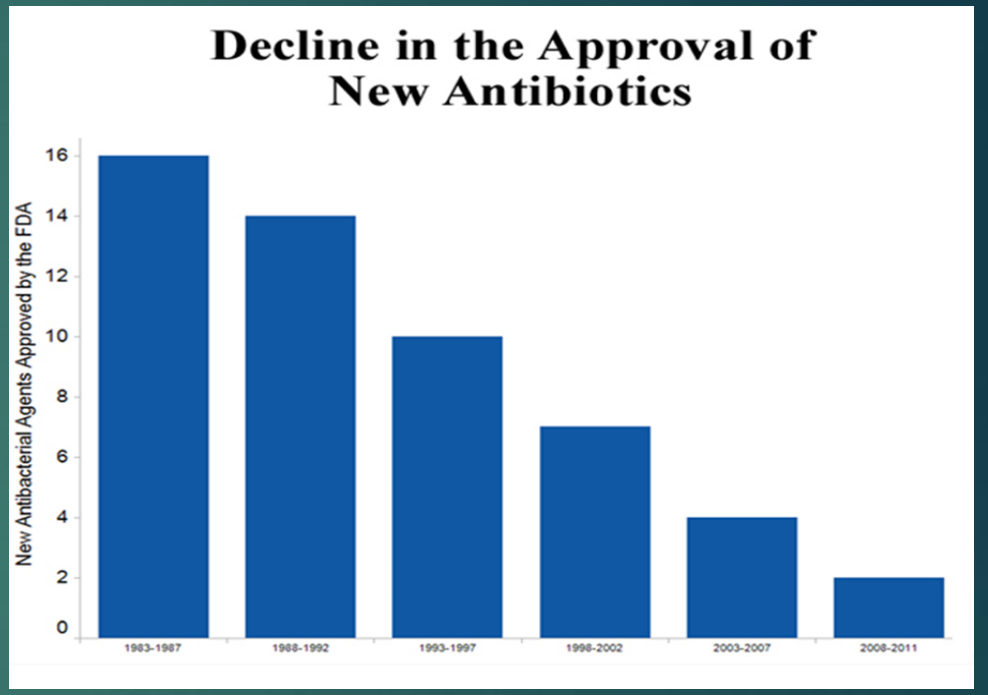
15 DEC 2014

Outline

- The crisis of antibiotic resistance
- The emergence of ‘superbugs’
- The decline of antibiotic development
- New strategies fights against resistant pathogens
- Probiotics
- Bacteriophage therapy
- Anti-virulence strategies

The crisis of antibiotic resistance





Superbugs are on the rise
Antibiotic resistance is ancient
Long term persistence of antibiotics resistance

Antibiotic development is dwindling
Pharmaceutical firm abandon antibiotics development: economic and regulatory barriers.

http://www.theatlantic.com/business/archive/2011/06/how-superbugs-will-affect-our-health-care-costs/240454

Strategies to fight against resistant pathogens

- **Preserving available antibiotics**
  - ✓ Appropriate use of antibiotics
  - ✓ Inhibitors of resistant enzymes and antibiotic efflux
  - ✓ Silence resistant genes
- **New antibiotics**
  - ✓ Structural modification of existing drugs
  - ✓ New sources of antimicrobial chemicals-natural products, ocean
- **New strategies**
  - ✓ Probiotics
  - ✓ Bacteriophage therapy
  - ✓ Anti-virulence strategies

Antibiotics

Probiotics-'good' bacteria

Live microorganisms which when administered in adequate amounts confer a health benefit on the host. (Lactobacillus group:genera Lactobacillus, Enterococcus, Streptococcus, Lactococcus, Pediococcus, Bifidobacterium and Leuconostoc)

What's new…

- The importance of gut microbiota
- ✓ 90%
- ✓ Break down food
- ✓ Clean the gut waster
- ✓ Suppress bad bacteria
- ✓ …
- Imbalance and diseases
- Antibiotic associated infections
- ✓ Recurrent *C. difficile* infection

http://www.dfwchild.com/Fort-Worth/features/1014/Keeping-Kids-Healthy-With-Probiotics

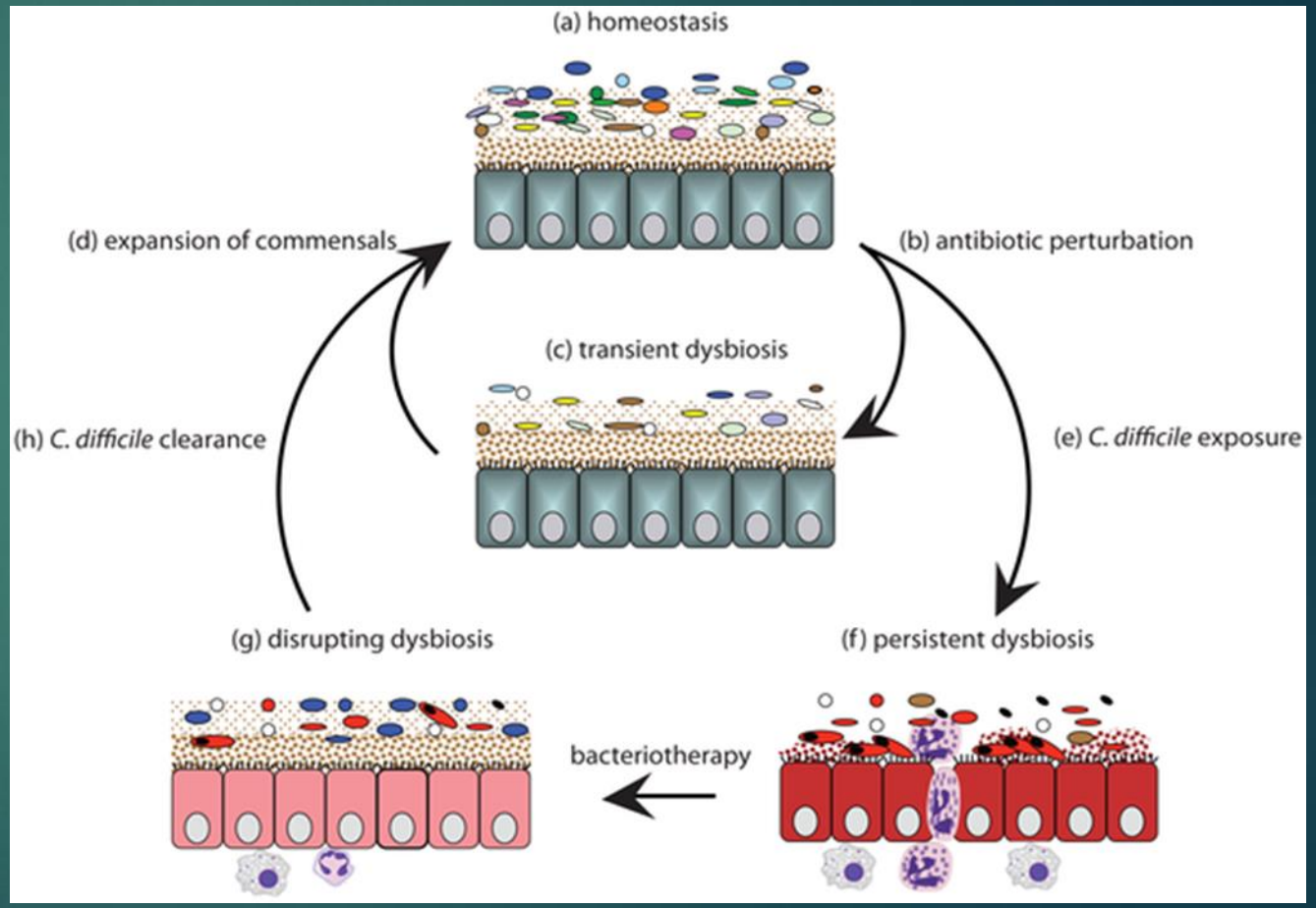
Probiotics- ‘good’ bacteria fight against ‘bad’ones

