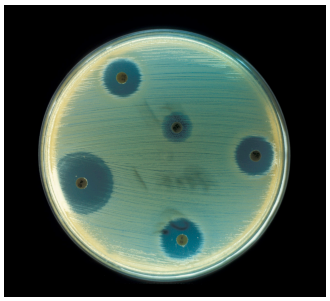
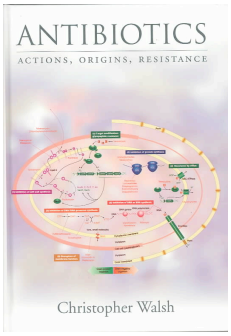


Mechanistic Classes of Antibacterials

Benjamin D. Horning
Group Meeting November 30, 2011



http://images.agoramedia.com/cs/eh/cs_diarrhea_antibiotics_causing_diarrhea_article.jpg http://www.irishhealth.com/content/image/853/Image1.jpg

Walsh, C. T. *Antibiotics: Actions, Origins, Resistance*, American Society for Microbiology Press, Washington DC, 2003

Antibacterials- A Subclass of Antibiotics

- An antibiotic is "a chemical substance having the capacity, in dilute solution, to kill or inhibit growth of microorganisms." This definition includes antifungals and antiprotozoals. Antibiotics travel inside the body to fight microorganisms, antiseptics are used externally, and disinfectants are for non-living surfaces.

antimicrobials

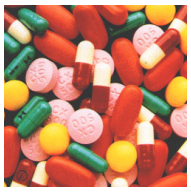
antibiotics

disinfectants

applied to non-living objects

antiseptics

for external applications to living organisms



antibacterials

for internal or external use

antifungals

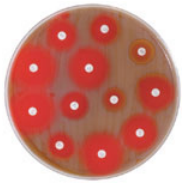
kill fungus

antiprotozoals

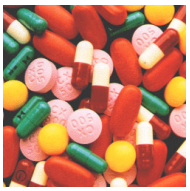
kill protozoans (single-celled eukaryotes)

http://www.lysol.com/images/products/no-mess-automatic-toiletbowl-cleaner.png, http://www.couponmamacentral.org/wp-content/uploads/2011/09/purell.jpg, http://www.medexpressrx.com/blog/wp-content/uploads/2010/07/antibiotics4.jpg, http://drugster.info/drug/medicament/22969/, http://modernmedicalguide.com/wp-content/uploads/2010/03/Antiprotozoal-Drugs.jpg

Antibacterials- A Subclass of Antibiotics

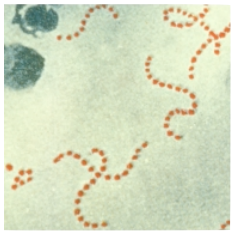


in vitro antibacterials

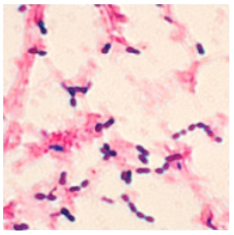


human antibacterials

veterinary and feedstock antibacterials



S. pyogenes



S. pneumoniae

S. mutans

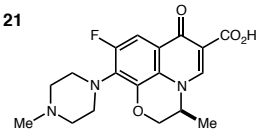
Streptococcus pyogenes - strep throat, rheumatic fever, scarlet fever, necrotizing fasciitis
Streptococcus pneumoniae - (bacterial) pneumonia
Streptococcus agalactiae - meningitis, (bacterial) pneumonia
Escherichia coli - gastroenteritis, urinary tract infections, sepsis, diarrhea
(Methicillin-resistant) Staphylococcus aureus (MRSA) - Impetigo, Staph infections, toxic shock syndrome

Image from: http://inst.bact.wisc.edu/inst/images/book_3/chapter_13/13-3.jpg

http://www.webcitation.org/5uJyti0mG http://www.medicinenet.com/sepsis/page4.htm

Top-Selling Antibiotics in the USA

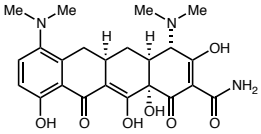
21



Levaquin (Levofloxacin)

Ortho-McNeil
$1,355 Million

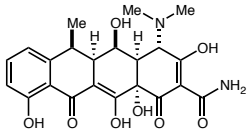
54



Solodyn (Minocycline)

Medicis
$673 Million

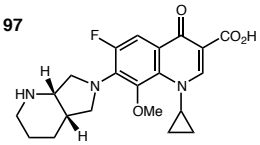
94



Doryx (Doxycycline)

Medicis
$673 Million

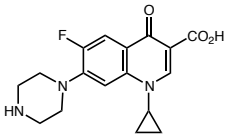
97



Avelox (Moxifloxacin)

Merck
$353 Million

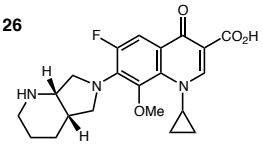
125



Ciprodex otic
(Cipro and Dexamethasone)

Alcon $255 Million

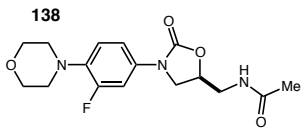
126



Vigamox (Moxifloxacin)

Alcon
$253 Million

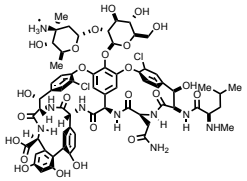
138



Zyvox (Linezolid)

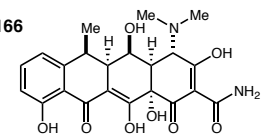
Pfizer
$223 Million

160



Vancocin (Vancomycin) ViroPharma
$192 Million

166

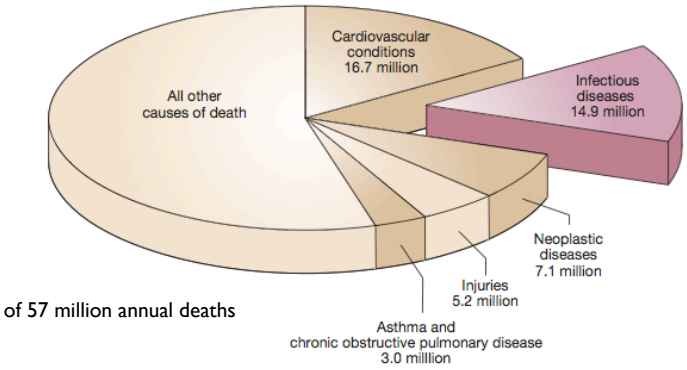


Oracea (Doxycycline)

Galderma
$187 Million

http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster

Antibiotics- Why You Should Care



of 57 million annual deaths

Infectious diseases	Annual deaths (million)
Respiratory infections	3.96
HIV/AIDS	2.77
Diarrhoeal diseases	1.80
Tuberculosis	1.56
Vaccine-preventable childhood diseases	1.12
Malaria	1.27
STDs (other than HIV)	0.18
Meningitis	0.17
Hepatitis B and C	0.16
Tropical parasitic diseases	0.13
Dengue	0.02
Other infectious diseases	1.76

Table 1. Dates of deployment of representative antibiotics and herbicides, and the evolution of resistance. [Source (*75*)].

EVOLUTION OF RESISTANCE TO ANTIBIOTICS AND HERBICIDES

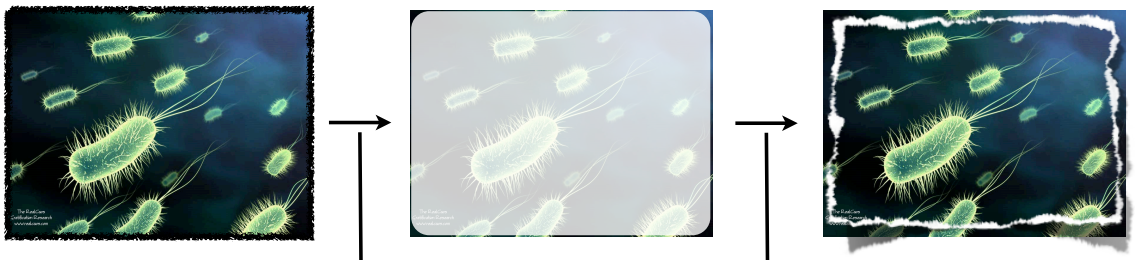
Antibiotic or herbicide	Year deployed	Resistance observed
Antibiotics		
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	late 1960s

- Vaccinations and antibiotics can cure or prevent the majority of infectious diseases currently afflicting humanity.
- Antibiotic use introduces evolutionary selection pressure to bacteria; Resistant strains are selected for, and cause antibiotics to become ineffective.
- Bacterial resistance has been observed for every class of antibiotic introduced, sometimes within one year.
- New therapies *will* be needed.

Graph from: Morens, D. M.; Folkers, G. K.; Fauci, A. S. *Nature* **2004**, *430*, 242-249

Table from: Palumbi, S. R. *Science* **2001**, *293*, 1786-1790

Strategies to Slow the Development of Antibiotic Resistance



10^8 bacteria
one error per 10^7 bases
10 mutants (~0.3% of genes)

antibiotic treatment

1 bacterium
selection for resistant bacteria

bacterial growth

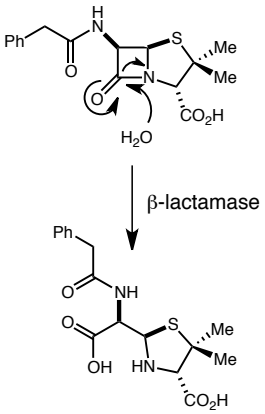
10^8 bacteria
completely resistant

- Overkill (multiple antibiotics) has worked well for HIV/AIDS, but not always applicable for bacteria (side effects).
- Direct observation therapy - continue antibiotic dose until no bacteria remain (not practical).
- Use narrow-spectrum antibiotics when applicable.
- Withhold the most powerful drugs - prevented vancomycin resistance for >30 years - difficult business model for pharma.
- Continue to develop new therapies and improve old therapies.

