

Beta-lactam antibiotics

Penicillins

Target - Cell wall - interfere with cross linking
Actively growing cells

Bind to **Penicillin Binding Proteins**

Enzymes involved in cell wall synthesis

Activity of an Antibiotic

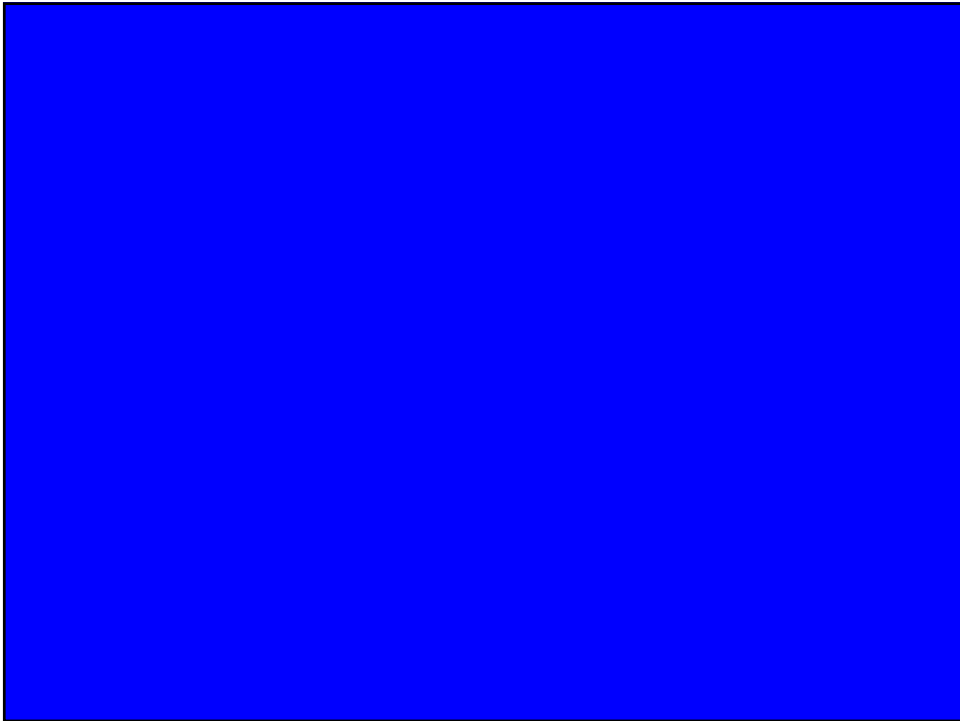
Affinity for target

Permeability properties
(ability to get to the target)

Stability to bacterial enzymatic degradation

Bacterial modifications:

- 1 – Mutate target - ? More than one protein
Importance of the target –
? Essential
2. Permeability – Size/charge considerations
? Substrate for an efflux pump
3. Selection for mutants that destroy the antibiotic