- Mechanism:

maintain microbial ecology

interspecific competition

- Probiotics
- ✓ Dietary supplements
- ✓ Microbiota transplantation
- Major concerns
- ✓ Efficiency, safety, mechanism
- ✓ Regulation

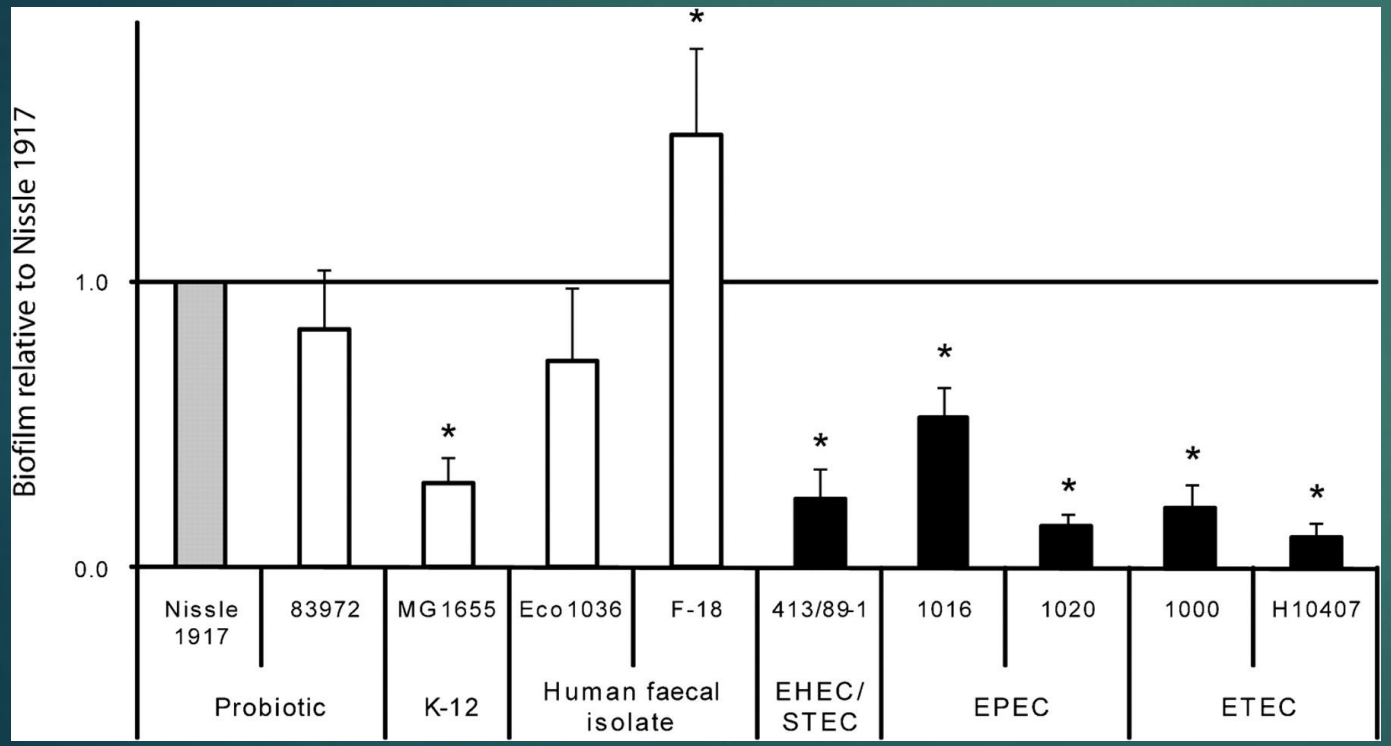


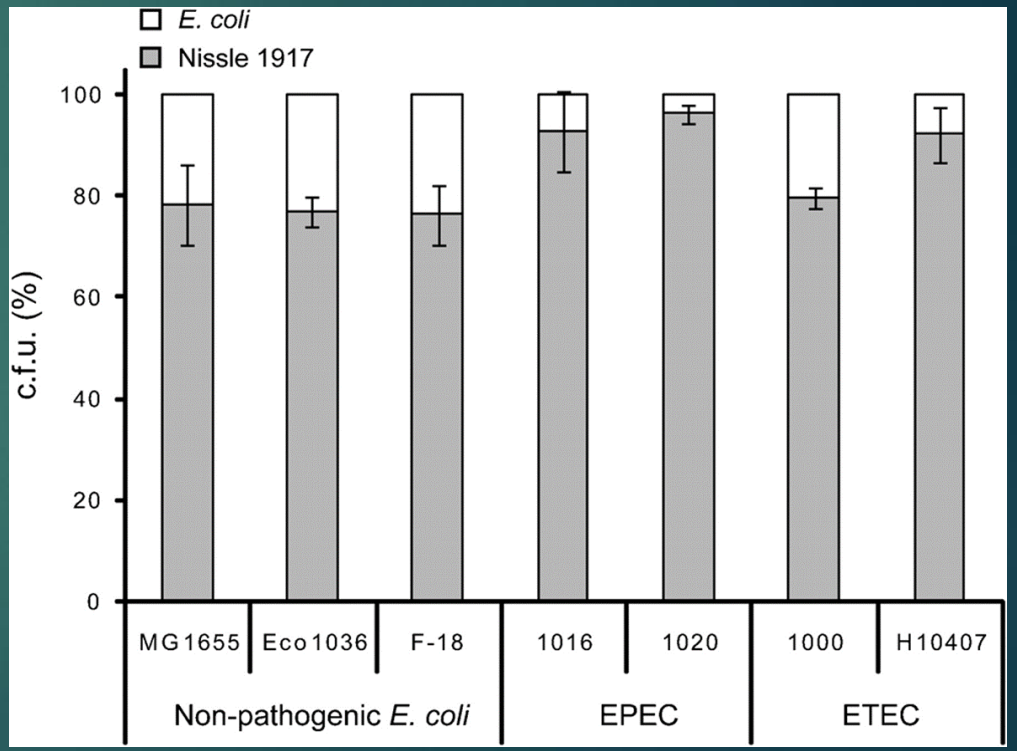
Lawley TD, Clare S, Walker AW, Stares MD, et al. (2012). PLoS Pathog

