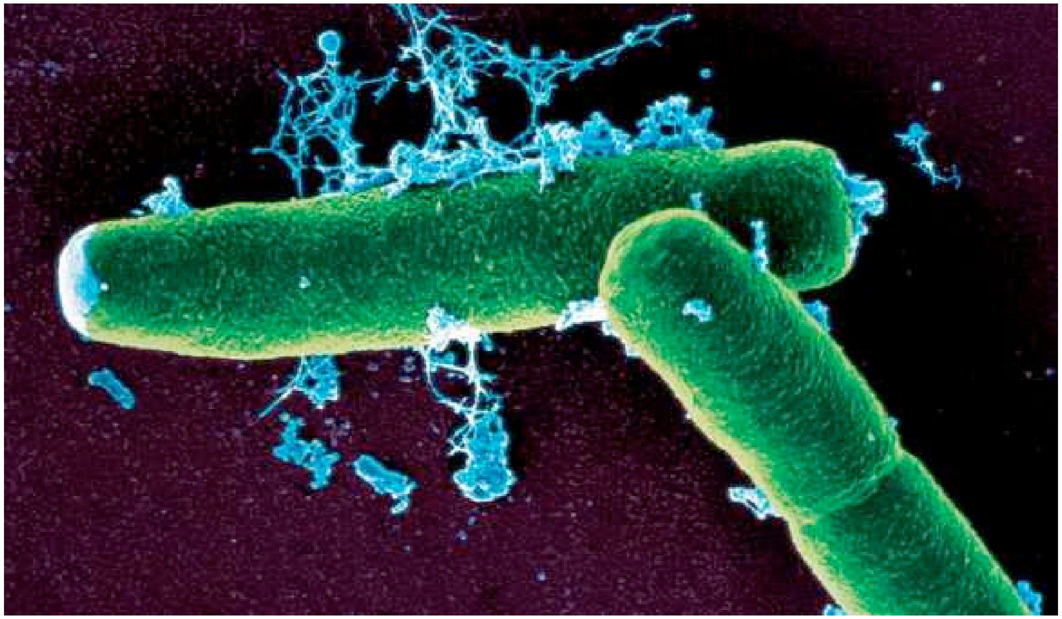
Antibiotics: A Frontier Reborn

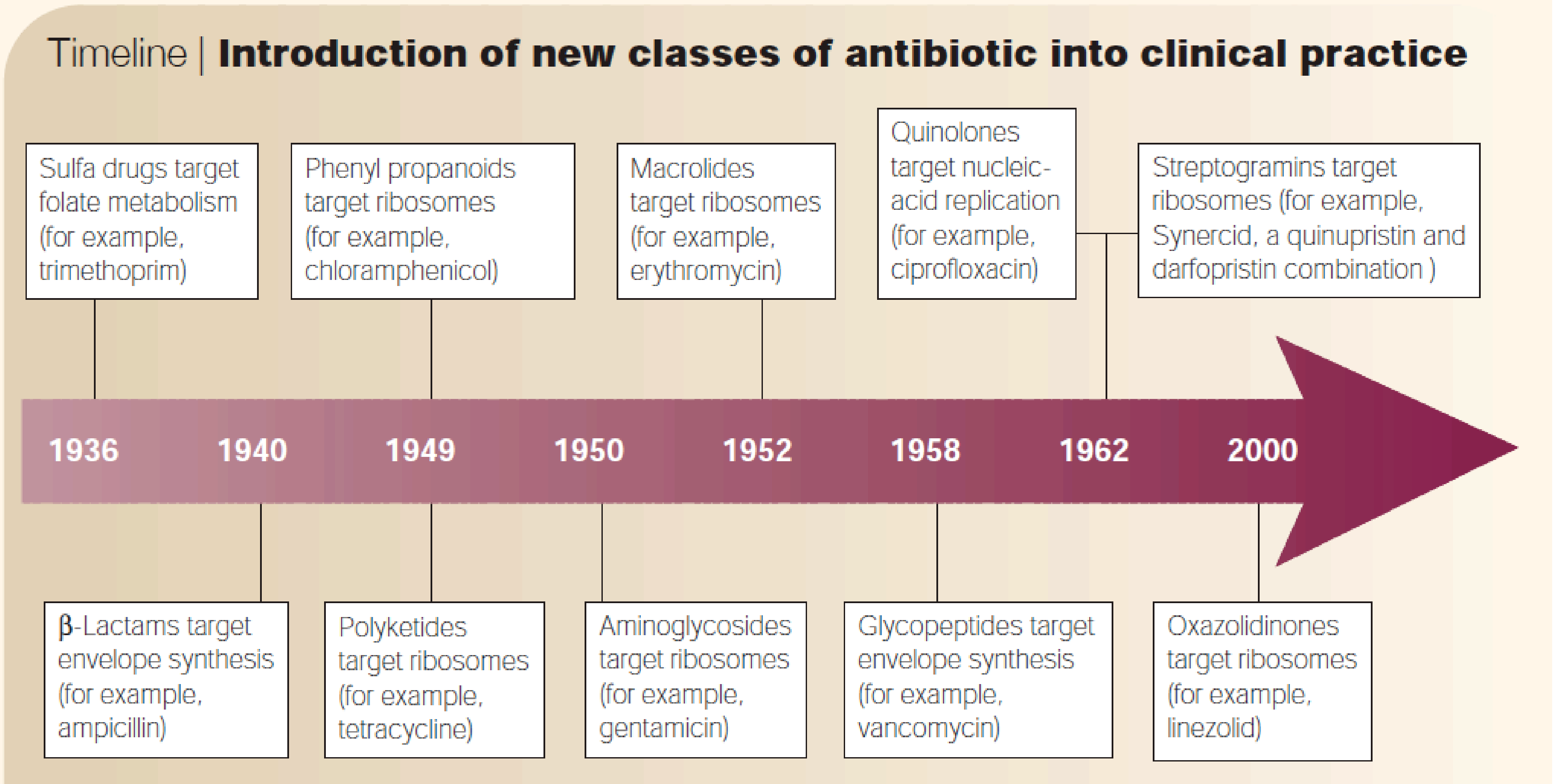


Joshua G. Pierce
Wipf Group

June 10, 2006

Antibiotics: A Frontier?

Wasn't that all done in the 40's and 50's?



Timeline | **Introduction of new classes of antibiotic into clinical practice**

Sulfa drugs target folate metabolism (for example, trimethoprim)

Phenyl propanoids target ribosomes (for example, chloramphenicol)

Macrolides target ribosomes (for example, erythromycin)

Quinolones target nucleic-acid replication (for example, ciprofloxacin)

Streptogramins target ribosomes (for example, Synercid, a quinupristin and darfopristin combination)

1936 1940 1949 1950 1952 1958 1962 2000

β-Lactams target envelope synthesis (for example, ampicillin)

Polyketides target ribosomes (for example, tetracycline)

Aminoglycosides target ribosomes (for example, gentamicin)

Glycopeptides target envelope synthesis (for example, vancomycin)

Oxazolidinones target ribosomes (for example, linezolid)

1 in 10 deaths in industrialized nations occur due to infectious disease. This number is 6 in 10 in under-developed nations. Even more troubling, the number of people in the US dying of certain infectious diseases has increased since the early 90's.

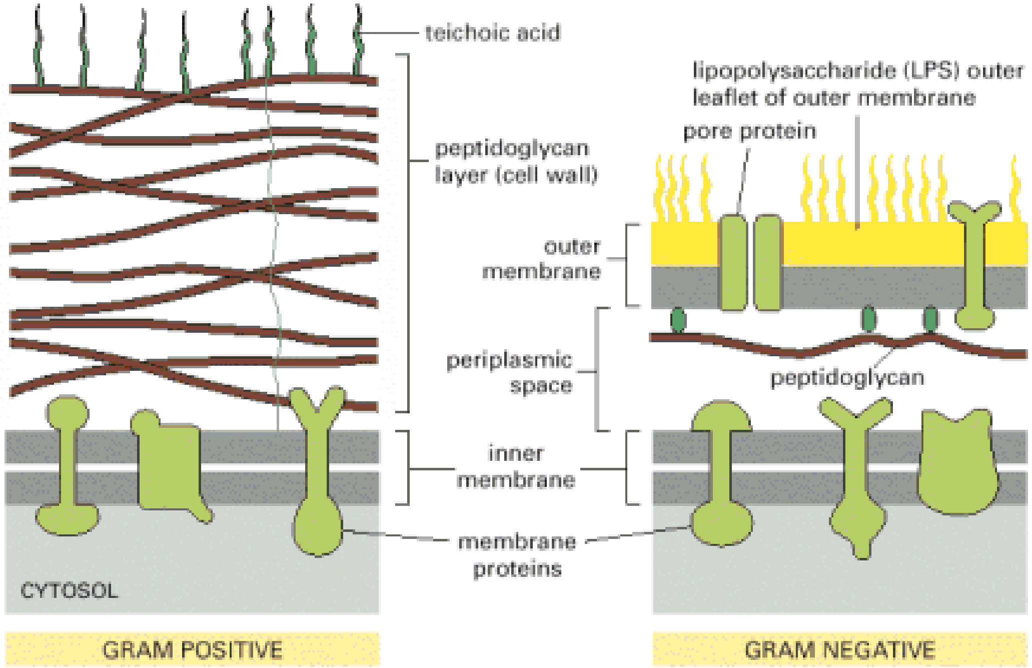
Walsh *Nature Reviews Micro*. **2006**, *1*, 65.

Gram Staining

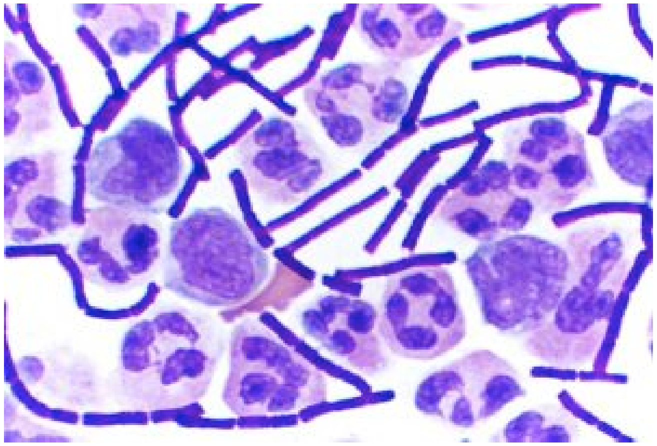
In 1884, Hans Christian Gram, a Danish doctor working in Berlin, accidentally stumbled on a method which still forms the basis for the identification of bacteria.

In Gram-positive bacteria, the purple crystal violet stain is trapped by the layer of peptidoglycan which forms the outer layer of the cell.

In Gram-negative bacteria, the outer membrane prevents the stain from reaching the peptidoglycan layer in the periplasm. The outer membrane is then permeabilized by acetone treatment, and the pink safranin counterstain is trapped by the peptidoglycan layer.

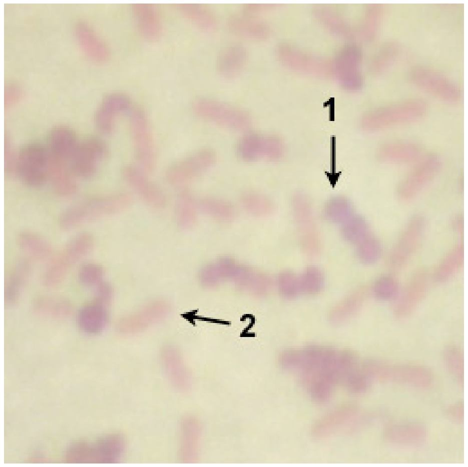


Gram Positive (rods)



1 - Gram Positive

2 - Gram Negative

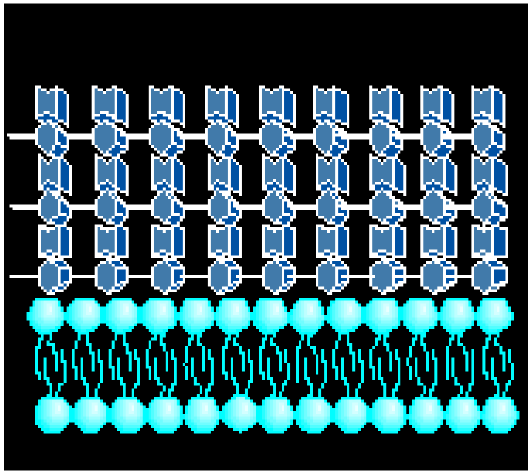


http://www-micro.msb.le.ac.uk/video/Gram.html

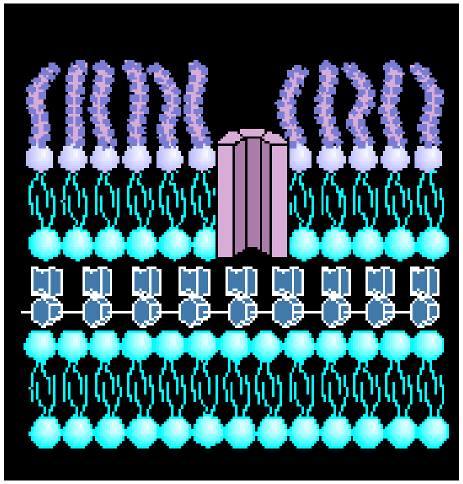
Gram Staining and Antibiotics

Whether a bacterium is Gram-negative or Gram-positive is often a good indicator of whether the bacteria can be destroyed using a given antibiotic.

Many antibiotics that are effective against gram positive bacteria are ineffective against gram negative, thereby making it imperative to distinguish the 2 types before a treatment is prescribed. The limiting pore size of the porin proteins in the outer membrane of gram negative bacteria (not present in gram positive) prevents entry of many antibiotics, including vancomycin.

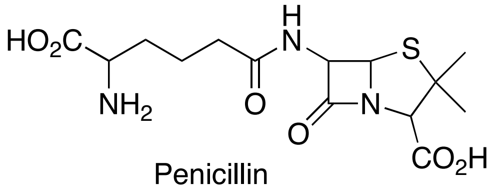


Gram positive bacteria contain a porous peptidoglycan layer that allows passage of most antimicrobial agents.



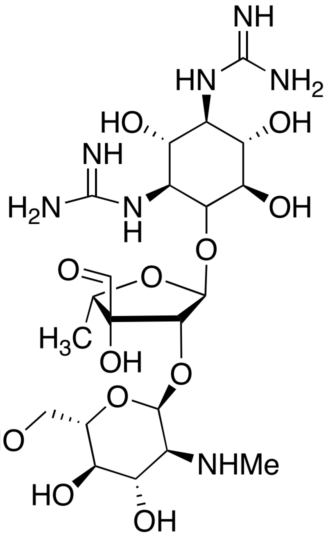
Gram negative bacteria contain 2 membranes. The outer membrand contains lipopolysaccharides (LPS) and porins which block many compounds from entry.