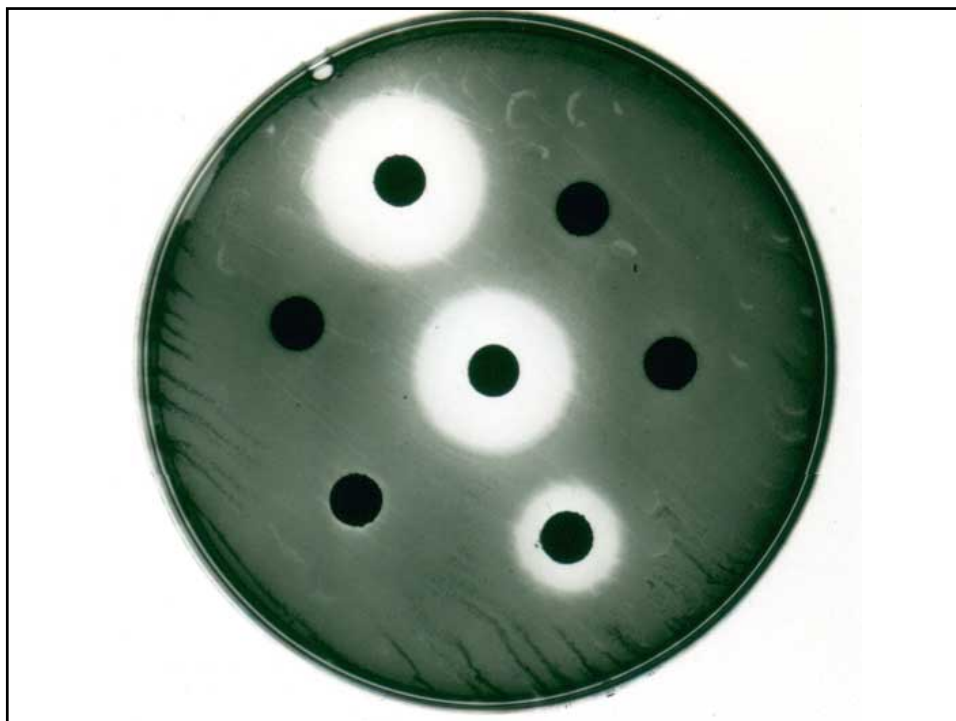
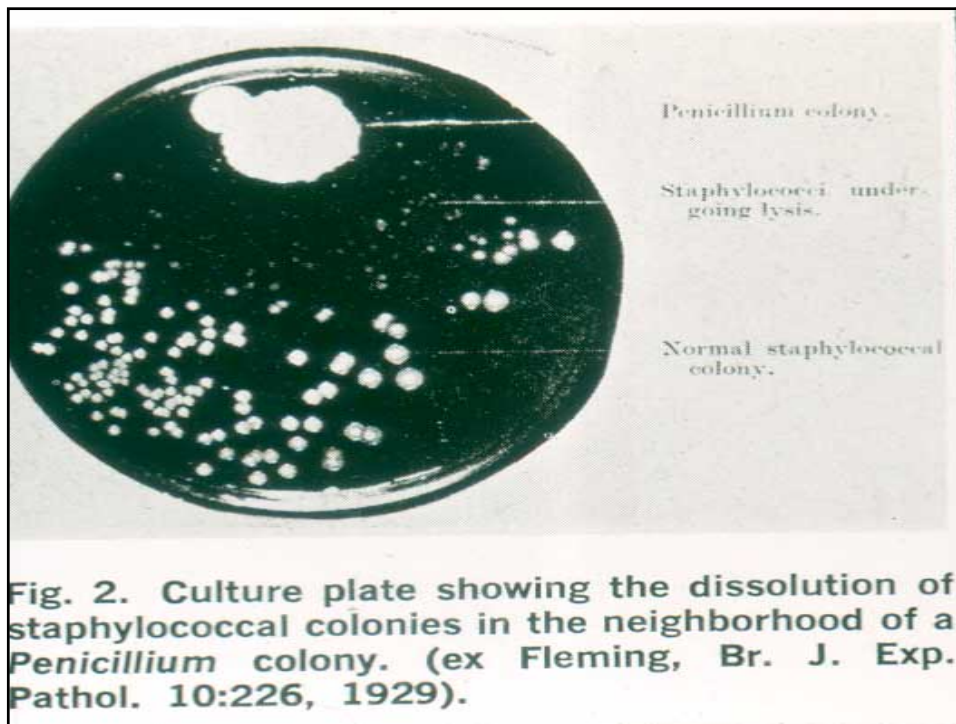
WHO discovered the penicillins??