Journal of Medical Microbiology (2010), **59**, 392–399 DOI 10.1099/jmm.0.008672-0

Probiotic *Escherichia coli* strain Nissle 1917 outcompetes intestinal pathogens during biofilm formation

Viktoria Hancock, Malin Dahl and Per Klemm



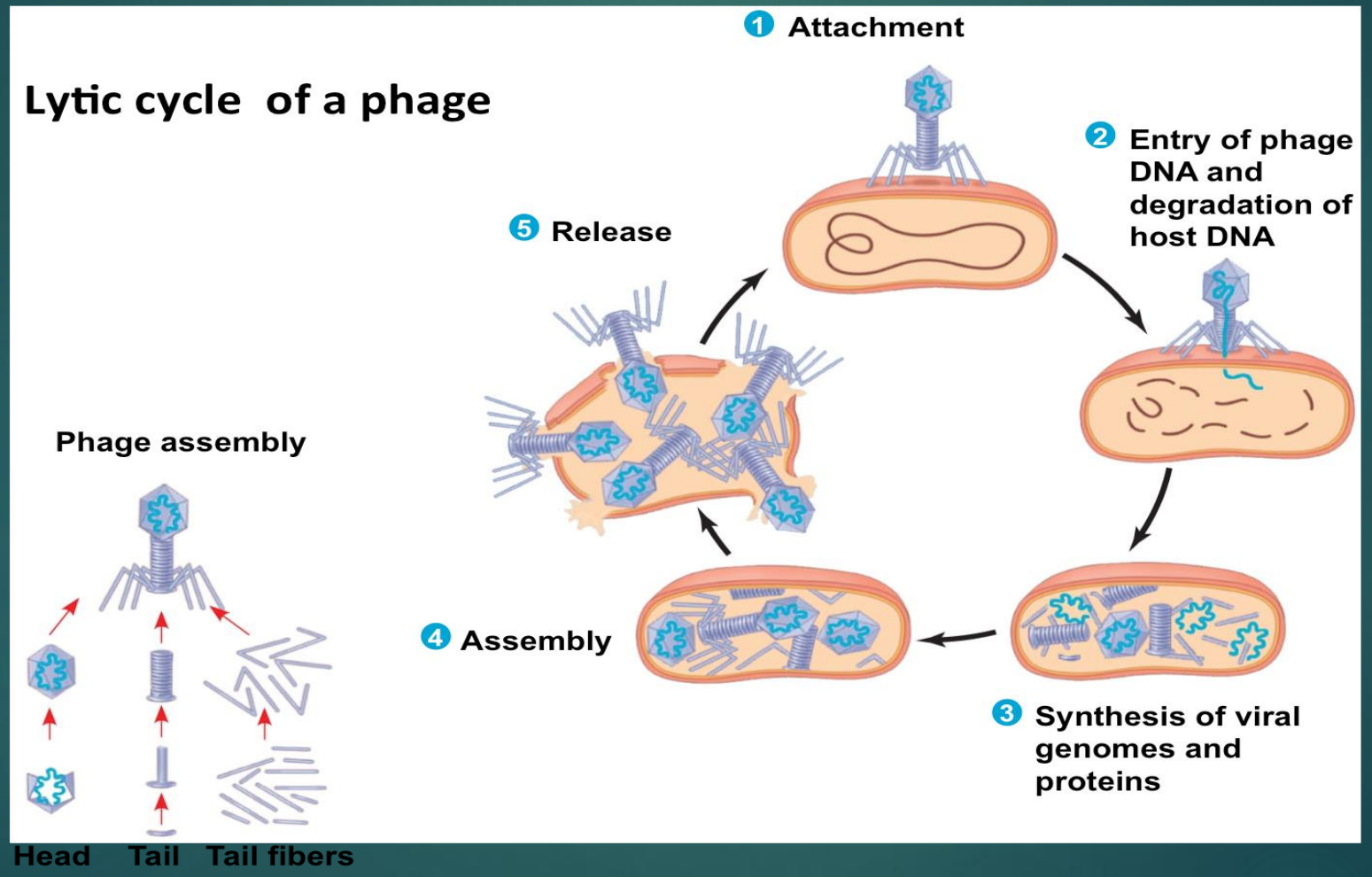


Bacteriophage therapy

- Bacteriophages, or simply 'phages', are viruses that infect and in some cases destroy bacterial cells.
- Phages are a natural part of the microbial ecosystem.
- Phage species are specific to particular bacterial species.
- The golden age in use of phage was in the 1930s.
- Phage ‘cocktail’

http://www.iflscience.com/health-and-medicine/new-antibiotic-free-treatment-could-tackle-drug-resistant-bacteria