Timetable of Antibiotic Discovery



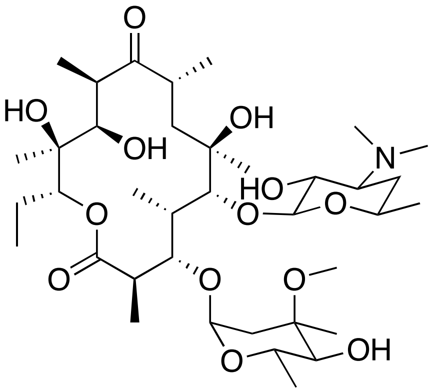
Penicillin

Discovered by Alexander Fleming in 1929. Florey and Chain (Britian/USA, 1939-1945) produced first commercial formulation



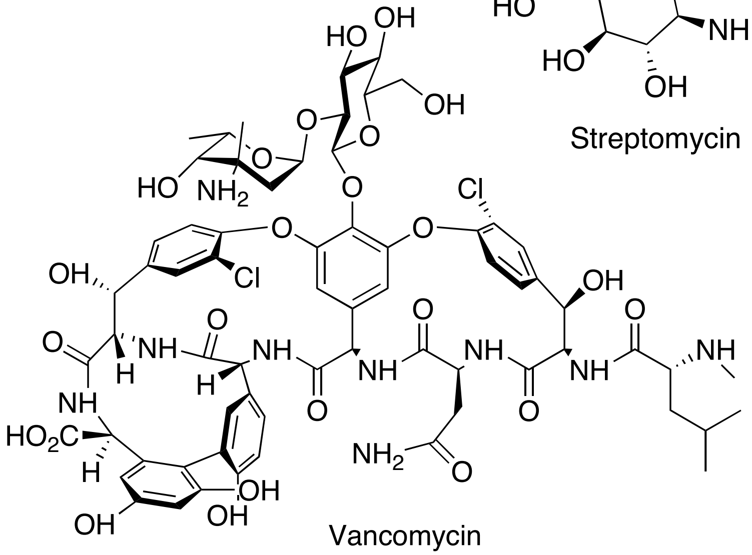
Streptomycin

First isolated on October 19, 1943 in the laboratory of Selman Abraham Waksman at Rutgers University by Albert Schatz, a graduate student in his laboratory. First effective treatment for TB.



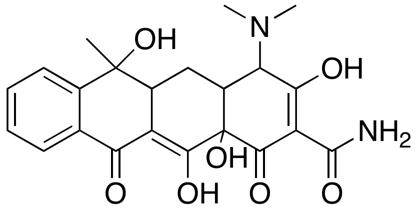
Erythromycin A

Abelardo Aguilar, a Filipino scientist, sent some soil samples to his employer Eli Lilly in 1949. Eli Lilly's research team, led by J. M. McGuire, managed to isolate Erythromycin from the metabolic products of a strain of *Streptomyces erythreus* found in the samples. The product was subsequently launched in 1952 under the brand name Ilosone®



Vancomycin

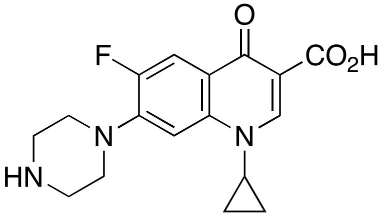
Discovered by Eli Lilly in 1956 (FDA approval 1958). Until recently, vancomycin was the last resort antibiotic for Methicillin resistant *S. Aureus* (MSRA) infections.



Tetracycline

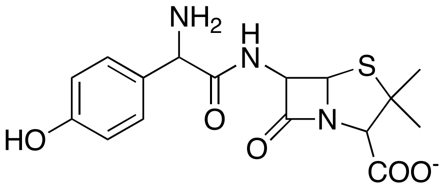
Tetracycline was first discovered by Lloyd Conover in the research departments of Pfizer. The patent for tetracycline was first issued in 1955. Began use in 1948.

Timetable of Antibiotic Discovery



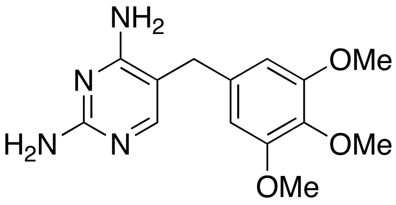
Ciprofloxacin

Developed by Bayer in 1987. Active against gram negative and gram positive bacteria. FDA approved Cipro for treatment of Anthrax in 2001.



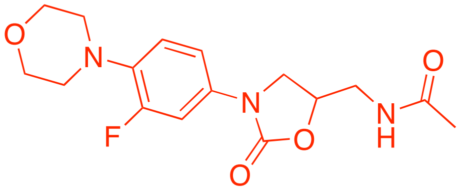
Amoxicillin

SmithKline Beecham patented Amoxicillin or amoxicillin/clavulanate potassium tablets and first sold the antibiotic in 1998 under the tradenames of Amoxicillin, Amoxil, and Trimox. Amoxicillin is the most prescribed antibiotic in the United States.



Trimethoprim

Trimethoprim was approved by the FDA in combination with sulfamethoxazole in 1973. It was approved as a single agent in 1980. Developed by GlaxoWellcome

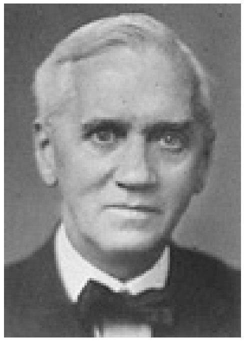


Linezolid

The oxazolidinone class was discovered by researchers at E.I. duPont de Nemours and reported in 1987. Pharmacia Corporation developed linezolid and FDA approval was granted in April 2000.

β-Lactam Antibiotics: Penicillin

“Chance Favors the Prepared Mind” - Louis Pasteur



Sir Alexander Fleming

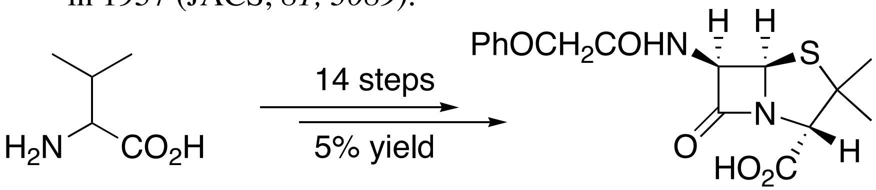
Ernst Boris Chain

Sir Howard Walter Florey

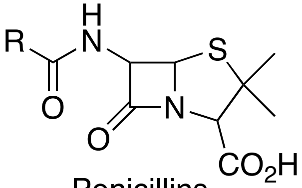
The Nobel Prize in Physiology or Medicine 1945
"for the discovery of penicillin and its curative effect in various infectious diseases"

The age of the β-lactam antibiotics began with Fleming noticing that mold growing on a culture plate was preventing the growth of bacteria (1929). While this was not the first evidence of such a phenomenon, Fleming was the first to connect the dots and suggest that penicillin could have medical benefits.

First practical synthesis developed by Sheehan in 1957 (JACS, *81, 3089)*.



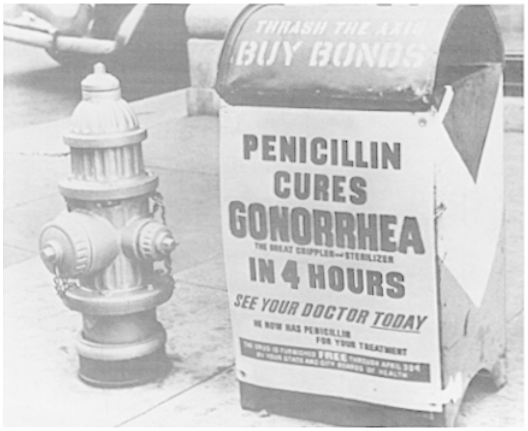
Penicillium chrysogenum, a mutant strain that produces 60x more Penicillin per mL of culture.



Penicillins

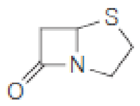
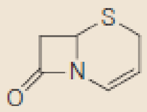
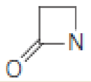
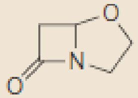
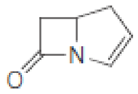
Fleming’s original culture dish

Miracle Drug!



β-Lactam Antibiotics: Discovery and Classes

The five main classes of β-lactam antibiotics

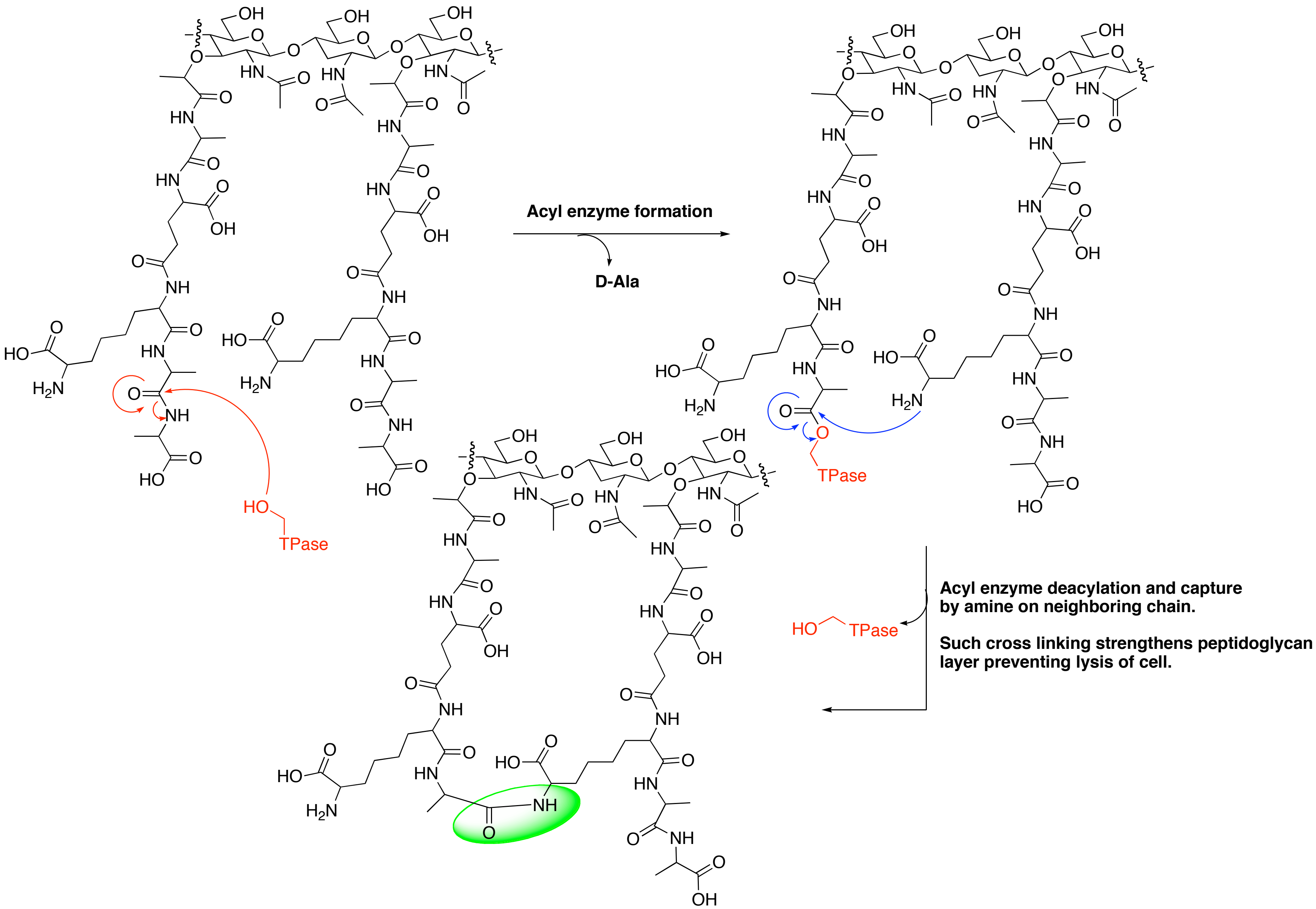
Structure	Class	Example	Source organism
	Penicillins	Penicillin G	*Penicillium chrysogenum*
	Cephalosporins/ cephamycins	Cephalosporin C	*Acremonium chrysogenum*
	Monobactams	Nocardicin A	*Nocardia uniformis* subsp. *tsuyamanensis*
	Clavams	Clavulanic acid	*Streptomyces clavuligerus*
	Carbapenems	Car	*Erwinia carotovora* subsp. *carotovora*

β-lactam antibiotics are the biggest and traditionally most important class of antibiotics accounting for 65% of the market and an estimated $18 billion in sales.

All classes are produced by fermentation or semi-synthesis except for the carbapenem class which is made through synthesis.

Biosynthesis of these compounds differ greatly between the classes however some can be inter-converted in bacteria.

Strengthening of Cell Walls Through Cross-linking



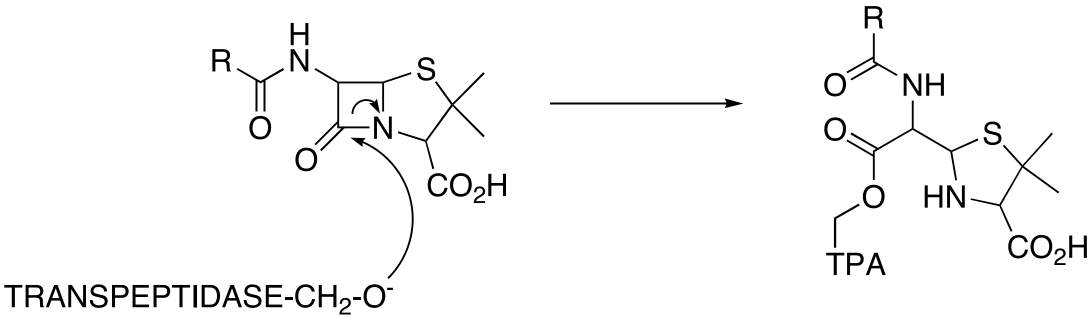
Acyl enzyme formation

D-Ala

Acyl enzyme deacylation and capture by amine on neighboring chain.

Such cross linking strengthens peptidoglycan layer preventing lysis of cell.

β-Lactam Antibiotics: Function



β-lactams inhibit transpeptidase by mimicking its substrate, the terminal D-Ala—D-Ala.

Transpeptidase attacks the β-lactam ring of penicillin, forms a covalent bond that is slow to hydrolyze; enzyme is deactivated.

Normally, the enzyme forms a temporary bond with D-Ala that is rapidly broken by the side chain of lysine.

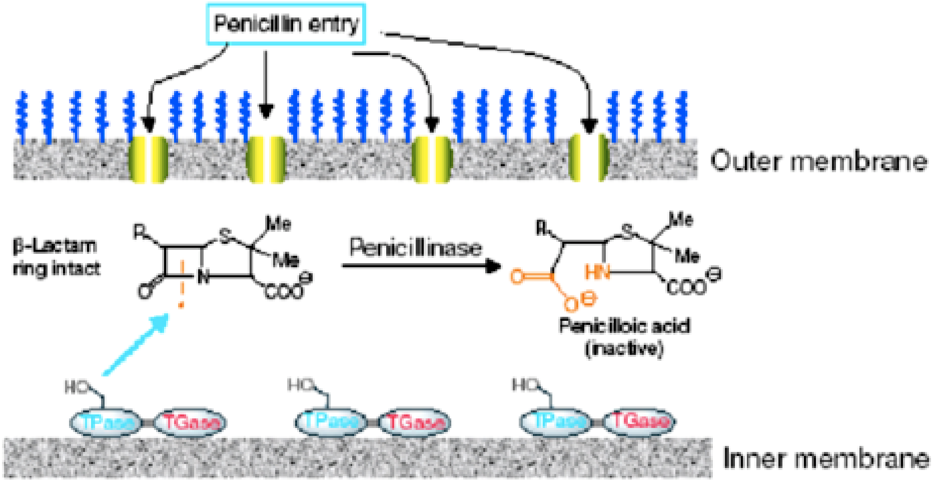
The β-lactam antibiotics also stimulate the activity of autolysins. These are enzymes that are responsible for the natural turnover of cell wall polymers to permit growth of the cells.