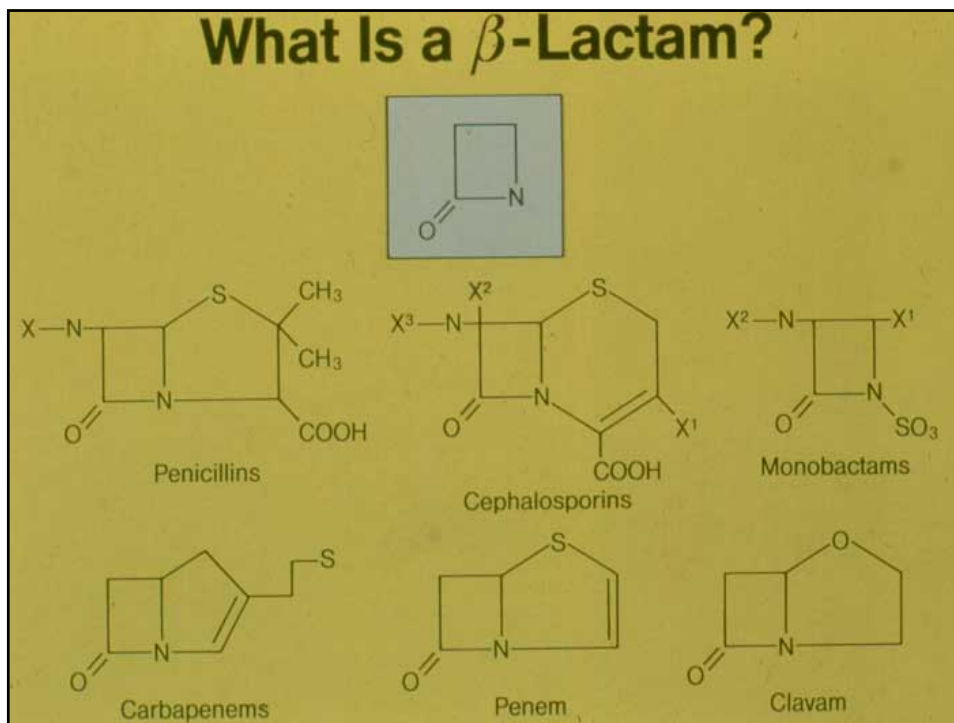
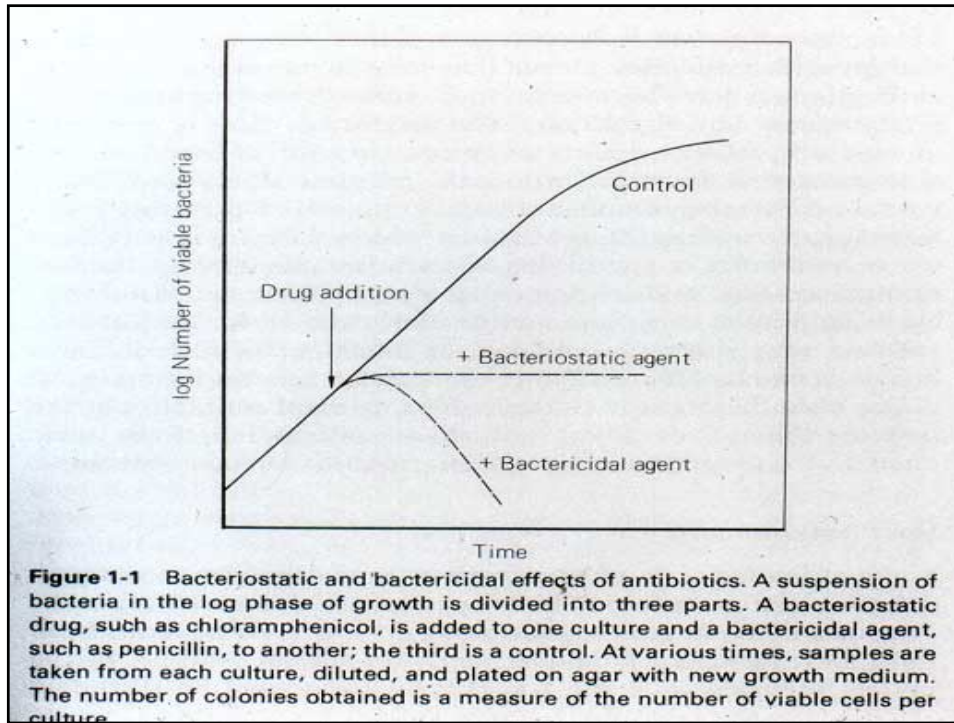
Abess Hildegarde von Bingen ?