Mechanism of phage therapy



http://cis.payap.ac.th/?p=3759

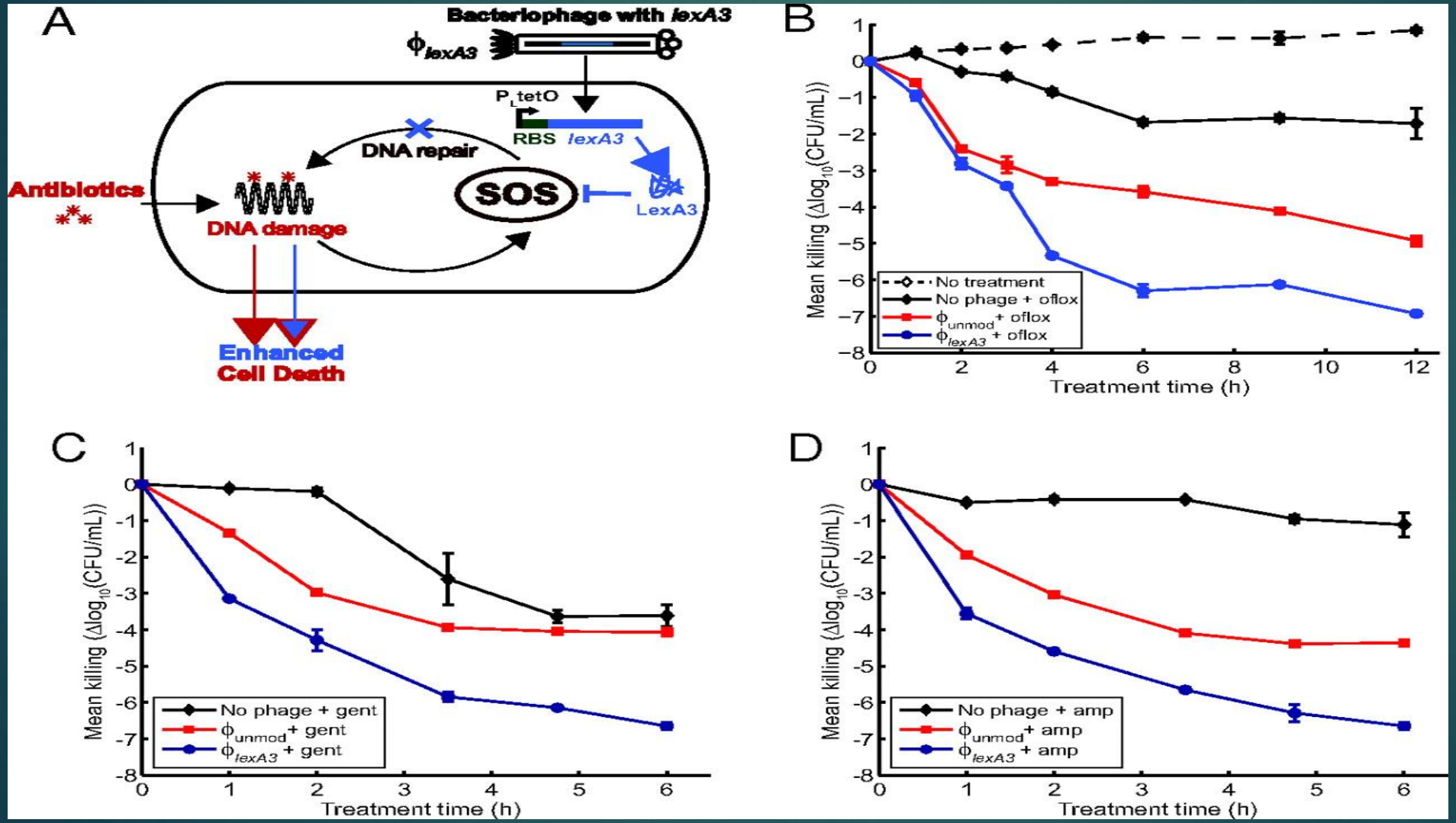
Bacteriophage therapy

- **Advantages**
- ✓ Phage therapy is possible in all bacterial infections
- ✓ Phage coevolving with bacteria
- ✓ Specific- no effect on healthy microflora
- ✓ And so on…
- **Challenges**
- ✓ Safety issue
- ✓ Precise and quick diagnosis are needed before prescribing a phage treatment
- ✓ Difficulties in getting the approval of phage ‘cocktail’ and intellectual property issue

Engineered bacteriophage targeting gene networks as adjuvants for antibiotic therapy

PNAS

Timothy K. Lu[a,b] and James J. Collins[b,1]



Engineered *lexA3* bacteriophage enhances killing of wild-type *E. coli* EMG2 bacteria by bactericidal antibiotics.

Bacteriophage endolysins

- Endolysins (or lysins) are highly evolved enzymes produced by phage to digest the bacterial cell wall for phage progeny release.
- Lysins exert their lethal effects by forming holes in the cell wall through peptidoglycan digestion.
- NO living viruses involved-

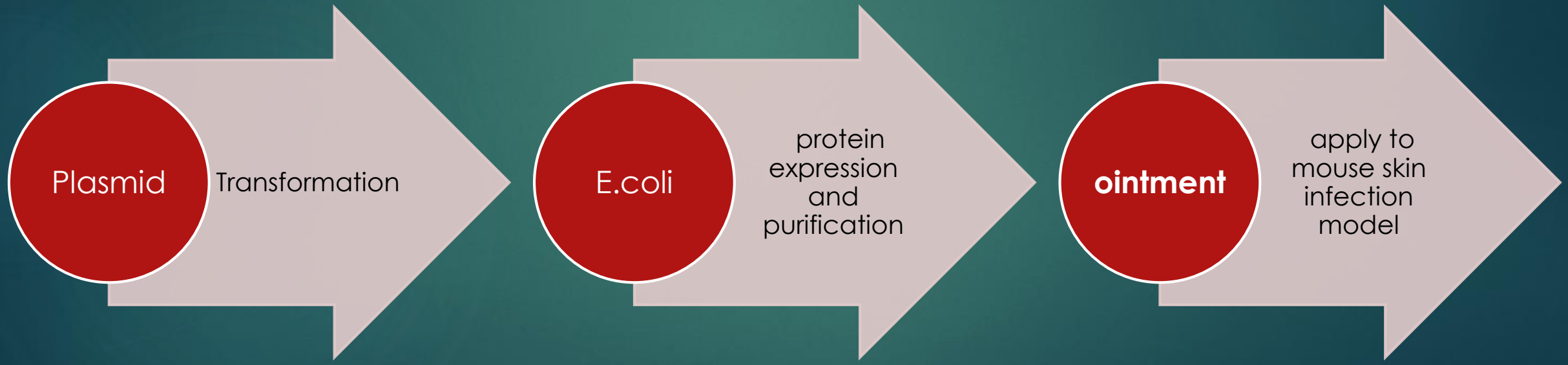
A Novel Chimeric Lysin Shows Superiority to Mupirocin for Skin Decolonization of Methicillin-Resistant and -Sensitive *Staphylococcus aureus* Strains[▽]