Through either mechanism the cell wall becomes weakened and the cell dies due to osmotic pressure and collapse.

How Does Resistance Develop?

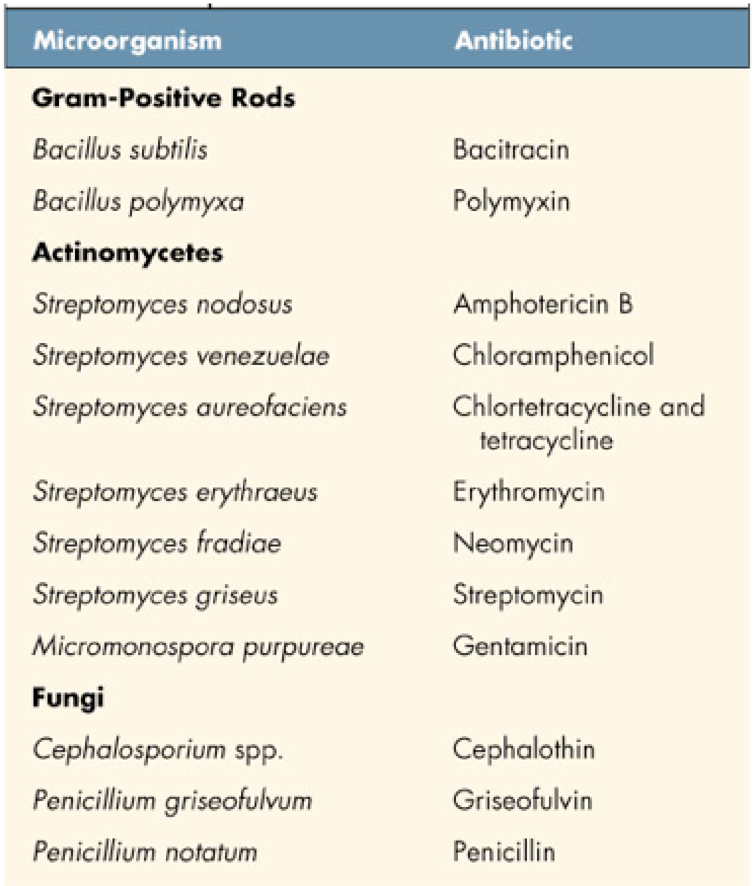
DRUG	INTRODUCTION	APPEARANCE OF RESISTANCE
Penicillin	1943	1946
Streptomycin	1945	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1964	late 1960’s

Self Protection Mechanisms Can Cause Resistance:



β-lactamases make up 4 classes of enzymes (A-D) that have broad specificity for a variety of β-lactam substrates.

Many antibiotics arise from microbial sources:



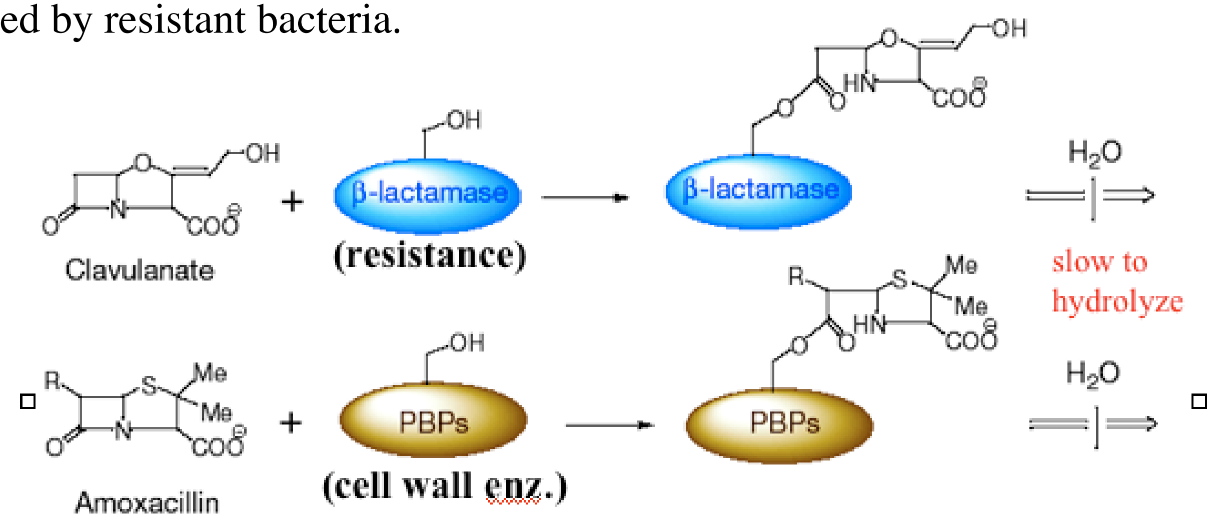
Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Bacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Streptomyces erythraeus	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpureae	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium notatum	Penicillin

Roughly 90,000 people in the United States acquire fatal infections in hospitals every year, according to data from the Centers for Disease Control and Prevention in Atlanta. Nearly three-fourths of those deaths can be traced to antibiotic-resistant microbes.

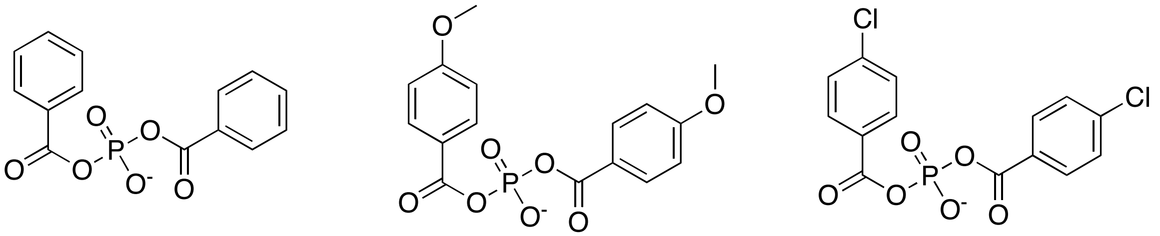
Fighting Resistance of β-Lactam Antibiotics:

A Combination Drug Approach

Augmentin (GlaxoSmithKline) is a popular drug that combines amoxicillin with clavulanic acid—a chemical that inactivates an antibiotic-neutralizing enzyme secreted by resistant bacteria.



Novel diaroyl phosphates that inhibit class A-D β-lactamases - more effective than clavulanic acid and are intriguing candidates for further development.



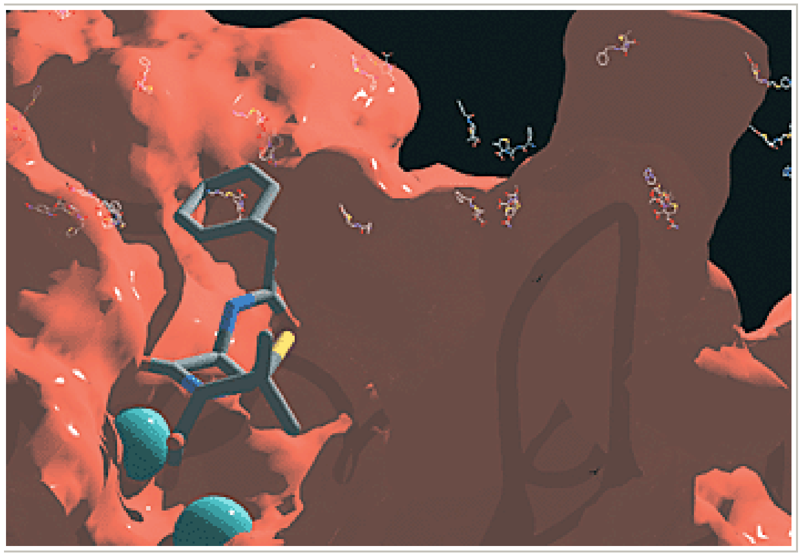
Pratt *et al. Biochemistry*, **2005**, *44*, 16121.

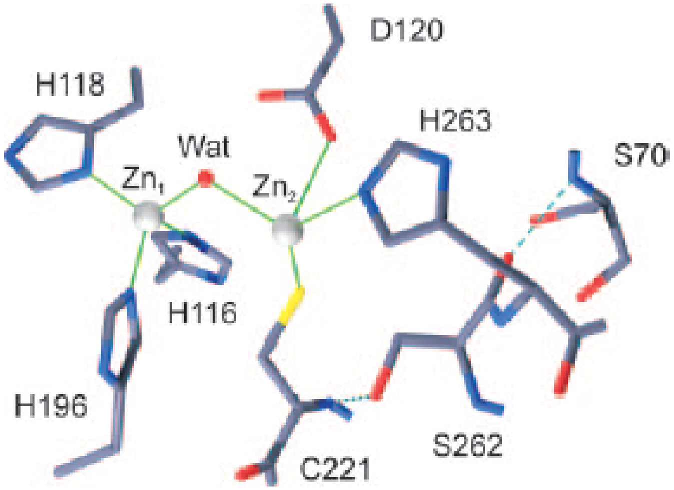
Outflanking the Bacteria:

A Directed Evolution Approach

While there are effective inhibitors of various lactamases, metallo-β-lactamases are the latest generation and confer resistance to most all existing lactam antibiotics.

Experiment demonstrated that it was the mutations in the second coordination sphere of Zn (II) (Gly 262 -> Ser and Asn 70 -> Ser)

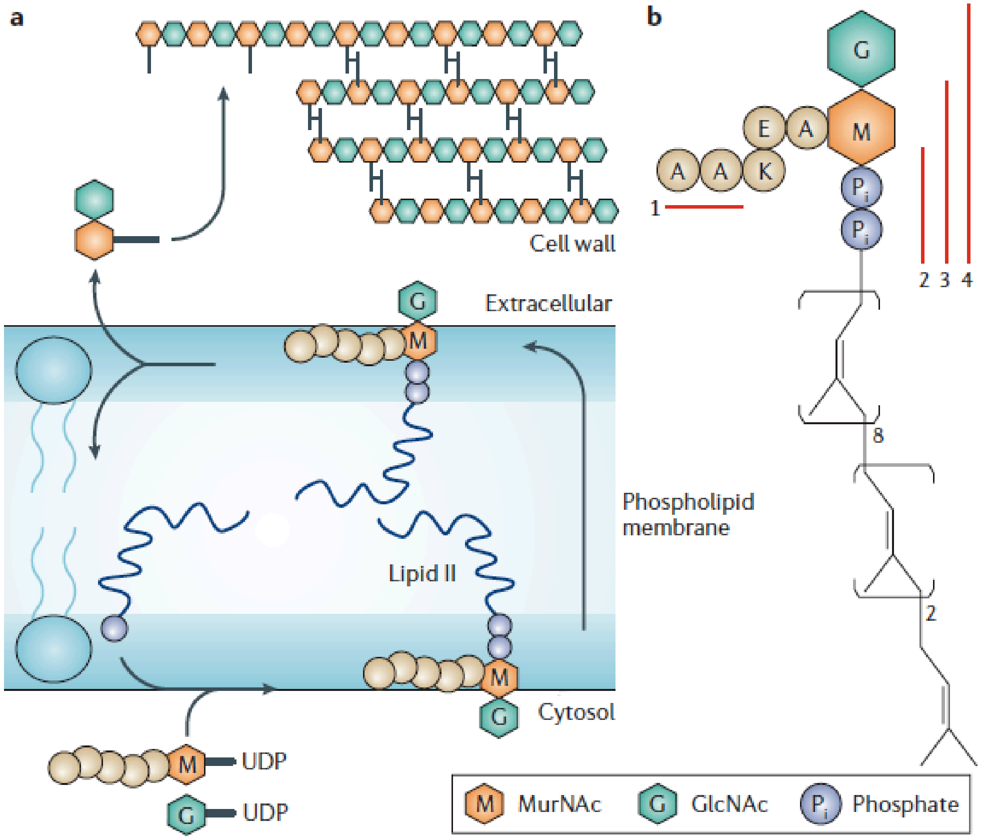




Directed evolution was demonstrated to be an effective way to mimic mutations that occur in clinical settings.

The catalytic efficiency, not just the binding affinity, was shown to be essential in the substrate scope of lactamases -- subtle changes in the second coordination sphere elicit substantial changes around Zn center.

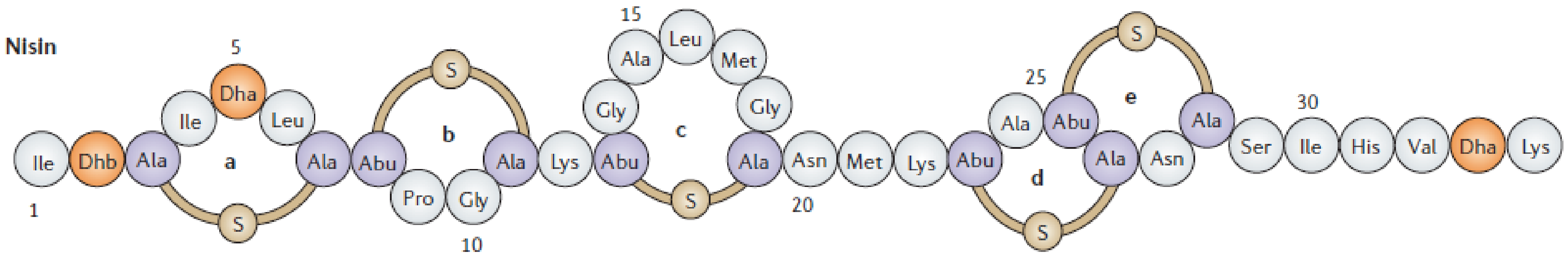
Lipid II: Targeting Cell Wall Synthesis



Lipid II has been a target for antibacterial development since the discovery of vancomycin.

Lipid II is thought to be the bottle neck in cell wall synthesis and therefore is an ideal target for antibiotics.

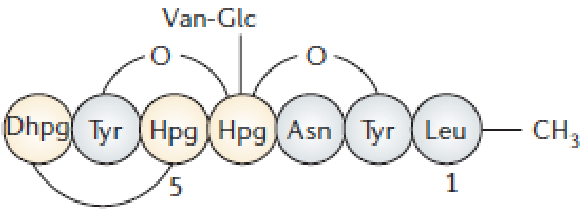
Nisin, discovered in 1920 has become one of the most widely used antibiotics in the food industry, however the lantibiotic class has not made it to the clinic due to poor pharmacokinetics.



