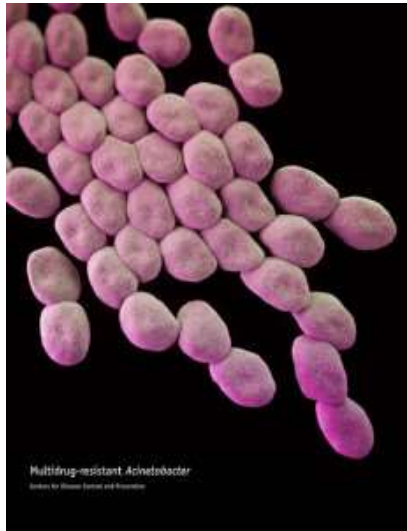


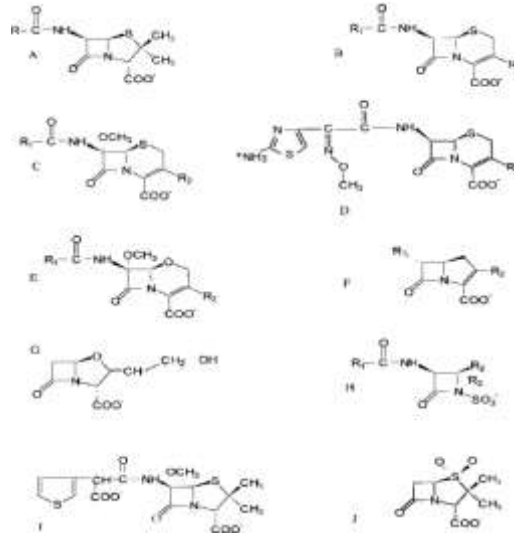
# Antibiotics and alternative strategies to control infections



ciss.blog.olemiss.edu

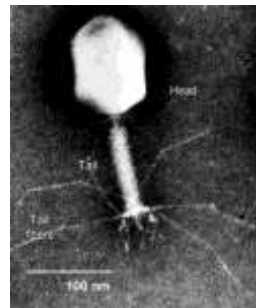


<http://blog.microbiologics.com/wp-content/uploads/2015/12/Acinetobacter-baumanni-232x300.jpg>



[www.biochemj.org/bj/330/0581/bj3300581.htm](http://www.biochemj.org/bj/330/0581/bj3300581.htm)

**Dr. Vassie Ware**  
**Bioscience in the 21<sup>st</sup> Century**  
**10/16/2019**



Head Space - WordPress.com



Wikipedia

# ***OUTLINE***

1. Your thoughts about the value of antibiotics
2. General information about antibiotics and their targets
3. Development of bacterial antibiotic resistance
4. How do we respond to growing antibiotic resistance problem?
5. Reprise: Alternative strategies - Phage Therapy

# PERSPECTIVE

- **Widespread use of antibiotics after WWII to improve global health**
- **Increasing antibiotic resistance in bacterial pathogens coupled with a lag in the development of additional antibiotics by pharmaceutical companies poses an escalating problem in the 21<sup>st</sup> century**

**2005: ~19,000 deaths from bacterial infections.**

**Today: 2 million people infected; ~23,000 deaths/year in US from bacterial infections!!! (from cdc.gov)**

- **Challenge to design effective new generation antibiotics among the growing impact of superbugs, overuse of antibiotics, and decline in research and development of new prospects**
- **Use of structure-based drug design to develop novel drugs based on high resolution structures of drug targets and their resistance mutants**



## Who said this and what was the antibiotic?

"When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bacteria killer,"  
....would later say, "But I suppose that was exactly what I did."

# Antibiotic Basics

# Antibiotics

- Natural or synthetic compounds that either kill (bactericidal) or inhibit growth (bacteriostatic) of bacteria (or other microorganisms)
- Antibiotics may be classified in several ways. Most common classification schemes are based on chemical structure of the antibiotic

# Antibacterial agents, suitable for therapy:

## Natural –

Derived from natural sources such as fungi and soil bacteria.