Mina Pastagia,[1,2*] Chad Euler,[1] Peter Chahales,[1] Judilyn Fuentes-Duculan,[2] James G. Krueger,[2] and Vincent A. Fischetti[1]

MICROBIAL DRUG RESISTANCE
Volume 18, Number 3, 2012

DOI: 10.1089/mdr.2012.0025

The development of ClyS ointment



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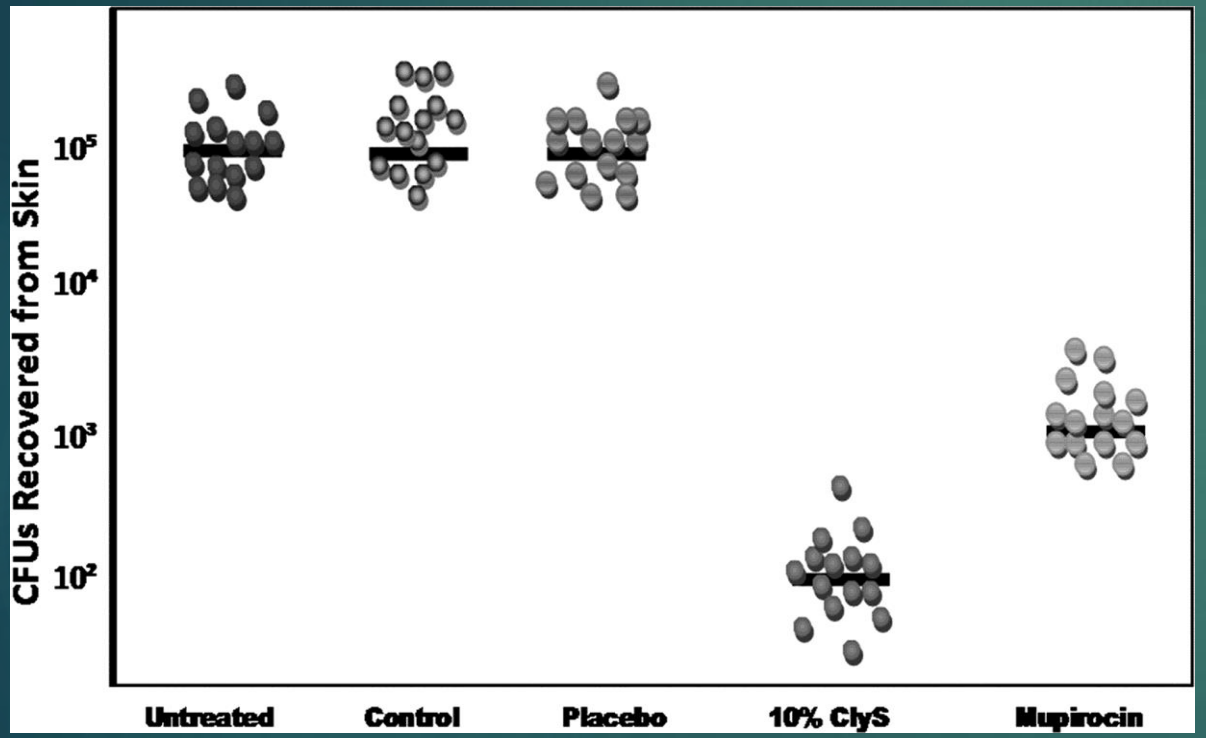
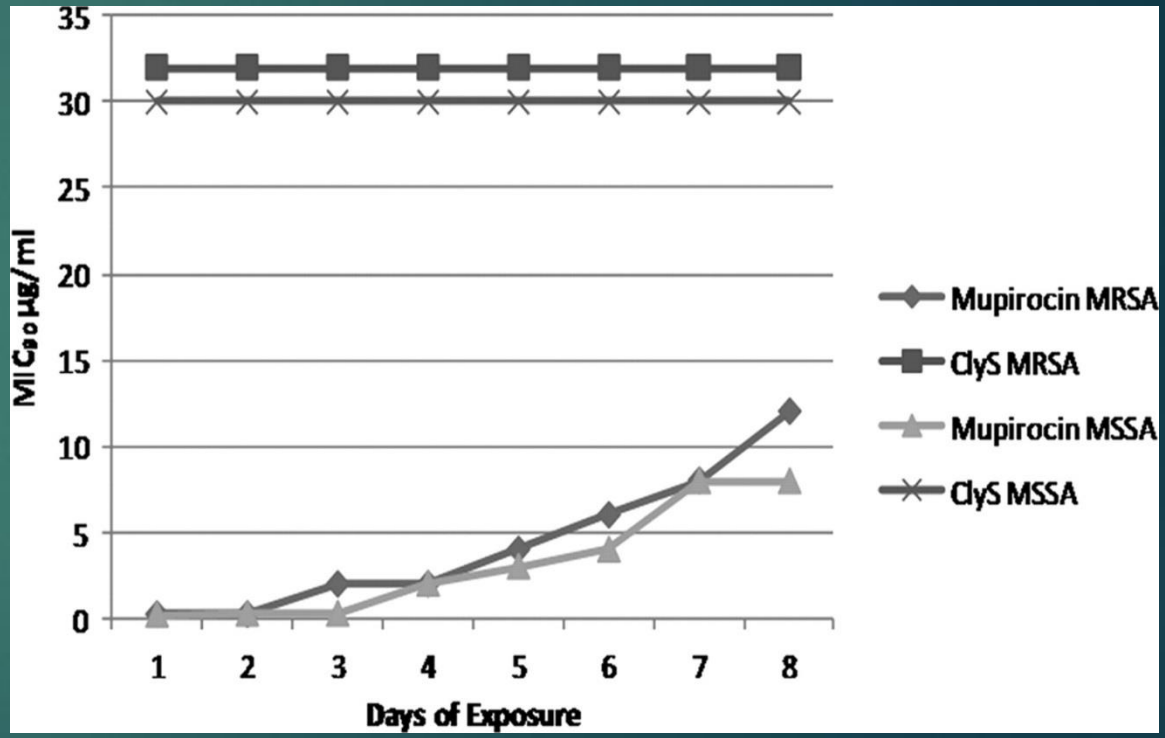
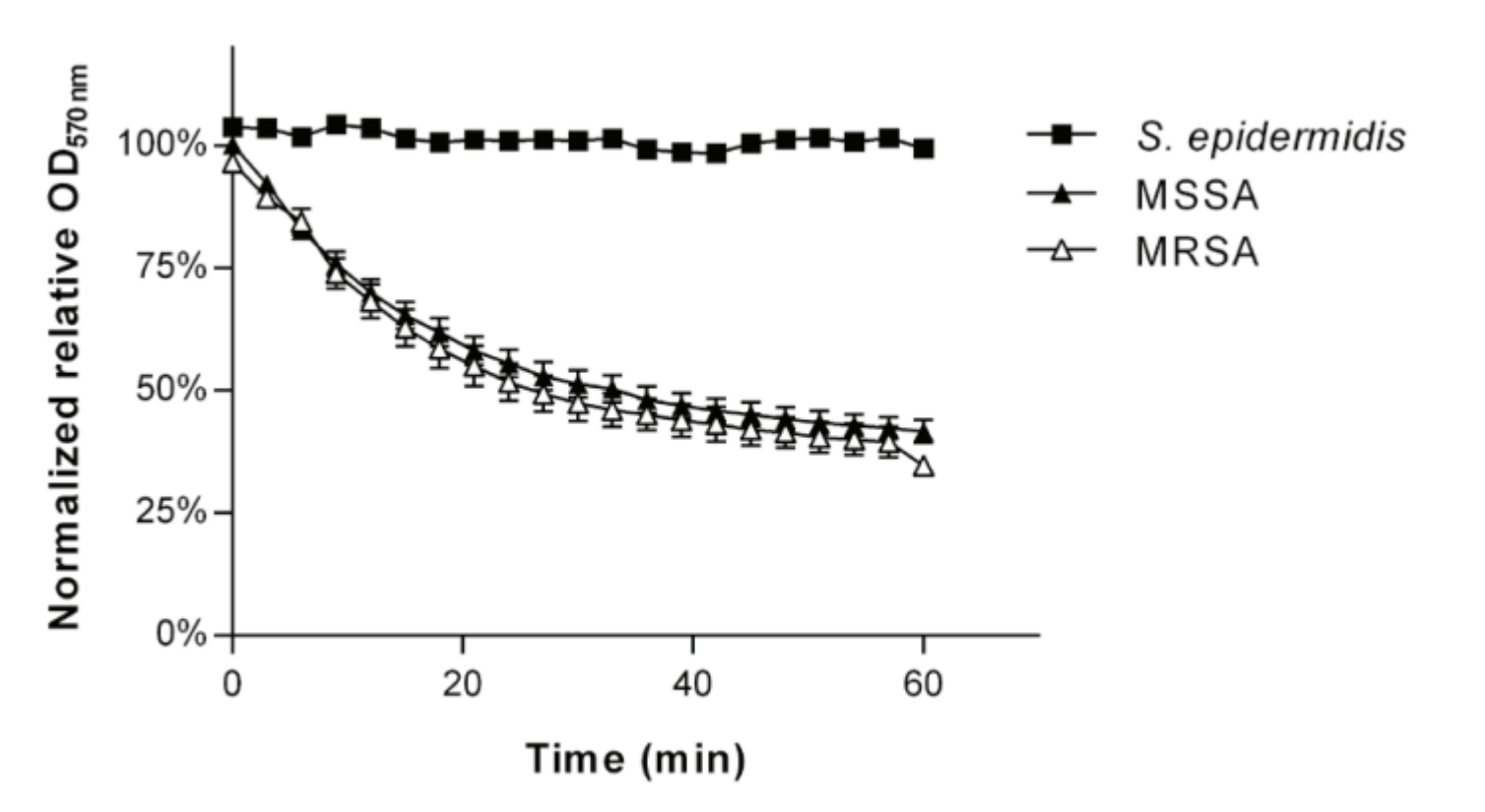