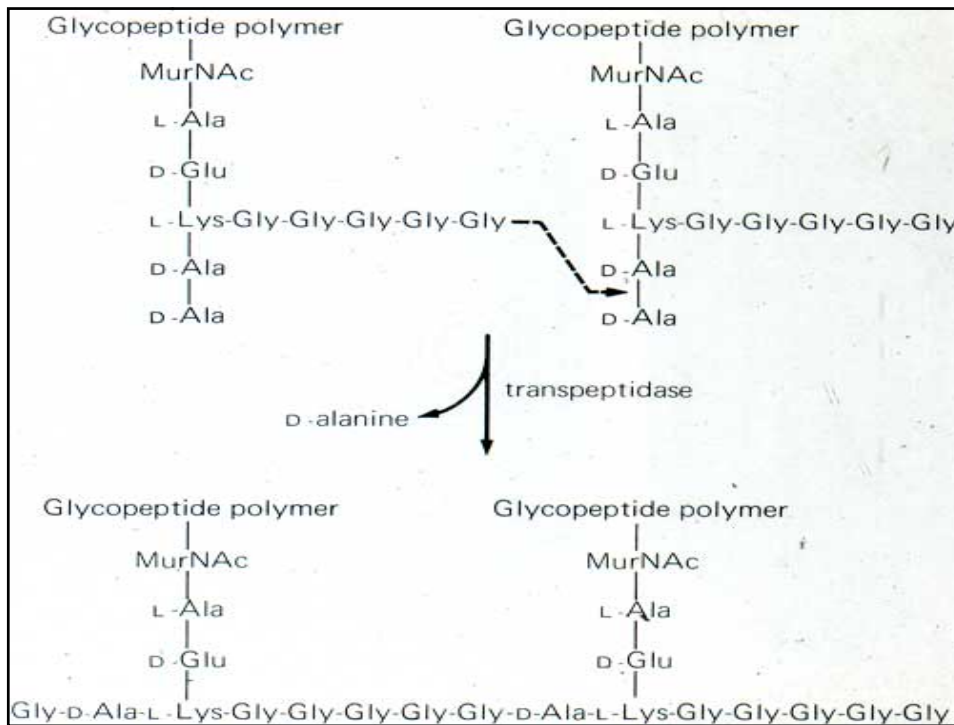
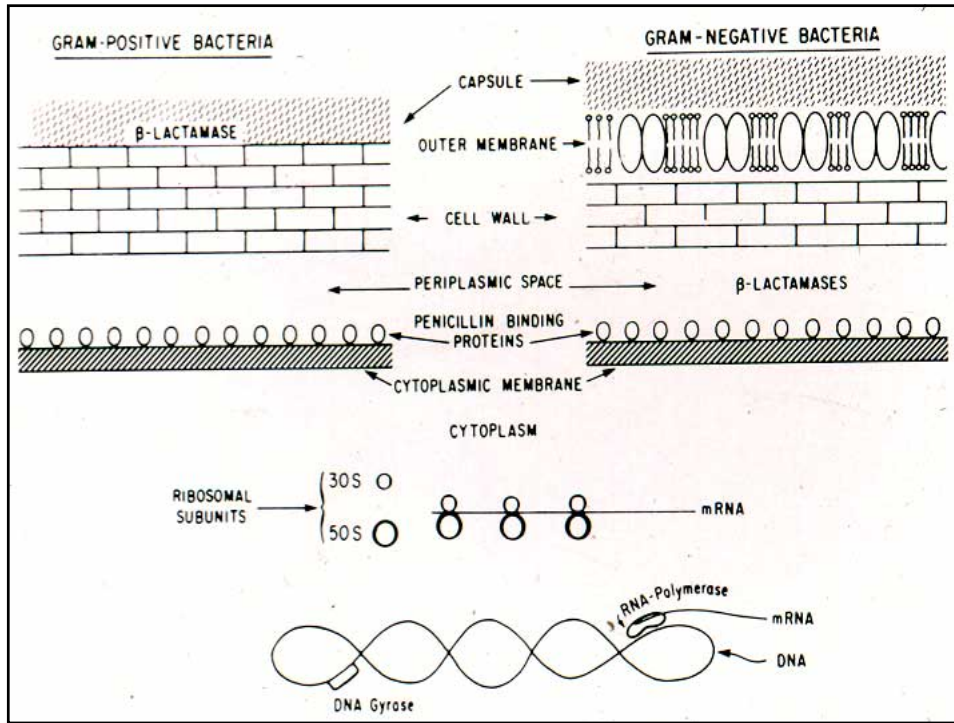
“Good things that grow on the sides of trees....”