Penicillin as the classic example, derived from the fungus *Penicillium*

Pharmaceutical industry produces penicillin from cultures of

*Penicillium chrysogenum* that are adapted for high yield

Others: many aminoglycosides from soil bacteria (e.g., streptomycin)

## Semi-synthetic -

Natural products that have been chemically modified to improve effectiveness of the product or to reduce side effects, etc

Examples include the  $\beta$ -lactams ampicillin, amoxicillin, etc, derived from fungi

## Completely synthetic –

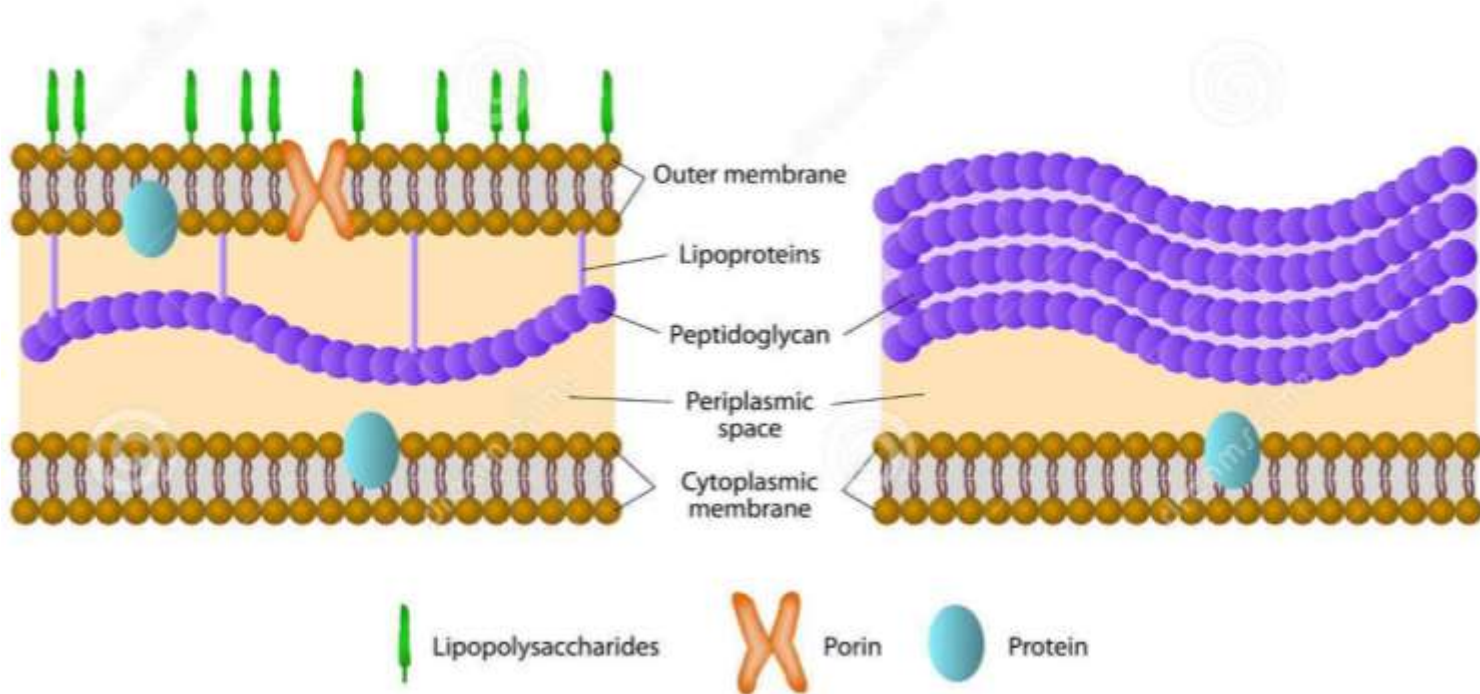
Products are synthesized completely in the laboratory