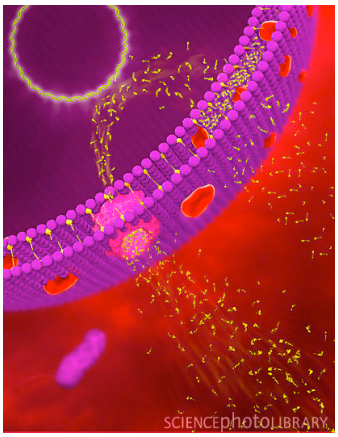
Palumbi, S. R. *Science* **2001**, *293*, 1786-1790

Bacterial Resistance - Three Flavors

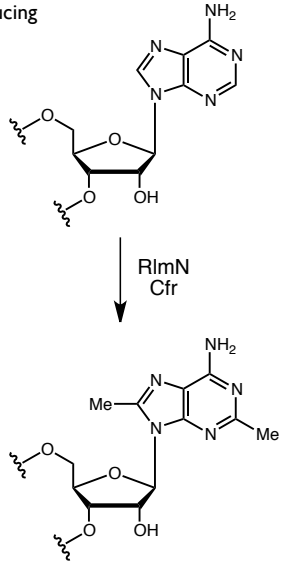
- Three types of bacterial resistance to antibiotics have been observed, coming either from random mutation under the selection pressure of antibiotics, or from antibiotic-producing bacteria. Resistance can be spread amongst bacteria via horizontal gene transfer.



antibiotic modification
(only natural products
and semisynthetics)



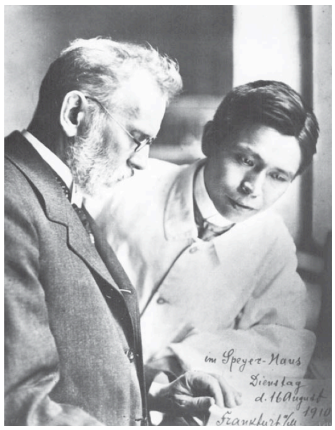
export pumps
(efflux)



enzymatic target
modification

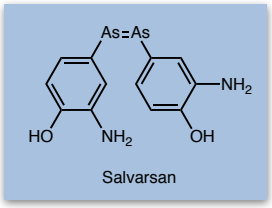
http://www.sciencephoto.com/image/151999/530wm/C0089313-Active_efflux,_artwork-SPL.jpg
Fujimori, D. G. *et. al.* J. Am. Chem. Soc. **2010**, *132*, 3953-3964

Paul Ehrlich and Drug Discovery

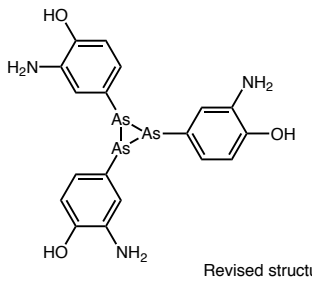


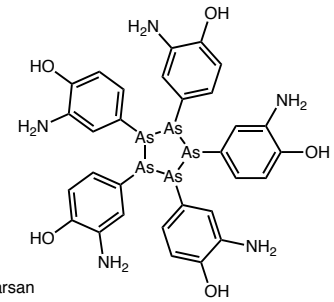
Paul Ehrlich and Sahachiro Hata
Frankfurt 1910

- Made seminial contributions in histology, haematology, immunology, oncology, microbiology and pharmacology.
- Alongside Ilya Mechnikov, won the Nobel Prize in Physiology or Medicine in 1908 "*in recognition of their work on immunity.*"
- Most famous for his discovery of Salvarsan (arsphenamine, #606), a compound for the treatment of syphilis, which was discovered during the first screen of a library of compounds for pharmaceutical activity, and later part of the first optimization of a lead, becoming the first blockbuster drug and presaging modern drug discovery.



Salvarsan

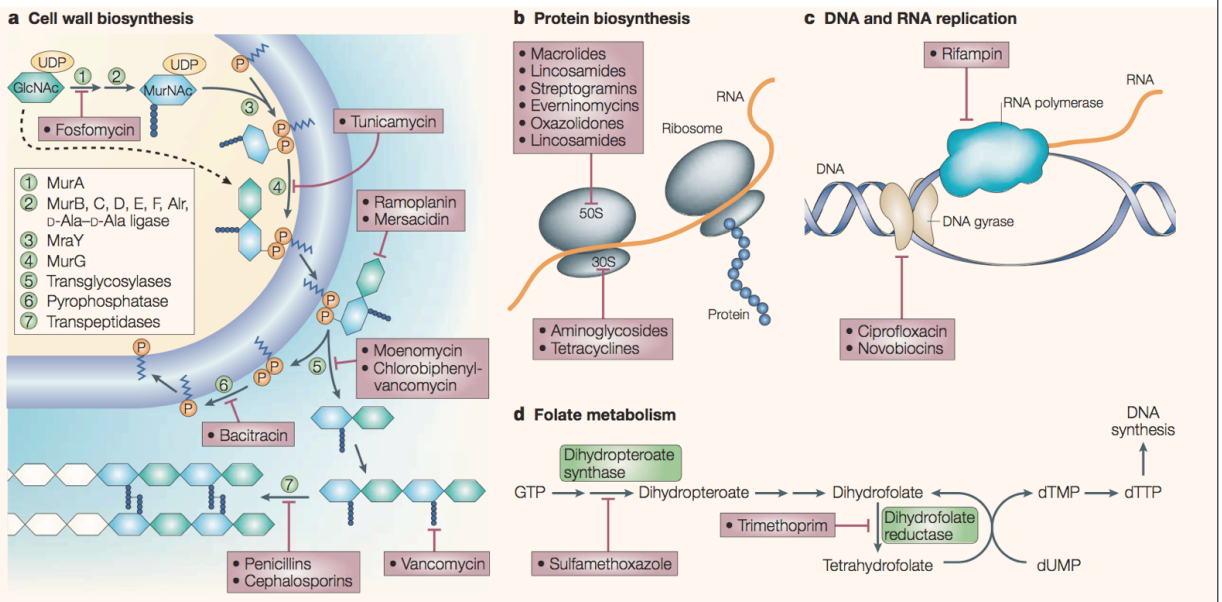




Revised structure of Salvarsan

Bosch, F.; Rosich, L. *Pharmacology* **2008**, *82*, 171-179 www.nobelprize.org/nobel_prizes/medicine/laureates/1908/
http://pubs.acs.org/cen/coverstory/83/8325/8325salvarsan.html
Lloyd, N. C.; Morgan, H. W.; Nicholson, B. K.; Ronimus, R. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 941-944

The Four Major Targets of Antibiotics

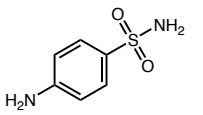


Walsh, C. T. *Nature Reviews Microbiology* **2003**, *1*, 65-70

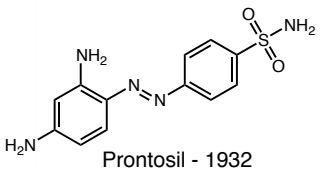
Walsh, C. T. *Antibiotics: Actions, Origins, Resistance*, American Society for Microbiology Press, Washington DC, 2003

The Four Major Targets of Antibiotics

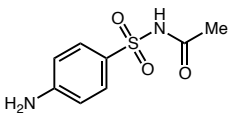
Antibiotics either target processes that are unique to bacteria - cell wall biosynthesis and folate metabolism - or processes that have different enough machinery to allow selective inhibition of bacterial over human versions - protein biosynthesis and DNA and RNA replication and repair.