In vivo activity of ClyS ointment versus that of placebo or mupirocin on tape-stripped mice infected with *S. aureus* 8325-4 or MRSA MW2.



In vitro resistance studies of ClyS and mupirocin. MIC90 values for MRSA and MSSA remain the same for ClyS but increase for mupirocin

Staphefekt-the first endolysin available for human use on intact skin



Specific lysis of MRSA and MSSA by Staphefekt

https://www.staphefekt.com/en/products

Staphefekt™ effectively kills MRSA & MSSA without disturbing normal skin flora

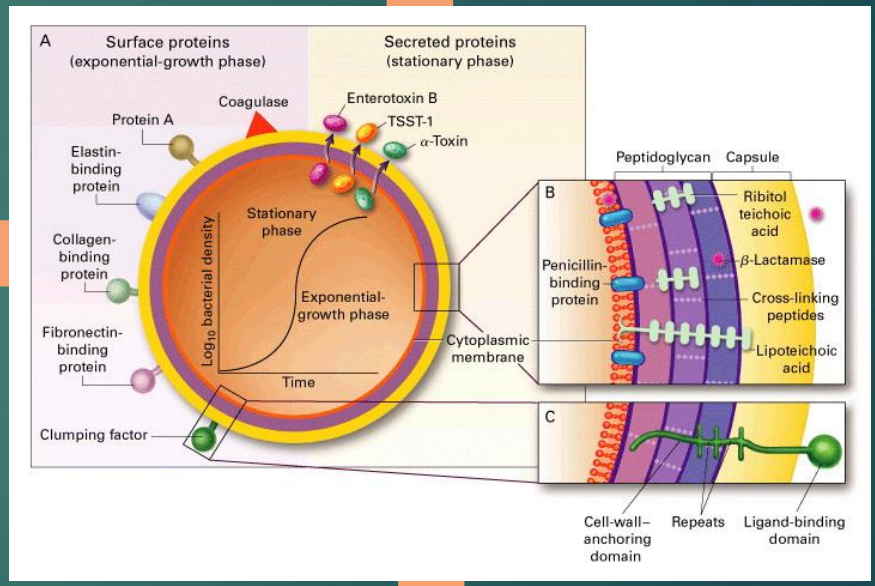
What is virulence ?