Sulfa drugs, folic acid analogs are examples

# Bacterial types distinguished by cell wall features

## GRAM-NEGATIVE

## GRAM-POSITIVE

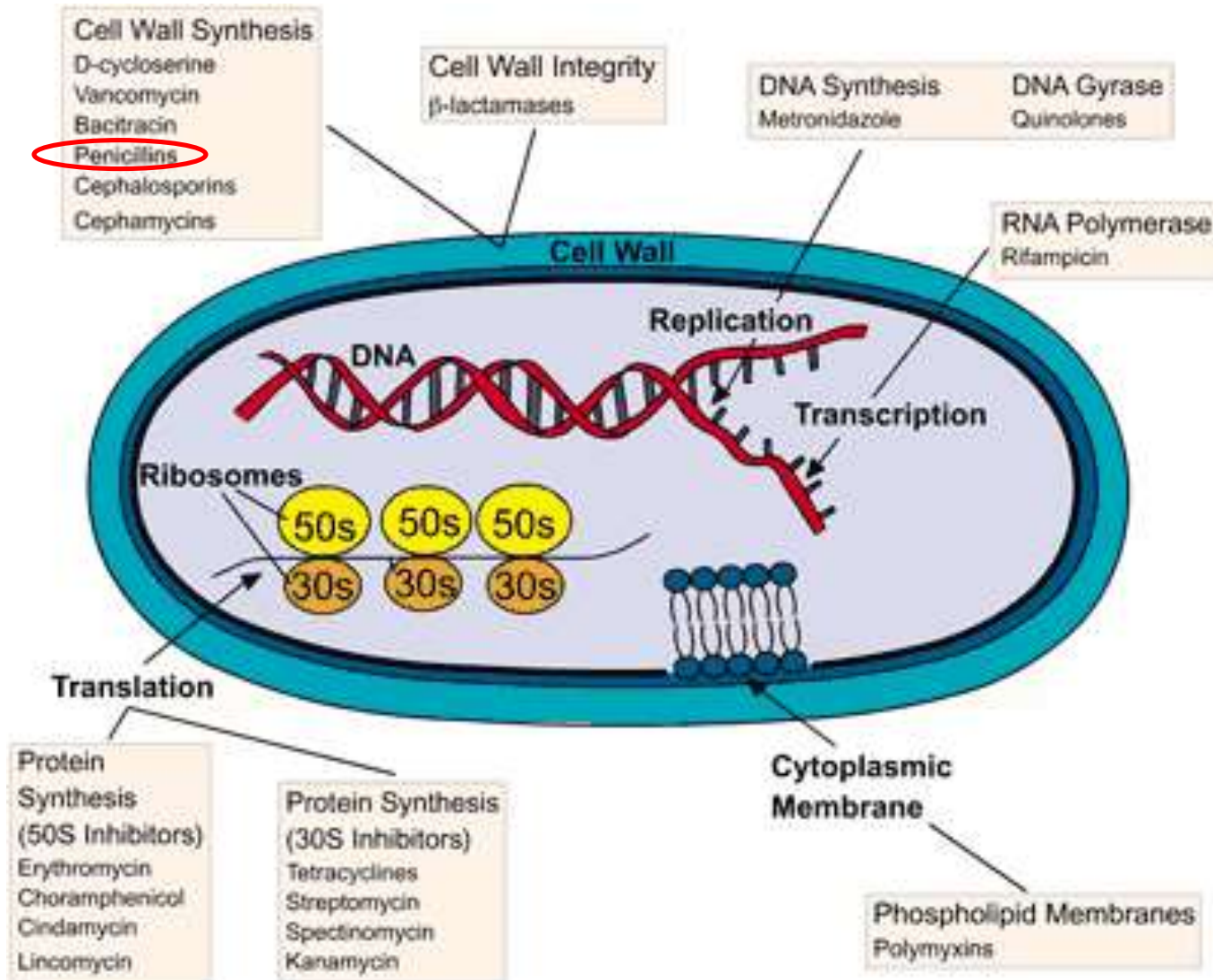


- *E. coli*
- *Acinetobacter baumannii*,
- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae*
- *Neisseria gonorrhoeae*

- *Streptococcus pneumoniae*
- *Clostridium botulinum*
- *Staphylococcus aureus*
- *Listeria monocytogenes*



# Antibiotic Targets in Bacterial Cells



# Antibiotic Resistance

# How do bacteria become resistant to antibiotics?

Bacteria acquire **genes** that encode proteins that shield or protect them from the effects of the antibiotic. Bacteria develop resistance by mutations in their proteins (derived from mutations in genes)

These genes may have arisen by **mutation** of existing genes

OR

they may have been acquired from *other* resistant bacteria through the **transfer of genetic information between bacteria**

Antibiotic resistance genes are often carried on **plasmids** and can be exchanged between bacteria.

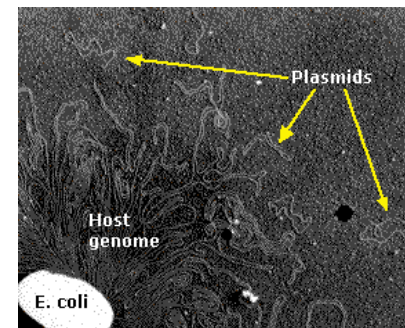


It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

[www.terra-thrive.com](http://www.terra-thrive.com)



[www.life.uiuc.edu](http://www.life.uiuc.edu)



[users.rcn.com](http://users.rcn.com)

# Resistance to Antibiotics can occur through two general genetic mechanisms

## 1. Intrinsic resistance

Some bacteria are naturally more resistant to certain classes of antibiotics than others.