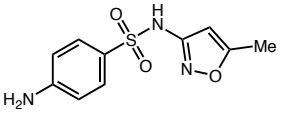
Sulfanilamide - 1936



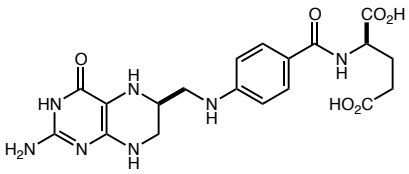
Prontosil - 1932



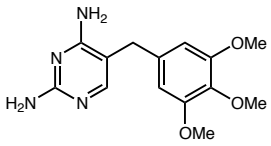
Sulfacetamide



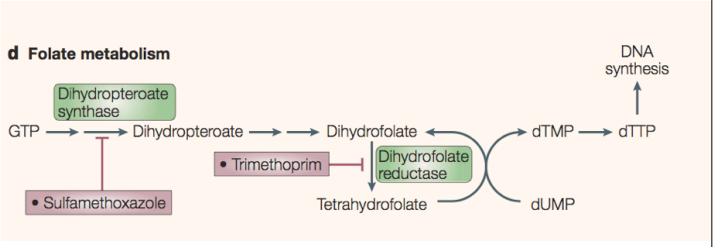
Sulfamethoxazole



Tetrahydrofolic acid



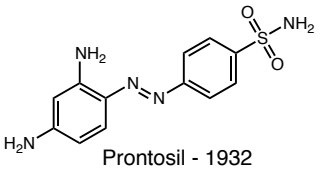
Trimethoprim - 1940s



Walsh, C. T. *Nature Reviews Microbiology* **2003**, *1*, 65-70

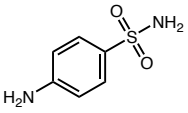
Walsh, C. T. *Antibiotics: Actions, Origins, Resistance*, American Society for Microbiology Press, Washington DC, 2003

Antibacterials Inhibiting Bacterial Folate Biosynthesis



Prontosil - 1932

in vivo metabolism



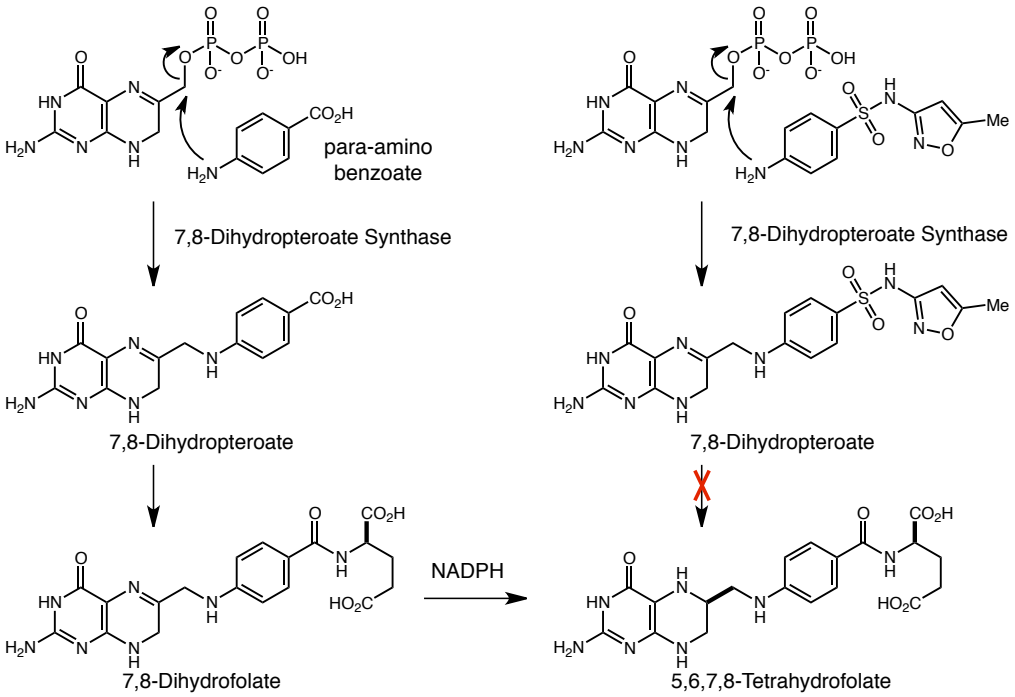
Sulfanilamide - 1936

- Prontosil was the first sulfa drug, discovered by Gerhard Domagk while working for Bayer AG.
- Bayer AG hoped to use its expertise in dyes to develop a Ehrlich-style "magic bullet" dye that could be selective for pathogenic bacteria, found Prontosil.
- Immensely successful as the first broad-spectrum antibiotic.
- Bayer AG's revenue stream was undercut when a team of French scientists found that Prontosil is a prodrug, and becomes sulfanilamide in the body, the patent for which had long ago expired.
- Massive product and marketing of sulfanilamide followed; One preparation, called Elixir Sulfanilamide, was a solution in ethylene glycol. This raspberry-flavored concoction caused over 100 deaths in 1937.
- In 1938, the FDA passed the Federal Food, Drug and Cosmetic Act, requiring safety tests for a variety of product. This is why we do clinical trials for all new medicines today.

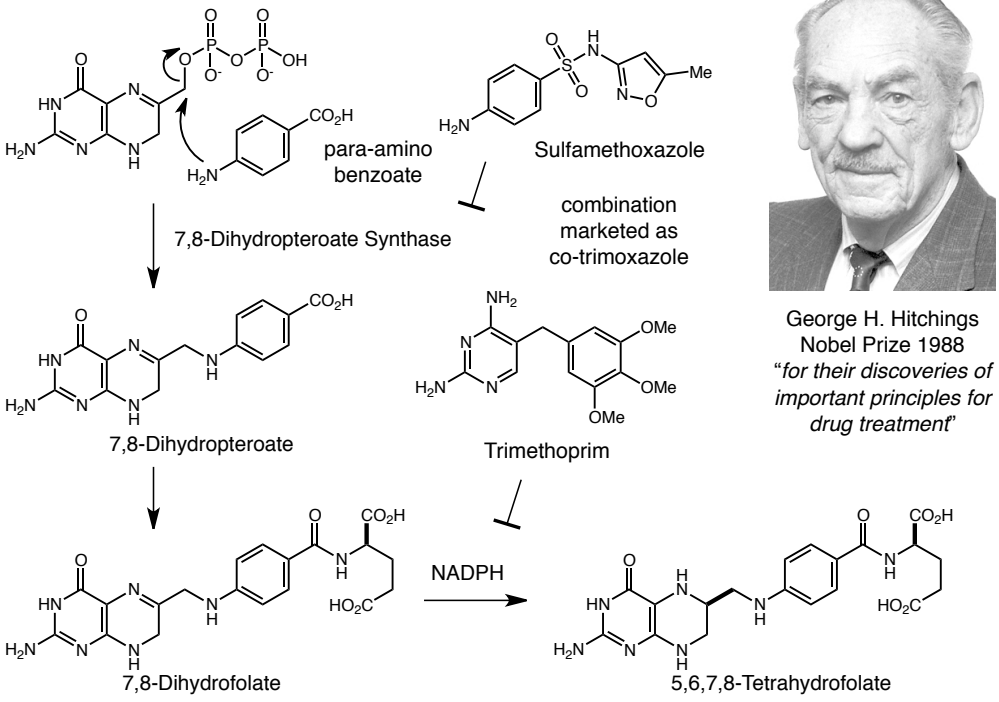
Gerhard Domagk
Nobel Prize 1939
"for the discovery of the antibacterial effects of prontosil"

http://www.nobelprize.org/nobel_prizes/medicine/laureates/1939/domagk.html#
http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm
for a history of clinical trials, see:
http://blogs.scientificamerican.com/guest-blog/2011/10/06/molecules-to-medicine-clinical-trials-for-beginners/

Sulfa Drugs - Tetrahydrofolate Biosynthesis in Bacteria

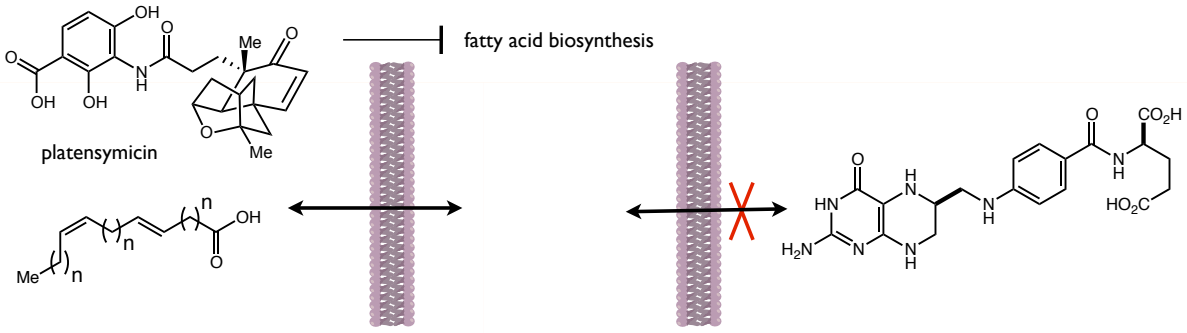


Sulfa Drugs - Tetrahydrofolate Biosynthesis in Bacteria

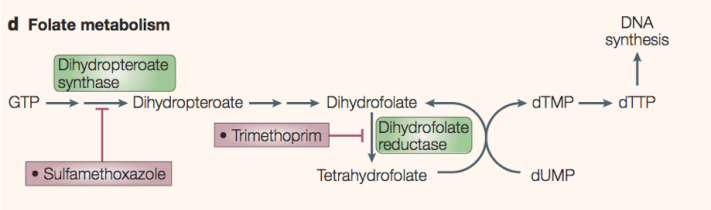


George H. Hitchings
Nobel Prize 1988
"*for their discoveries of important principles for drug treatment*"

Success and Failure with Bacterial Metabolite Biosynthesis



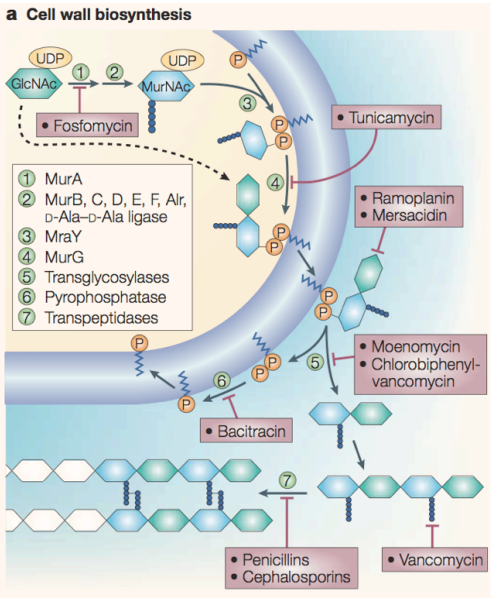
- Folate is an essential nutrient for humans, they cannot synthesize it.
- Bacteria must synthesize folate, and cannot obtain it from their environment.

