

**The Evolution of  
Antimicrobial  
Resistance**

**by**

**Sir Richard Sykes**

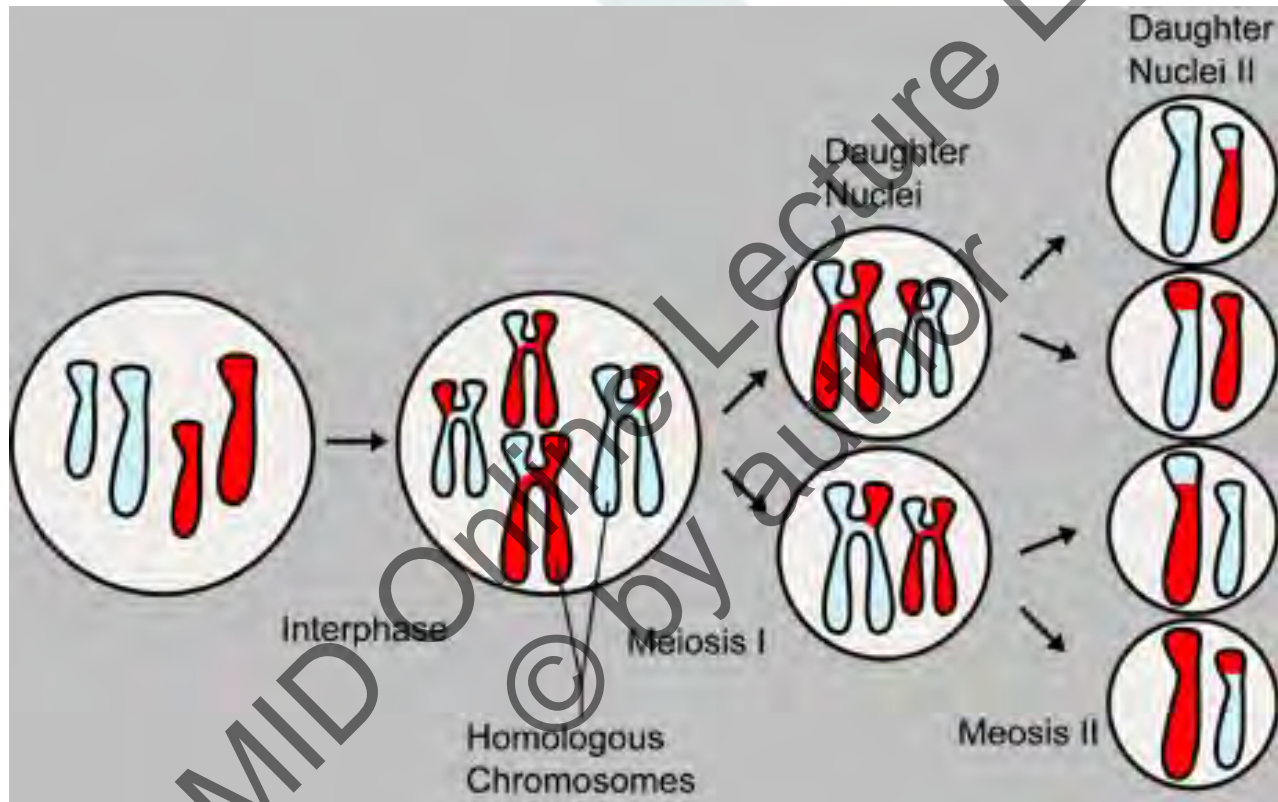
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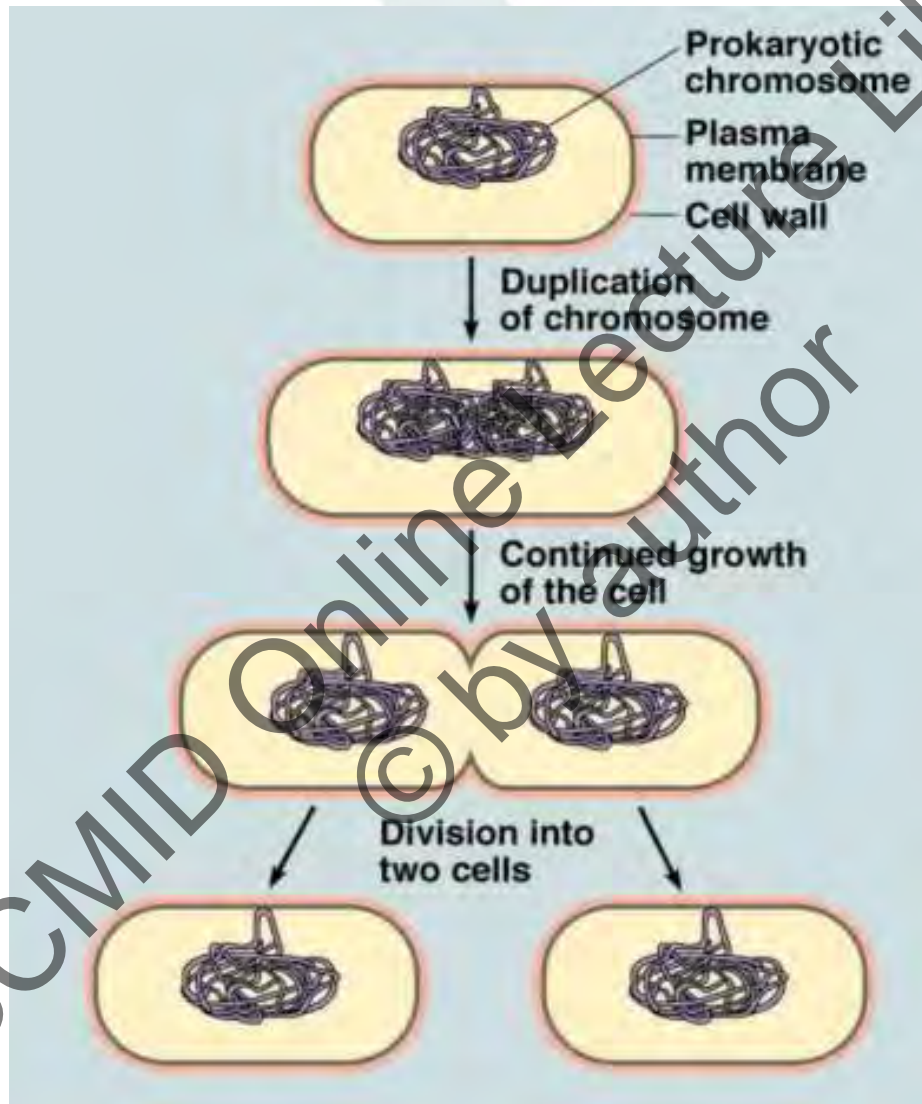
# Deep sea vent



# Meiosis



# Binary fission



# Major mechanisms of genetic transfer

- **Transformation** Uptake of naked DNA
- **Transduction** Transfer of DNA by phage
- **Congugation** © Transfer of DNA by cell to cell contact

# Plasmid

Plasmids are extra-chromosomal circular double standard DNA molecules separate from chromosomal DNA capable of replicating independently of chromosomal DNA.

Host to host transfer requires direct mechanical transfer by conjugation or uptake by transduction.

# Transposon

Transposons, or jumping genes, are sequences of DNA that can move around to different positions within the genome of a single cell (transposition).

They can jump from chromosome DNA to plasmid DNA and back, a good mechanism for developing multi resistant strains and causing mutations.

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# Integron

**Integron:** The integron is a gene capture system found in plasmids, chromosomes and transposons.

Pieces of DNA called gene cassettes can be incorporated expressed and disseminated.

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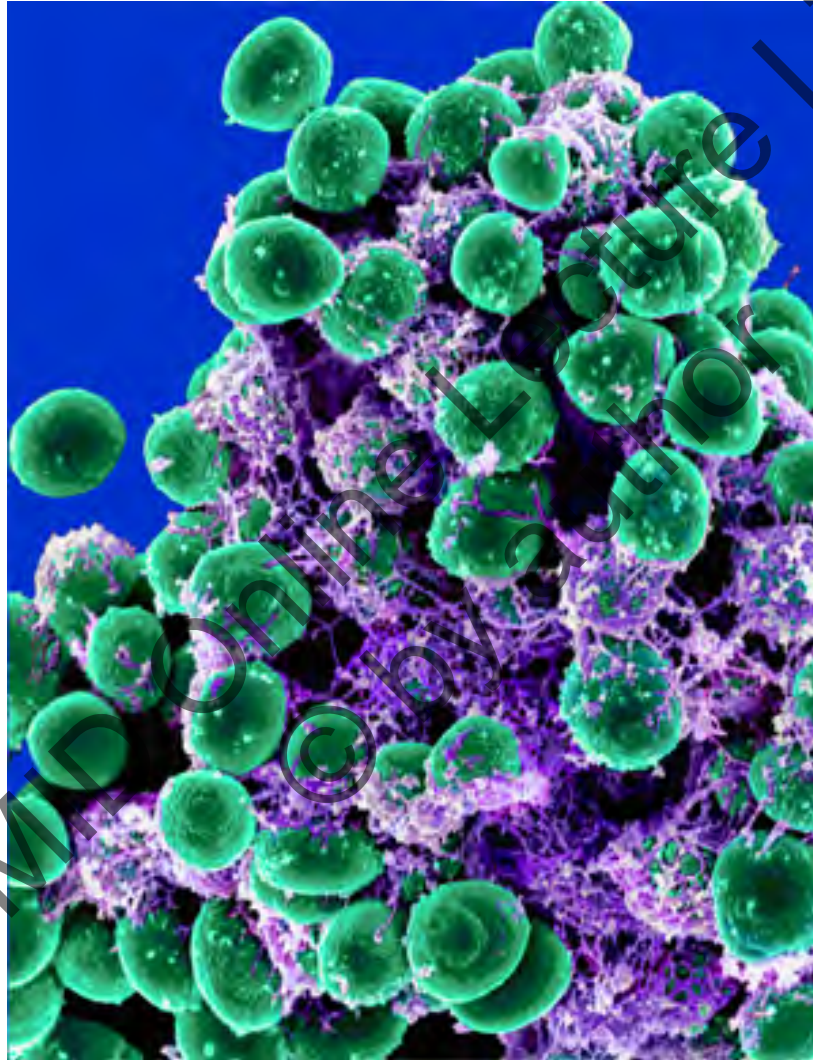
Flaming's laboratory reconstructed. St Mary's Hospital sees Trust