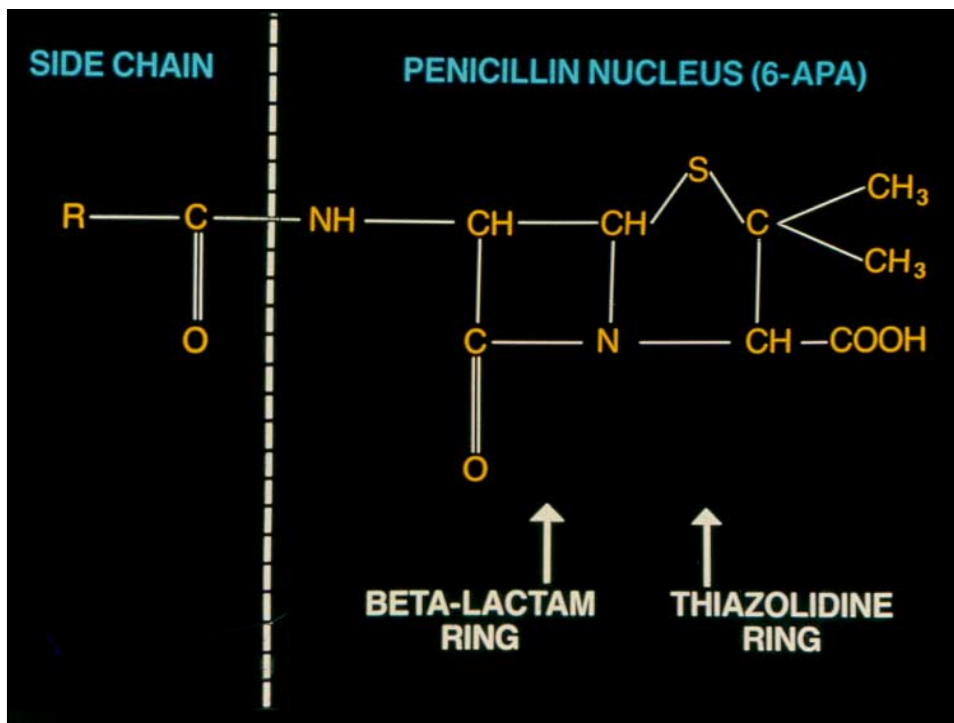
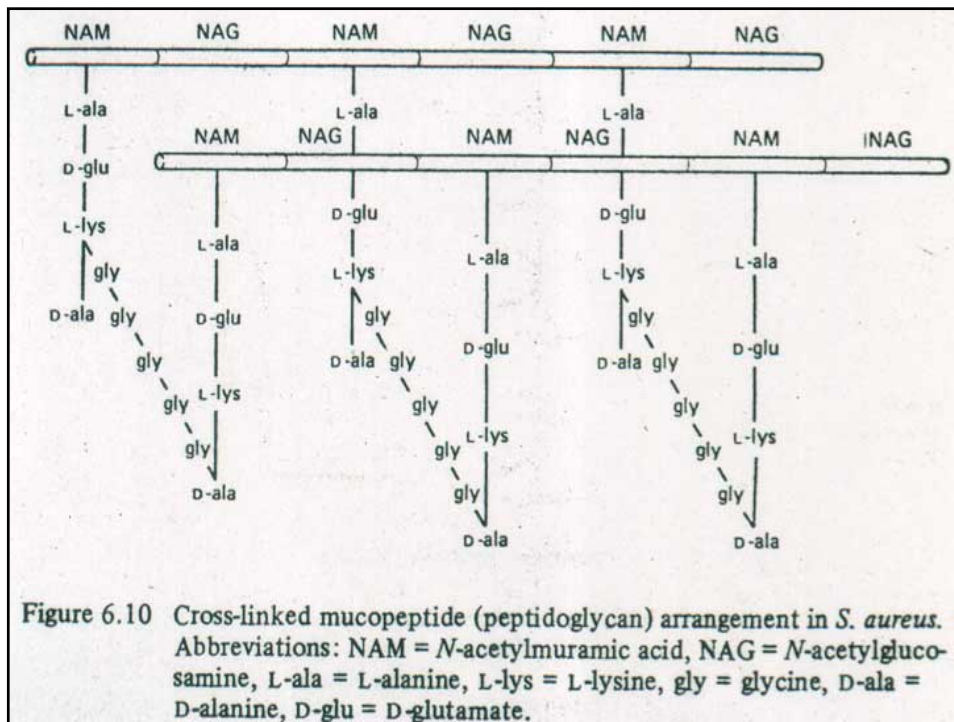
Fleming –