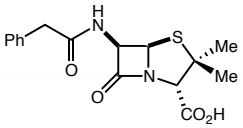


Zlitni, S. and Brown, E. D. *Nature* **2009**, *458*, 39-40

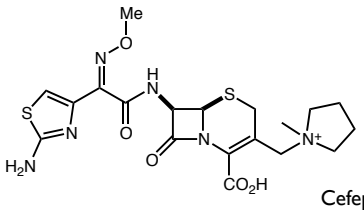
Walsh, C. T. *Antibiotics: Actions, Origins, Resistance*, American Society for Microbiology Press, Washington DC, 2003

The Four Major Targets of Antibiotics

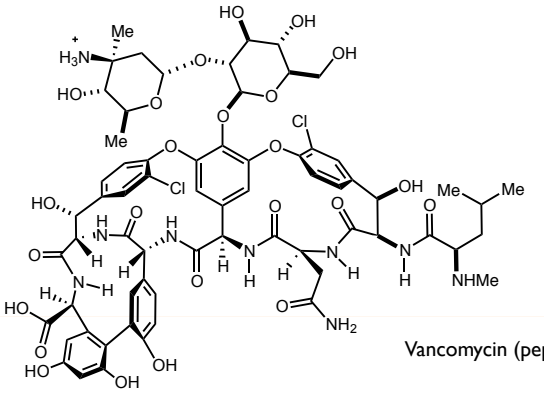




Penicillin G

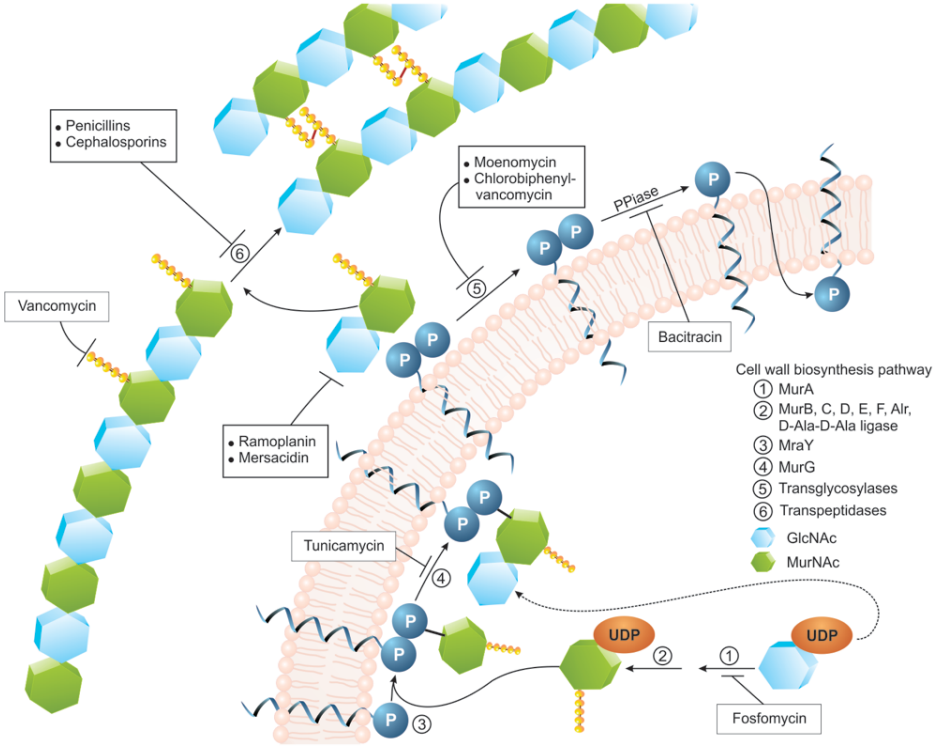


Cefepime (cephalosporin)



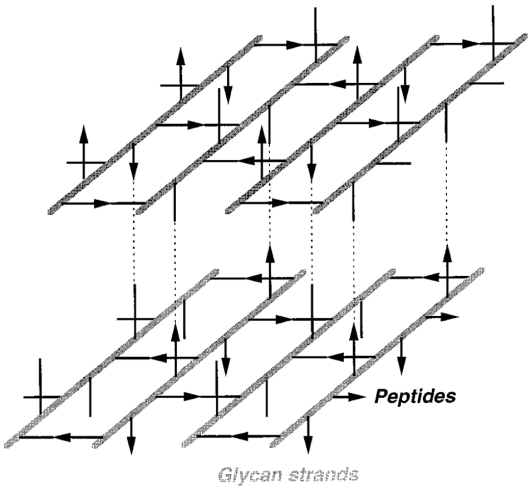
Vancomycin (peptidoglycan)

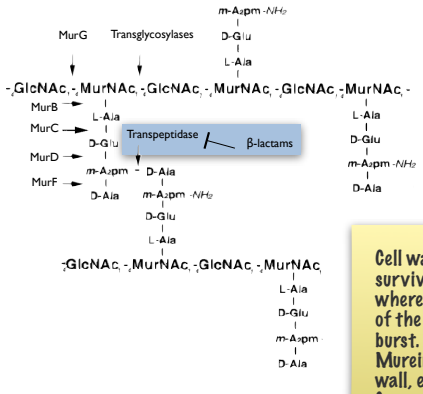
Antibacterials that Target Cell-Wall Biosynthesis



Images from: http://fernness.com/science-01.html

Antibacterials that Target Cell-Wall Biosynthesis



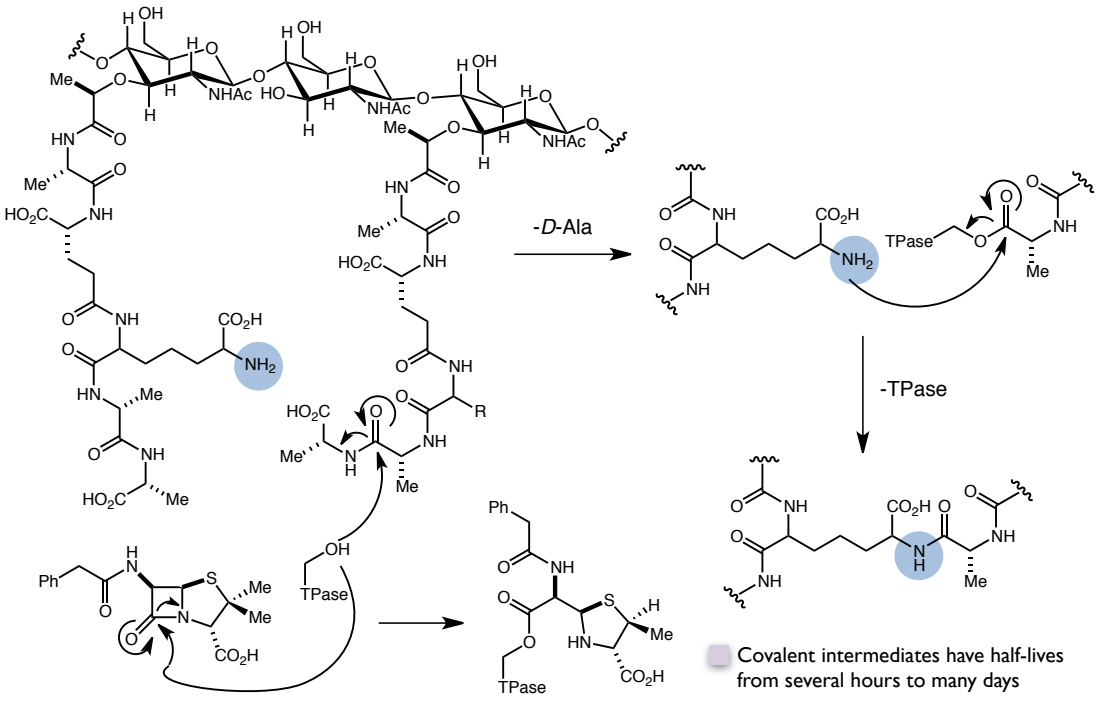


Cell wall allows cells to survive in hypotonic media, where otherwise swelling of the cell would cause it to burst.
Murein , greek word for wall, enzyme called MurA-G

- The cell wall is called murein, from the greek word for wall, and the enzymes involved in its construction are hence named MurA, MurB, etc.