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# Staphylococcus aureus

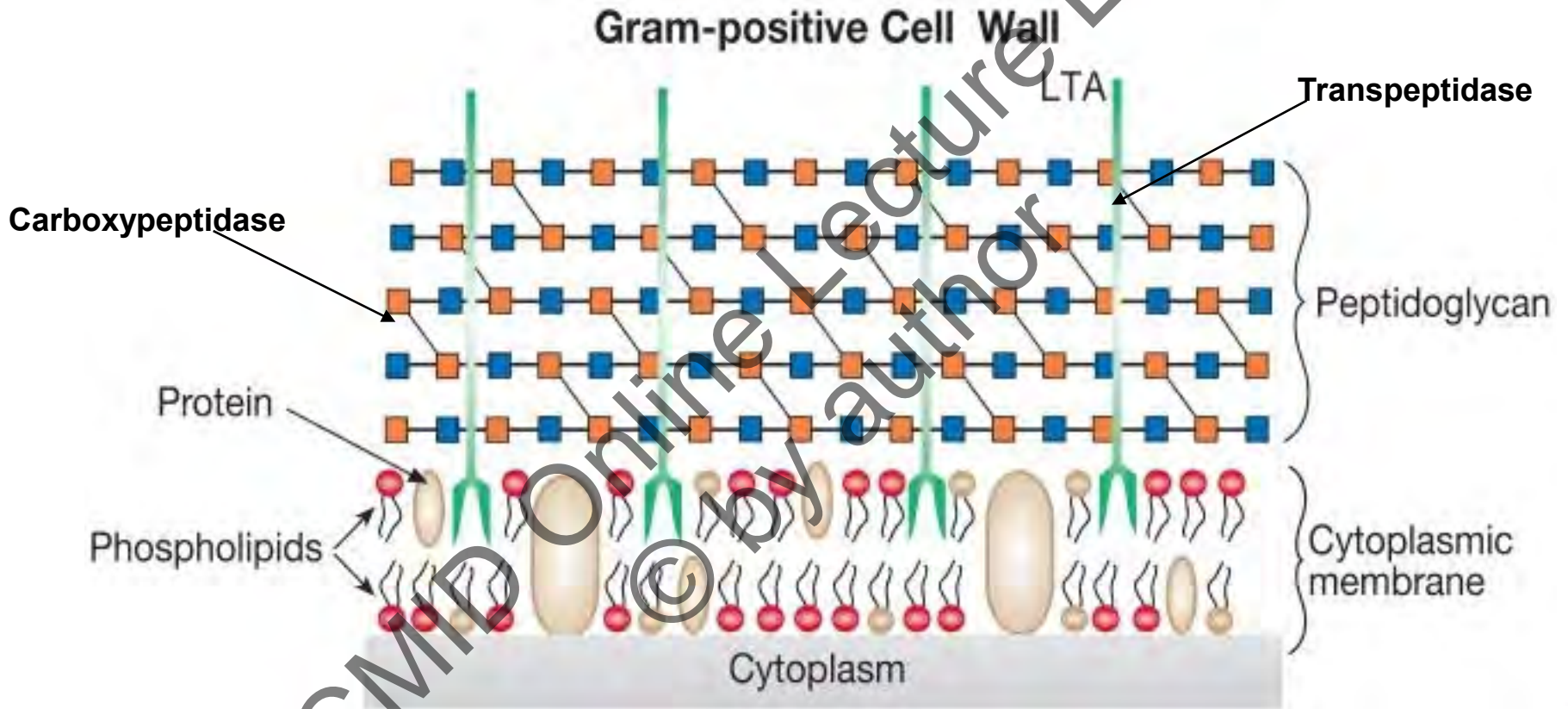


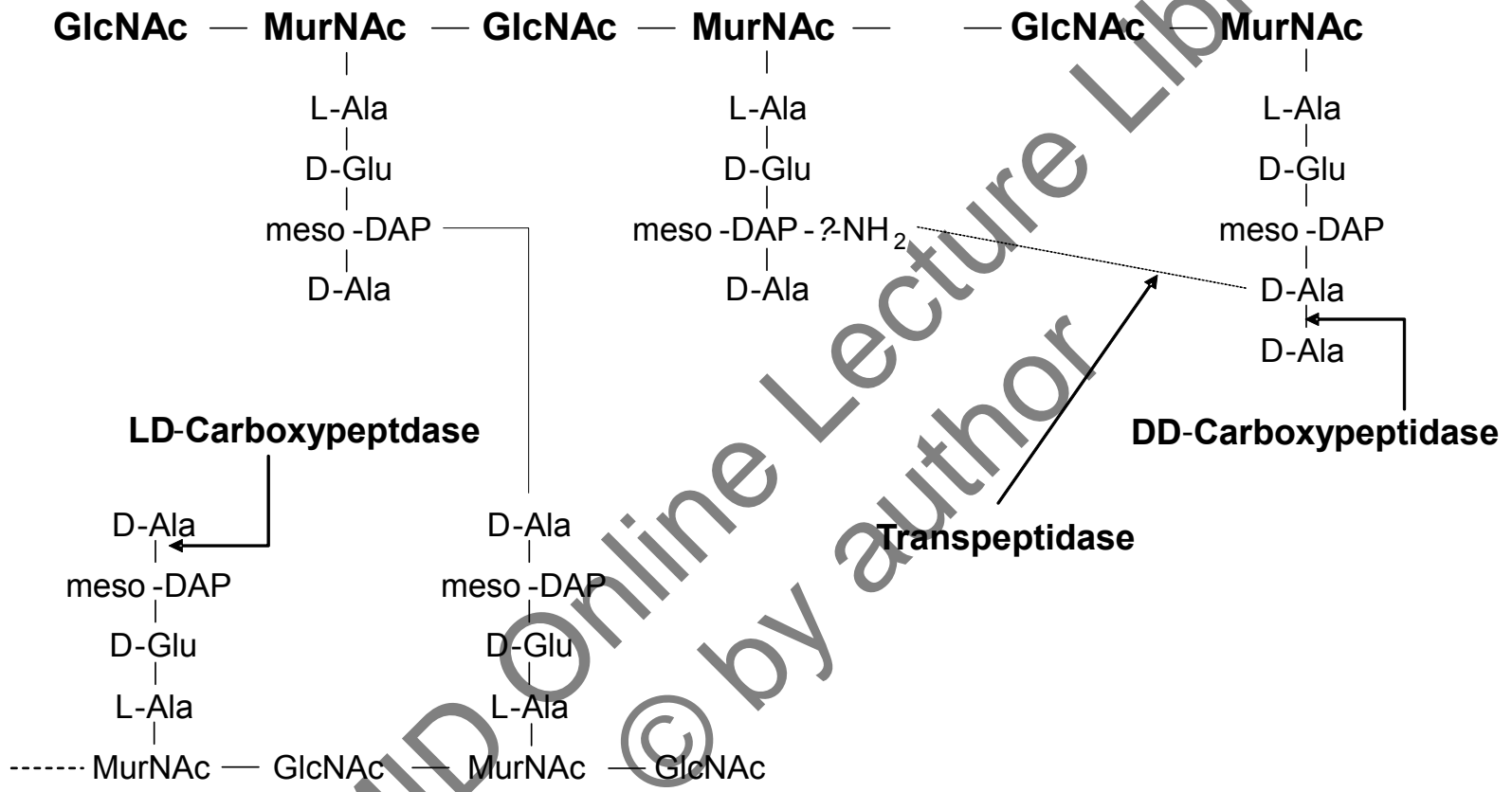
# Mechanism of antibiotic action



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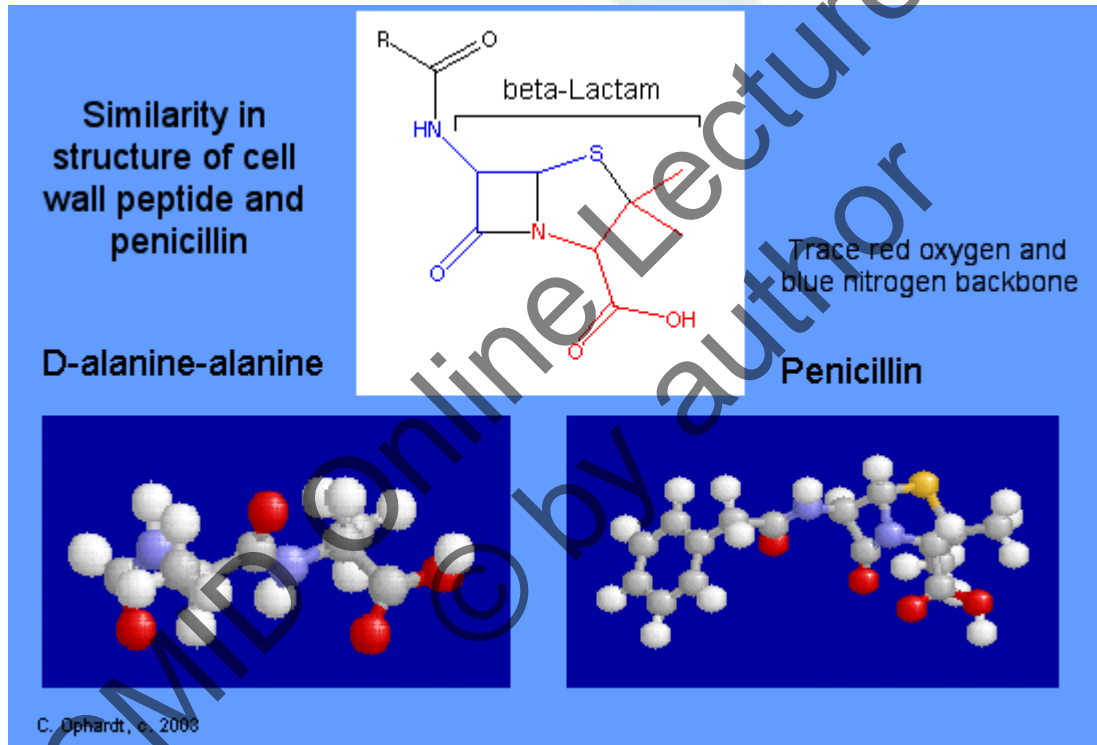