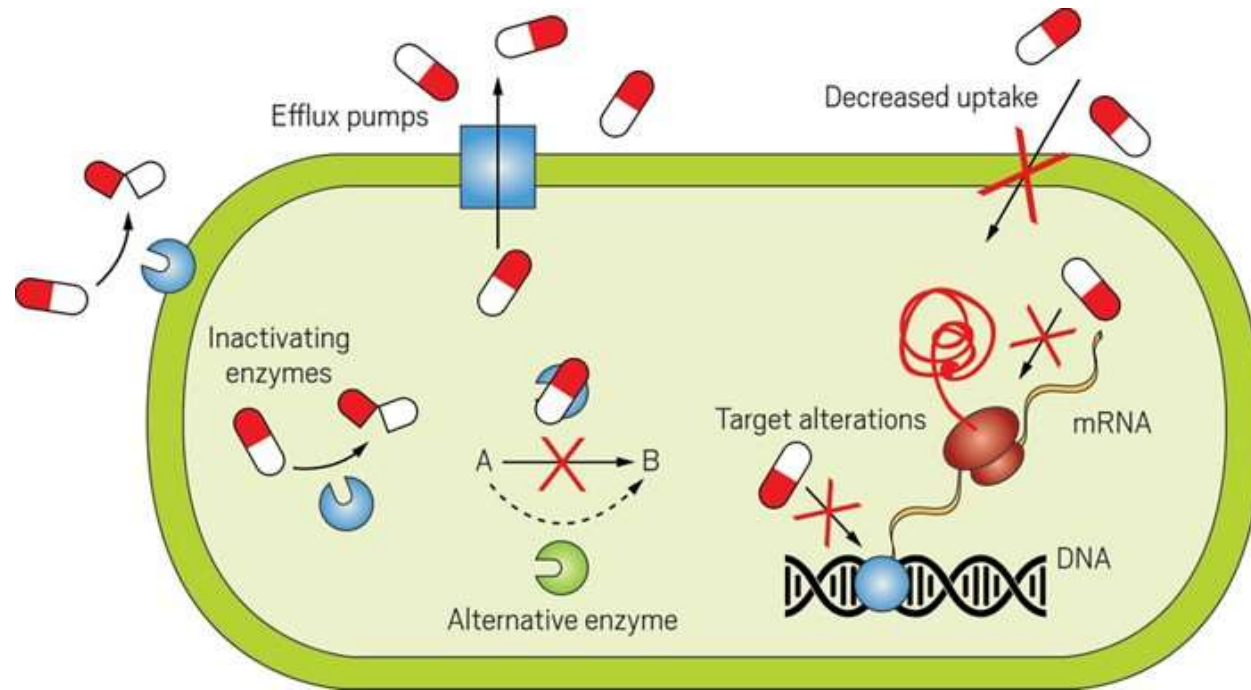
Examples:

- certain bacteria may lack a transport system for an antibiotic
- bacteria may lack the target of the antibiotic molecule
- the cell wall is covered with an outer membrane blocks entry of the antibiotic (as in the case for Gram negative bacteria).

## 2. Acquired resistance

Bacteria acquire resistance to antibiotics for which they were previously susceptible through

- spontaneous gene mutation (rate of  $10^{-8}$ – $10^{-9}$ ) and fixation of mutation in the population through rapid cell division (vertical evolution)
- **horizontal gene transfer** mechanisms, such as **conjugation**, **transformation**, or **transduction**. Impact of this can be significant. For example, in 10 years' time between 1985 and 1995, the percentage of ampicillin-resistant *Shigella* (causes intestinal illness) grew from 32% to 67%!