Images from: Höltje, J.-V. *Microbiol. Mol. Biol. Rev.* **1998**, *62*, 181-203

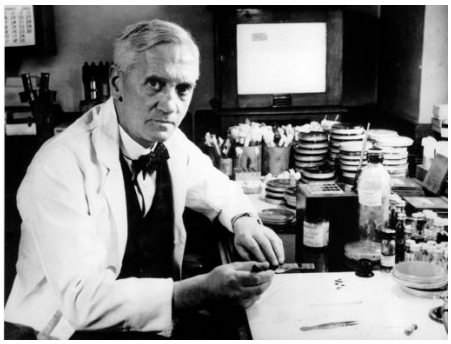
β-Lactams: Penicillins, Cephalosporins and Carbapenems



- Covalent intermediates have half-lives from several hours to many days

Walsh, C. T. *Antibiotics: Actions, Origins, Resistance*, American Society for Microbiology Press, Washington DC, 2003, p. 39

Discovery of Penicillin: Nobel Prize1945



Sir Alexander Fleming

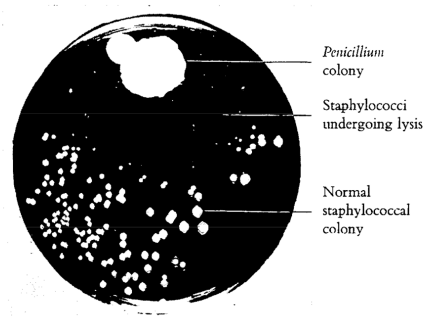
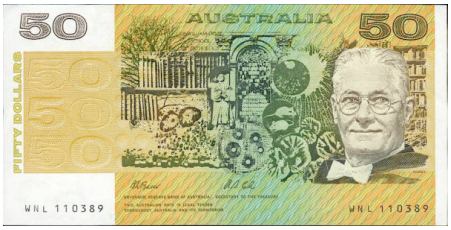


Fig. 1. Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a *Penicillium* colony.



Sir Howard Florey

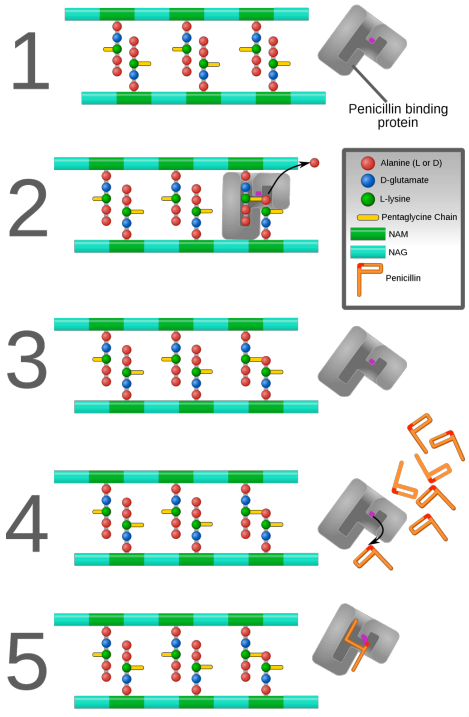
Dr. Ernst B. Chain

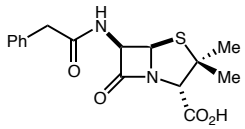
"for the discovery of penicillin and its curative effect in various infectious diseases"

assisted by Sir. Robert Robinson

http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/

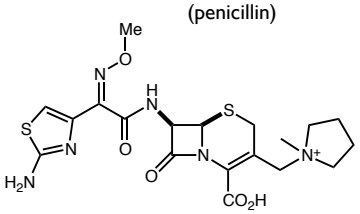
β-Lactams: Penicillins, Cephalosporins and Carbapenems





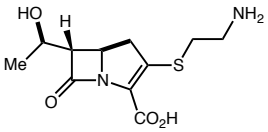
Penicillin G
(penicillin)

thiazolidine



Cefepime
(cephalosporin)

dihyrothiazine



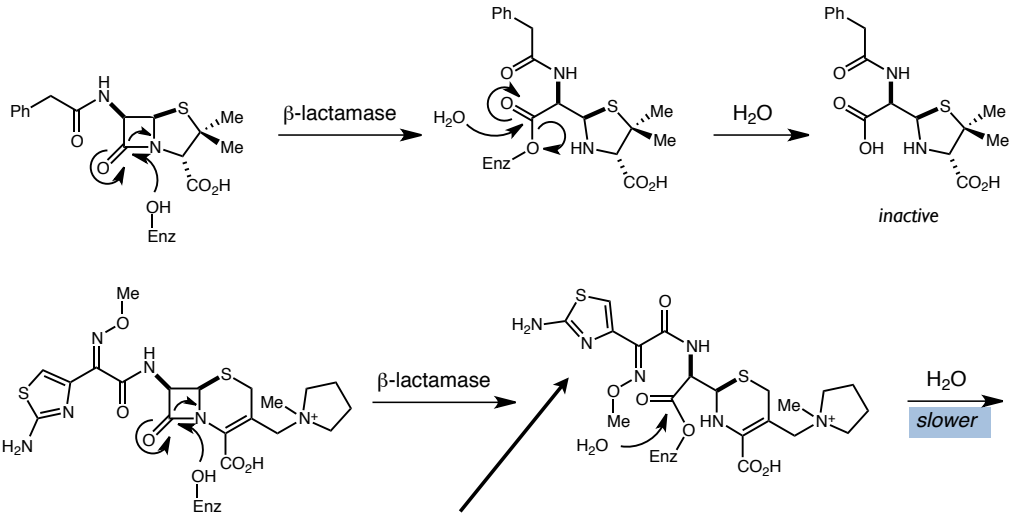
Thienamycin
(carbapenem)

dihydropyrrole

Structural modifications allow decreases susceptibility to β-lactamases.

β-Lactams: Resistance Mechanisms - β-Lactamases

- Costs of over $30 billion per year due to β-lactamase-mediated resistance

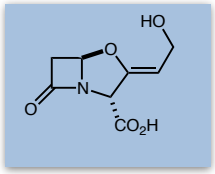


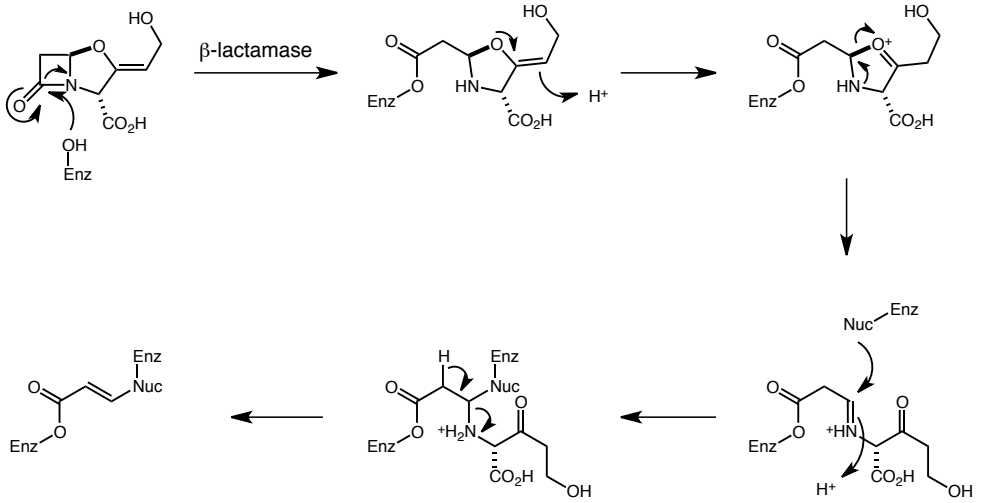
larger side chain slows hydrolysis by occluding water from the active site

Statistics from: Palumbi, S. R. *Science* **2001**, *293*, 1786-1790

β-Lactams: Resistance Mechanisms - β-Lactamase Inhibitors

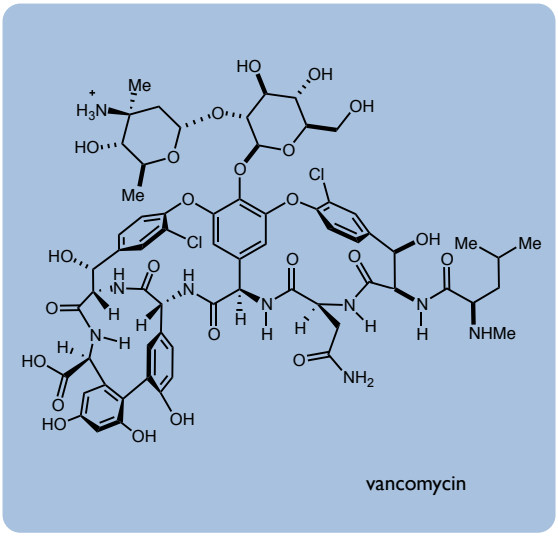
- Clavulanic acid (right) shows minimal activity against transpeptidases (penicillin-binding proteins) but is highly active against β-lactamases.
- A combination of Clavulanate and Amoxicillin is marketed by GlaxoSmithKline as Augmentin (and by Pfizer as Clavamox)