# Gram positive cell wall





Penicillin sensitive enzymes, involved in cell wall biosynthesis

# Structure of cell wall peptide and penicillin



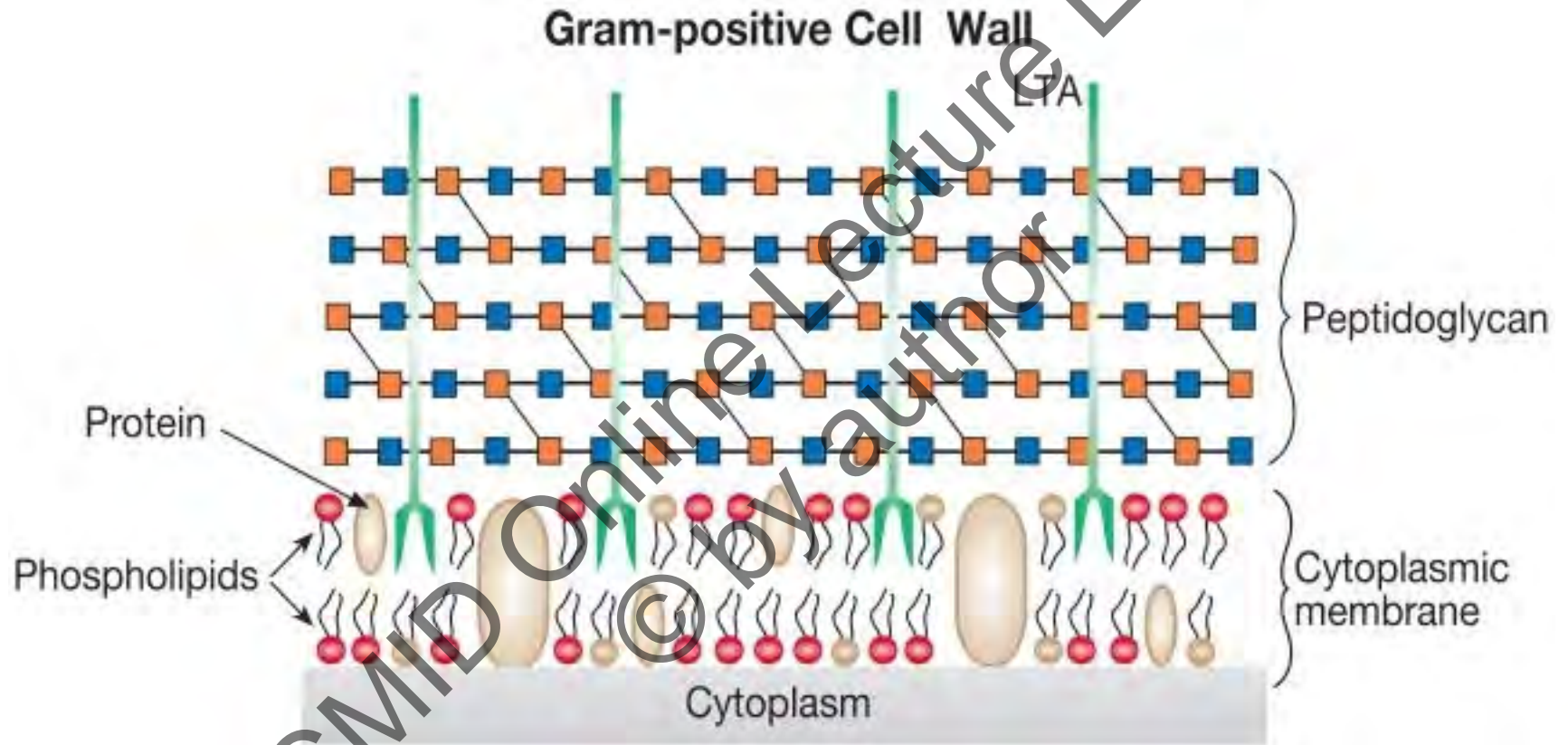
# Mechanism of antibiotic action



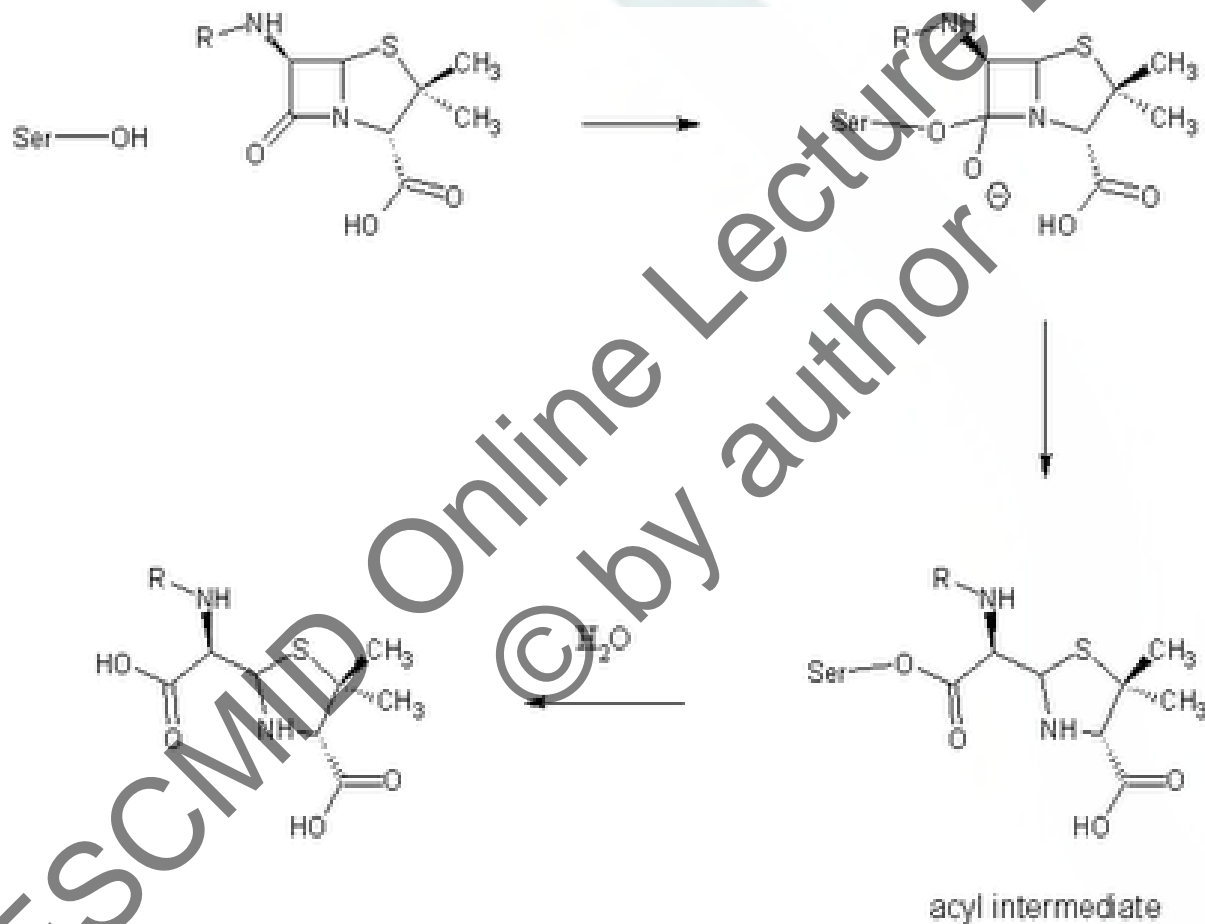
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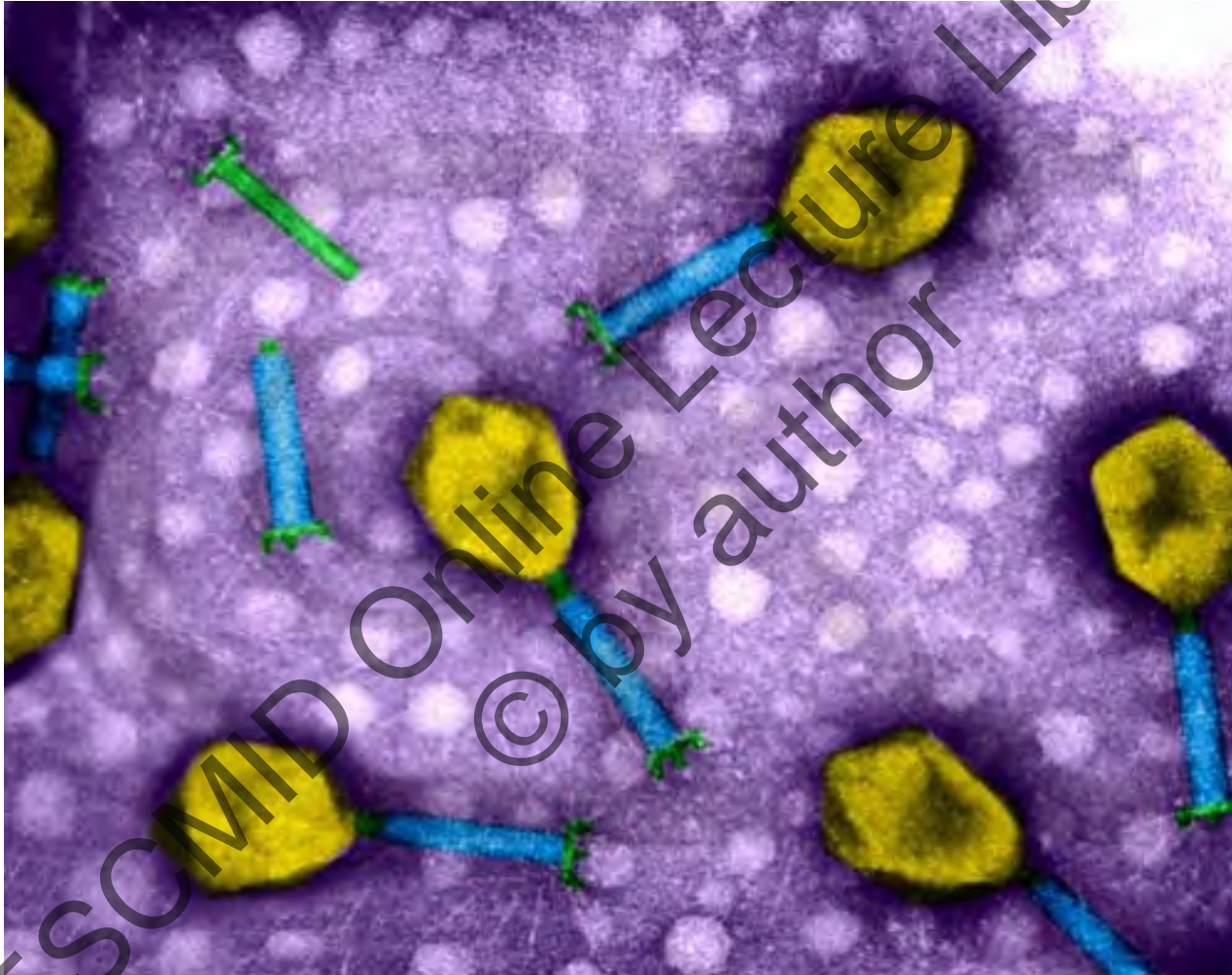
# Gram positive cell wall