- **Capacity to cause disease**
  - ✓ Adhesins
  - ✓ Toxins,proteases
  - ✓ Secretion systems

  And so on…
- **Global regulation**

Colonization

Immune evasion



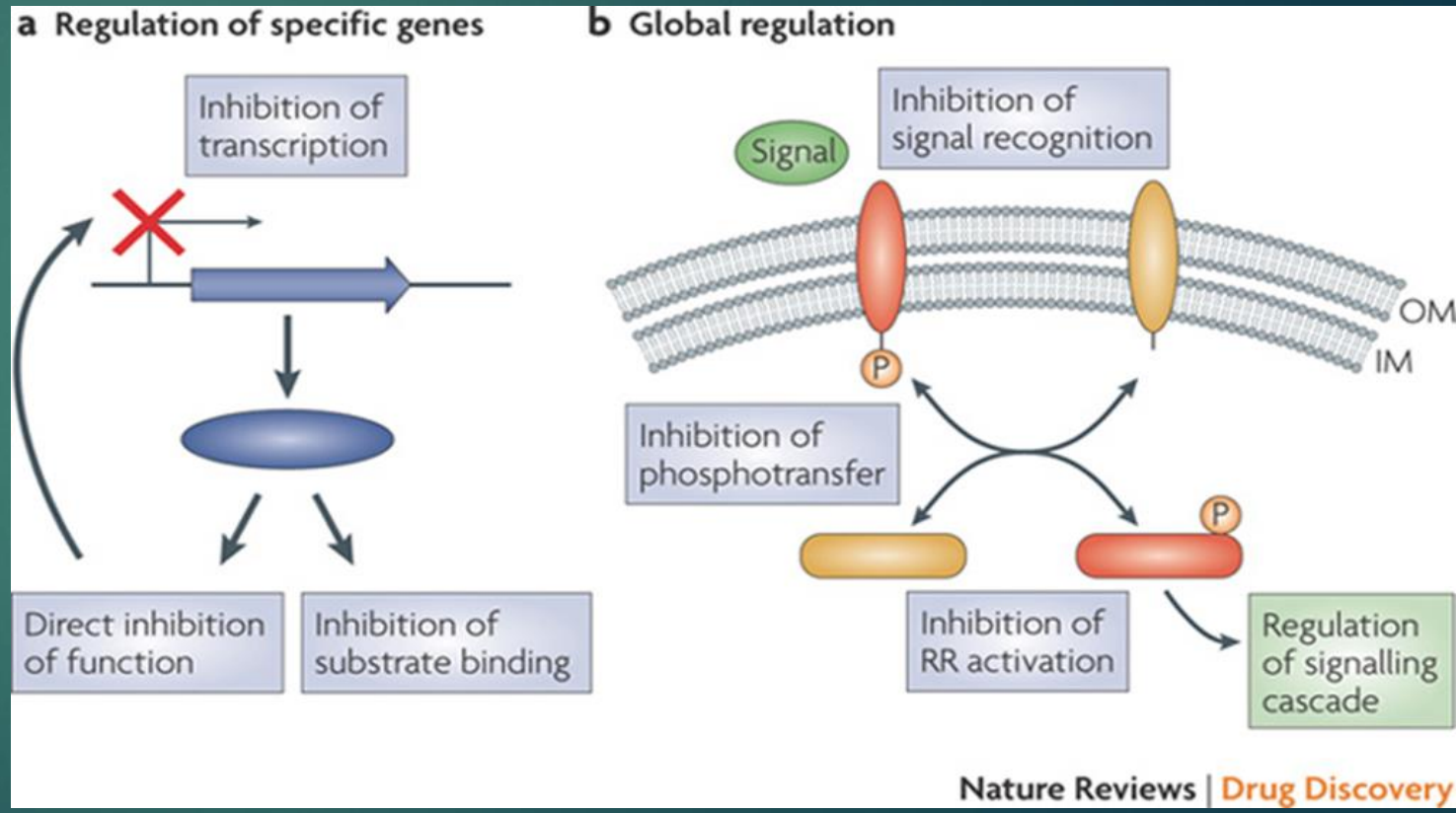
Resource acquisition

Host invasion

Lowy FD. N Engl J Med 1998;339:520-532

Anti-virulence strategies

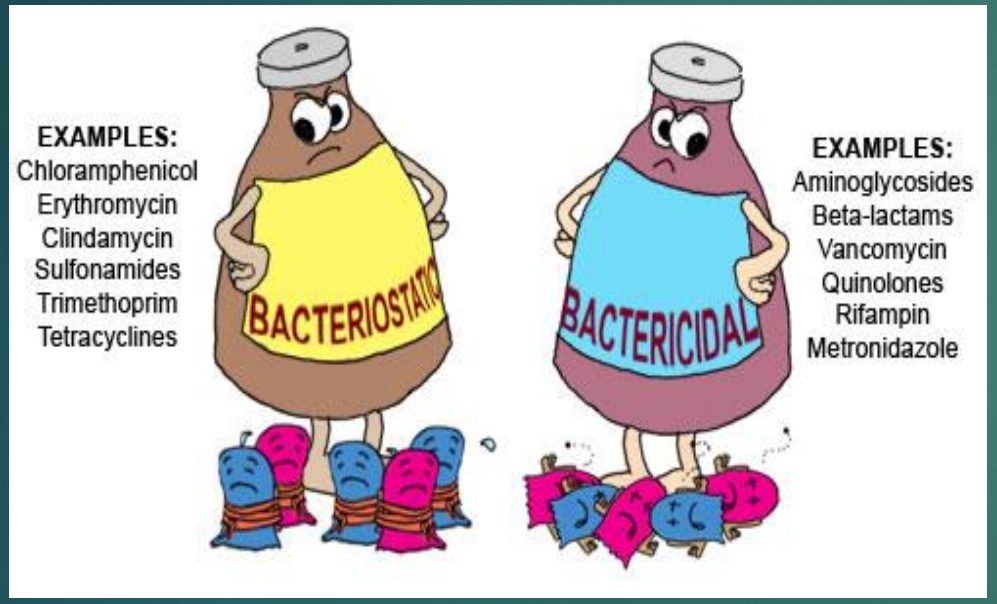
- **Block virulence factor induction, synthesis, or release**
  - ✓ Singal
  - ✓ Transcription
  - ✓ Assemble
  - ✓ Delivery
- **Inhibit the function**
  - ✓ Neutralization
  - ✓ Host receptor antagonist