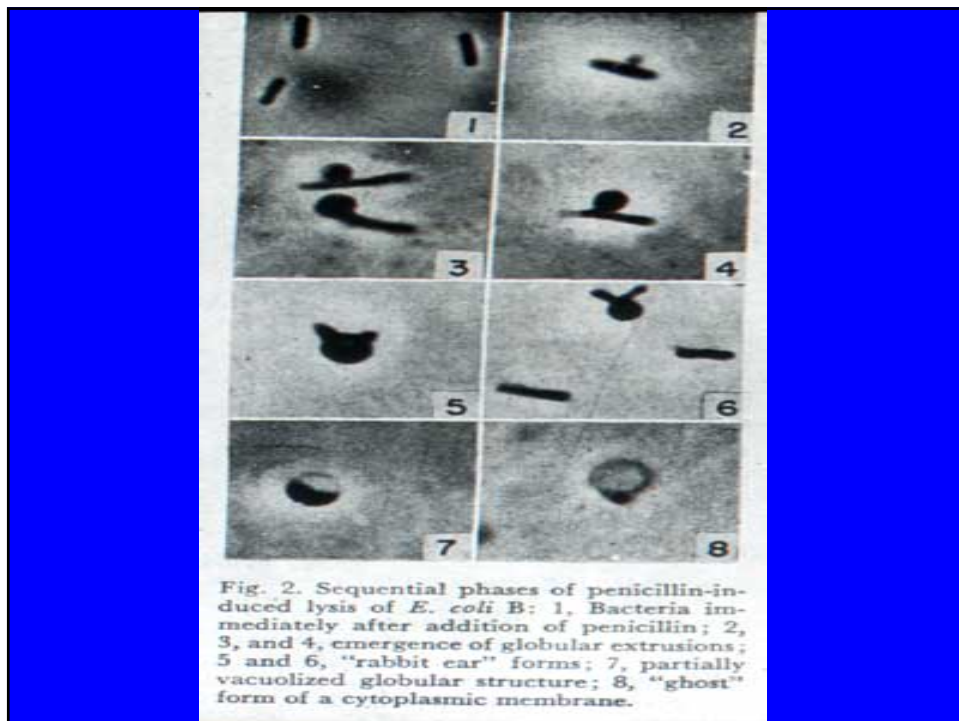
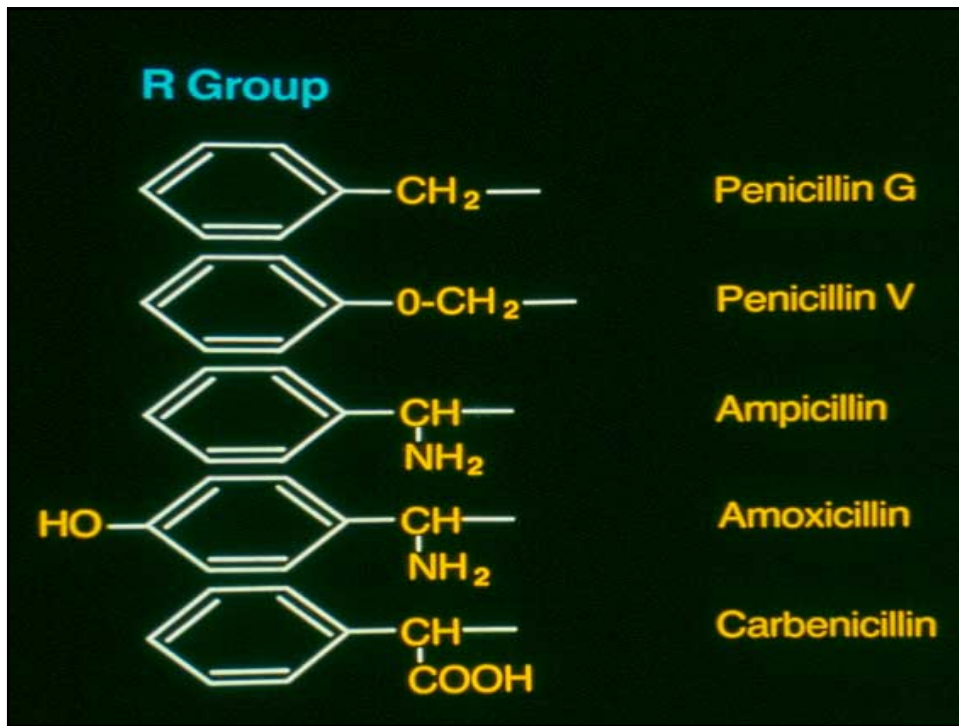
Florey – WWII....