# Inactivation of Penicillin by B- Lactamase

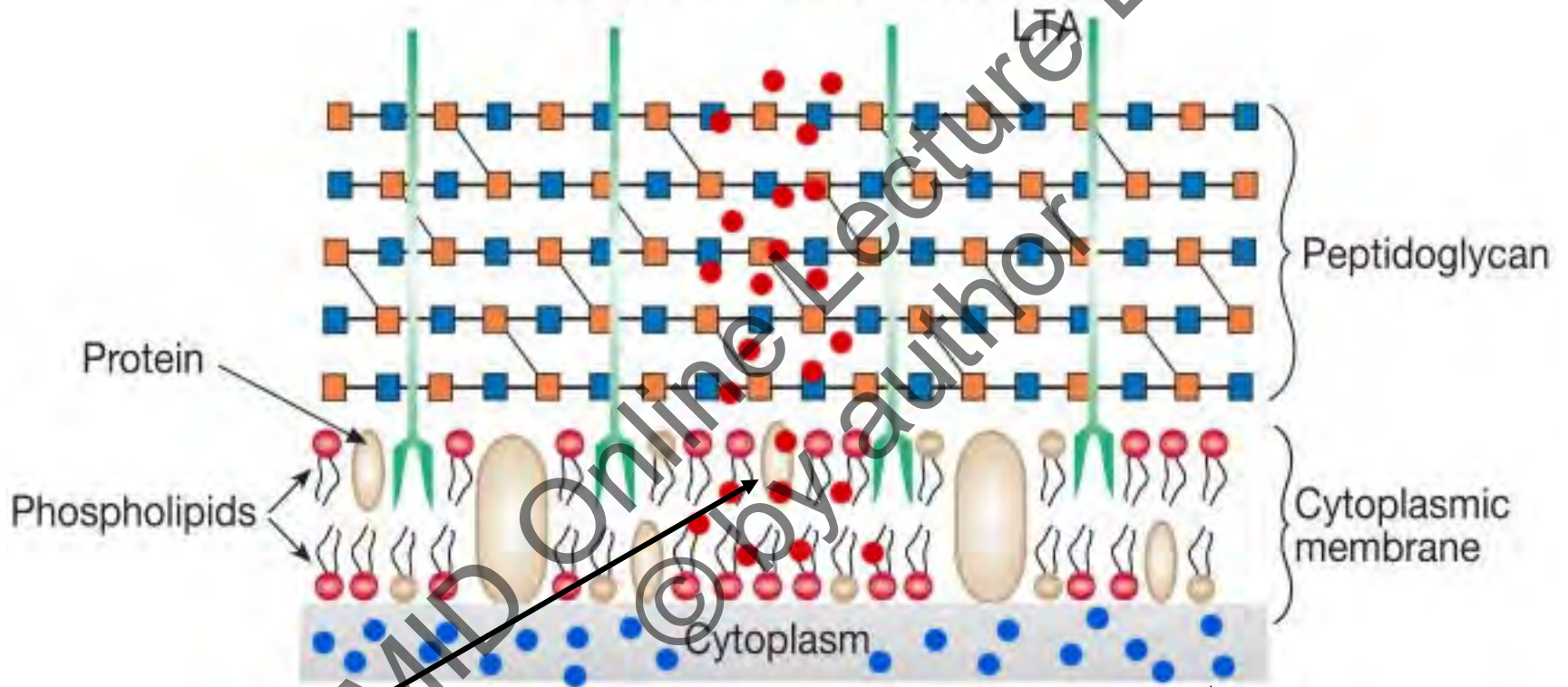


# Bacteriophage



# Gram positive cell wall

Gram-positive Cell Wall

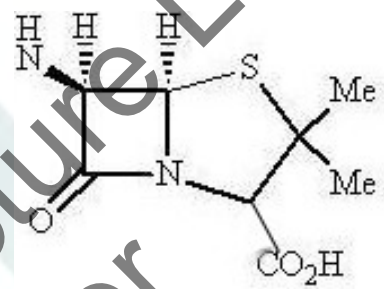


B-lactamase

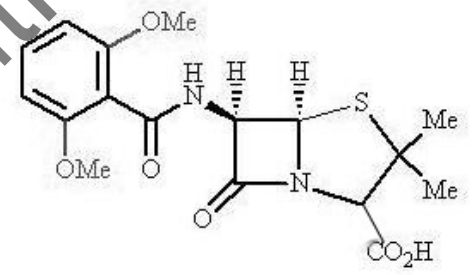
Transpeptidase

# Semi synthetic penicillins

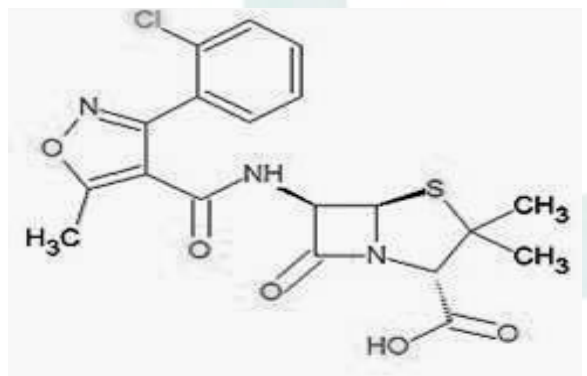
6-APA



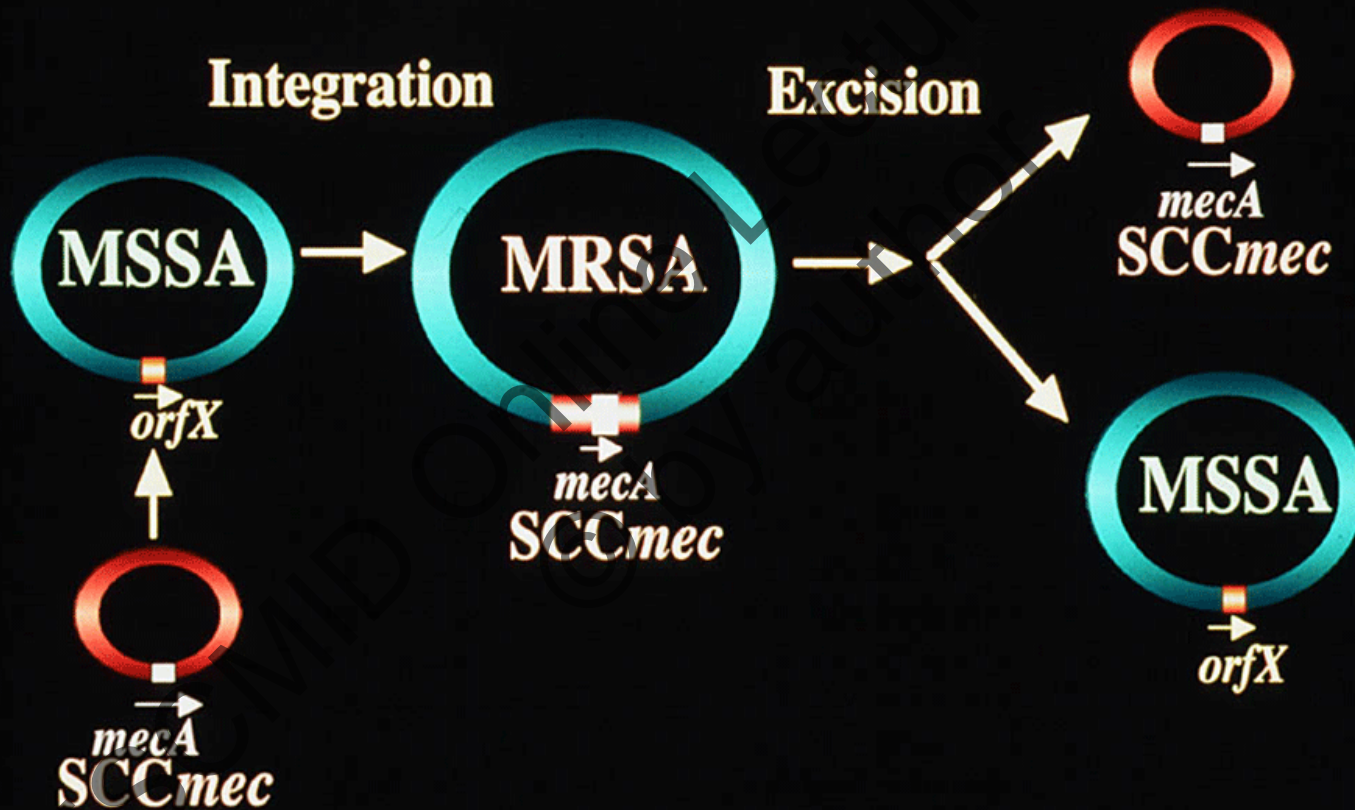
Methicillin



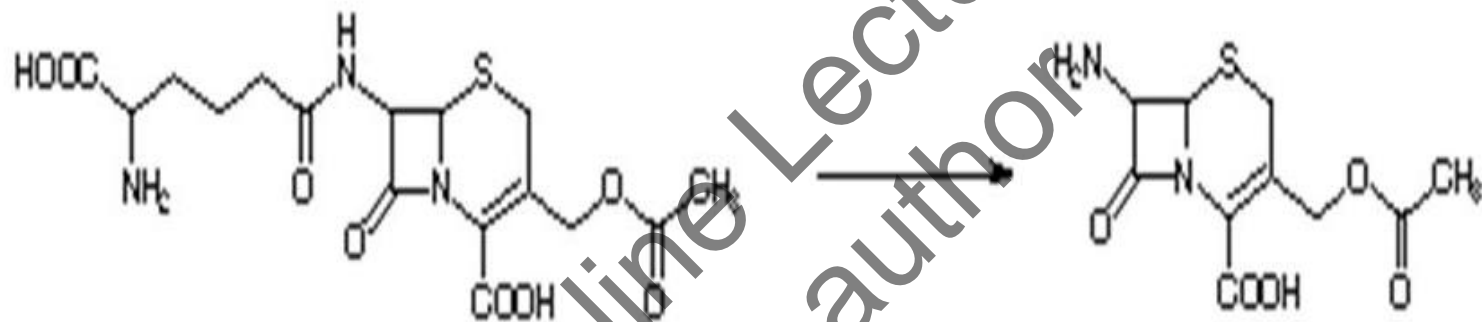
Cloxacillin



# Schematic representation of excision and integration of SCC<sub>mec</sub>



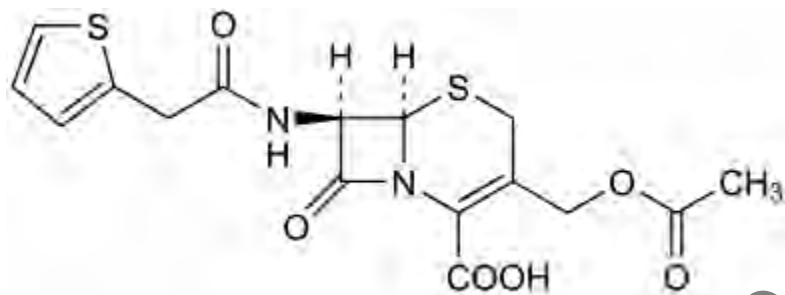
# Cephalosporin C – 7-ACA (capital c)



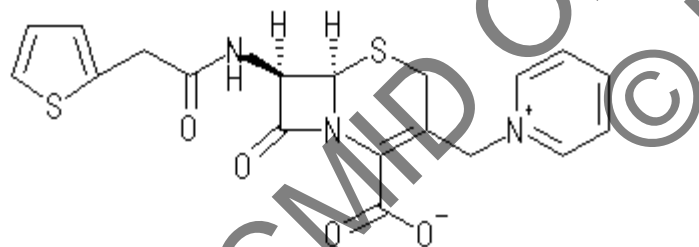
Cephalosporin C

7- Aminocephalosporanic acid  
(7-ACA)