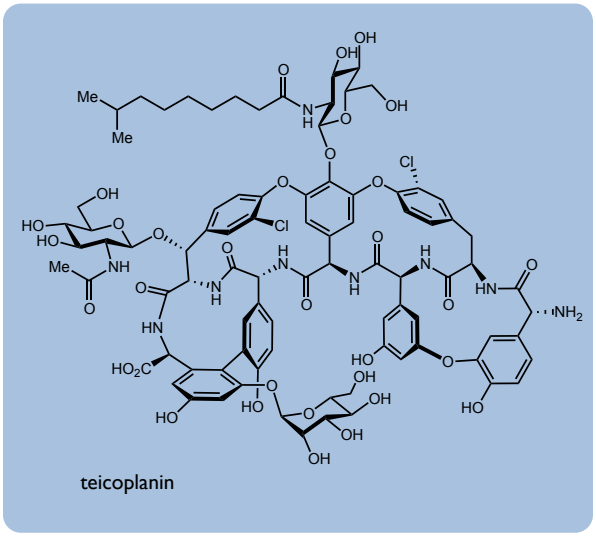




Statistics from: Palumbi, S. R. *Science* **2001**, *293*, 1786-1790

Aminoglycosides: Vancomycin and Teicoplanin





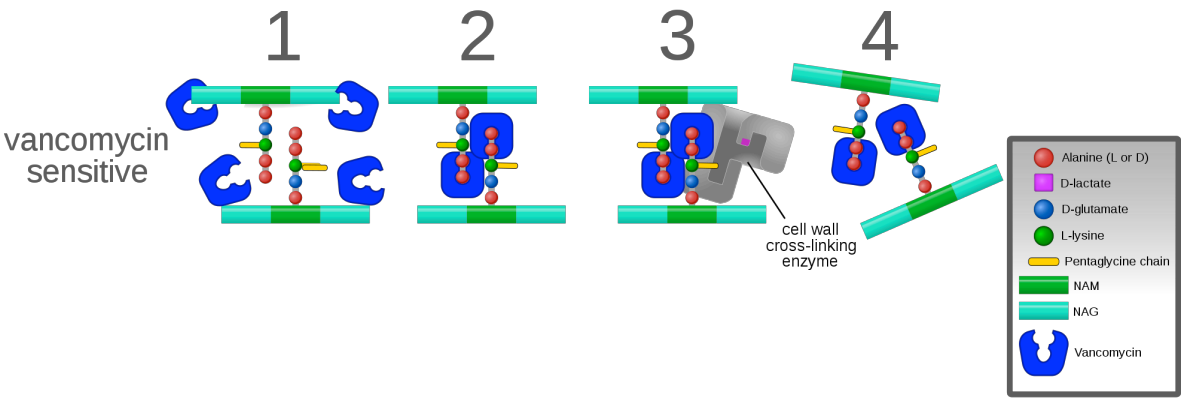
"The antibiotic of last resort"

Discovered in soil sample from Borneo, isolated by Eli Lilly chemist Edmund Kornfeld
>30 years before resistance observed (1953 to 1987)

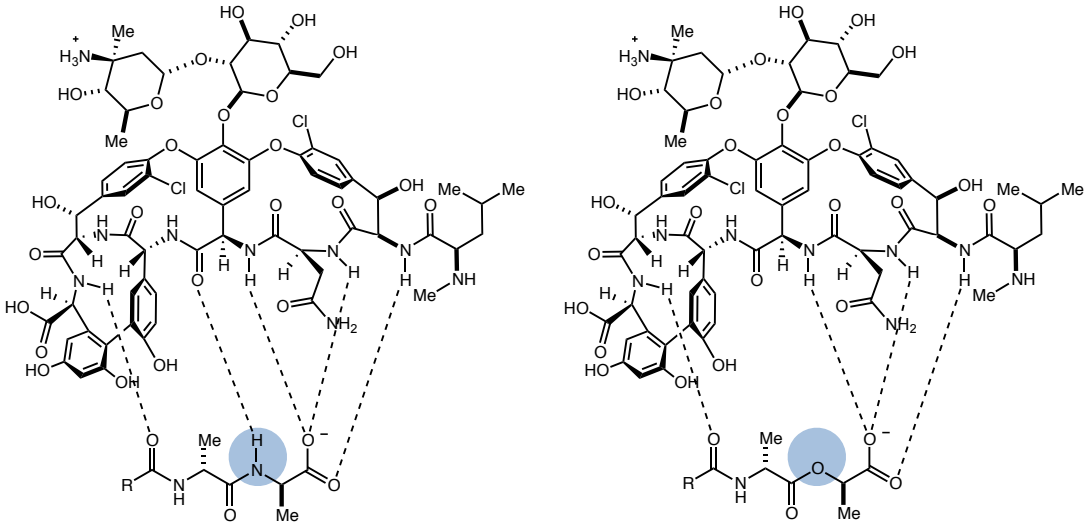
Marketed by Sanofi-Adventis
Approved in 2009

Chen, L.; Walker, D.; Sun, B.; Hu, Yanan; Walker, S.; Kahne, D. *Proc. Nat. Acad. Sci.* **2003**, *100*, 5658-5863

Aminoglycosides: Vancomycin and Teicoplanin

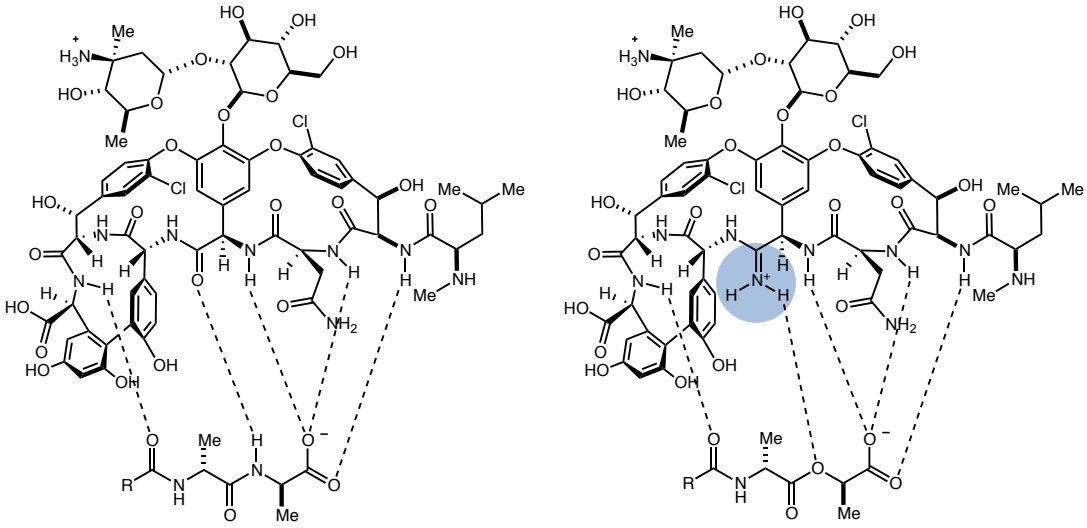


Aminoglycosides: Vancomycin Resistance



- Removing this single hydrogen-bond interaction reduces vancomycin affinity for the terminal dipeptide by 1,000-fold. Replacing the terminal D-Ala with D-Ser reduces affinity by 6-fold

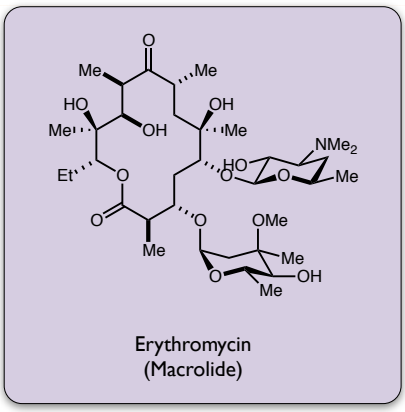
Aminoglycosides: Vancomycin Resistance



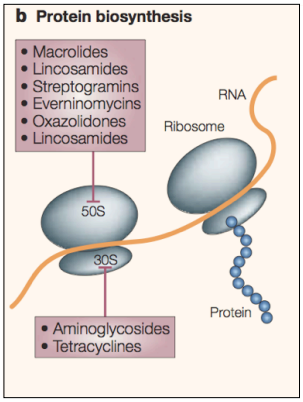
- Removing this single hydrogen-bond interaction reduces vancomycin affinity for the terminal dipeptide by 1,000-fold. Replacing the terminal D-Ala with D-Ser reduces affinity by 6-fold
- Boger, 2011 showed that activity can be returned by replacing the amide with an amidine

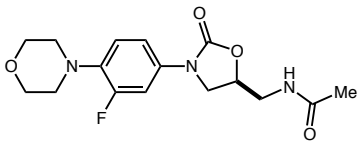
Xie, J.; Pierce, J. G.; James, R. C.; Okano, A.; Boger, D. L. *J. Am. Chem. Soc.* **2011**, *133*, 13946-13947

The Four Major Targets of Antibiotics

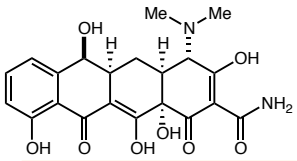


Erythromycin
(Macrolide)



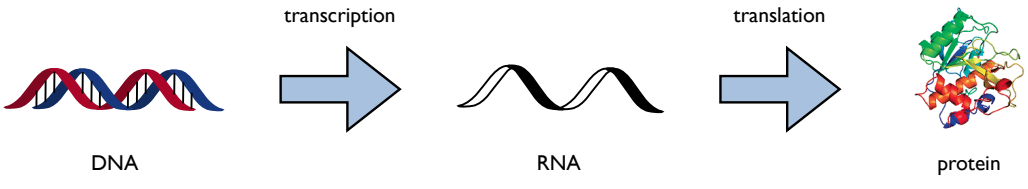


Linezolid
(Oxazolidinone)