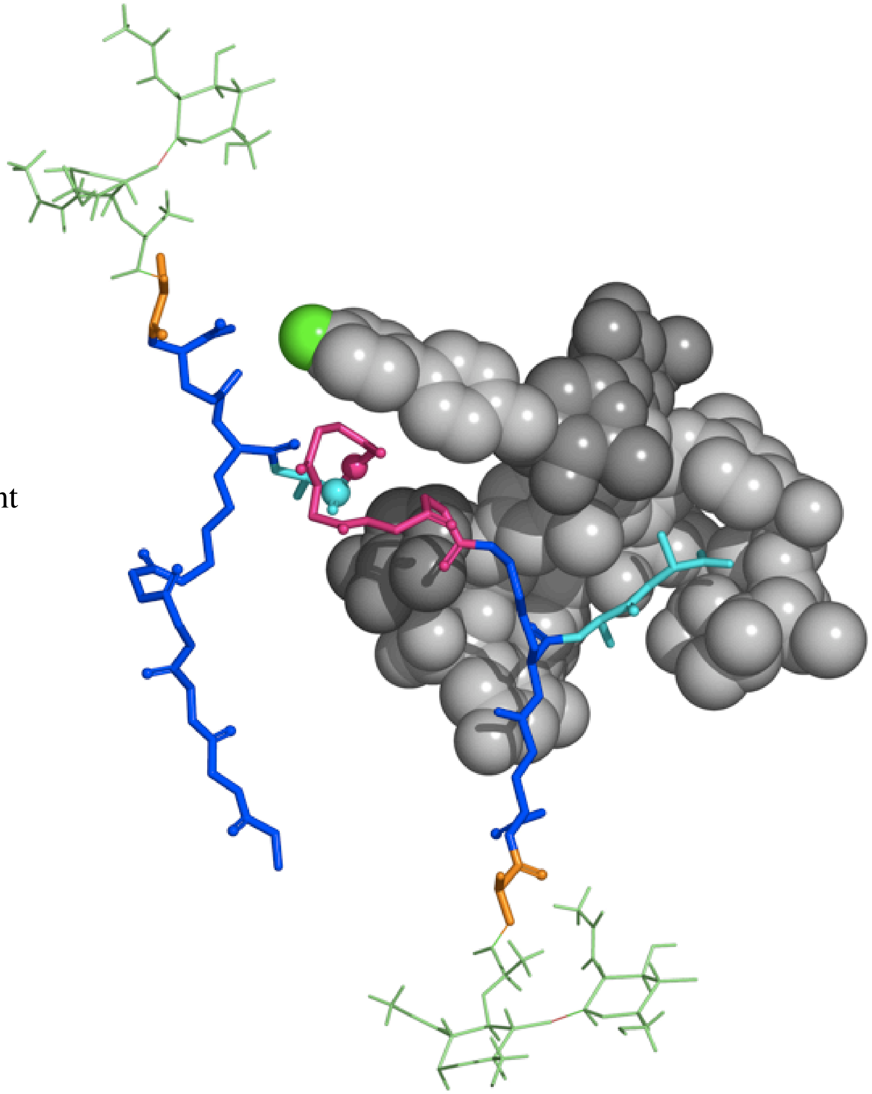
Kruijff and Breukink *Nature*, March **2006**

Vancomycin Function and Resistance

Vancomycin

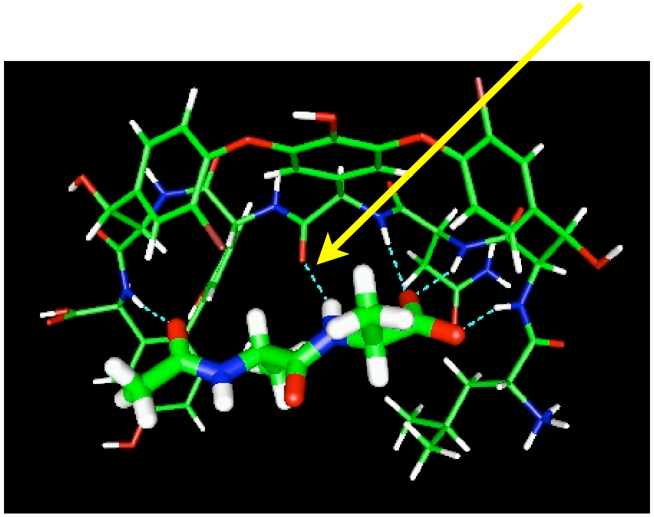


Structure of vancomycin and lipid II obtained through NMR and computational studies:



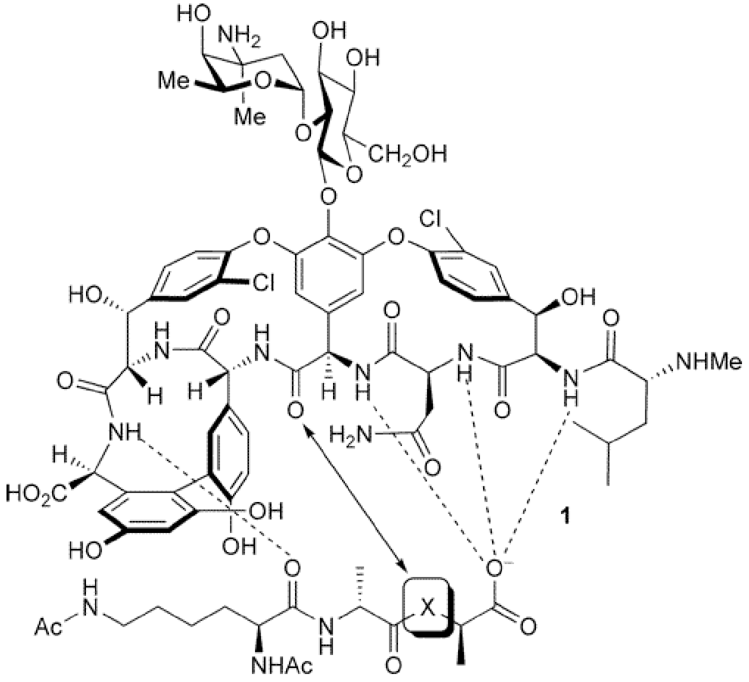
Vancomycin binds to the terminal D-Ala-D-Ala of Lipid II thereby inhibiting assembly of the cell wall.

Resistance is many derived from mutation of the terminal Ala to Lac, reducing binding by 1000 fold.



Hydrogen bond lost in Ala -> Lac mutant

Novel Strategies to Overcome Vancomycin Resistance



1

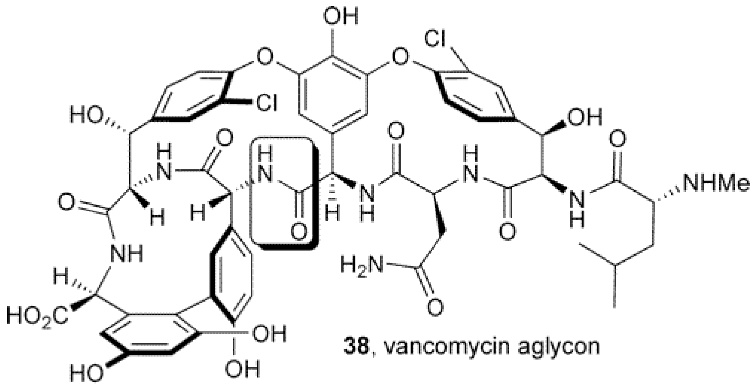
H-Bond
Increases K_a 10-fold (1.5 kcal/mol)

	K_a (M^{-1})	$\Delta G°$ (25 °C)
2, X = NH	4.4×10^5	7.7 kcal/mol
3, X = CH_2	3.3×10^4	6.2 kcal/mol
4, X = O	4.3×10^2	3.6 kcal/mol

Destabilizing lone pair interaction
Decreases K_a 100-fold (2.6 kcal/mol)

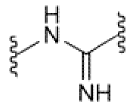
Hydrogen bonding and destabilizing electrostatic interactions account for observed vancomycin resistance.

Boger's Proposal:
Remove destabilizing interactions to create a compound with good binding properties with respect to wild-type and mutant binding site.



38, vancomycin aglycon

⇓ ⇓ ⇓

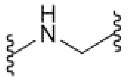


39

D-Ala-D-Lac
>>
D-Ala-D-Ala

40

D-Ala-D-Lac
>
D-Ala-D-Ala



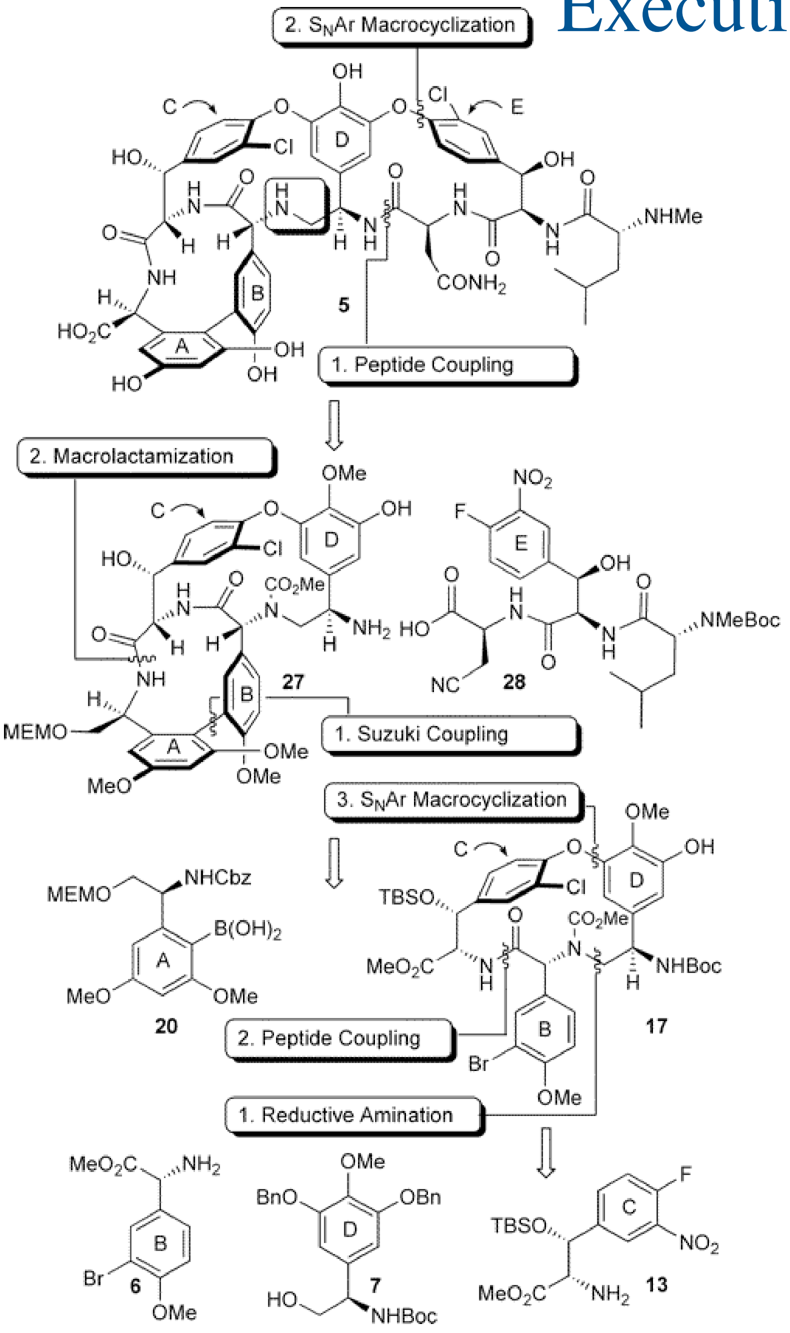
5

D-Ala-D-Lac
=
D-Ala-D-Ala

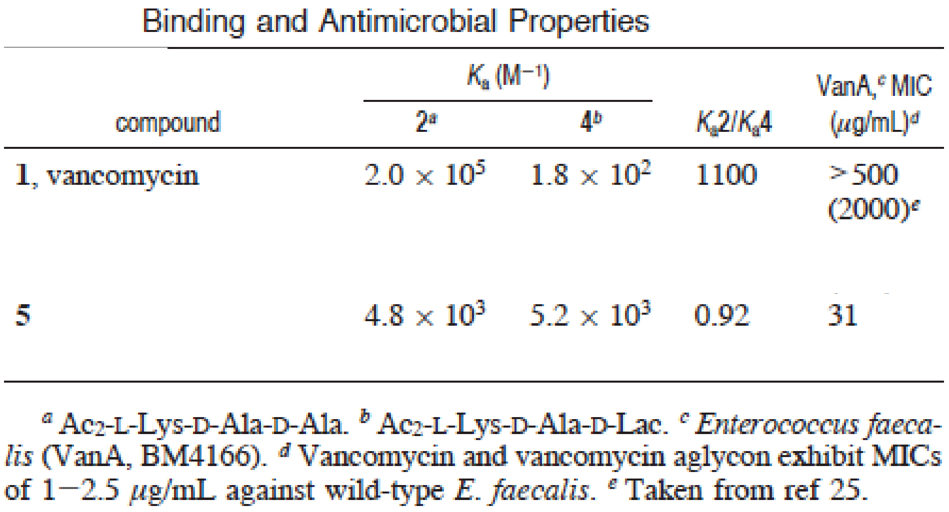
Previous attempts to overcome resistance have centered around making vancomycin more lipophillic, thereby increasing binding.

Boger *et al*. JACS, **2006**, *128*, 2885.

Execution of the Plan



Success!



Binding and Antimicrobial Properties

compound	K_a (M^{-1}) 2^a	4^b	K_a2/K_a4	VanA,^{c} MIC (μg/mL)^d
1, vancomycin	2.0×10^5	1.8×10^2	1100	>500 (2000)^e
5	4.8×10^3	5.2×10^3	0.92	31

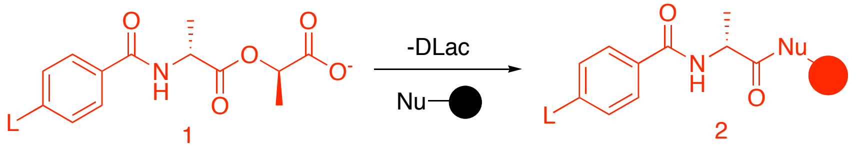
[a] Ac$_2$-L-Lys-D-Ala-D-Ala. [b] Ac$_2$-L-Lys-D-Ala-D-Lac. [c] *Enterococcus faecalis* (VanA, BM4166). [d] Vancomycin and vancomycin aglycon exhibit MICs of 1−2.5 μg/mL against wild-type *E. faecalis*. [e] Taken from ref 25.

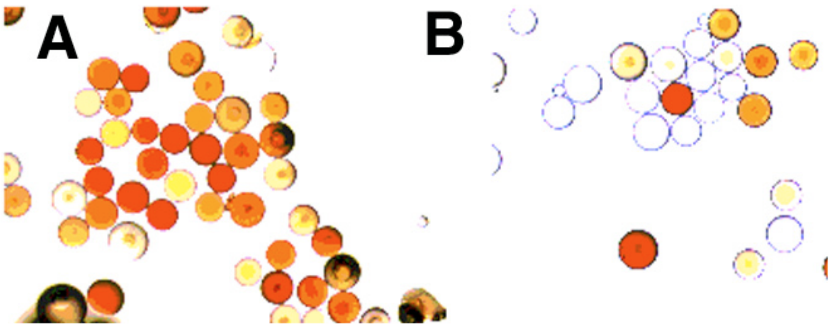
5 exhibited at 40-fold increase in affinity to D-Ala-D-Lac and a corresponding 35-fold reduction in affinity for D-Ala-D-Ala.

This represents the first derivative of vancomycin that addresses the resistance mutation directly and provides a compound that has dual-binding characteristics.

Overcoming Vancomycin Resistance with Small Molecules

Screen of a 300,000 member library for drugs that can cleave the D-Ala -- D-Lac bond (ie, find drugs that function like an enzyme). Initial screen utilized a red dye-labled probe. Solid supported peptides were then screened (A) and then the beads washed (B).