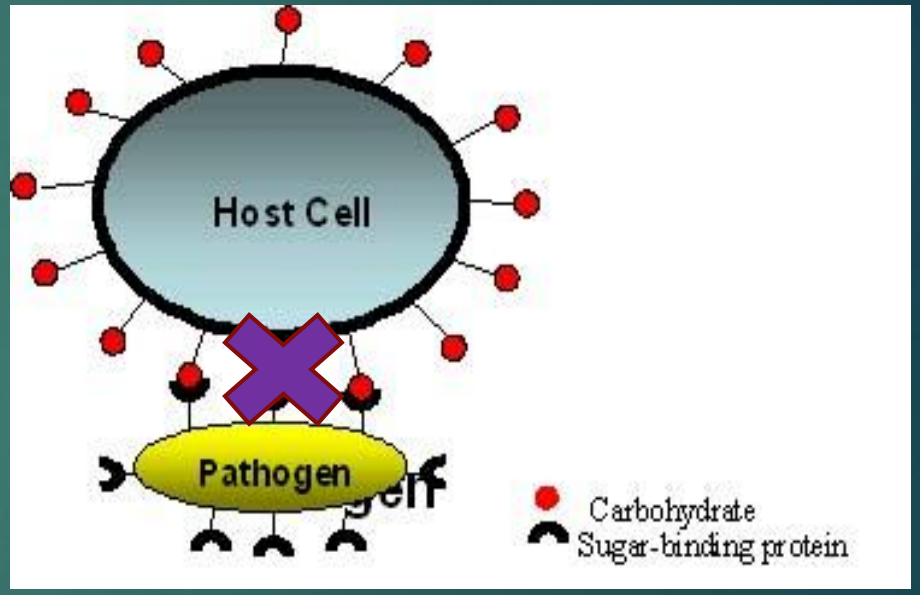
Vanessa Sperandio. Nature Reviews Drug Discovery 9.2 (2010): 117-128

Anti-virulence strategies

Antibiotics VS Anti-virulence



Kill or inhibit cell growth



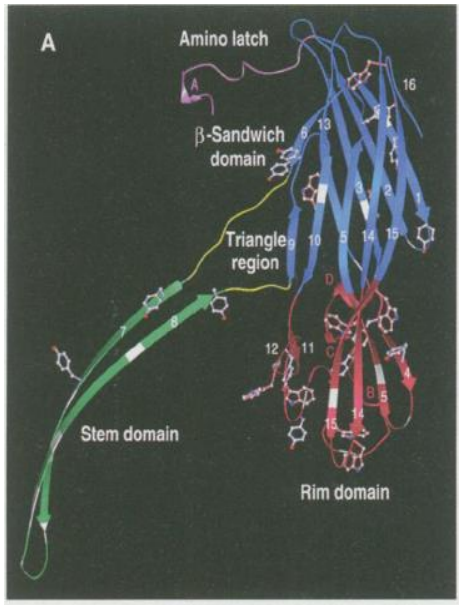
Interrupt infection

http://www.surface.mat.ethz.ch/research_old/functional_biointerface/GlycoSurf

http://www.smallerquestions.org/blog/2013/7/11/antibiotics-damage-human-cells.html

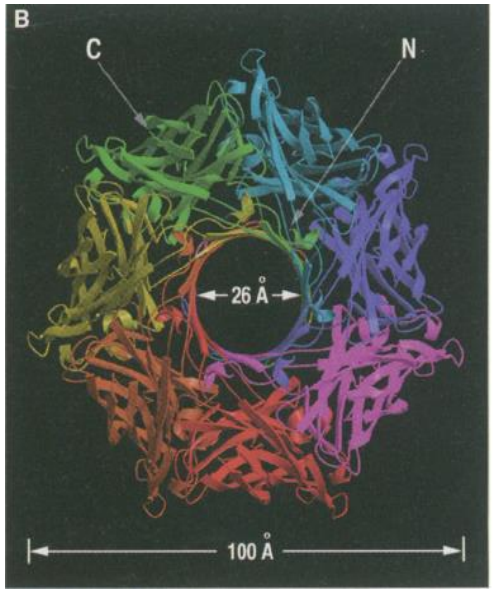
Anti-virulence strategies against MRSA

Alpha-hemolysin (α-toxin)



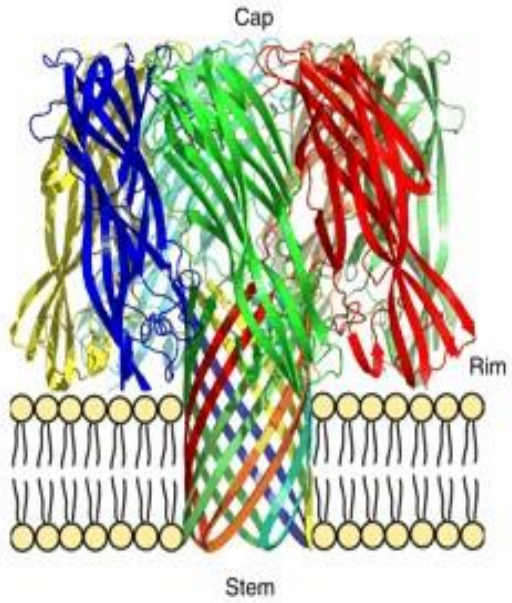
Monomer:33.2kD

L. Song et al.,*Science*,1996



Heptamer:232.4kD

L. Song et al.,*Science*,1996



Pore formation

J.Lakmal et al., *JBC*,2006

1. α-toxin is an essential virulence in SA
2. α-toxin form pore on cell membrane and lysis host cells
3. Metalloprotease 10 (ADAM10) is a cellular receptor for α-toxin

INFECTION AND IMMUNITY, July 2009, p. 2712–2718 Vol. 77, No. 7
0019-9567/09/$08.00+0 doi:10.1128/IAI.00115-09

Anti-Alpha-Hemolysin Monoclonal Antibodies Mediate Protection against *Staphylococcus aureus* Pneumonia▽

Brook E. Ragle[1] and Juliane Bubeck Wardenburg[1,2]*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2010, p. 298–304 Vol. 54, No. 1
0066-4804/10/$12.00 doi:10.1128/AAC.00973-09

Prevention and Treatment of *Staphylococcus aureus* Pneumonia with a β-Cyclodextrin Derivative▽

1. antibody: **neutralize** α-toxin
2. β-Cyclodextrin derivatives：**block the pore** formation
3. ADAM10 Inhibitor: **inhibit binding** of α-toxin to host cell

JID 2014:210

Targeting *Staphylococcus aureus* α-Toxin as a Novel Approach to Reduce Severity of Recurrent Skin and Soft-Tissue Infections

Georgia R. Sampedro,[1,2] Andrea C. DeDent,[1,2] Russell E. N. Becker,[2] Bryan J. Berube,[2] Michael J. Gebhardt,[2] Hongyuan Cao,[3] and Juliane Bubeck Wardenburg[1,2]

Summary

- Antibiotic resistance pathogens continue to rise, while antibiotic development is dwindling
- Probiotics : 'Good' bacteria fight against 'bad' ones
- Bacteriophage therapy: 'Viruse' fight against pathogens
- Anti-virulence strategies: Strategies aim to interrupt pathogen-host interaction

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Thanks for your attention