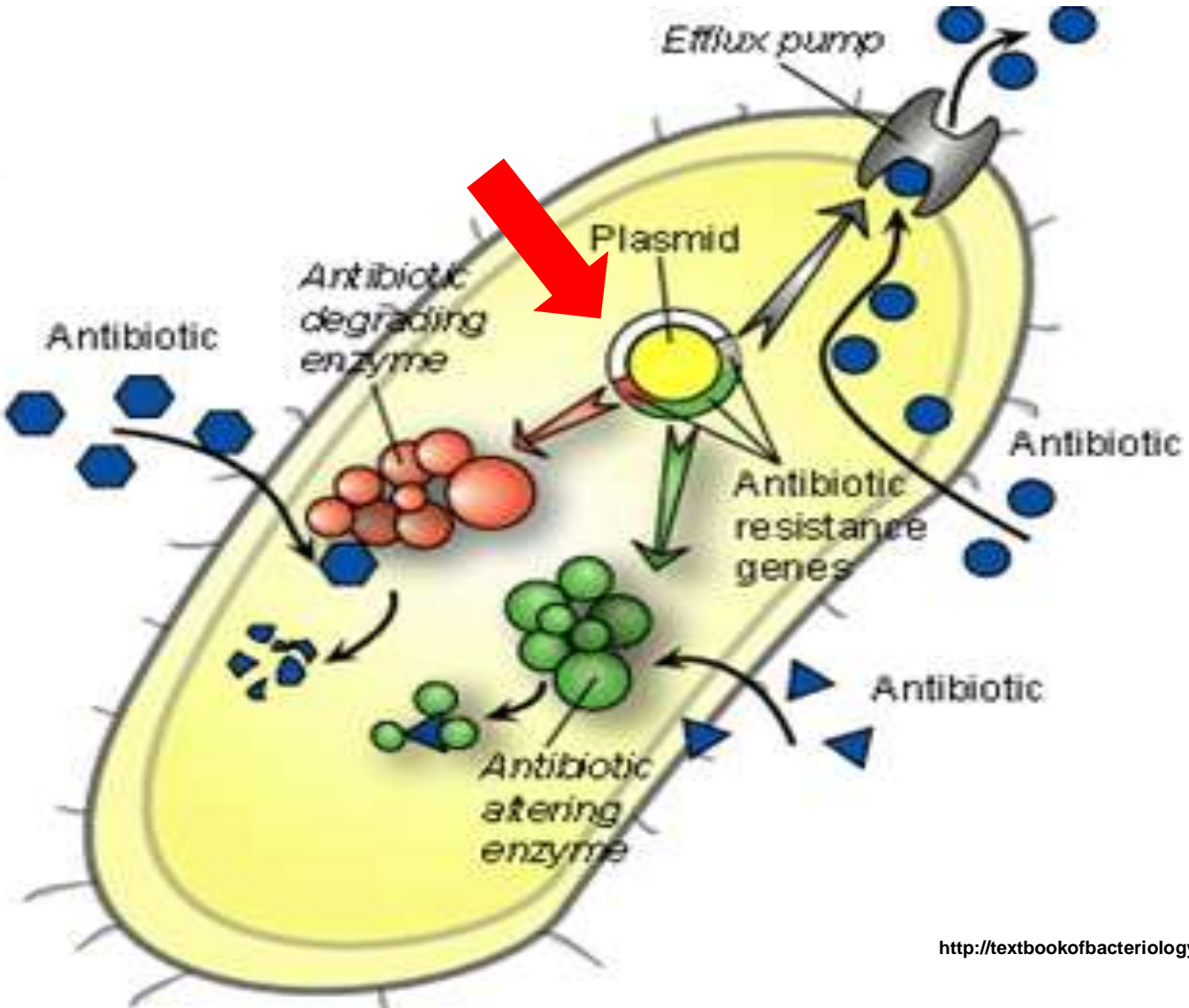


## Antibiotic resistance mechanisms

Pathogens have evolved several mechanisms to neutralize antibiotics:

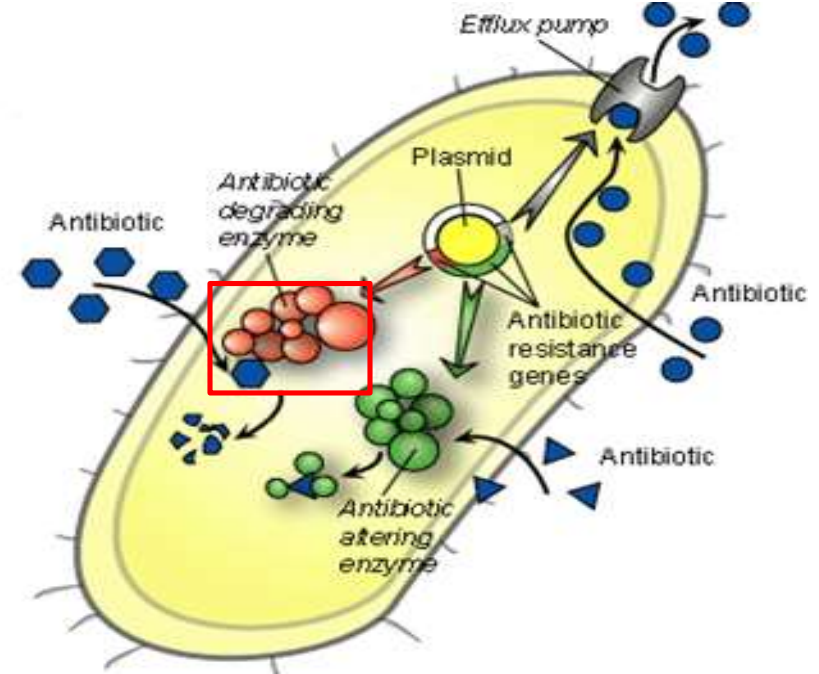
- They can use inactivating enzymes such as  $\beta$ -lactamases to destroy antibiotics containing  $\beta$ -lactam rings.
- They can increase the production of efflux pumps to spit antibiotics back out of the cell.
- They can alter the composition of their cell wall to decrease antibiotic uptake.
- They can alter the genetic targets of some antibiotics.
- They can replace enzymes targeted by antibiotics with alternative enzymes that carry out the same function.