# Cephalothin and Cephaloridine



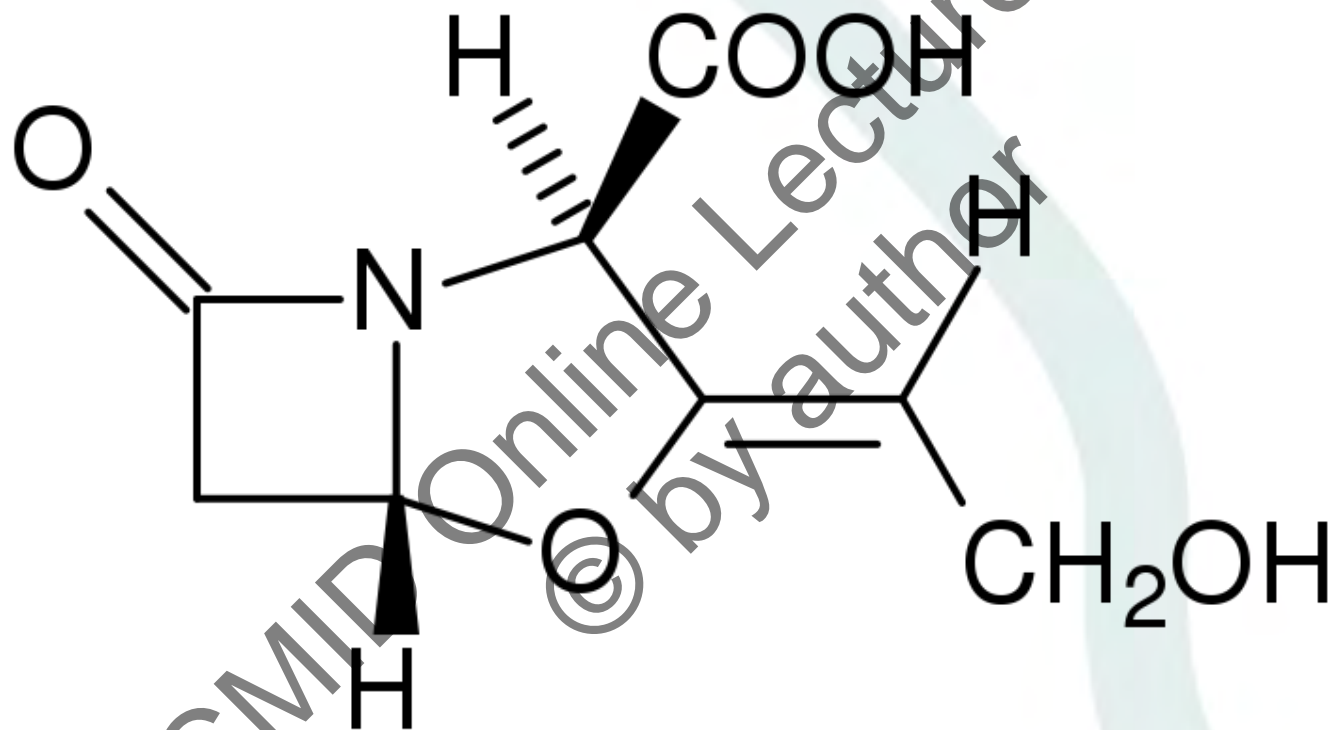
**Cephalothin**



**Cephaloridine**



# Clavulanic acid



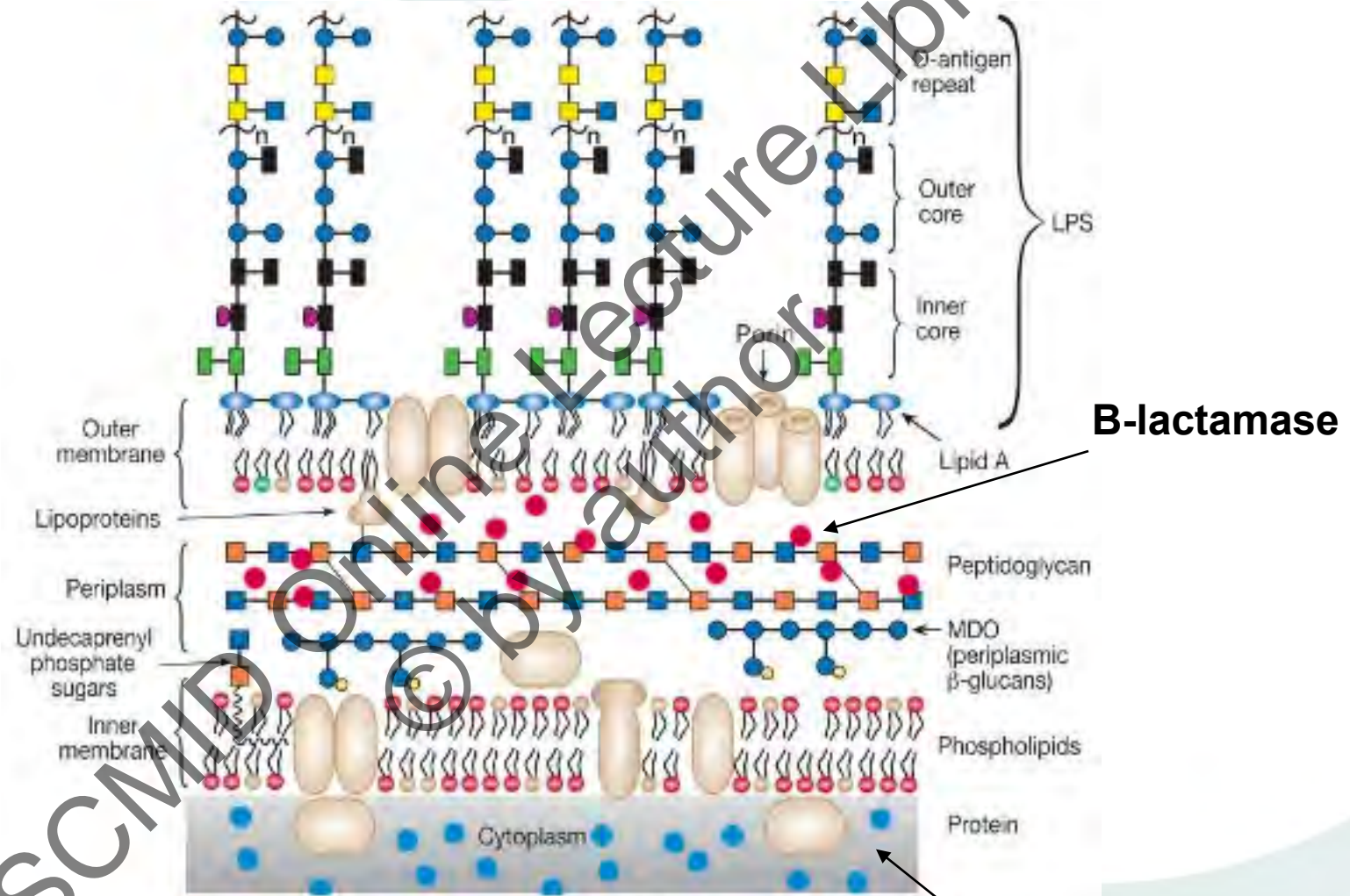
# The mechanisms of antibiotic resistance in staphylococci

- **Enzymatic inactivation:**  $\beta$ -lactams and aminoglycosides
- **Alteration of target:** methicillin, macrolides, vancomycin
- **Antibiotic trapping:** vancomycin and daptomycin
- **Efflux pumps:** Fluoroquinolones and tetracyclines.