Penicillin binding proteins

Transpeptidases

Carboxypeptidases

Differ in Gram (+) and in Gram (-) bacteria

Differ in abundance

Beta-lactamases - cleave the beta-lactam ring -
inactivate the drug -

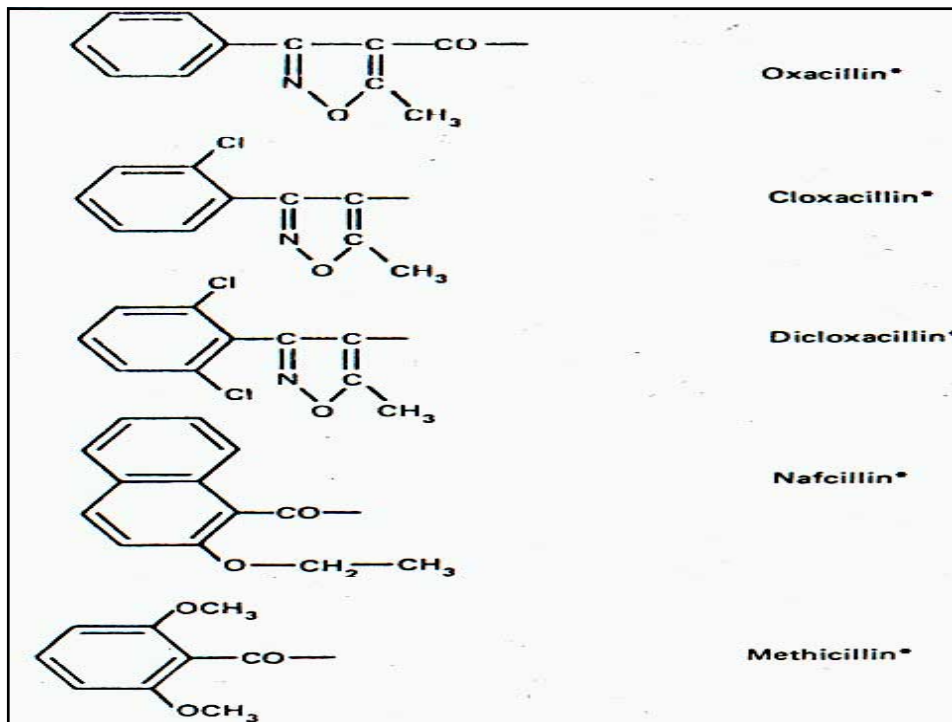
Open ring - can't bind to the target

Co-evolved with the penicillin binding proteins

Share a ser-X-X-lys - binding site for interactions

Gram positives - Secreted into the environment

Gram negatives - Secreted into the periplasmic space



Anti-staphylococcal penicillins

Strategy - Add a bulky side group to block beta-lactamase

(Methicillin) - renal toxicity

Nafcillin

Oxacillin

Cloxacillin (di-clox) - oral drugs

Beta-lactamases

Regulation - Constitutive - Chromosomal (*E.coli*)

Plasmid mediated -
copy number dependent

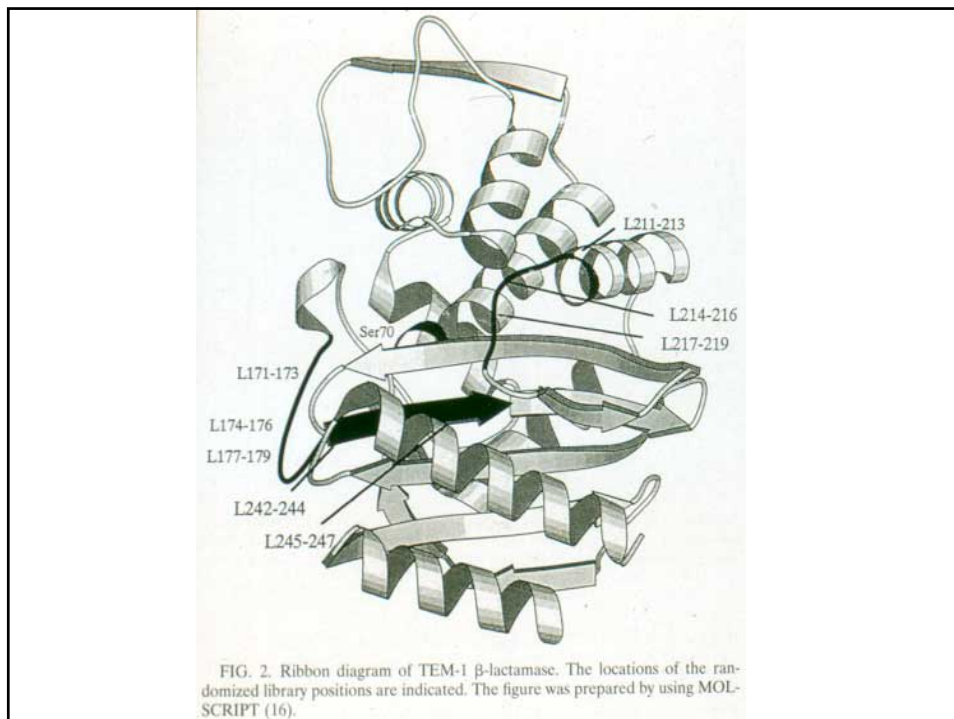
Inducible - chromosomal - SPACE
organisms - as a model