# Plasmid-encoded genes that can activate an antibiotic



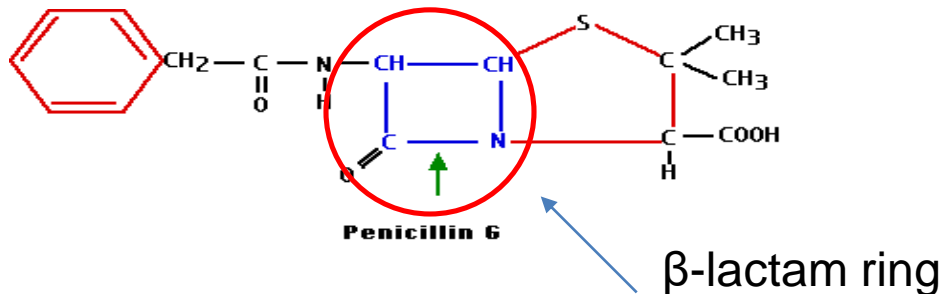


Several mechanisms (shown in red) exist to inactivate an antibiotic. Mechanism(s) used depend on the genes found in the resistant bacteria of interest, such as:



### Synthesis of enzymes that breakdown the antibiotic:

Penicillinase (a type of  $\beta$ -lactamase, breaks the  $\beta$ -lactam ring, thereby destroying the antibiotic). Other enzyme types are also prevalent (e.g., cephalosporinases). New Delhi metallo-beta lactamase (NDM-1), an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics (creating resistant “superbugs”)



# Case study

Strategies by industry to overcome resistance to  $\beta$ -lactams :

Bacteria produce enzymes called **lactamases** that disable antibiotics containing the classic  $\beta$ -lactam ring scaffold.

Pathogens have evolved ~2700 enzymes known to inactivate  $\beta$ -lactams.

Only so many ways to modify the ring scaffold to produce new generations of  $\beta$ -lactams. Therefore, one strategy is to develop lactamase inhibitors can overcome resistance mechanisms, at least for a little while.



# Antibiotic resistance is one of biggest health challenges - Alerts by the Centers for Disease Control (CDC)

Urgent Threats	Serious Threats	Concerning Threats
<ul style="list-style-type: none"><li>• <a href="#">Clostridioides difficile</a></li><li>• <a href="#">Carbapenem-resistant Enterobacteriaceae (CRE)</a></li><li>• <a href="#">Drug-resistant Neisseria gonorrhoeae</a></li></ul>	<ul style="list-style-type: none"><li>• <a href="#">Multidrug-resistant Acinetobacter</a></li><li>• <a href="#">Drug-resistant Campylobacter</a></li><li>• <a href="#">Fluconazole-resistant Candida</a></li><li>• <a href="#">Extended-spectrum Beta-lactamase producing Enterobacteriaceae</a></li><li>• <a href="#">Vancomycin-resistant Enterococcus (VRE)</a></li><li>• <a href="#">Multidrug-resistant Pseudomonas aeruginosa</a></li><li>• <a href="#">Drug-resistant non-typhoidal Salmonella</a></li><li>• <a href="#">Drug-resistant Salmonella Serotype Typhi</a></li><li>• <a href="#">Drug-resistant Shigella</a></li><li>• <a href="#">Methicillin-resistant Staphylococcus aureus (MRSA)</a></li><li>• <a href="#">Drug-resistant Streptococcus pneumoniae</a></li><li>• <a href="#">Drug-resistant Tuberculosis</a></li></ul>	<ul style="list-style-type: none"><li>• <a href="#">Vancomycin-resistant Staphylococcus aureus (VRSA)</a></li><li>• <a href="#">Erythromycin-Resistant Group A Streptococcus</a></li><li>• <a href="#">Clindamycin-resistant Group B Streptococcus</a></li></ul>

<https://www.cdc.gov/drugresistance/biggest-threats.html>

[2013 data; new data expected fall 2019]

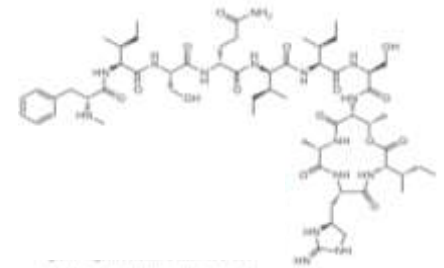
## New Discoveries and Stakeholders in Antibiotic Resistance Fight