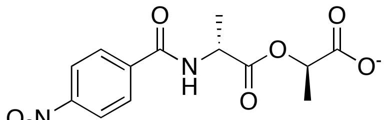




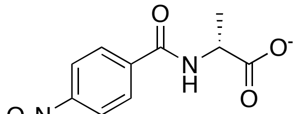
Raw Screen After DMSO wash

Red Beads = Hit

Also tested under aqueous conditions utilizing UV absorption:

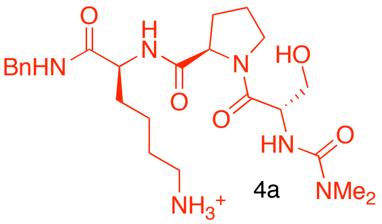


3

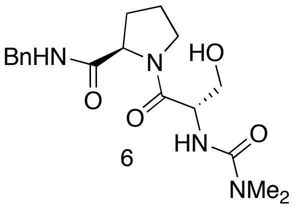


4

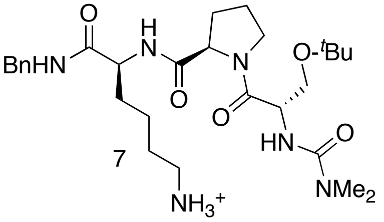
Combinatorial library of 300,000 tri-peptide derivatives yielded 3 hits - all contain a N-terminal serine and an intramolecular hydrogen bond!



4a

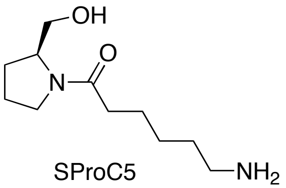


6



7

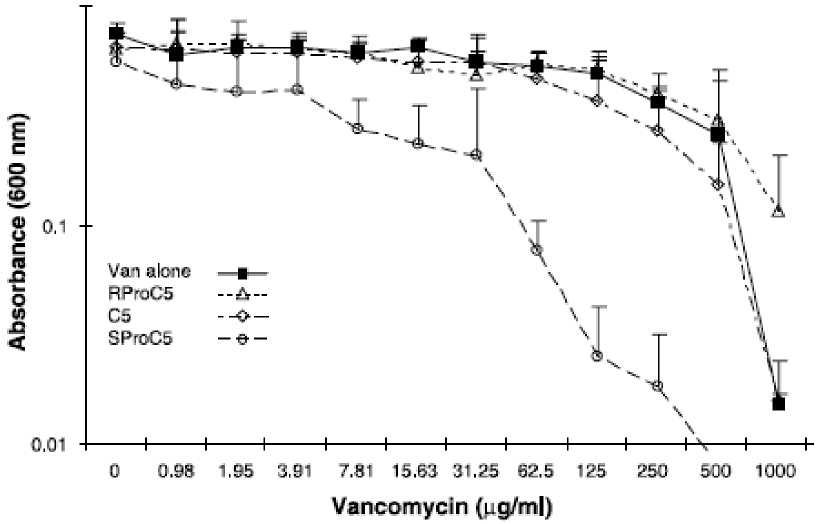
Necessary pharmacophore obtained though computer modeling studies:



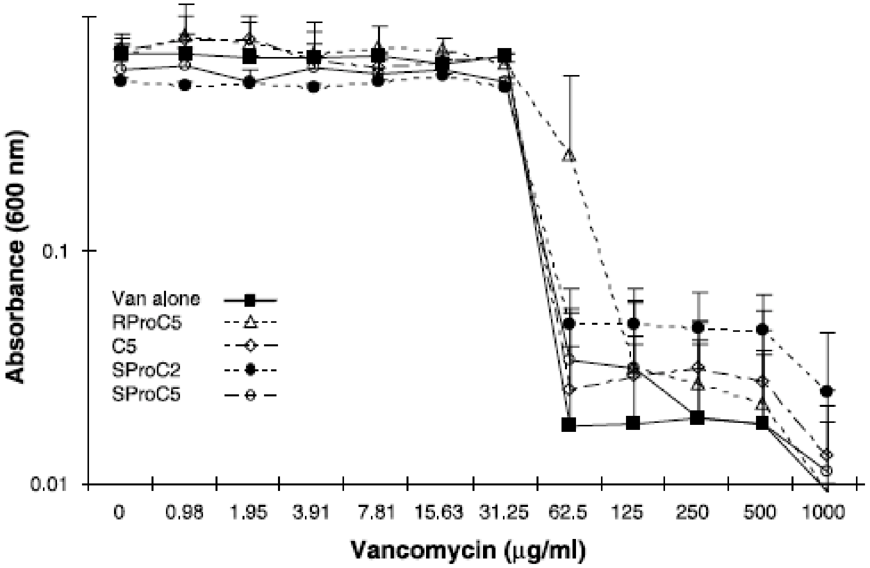
SProC5

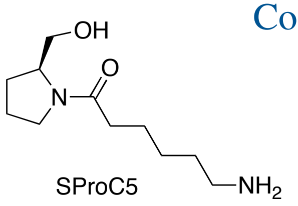
Conformation Specific!

Specificity of SProC5 against C5 and RProC5 against vancomycin resistant strain EF228.

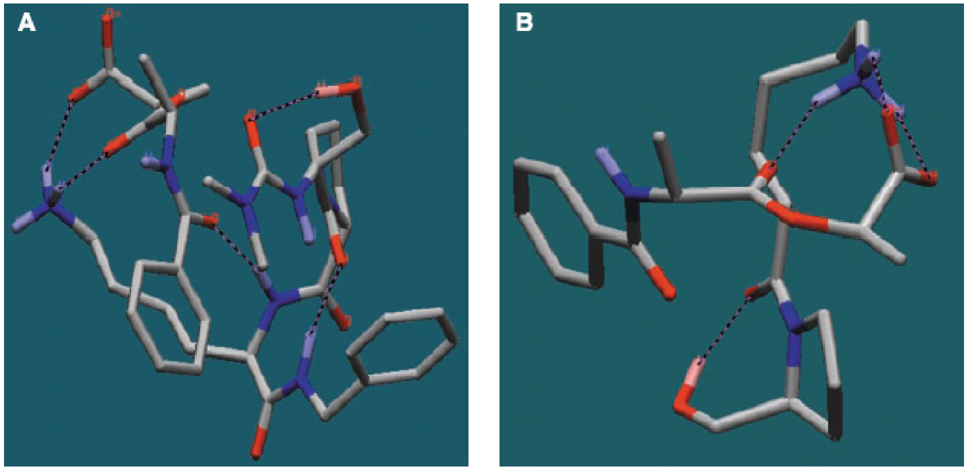


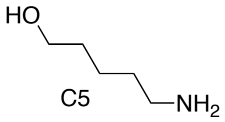
Vancomycin sensitive strain that does not contain D-Ala-D-Lac is unaffected by addition of synthetic molecules.




SProC5

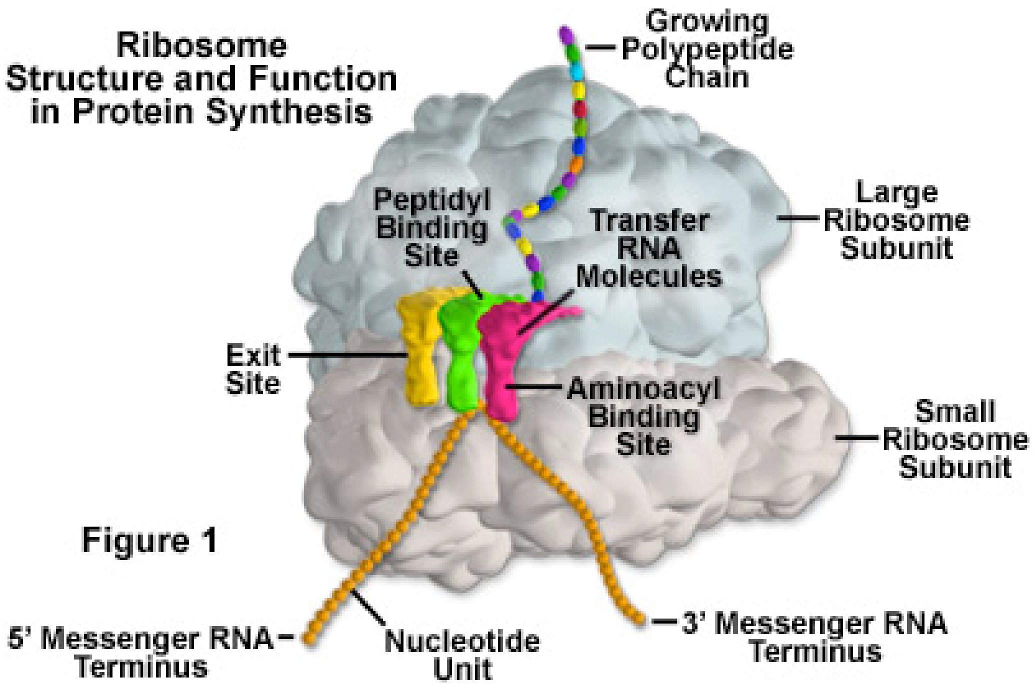
Computer generated model of 4a (A) and SProC5 (B) with PhNH-D-Ala-D-Lac




C5

Restoration of vancomycin activity with small molecules is a promising strategy, and provides a facile alternative to modifying the core structure of vancomycin.

Targeting Protein Synthesis: The Ribosome



A ribosome is an organelle composed of RNA and ribosomal proteins (known as a ribonucleoprotein or RNP). It translates Messenger RNA (mRNA) into a polypeptide chain (e.g., a protein).

Half of all naturally occurring antibiotics target protein synthesis.

Translation in Prokaryotes

Initiation

Initiation of translation involves the small ribosomal subunit binding to the 'start' codon on the mRNA, which indicates where the mRNA starts coding for the protein. In bacteria, the protein starts with the modified amino acid N-formylmethionine (f-Met). The binding of the small subunit to the correct place on the mRNA is facilitated by base pairing to a series of bases known as the Shine-Dalgarno sequence, located about 7 nucleotides before the start site.

Elongation

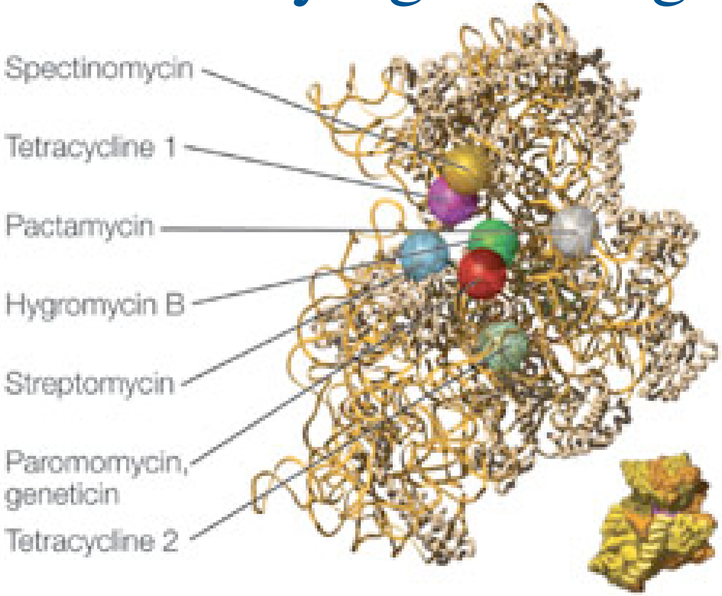
The large 50S subunit forms a complex with the small 30S subunit, and elongation proceeds. First, the Met-tRNAi enters the P-site of the ribosome and base-pairs with the start codon. Then another aminoacylated tRNA enters the A site of the ribosome and base pairs with the mRNA. Correct base pairing between mRNA codon and the tRNA anti-codon results in accommodation of the tRNA. Ribosome catalyzed peptidyl transfer joins the two adjacent amino acids by a newly formed peptide bond; the amino acid on the P site leaves its tRNA and joins the mRNA at the A site. Finally translocation occurs; shifting the peptidyl tRNA into the P-site leaving the A-site empty for a newly incoming tRNA.

Termination

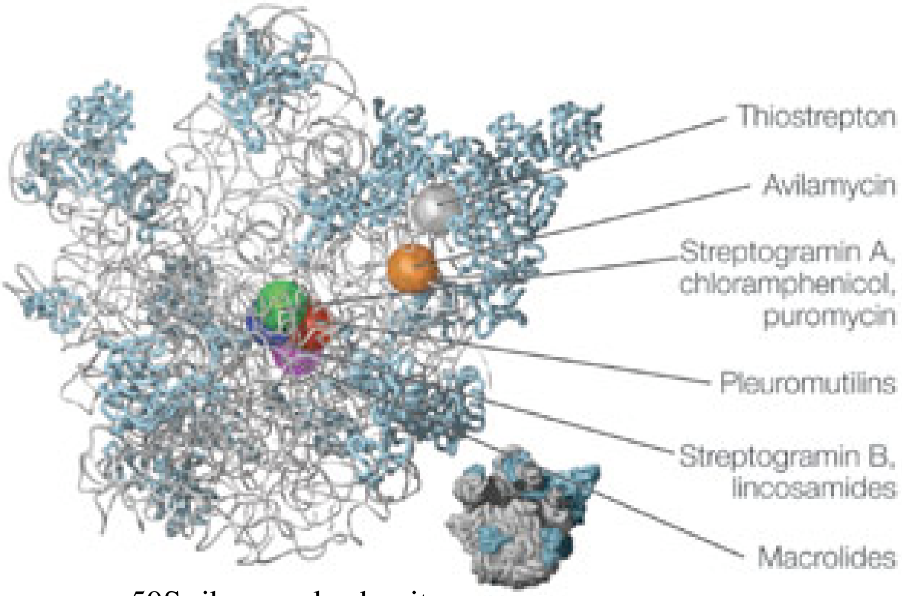
This procedure repeats until the ribosome encounters one of three possible stop codons, where translation is terminated. This stalls protein growth, and release factors, proteins which mimic tRNA, enter the A site and release the protein into the cytoplasm.

Antibiotics can disrupt any step in this cycle to either slow bacterial growth or kill bacteria.