# Pseudomonas aeruginosa



# Pseudomonas cell wall



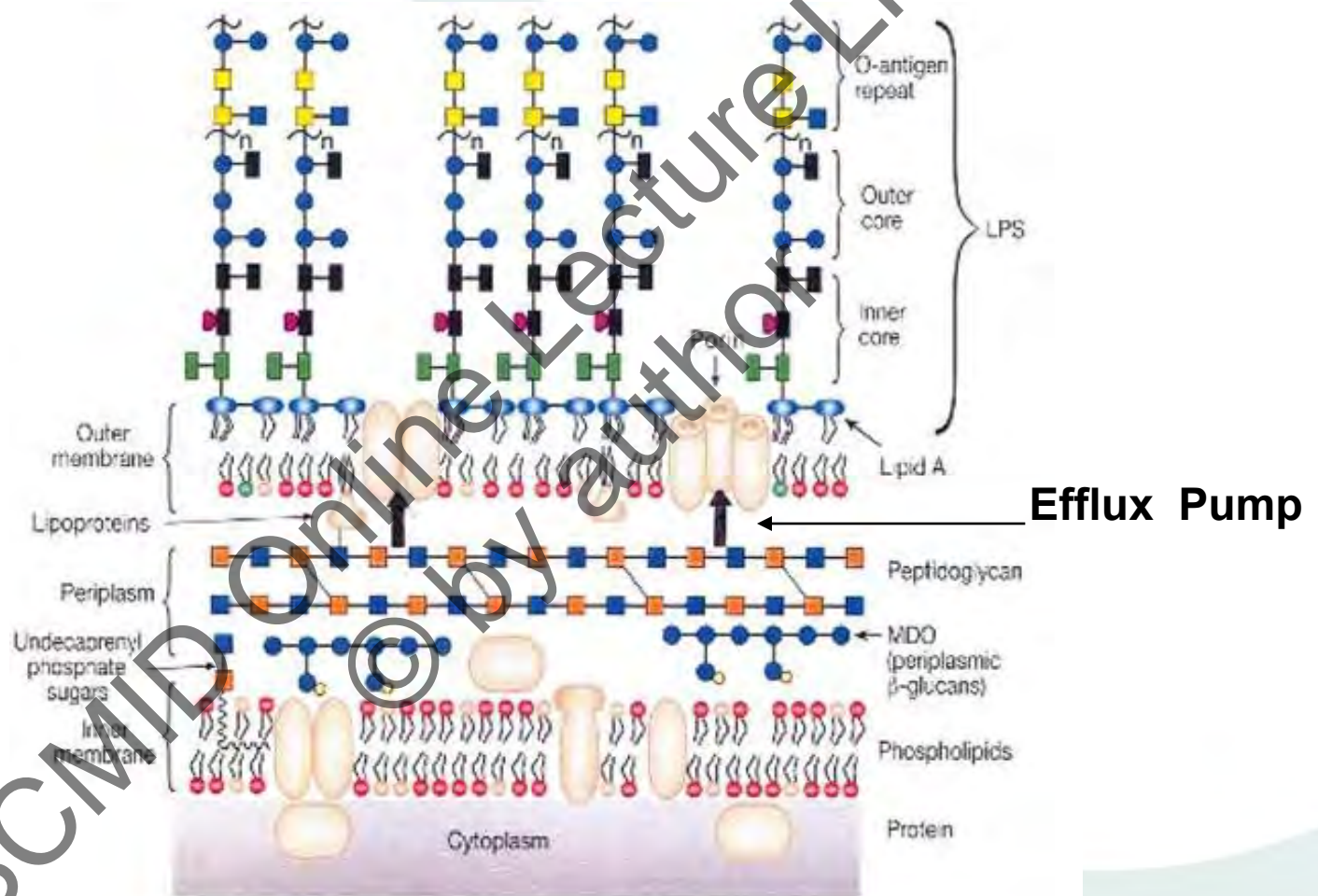
**B-lactamase**

**Transpeptidase**

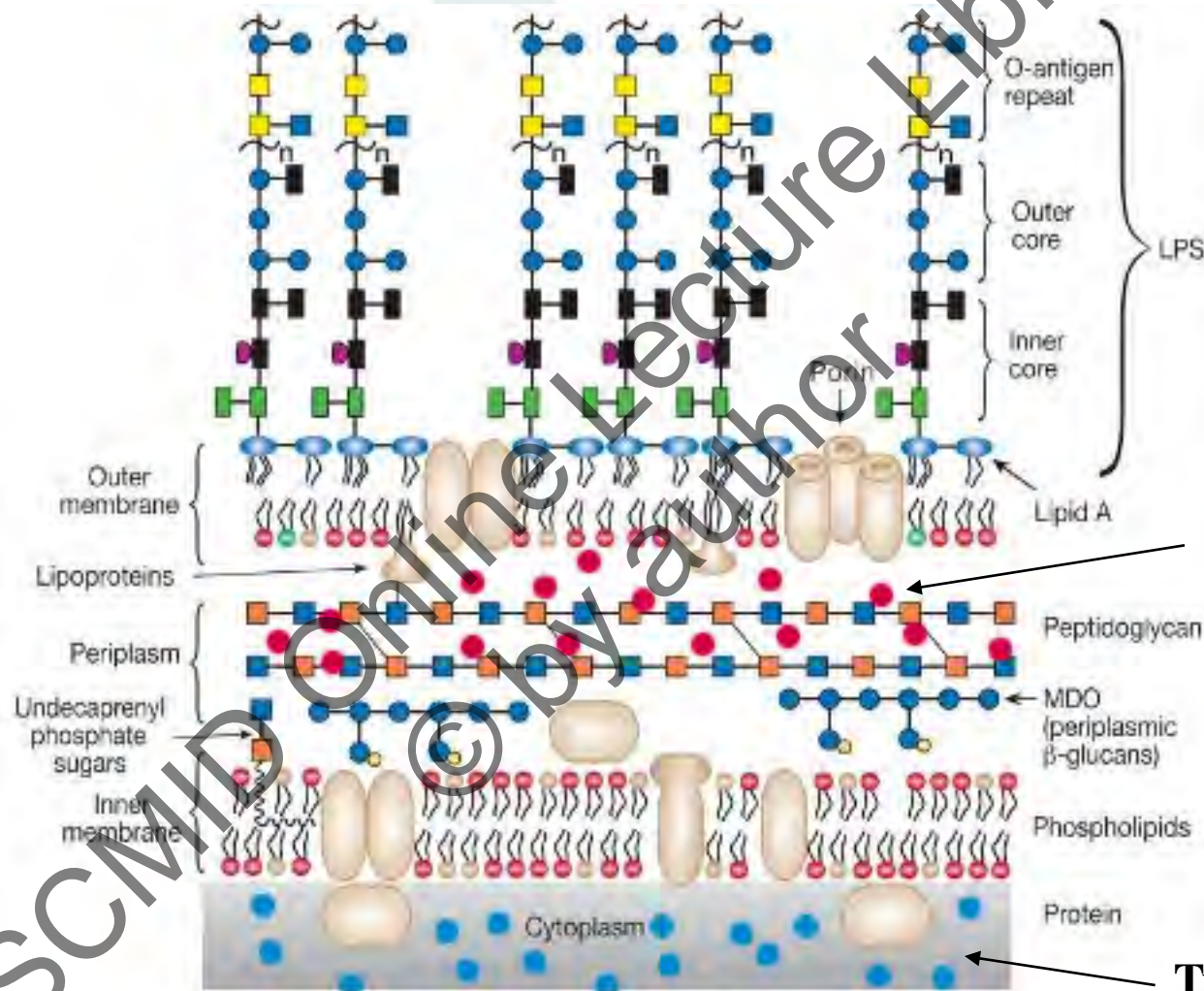
# Efflux Systems in Pseudomonas

- An energy dependent pump
- An outer membrane porin
- A linker protein which couples the two membrane proteins together