# Promising discoveries:

A new antibiotic called teixobactin isolated from a newly discovered bacterial species, *Eleftheria terrae*, kills pathogens without detectable resistance

Significance of this discovery:

- A new class of antibiotic active against Gram positive bacteria (e.g., *Staphylococcus aureus*, *Mycobacterium tuberculosis*)
- First new class of antibiotic discovered in ~30 years
- Binds to lipids (NOT proteins) which are precursors to cell wall synthesis
- Discovered with a new isolation method of culturing bacteria in soil using iChip
- Discovery improves hopes of isolating new antibiotics using different culturing methods
- In preclinical trials



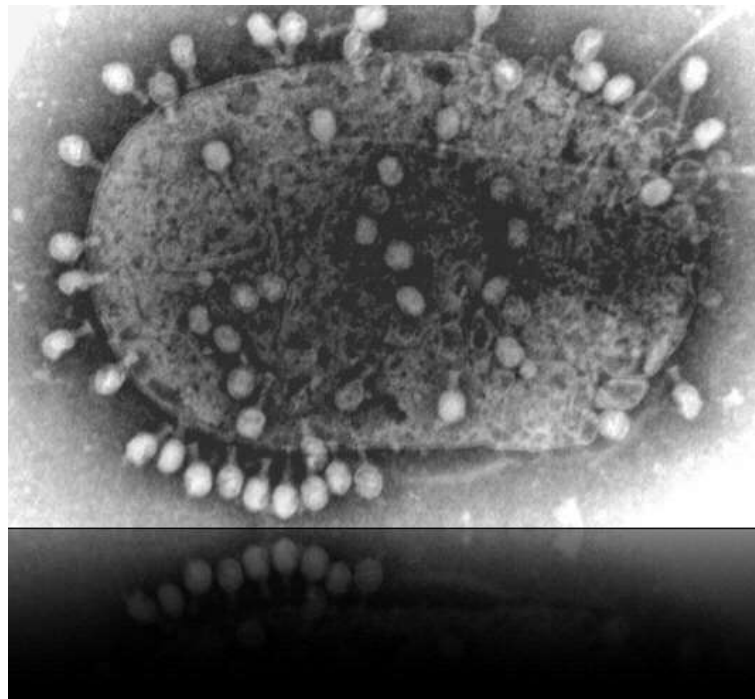
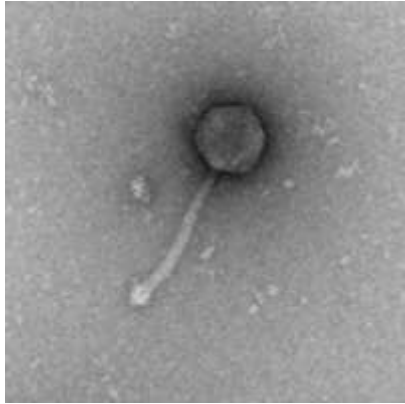
# What can government do to help solve the antibiotic crisis?



Three main components to the report (2014):

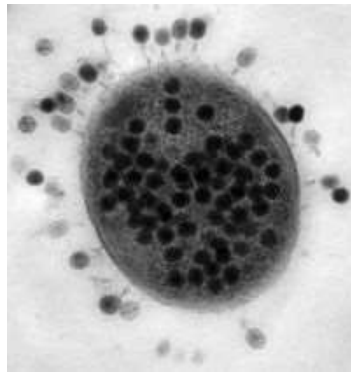
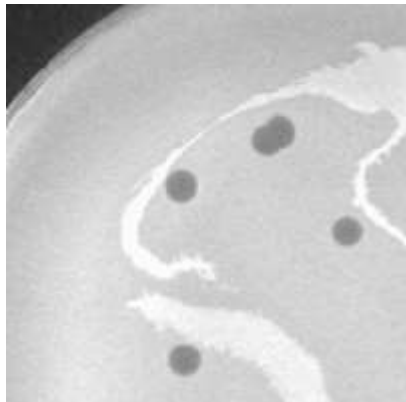
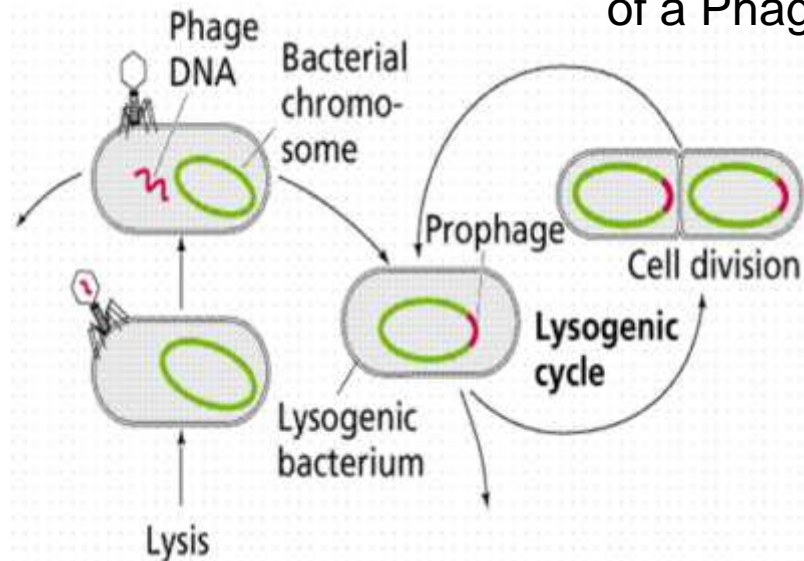
- improve surveillance of antibiotic-resistant bacteria and stop outbreaks;
- increase the life of current antibiotics and develop new ones, as well as promote research accelerating clinical trials;
- increase economic incentives to develop new antibiotics.