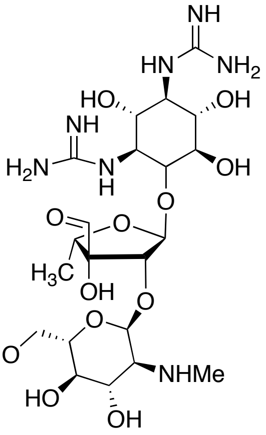
Varying Binding Sites for an Array of Drugs



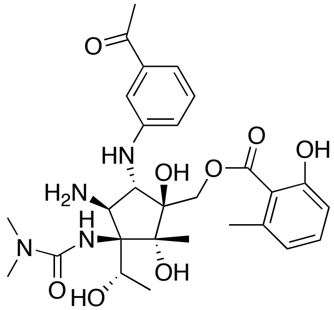
30S ribosomal subunit



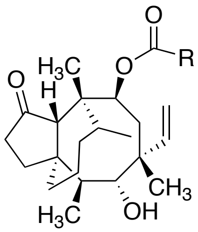
50S ribosomal subunit



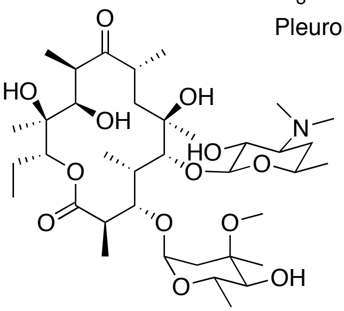
Streptomycin



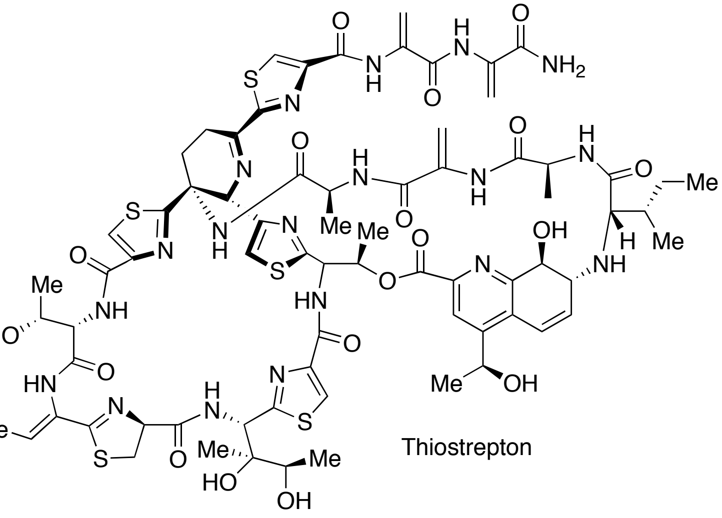
Pactamycin



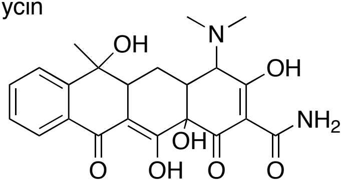
Pleuromutilins



Erythromycin A
(macrolide class)

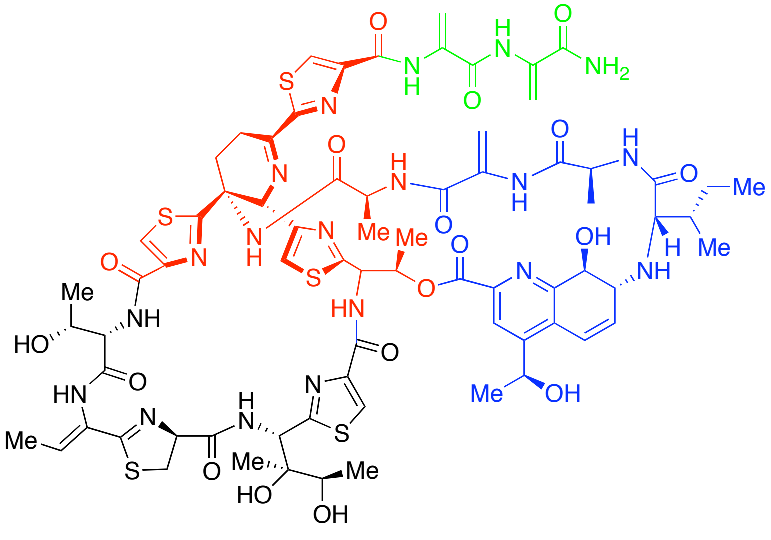


Thiostrepton

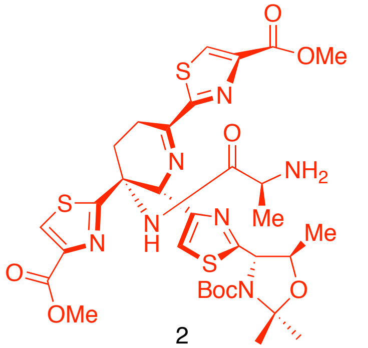


Tetracycline

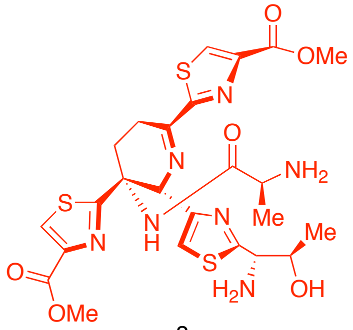
Simplifying Nature



thiostrepton



2



8

Thiostrepton, a thioazole-containing antibiotic first isolated from Streptomyces azureus in 1954, inhibits ribosome function, displaying activity against Gram- positive bacteria and *Plasmodium falciparum*, the causal agent of malaria.

Use in humans is limited by its low solubility in water and poor bioavailability.

Low molecular weight of **2** may enable its use as a lead for human antibiotics withimproved pharmacological profiles compared to thiostrepton.

Target Oriented Synthesis!

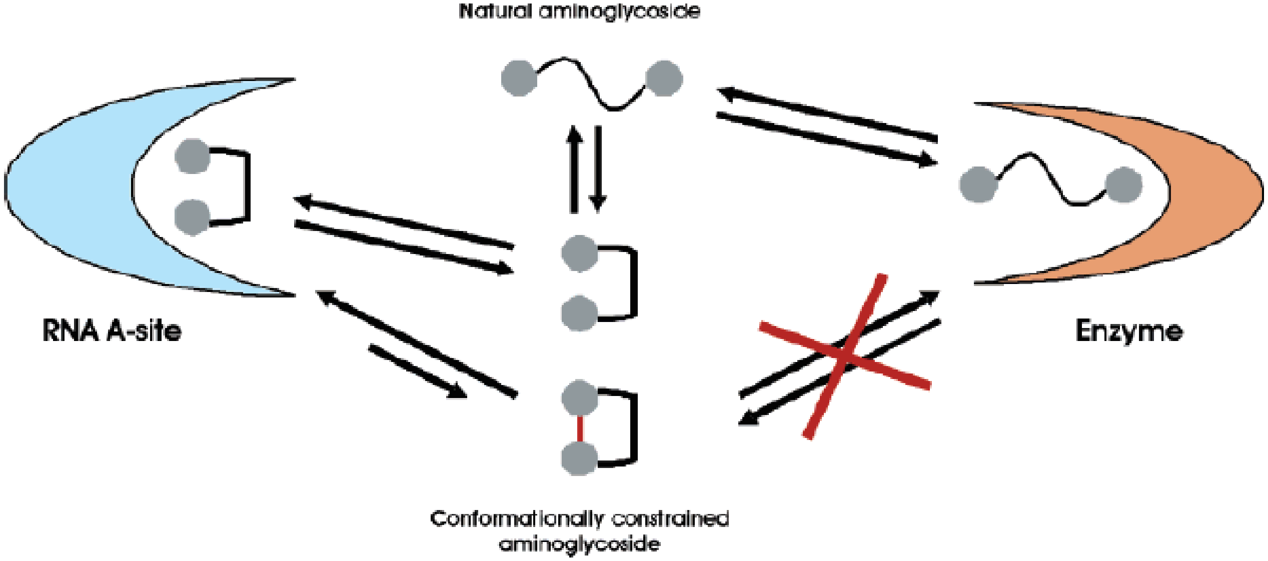
compound	MIC (μM)[a] MRSA[b]	VREF[c]	EC[d]	HD$_{50}$[e] (μM)
vancomycin	1.0	NA[f]	NA	ND[g]
teicoplanin	0.5	ND	NA	ND
thiostrepton (1)	0.2	1.0	NA	> 200
2	5.0	5.0	NA	150
3	NA	NA	NA	ND
4	NA	NA	NA	> 200
5	NA	NA	NA	> 200
6	NA	NA	NA	ND
7	NA	NA	NA	ND
8	15.0	ND	NA	> 200

[a] Minimum inhibitory concentration. [b] Methicillin-resistant *Staphylococcus aureus* ATCC 33591. [c] Vancomycin-resistant *Enterococcus faecalis* ATCC 51575. [d] *Escherichia coli* ATCC 29425. [e] Concentration required to hemolyze 50% of human red blood cells. [f] NA: not active at the highest concentration tested (50 μM). [g] ND: not determined.

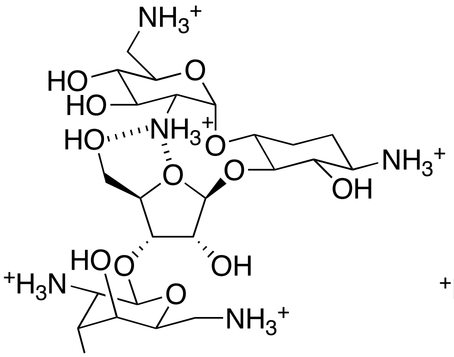
Nicolaou *et al.* JACS, **2005**, *127*, 15042.

Aminoglycosides Revisited:

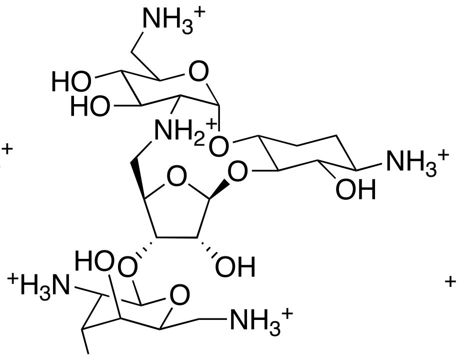
Conformational Locking



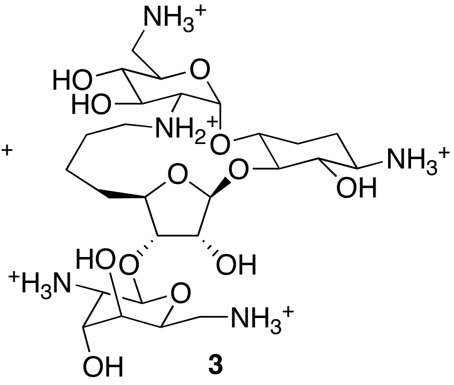
Many antibiotics, including aminoglycosides, are inactivated by enzymes that trap the compounds while they are in their “non-binding” conformations.



Neomycin B (**1**)



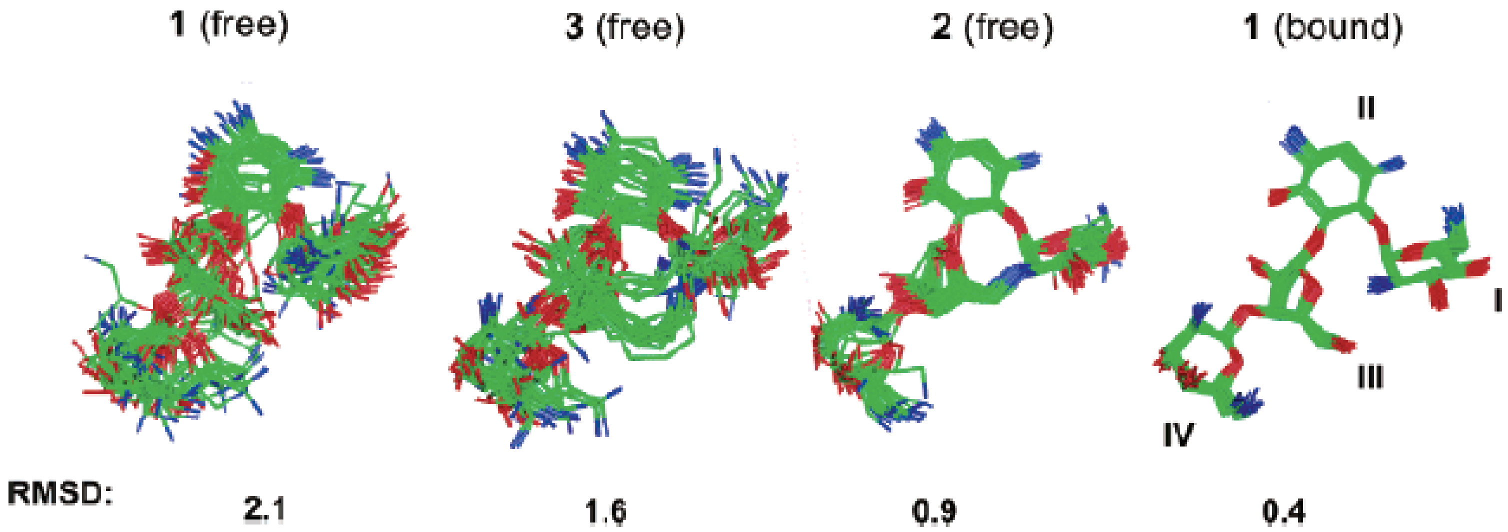
2

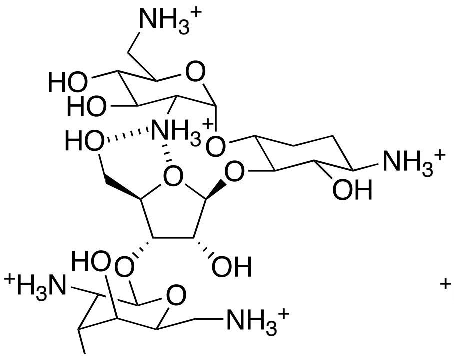


3

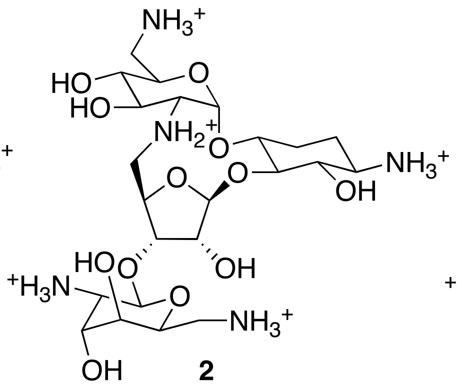
Bastida *et al.* *JACS*, **2006**, *128*, 100.

Conformational Rigidity

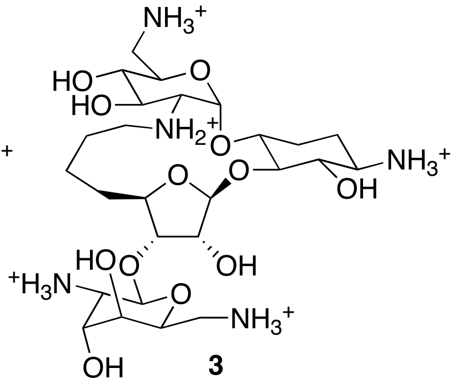




Neomycin B (**1**)



2



3

MIC (μg/mL)	*E. coli* (non-resistant)	3	20
	E. coli DH5α (resistant)	60	20

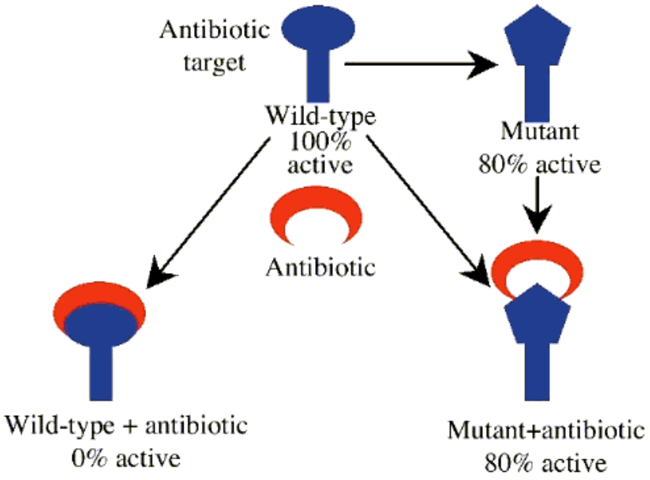
Although both 2 and 3 resist inhibition by enzymes, they had lower binding affinities to their target, attributed to loss of hydroxy functionality - current work is aiming to address this problem.

Anticipating the Resistance

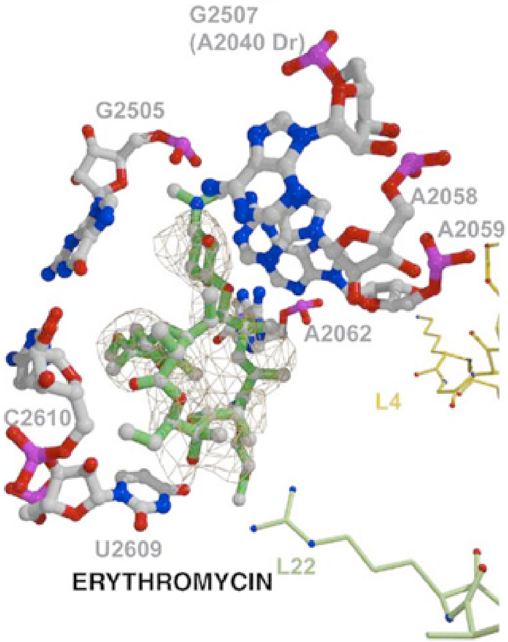
Resistance to these naturally occurring antibiotics is typically acquired by one of two mechanisms, either by transferal of resistance from other bacteria or spontaneously through a mutation in the bacterial chromosome.