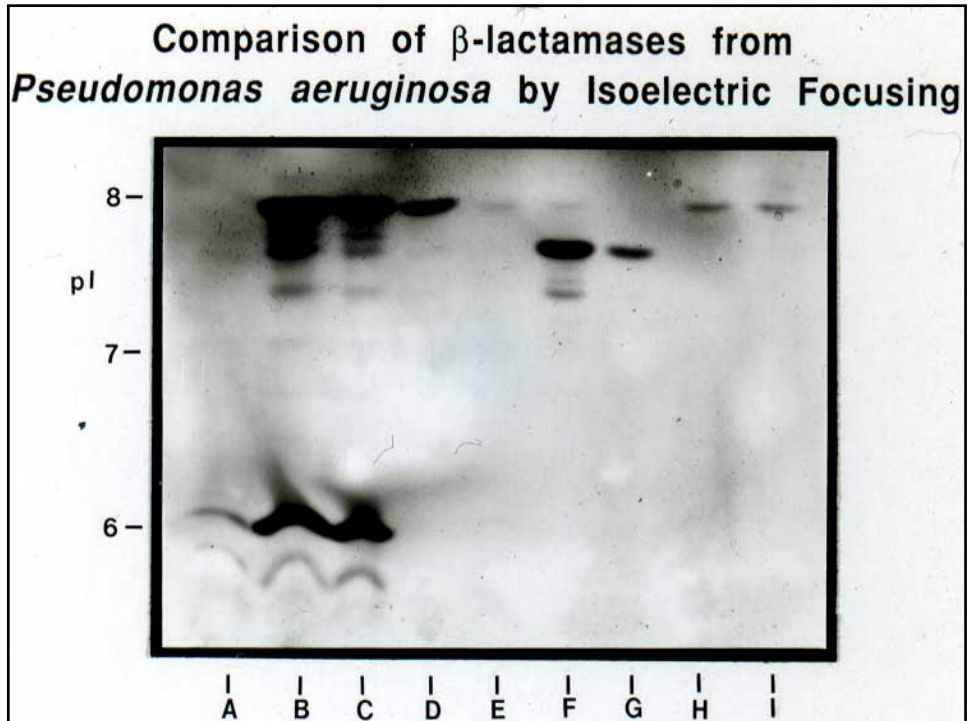
2-component signaling - (*ampD*, *ampE*, *ampR*)

Sensor

Response regulator

Transcriptional activator





Drugs in clinical use:

Penicillin G, VK

Ampicillin (+) clavulanic acid (beta-lactamase inhibitor)

(oral or parenteral)

Piperacillin - anti-*Pseudomonas* (+tazobactam)

(parenteral)

Spectrum - gram positive and gram negative -

Not inherently beta-lactamase stable

Spectrum - dependent upon permeability properties

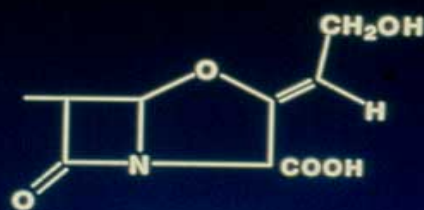
Add a beta-lactamase inhibitor

Clavulanic acid -
Sulbactam
Tazobactam

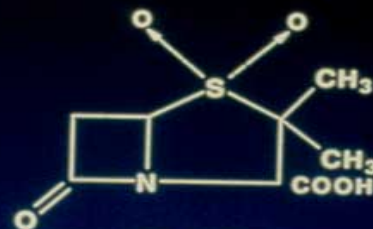
Expands spectrum of activity
Anaerobes

NOT effective against the beta-lactamases of the
SPACE organisms

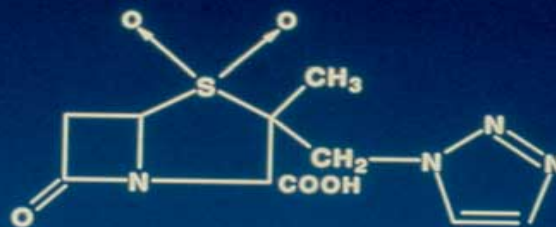
β -LACTAMASE INHIBITORS



Clavulanate



Sulbactam



Ta20bactam

Pharmacology of the penicillins

Absorption - Amoxicillin - acid stable
dosing - give more - longer intervals
Augmentin - amox + clav - diarrhea

Metabolism - minor

Excretion - Renal - tubular secretion
Increase serum levels with probenecid
Biliary - only ureido penicillins
Nafcillin

Distribution - Anions - charged - extracellular space
CSF - with inflammation
Concentrated in urine