Tetracycline

Antibiotics Blocking Bacterial Protein Biosynthesis



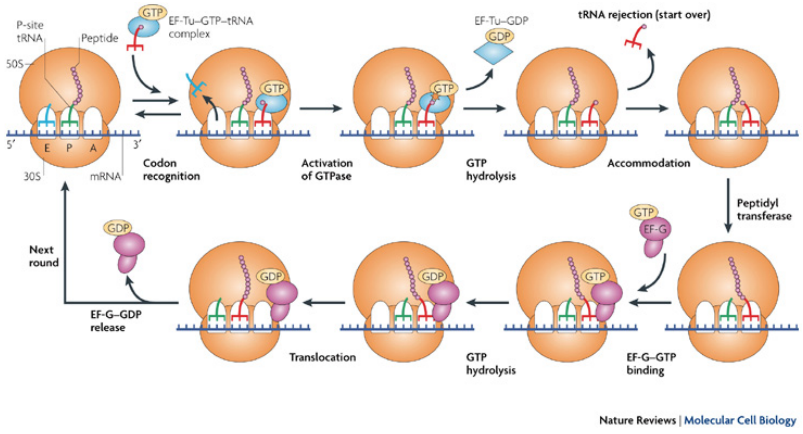
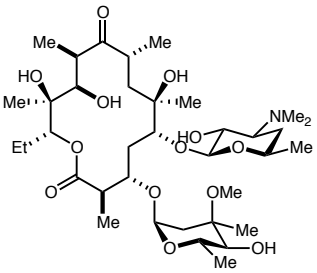
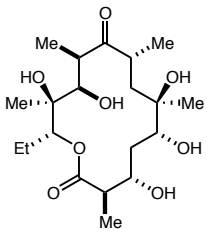


Figure from: Steitz, T. A. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 242-253

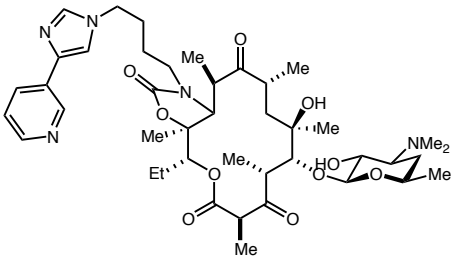
Antibiotics Blocking Protein Biosynthesis: Erythromycin



Erythromycin



Erythronolide
(Erythromycin aglycone)

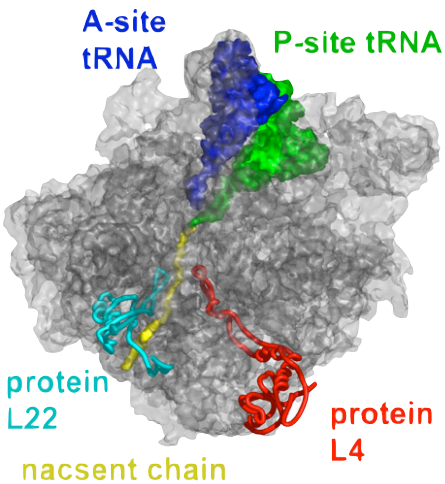


Telithromycin

- First isolated by Eli Lilly Scientist J. M. McGuire from soil samples collected by A. Aguilar which contained *Saccharopolyspora erythraea,* a species of actinomycete (major group of antibacterial-producing bacteria)
- Acid-instability hampered widespread application of early derivatives; Mono-deglycosylation, C-6 methylation and carbamate introduction aided in newer generations.

First total synthesis: Woodward, R. B. *et. al. J. Am. Chem. Soc.*, **1981**, 103, 3210–3213

Erythromycin Binds to the Ribosome Exit Tunnel



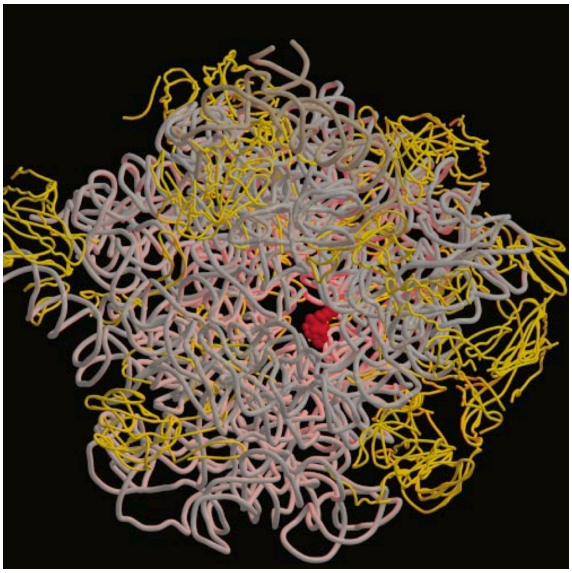


Image from: http://www.weizmann.ac.il/sb/faculty_pages/Yonath/10A-1.jpg

Figure from: Schlünzen, F. *et. al. Nature* **2001**, *413*, 814-821

Antibiotics Blocking Protein Biosynthesis: Erythromycin

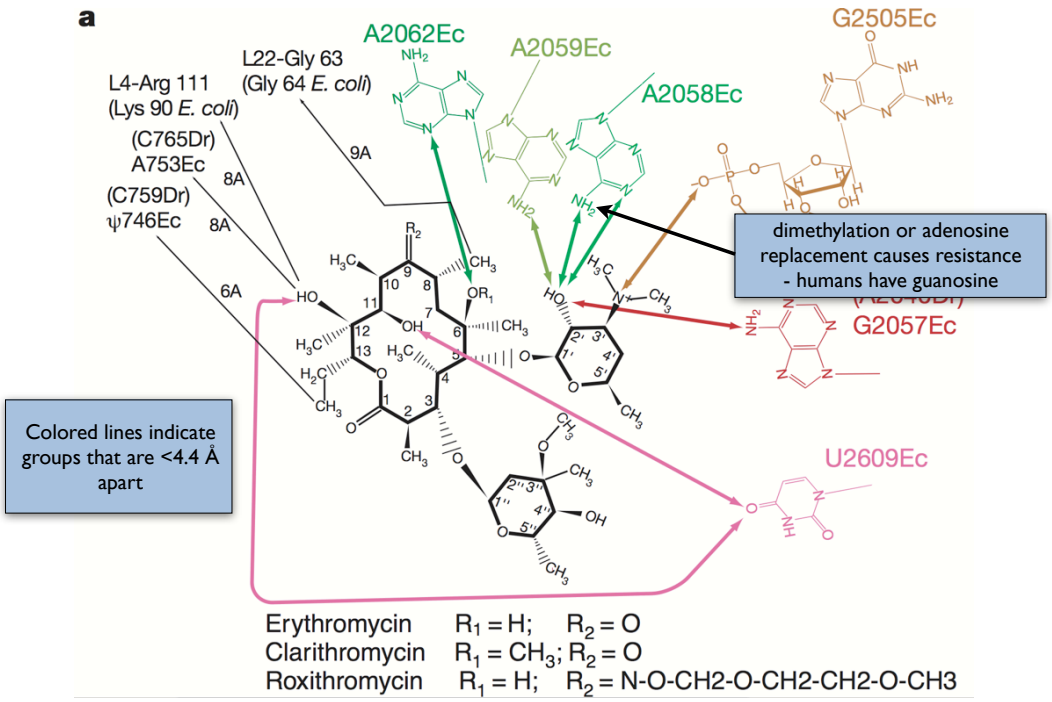
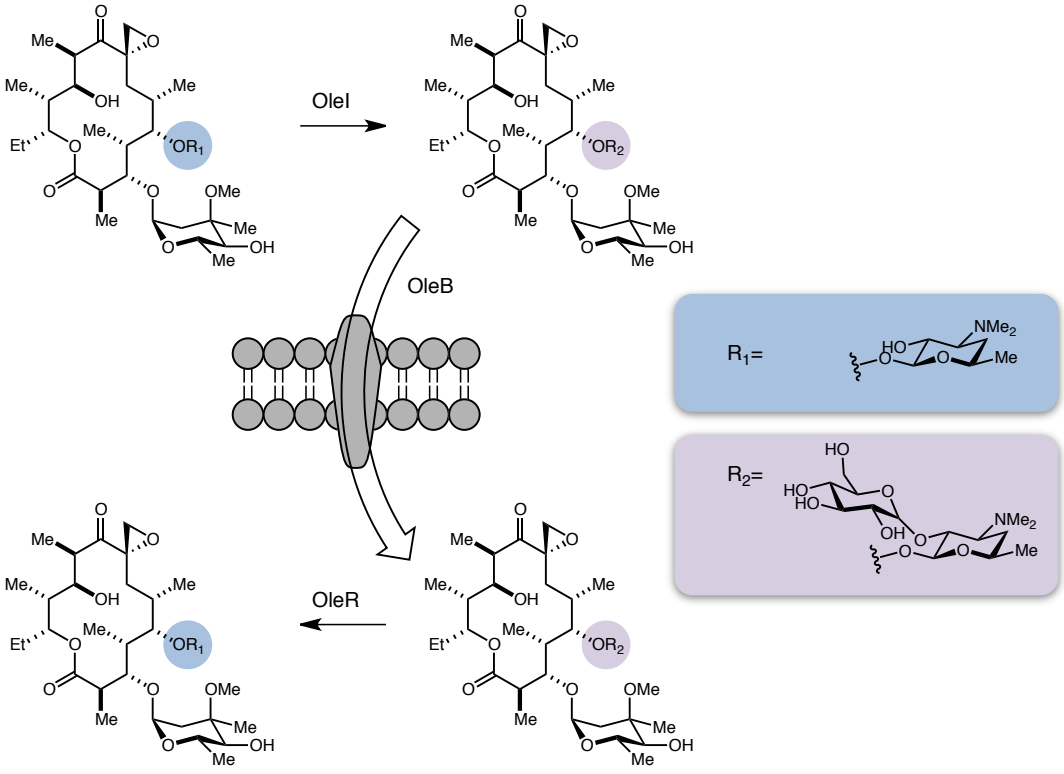