While drugs in development can be tested against known resistant clinical isolates, this does not give any information about what new mutants might arise when a new antibiotic is introduced to the market.

If the viable mutations of a rRNA drug target are known, the components of the target required for function can be identified and new drugs developed to specifically recognize the essential components of the target.



RiboNovix
(Biotech start-up)



Can we design new drugs that bacteria can not become resistant to through mutation?

Once a Mutant, Always a Mutant

Resistance carries a cost: resistant bacteria grow more slowly under normal conditions, pay a 10-20% fitness cost

- Replicating extra plasmid DNA is costly to the cell
- Ribosomal mutations that confer resistance slow protein production

When we stop using an antibiotic, does resistance go away?

- Can we reverse selection, and favor the vulnerable bacteria instead?

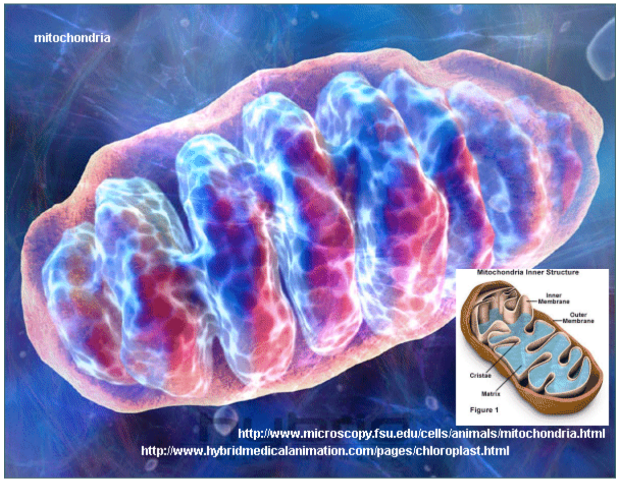
Experiments show bacteria quickly evolve compensatory mutations that lower the costs of resistance, instead of just losing resistance.

- Recent results suggest that once we select resistant bacteria, we may be stuck with them permanently!

illustration: Don Smith

Levin et al. 2000, *Genetics* 154: 985-997

Mitochondrial Effects: Significant Problem



http://www.microscopy.fsu.edu/cells/animals/mitochondria.html
http://www.hybridmedicalanimation.com/pages/chloroplast.html

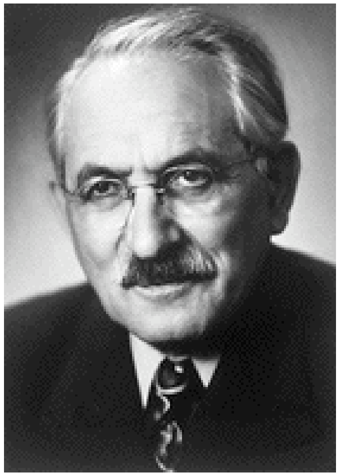
According to the endosymbiotic theory mitochondria originated as separate prokaryotic organisms which were taken inside the cell as endosymbionts. Mitochondria developed from proteobacteria and have evolved to be the "power plant" for the cell.

Antibiotics that function by inhibiting bacterial ribosomes sometimes also inhibit mitochondrial ribosomes and thus mitochondrial protein synthesis. Mitochondrial toxicity has been implicated in hearing loss caused by amino glycosides, and bone marrow depression caused by chloramphenicol and the recently released Zyvox (linezolid).

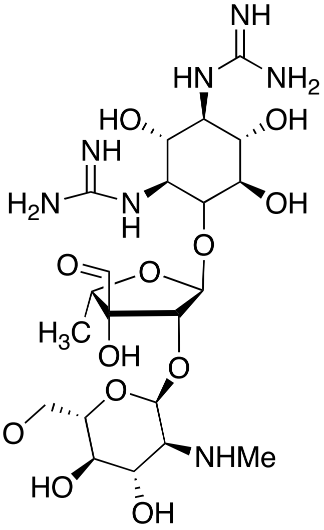
This type of side-effect is usually unnoticed until long term treatment has been performend since mitchondrial turnover is slow.

Compounds with higher selectivity are required to overcome this problem.

The Streptomycin Story



Selman Waksman
(1888-1973)



Streptomycin

Albert Schatz
(1920-2005)

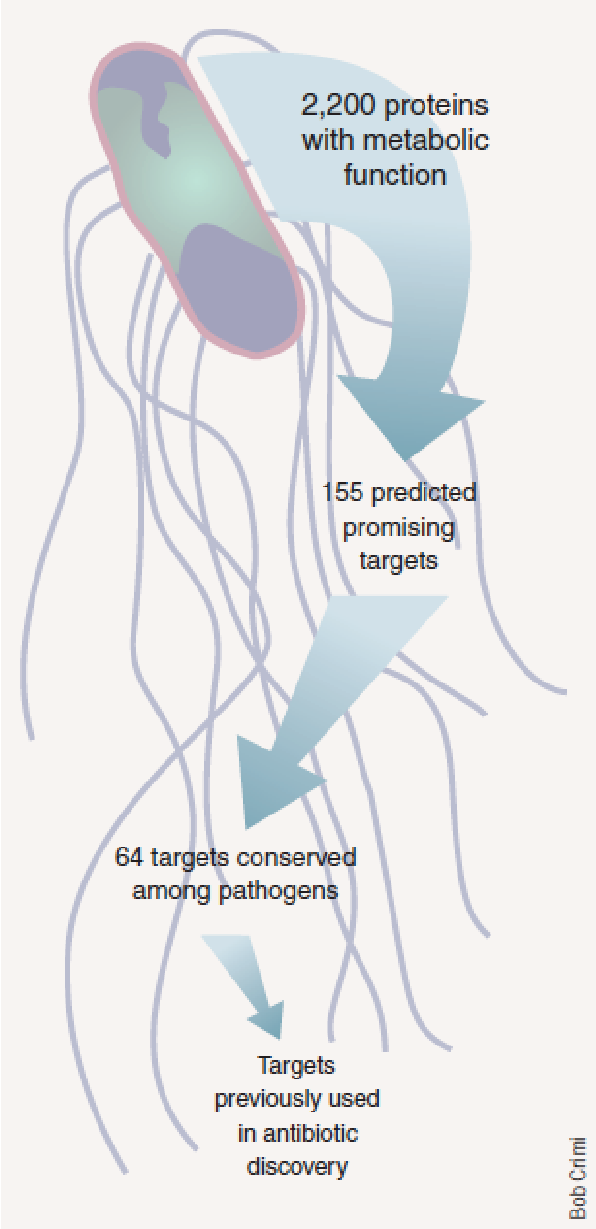
Streptomycin was discovered in the labs of Selman Waksman ("Father of Antibiotics") in 1943 by Albert Schatz, a graduate student in his group. Waksman discovered many antibiotics during his career, including actinomycin, neomycin, and clavacin.

At some point, Waksman made an arrangement with Rutgers to share in the royalties the university was obtaining from Merck, and this led to litigation by Schatz. He had been an undergraduate at Rutgers and then joined Waksman's team, first as an assistant, then as a doctoral research student. He defended his dissertation on streptomycin in 1945, and then left Rutgers to work in California. Schatz later sued Rutgers and Waksman for part of all royalties and has pursued credit for being "co-discoverer" of streptomycin -- a case that he won, but one that ruined his career.

What we have here, then, is a high-level version of the old story about the mechanic who fixed a faulty engine with a single hammer blow. When the motorist protested that the charge of $100 was excessive, he was told, "Hitting costs only $5, the $95 is for knowing where to hit."

Lawrence. *Nature*, **2002**, *415*, 835.

Out of Targets?



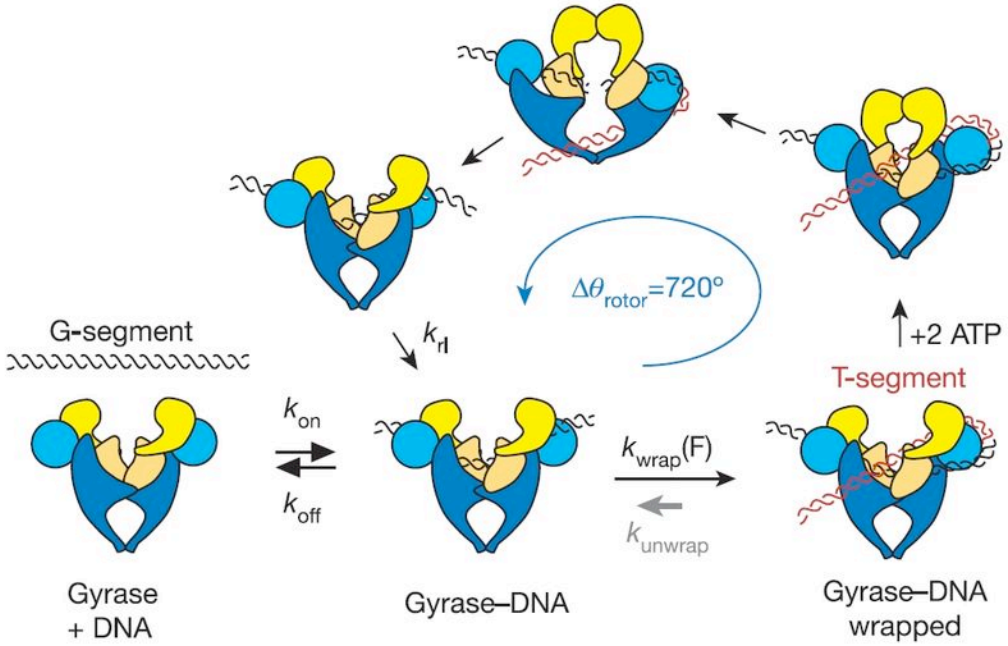
Recent work by Becker and co-workers has employed genomics and computational methods to screen bacterial genes that are involved in metabolic function across multiple bacteria strains.

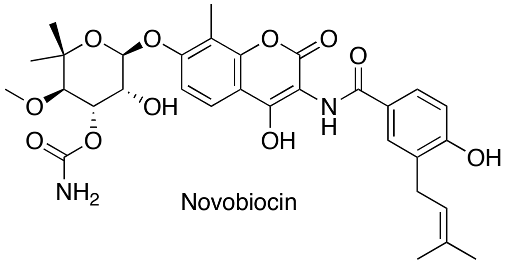
Although the screen has been seen as too narrow or too broad by others, all 64 discovered targets were previously known and investigated.

Are all good targets being investigated? Or is the field of structural biology and genomics not choosing and eliminating the correct targets?

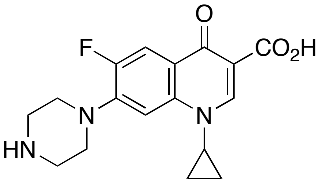
Becker *et al*. *Nature*, **2006**, *440*, 303.

Targeting DNA Gyrase





Novobiocin



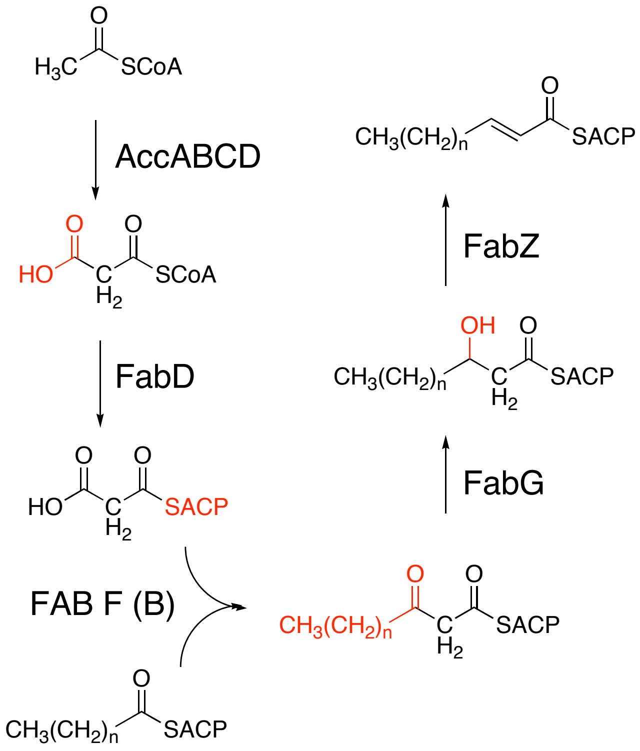
Ciprofloxacin

DNA gyrase only found in bacteria - not in eukaryotes. Cipro has become one of the most used antibiotics, even though its side effects are numerous.

Side Effects Attributed to Cipro:

Abnormal dread or fear, achiness, bleeding in the stomach and/or intestines, blood clots in the lungs, blurred vision, change in color perception, chills, confusion, constipation, convulsions, coughing up blood, decreased vision, depression, difficulty in swallowing, dizziness, double vision, drowsiness, eye pain, fainting, fever, flushing, gas, gout flare up, hallucinations, hearing loss, heart attack, hiccups, high blood pressure, hives, inability to fall or stay asleep, inability to urinate, indigestion, intestinal inflammation, involuntary eye movement, irregular heartbeat, irritability, itching, joint or back pain, joint stiffness, kidney failure, labored breathing, lack of muscle coordination, lack or loss of appetite, large volumes of urine, light-headedness, loss of sense of identity, loss of sense of smell, mouth sores, neck pain, nightmares, nosebleed, pounding heartbeat, ringing in the ears, seizures, sensitivity to light, severe allergic reaction, skin peeling, redness, sluggishness, speech difficulties, swelling of the face, neck, lips, eyes, or hands, swelling of the throat, tender, red bumps on skin, tingling sensation, tremors, unpleasant taste, unusual darkening of the skin, vaginal inflammation, vague feeling of illness, weakness, yellowed eyes and skin.

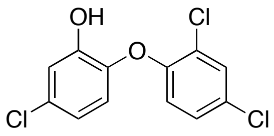
Targeting Fatty Acid Synthesis: Possible Breakthrough



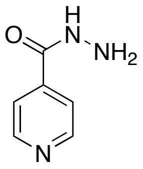
While compounds that target fatty acid synthesis have been known for decades, no current drugs target this pathway.

It is thought that few inhibitors of this pathway exist in nature due to the similarity of this pathway to polyketide synthesis.