# An Alternative to Antibiotics



<http://www.bacteriophagetherapy.info>

## The Life Cycle of a Phage



<http://en.citizendium.org/wiki/Bacteriophage>

# Alternative strategies to control human infections



Bacteriophages could be a resource for fighting drug-resistant bacterial infections.

MICROBIOLOGY

## Phage therapy gets revitalized

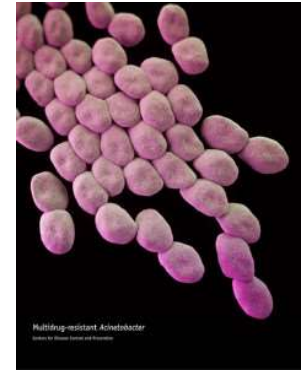
*The rise of antibiotic resistance rekindles interest in a century-old virus treatment.*

- Widely used in Russia, Poland, Georgia; nearly a century of research on phages at Eliava Institute in Georgia (1923)
- First European large, multicenter clinical trial of phage therapy for human infections called Phagoburn
- Novel Phage Therapy Saves Patient with Multidrug-Resistant Bacterial Infection in US (collaboration between UCSD, U.S. Navy Medical Research Center – Biological Defense Research Directorate (NMRC-BDRD), Texas A&M University, AmpliPhi, San Diego State University)
- Development of phage cocktails with multiple phage within. Why?



# Phage Therapy Case Study

- March 2016: first known person in USA to be treated by IV bacteriophage therapy - Tom Patterson, Ph.D., psychiatrist from UCSD
- Contracted life-threatening infection with MDR strain of *Acinetobacter baumannii* (Gram negative) in Egypt in 2015. Patient in months-long coma
- At UC San Diego Health, received emergency approval (emergency investigational new drug application) for FDA for IV phage therapy specifically targeting *A. baumannii*.
- Condition improved almost immediately
- Rationale for exploring this as alternative to antibiotics amid growing resistance problem.



<http://blog.microbiologics.com/wp-content/uploads/2015/12/Acinetobacter-baumannii-232x300.jpg>

# Phage therapy: advantages and challenges

## Advantages:

- Phages typically infect one bacterial type (or very closely related types); advantage over broad-spectrum antibiotics
- Phages are plentiful in the biosphere ( $10^{31}$ )
- Phages require bacteria for replication; therefore they replicate where the pathogen resides (if accessible)
- Generally thought to be safe (commonly used prior to antibiotic revolution after WWII)
- Indiscriminate against antibiotic-sensitive and antibiotic-resistant bacteria

## Challenges:

- More research needed to determine efficacy and safety
- Accessibility challenges for pathogens that are intracellular (for example, TB at certain stages)
- Delivery challenges to get to target and to avoid neutralization by immune system
- Can be carriers of other genetic material and deliver to bacterial pathogen (transduction)



# SUMMARY

- Bacterial antibiotic resistance is an increasingly serious global health problem
- Several mechanisms exist that allow bacteria to escape the effects of antibiotics
- Global scientific research imperatives:
  - Development of new derivatives of antibiotics
  - Discovery of new classes of antibiotics with novel mechanisms of action
  - Development of new approaches to treating bacterial infections
- Government and industrial partnerships are essential to foster new antibiotic drug development
- Bacteriophages are being used in phage cocktails as an alternative strategy to treat infection