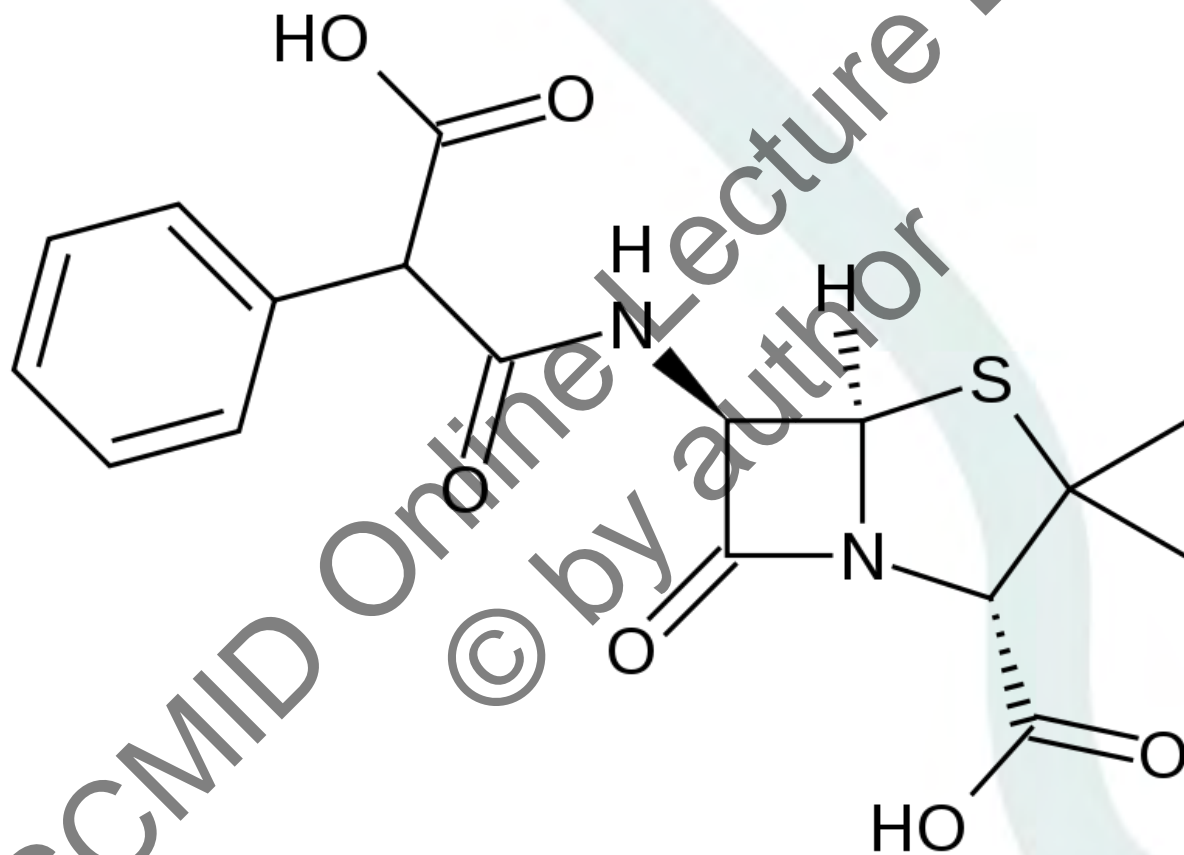
# Antibiotic efflux



# Pseudomonas cell wall

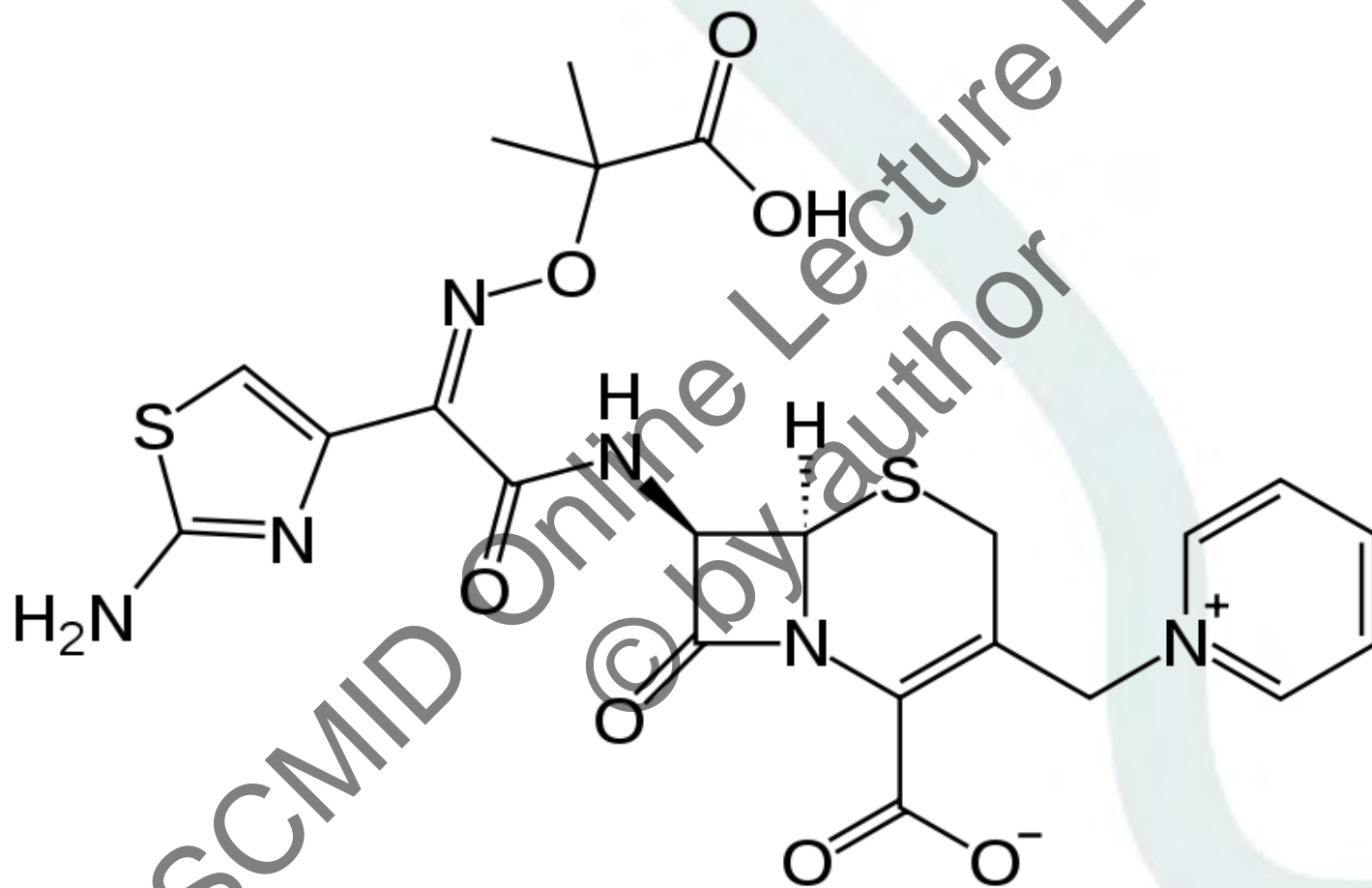


# Carbenicillin

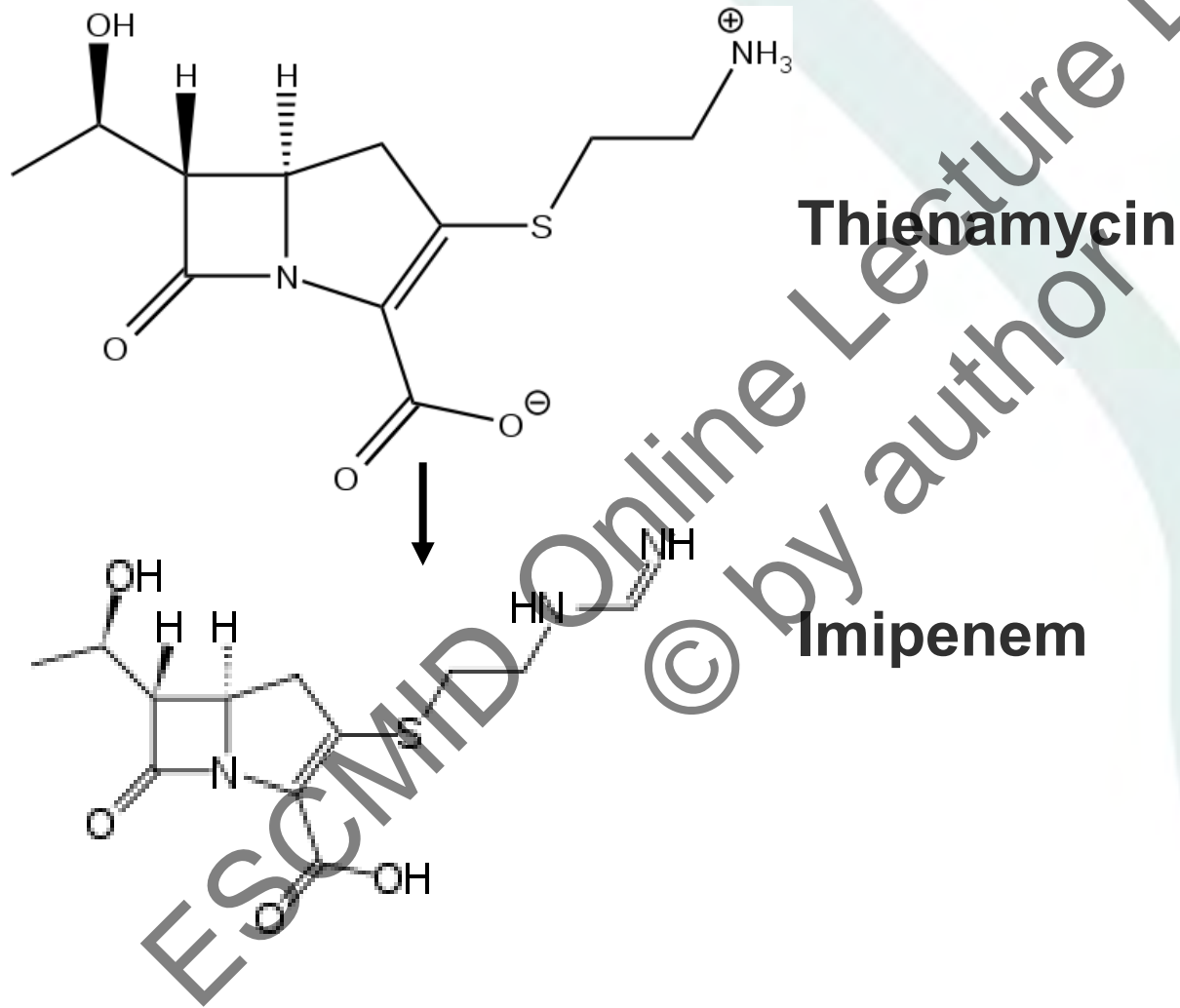




# Ceftazidime

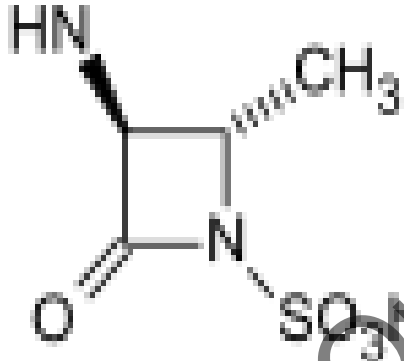


# Thienamycin - imipenem

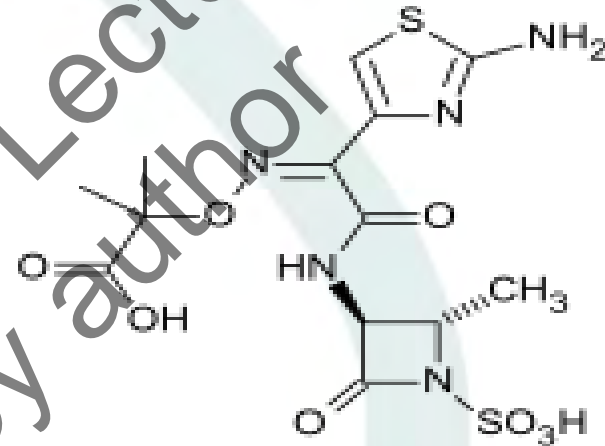


# Monobactams

Monobactam

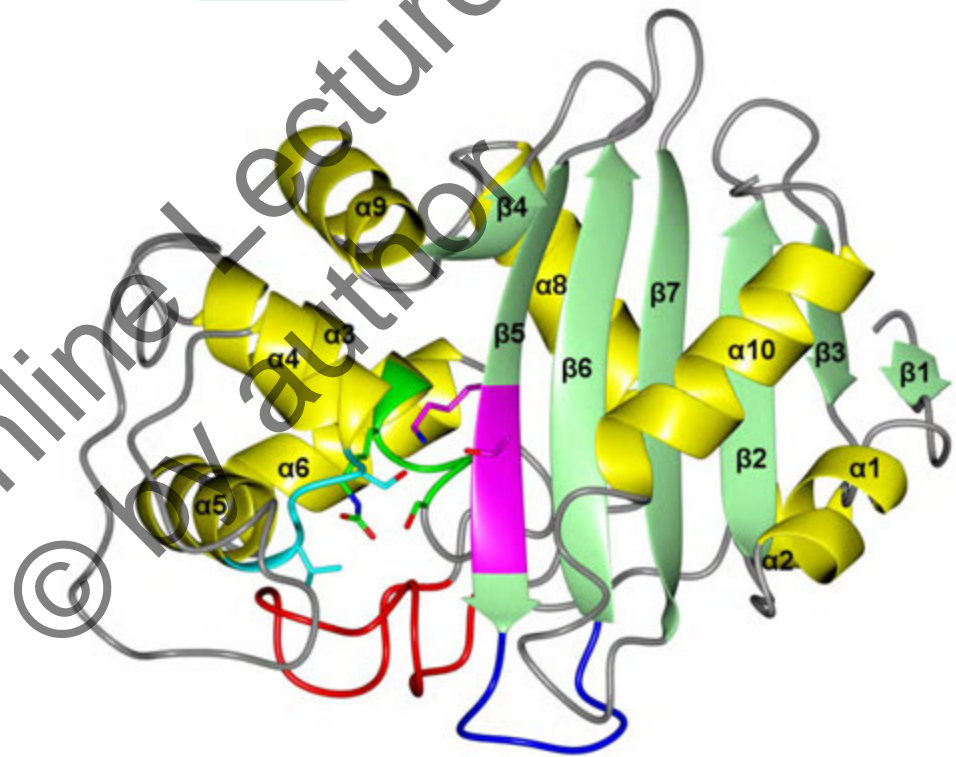


Aztreonam



# Number of Discrete $\beta$ -lactamases Identified

- 1972 - 13
- 1999 - 282
- 2004 - 532
- 2010 - >950



# $\beta$ -lactamases of Pseudomonas

## CLASS

- A Carbenicillinases (PSE)  
Extended spectrum  $\beta$ -lactamases (ESBL)
- B Metallo  $\beta$ -lactamases
- C Cephalosporinases
- D Oxacillinases

# Class A $\beta$ -lactamases

PSE 1-4 – Transposon mediated

ESBL – TEM type

SHVs

PER

VeB

GES

Dissemination by plasmids and integrons

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# Class B $\beta$ -lactamases

- Metallo  $\beta$ -lactamases
- Carbapenemases

VIM

IMP

GIM

SIM

SPM – gene cassettes and  
integrons and transposons

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# Class C $\beta$ -lactamases

- Cephalosporinases
- AmpC gene

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# Class D $\beta$ -lactamases

- Oxacillinases

- 5 groups

Chromosomal

Plasmid mediated

Integron

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# Mechanisms of Resistance

1. **Enzymatic inactivation**  
 $\beta$ -lactams  
Aminoglycosides
2. **Efflux mechanisms** effective against all antibiotics
3. **Alteration of target site**  
Aminoglycosides  
Fluroquinolones
4. **Porin exclusion**  
Carbapenems



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