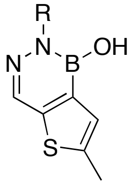
Known Inhibitors of Various Steps in Fatty Acid Synthesis:



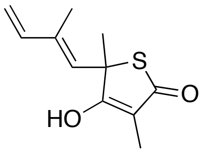
triclosan



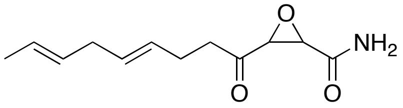
isoniazid



diazoborine

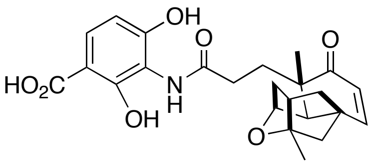


thiolactomycin



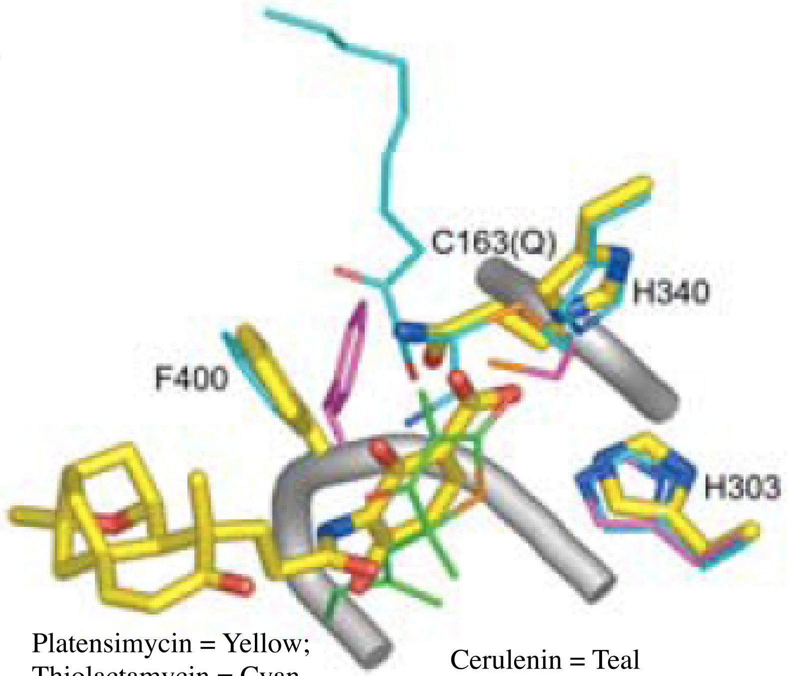
cerulenin

Platensimycin



platensimycin

Discovered by a Merck team during a novel screen of 250,000 compounds. Found to be potent inhibitor of FabF.



Platensimycin = Yellow;
Thiolactamycin = Cyan

Cerulenin = Teal

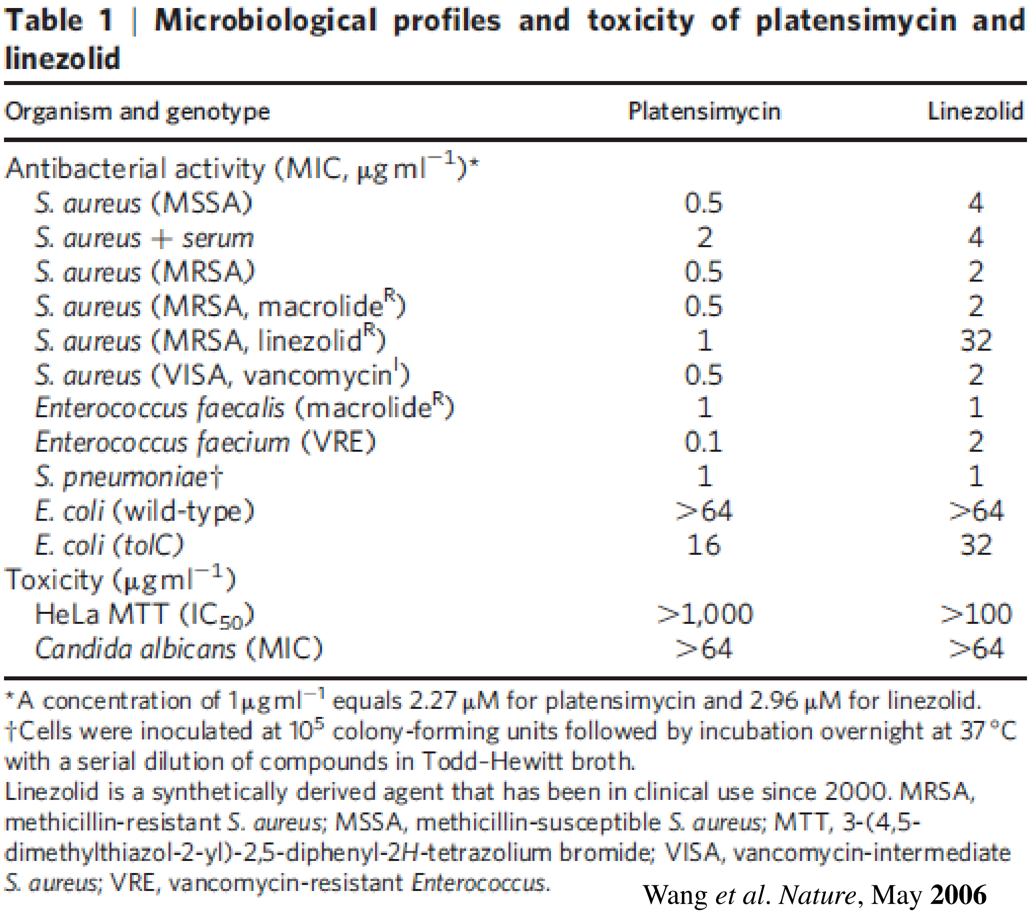


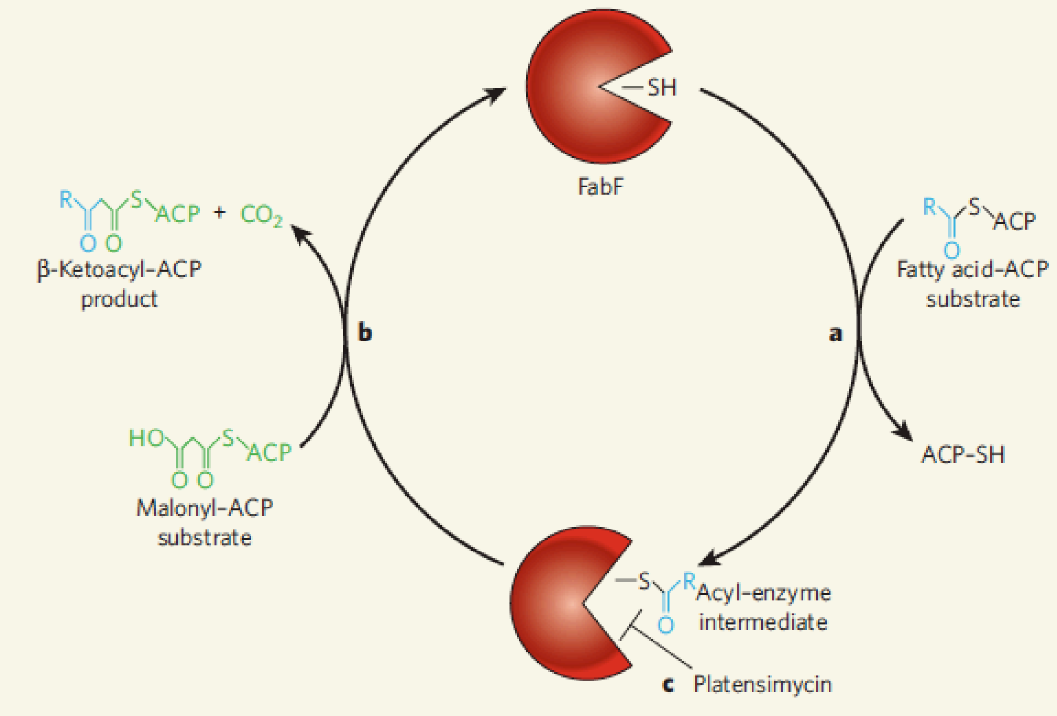
Table 1 | Microbiological profiles and toxicity of platensimycin and linezolid

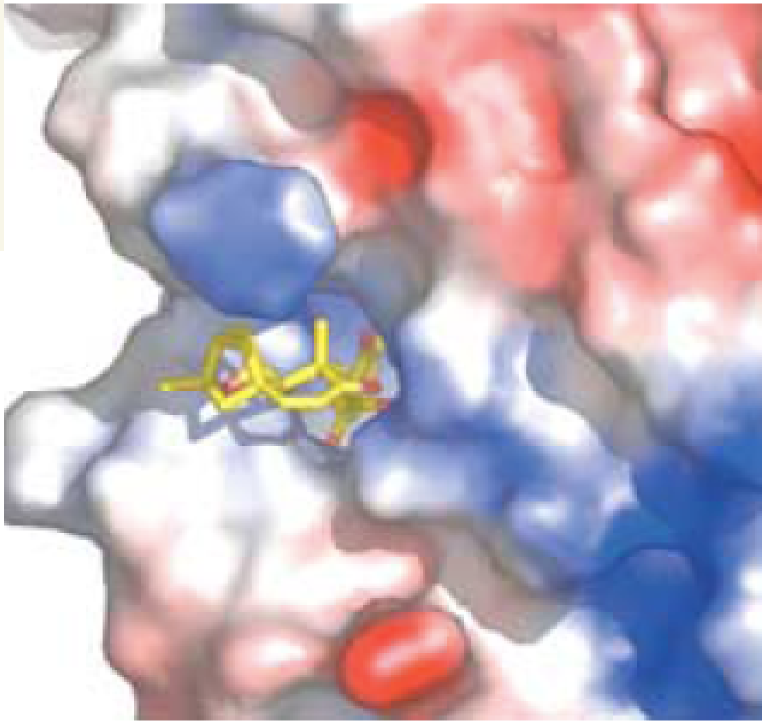
Organism and genotype	Platensimycin	Linezolid
Antibacterial activity (MIC, μg ml^{-1})*		
S. aureus (MSSA)	0.5	4
S. aureus + *serum*	2	4
S. aureus (MRSA)	0.5	2
S. aureus (MRSA, macrolide^{R})	0.5	2
S. aureus (MRSA, linezolid^{R})	1	32
S. aureus (VISA, vancomycin^{I})	0.5	2
Enterococcus faecalis (macrolide^{R})	1	1
Enterococcus faecium (VRE)	0.1	2
S. pneumoniae†	1	1
E. coli (wild-type)	>64	>64
E. coli (*tolC*)	16	32
Toxicity (μg ml^{-1})		
HeLa MTT (IC$_{50}$)	>1,000	>100
Candida albicans (MIC)	>64	>64

*A concentration of 1 μg ml^{-1} equals 2.27 μM for platensimycin and 2.96 μM for linezolid.
†Cells were inoculated at 10^{5} colony-forming units followed by incubation overnight at 37 °C with a serial dilution of compounds in Todd-Hewitt broth.
Linezolid is a synthetically derived agent that has been in clinical use since 2000. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide; VISA, vancomycin-intermediate *S. aureus*; VRE, vancomycin-resistant *Enterococcus*.

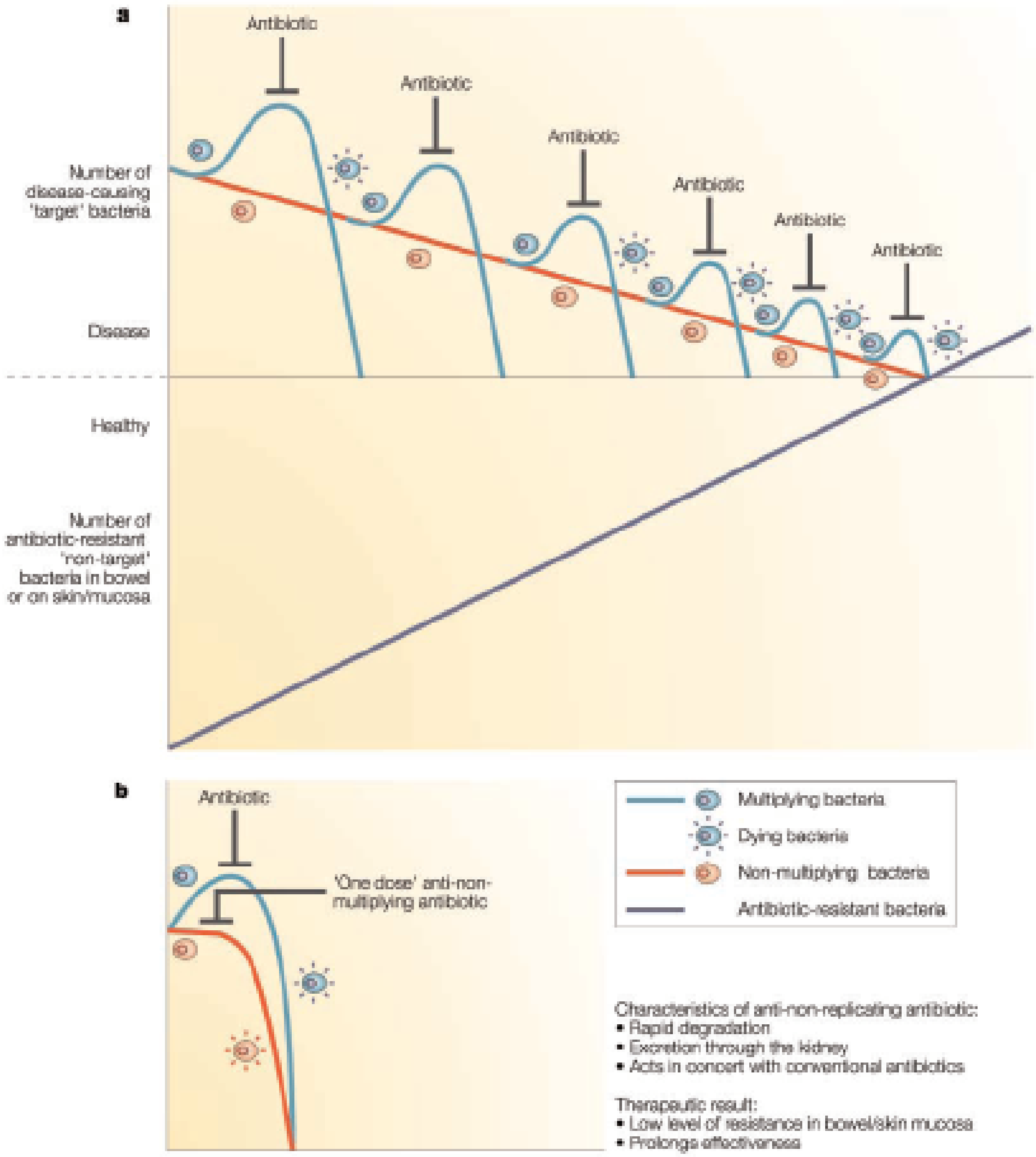
Wang *et al*. *Nature*, May **2006**

Platensimycin Binds to Acyl-Enzyme Intermediate





No Existing Drugs Target Non-Multiplying Bacteria



Characteristics of anti-non-replicating antibiotic:
- Rapid degradation
- Excretion through the kidney
- Acts in concert with conventional antibiotics

Therapeutic result:
- Low level of resistance in bowel/skin mucosa
- Prolongs effectiveness

The Billion Dollar Question:

How can we target non-multiplying bacteria with small molecules?

Conclusions and Future Directions

A major frontier of science in the 40-60's, antibiotic development was greatly reduced until recently.

The modification of current drugs or the use of a multi-drug treatment has been shown to fend off some resistant bacteria for the short term. Time will tell the long term effectiveness of these strategies and will hopefully also bring better solutions though further understanding of structure/activity relationships.

The discovery of platensimycin highlights the fact that novel compounds with interesting targets are still out there to be discovered.

With old and new strains of bacteria becoming resistant to all current drugs, and new drug resistance for many classes only taking months, the development of new antibiotics that have novel targets is more important now than ever.

Since naturally produced antibiotics already have resistance mechanisms in bacteria, novel synthetic antibiotics that are designed to target specific and essential targets should yield drugs that are highly effective.

The topics covered here, along with the many that were not including peptide based and enediyne based antibiotics, will provide a wealth of new therapies for future generations.