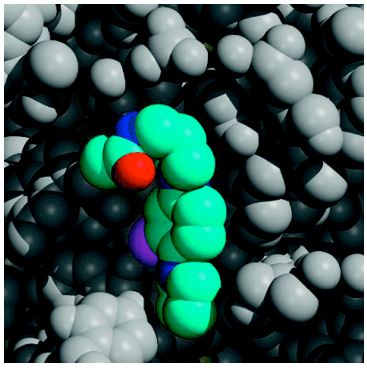
Figure from: Schlünzen, F. *et. al. Nature* **2001**, *413*, 814-821

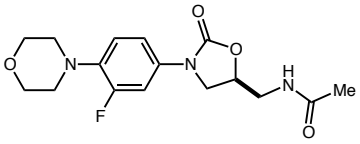
Erythromycin Resistance in Bacteria



Adapted from: Quiros, L. M. *et. al. Mol. Microbiol.* **1998**, *28*, 1177-1185

Antibiotics Blocking Protein Biosynthesis: Linezolid (Zyvox)

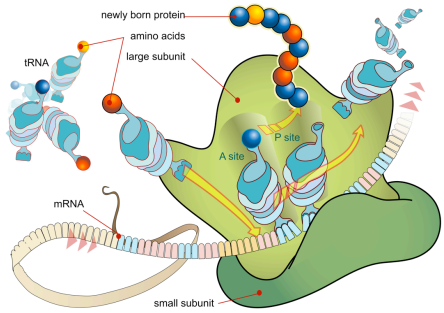




Linzeolild (Zyvox)

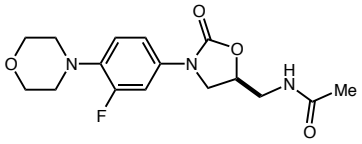
Pfizer, $223 million in 2010

- Antibacterial effects of oxazolidinone originally discovered by DuPont, abandoned due to toxicity issues. Pharmacia/Upjohn later salvaged the product and (after being incorporated by Pfizer) released Zyvox in 2000.
- To date, Zyvox is the only oxazolidinone clinically approved, but many others are currently in clinical trials
- Represents the first widely-used novel antibiotic structural class since the 1960s (fluoroquinolones)
- Differences in binding site between other protein biosynthesis inhibitors prevents cross-resistance

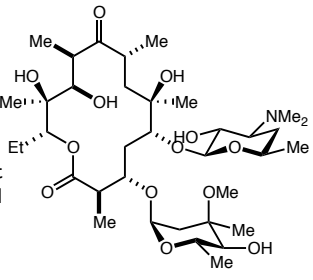


Structure from: Ippolito, J. A. *et. al. J. Med. Chem.* **2008**, *50*, 3353-3356

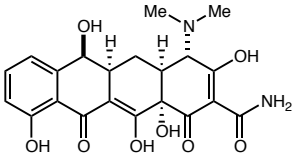
Antibiotics Blocking Protein Biosynthesis: Tetracycline



Macrolides and oxazolidinones interact with the 50S ribosomal subunit



Tetracyclines interact with the 30S ribosomal subunit



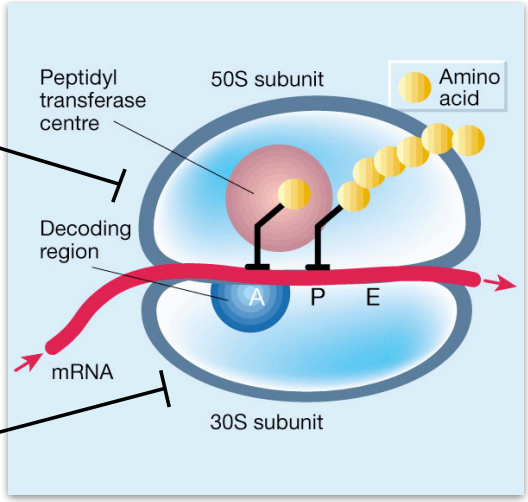
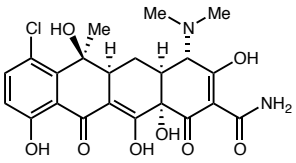
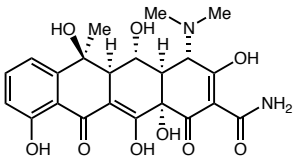


Figure from: Williamson, J. R. *Nature* **2000**, *407*, 306-307

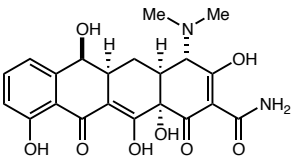
Antibiotics Blocking Protein Biosynthesis: Tetracycline



chlorotetracycline
(aureomycin)

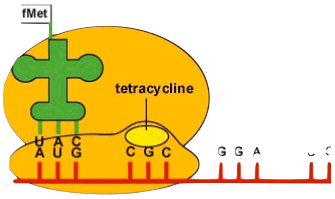


oxytetracycline
(terramycin)



tetracycline
(acromycin)

- Chlorotetracycline (aureomycin) was the first tetracycline antibiotic, discovered in a soil sample in 1948 (again biosynthesized by actinomycetes)
- Oxyotetracycline (terramycin) was subsequently discovered in 1949 by a nascent Pfizer, and was the subject of the first mass-marketing drug campaign. This drug put Pfizer on the map.
- R. B. Woodward and Pfizer collaborated to solve the structure of terramycin, mostly succeeding (mis-assigned one stereocenter)
- Hydrogenation of aureomycin gave the deschloro product, which maintained activity, and was one of the first semi-synthetic antibiotics.

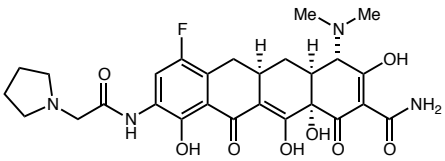


Baran group meeting on Tetracyclines (http://www.scripps.edu/chem/baran/html/meetingschedule.html)
Chopra, I.; Roberts, M. *Microbiol. Mol. Biol. Rev.* **2001**, *65*, 232-260

Novel Tetracyclines from Tetraphase

Andrew G. Myers
Profssor of Chemistry
Harvard University

TETRAPHASE PHARMACEUTICALS



TP-434

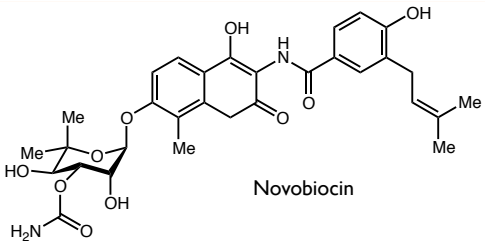
- Fully synthetic tetracyclines overcome bacterial resistance problems in ways that semisynthetics are unable to.
- Business plan includes developing new broad spectrum antibiotics as well as narrow-spectrum inhibitors.

Tetraphase Pipeline

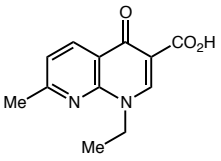
Program	Target Indications	Preclinical	IND Enabling Studies	Phase I	Phase II
TP-434 Broad Spectrum IV	cIAI ABSSSI HAP/VAP				
TP-434 Broad Spectrum Oral Stepdown	cIAI ABSSSI HAP/VAP				
TP-2758 MDR Gram-negative IV/Oral	cUTI				
TP-834 IV/Oral Monotherapy	CABP (including MRSA and atypicals)				
Other Assets					

http://tphase.com/

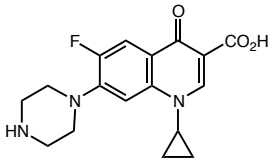
Antibiotics Interfering with DNA Replication and Transcription



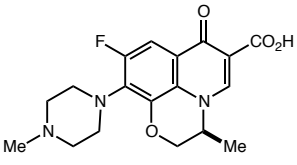
Novobiocin



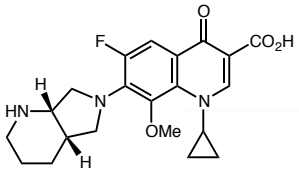
Nalidixic acid



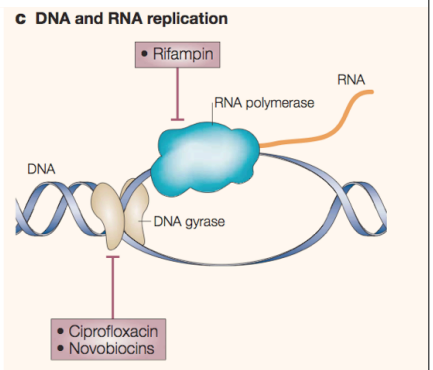
Ciprofloxacin



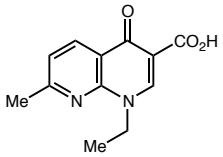
Levofloxacin



Moxifloxacin

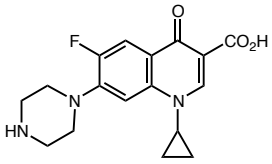


Fluoroquinolones Affecting DNA Replication and Transcription



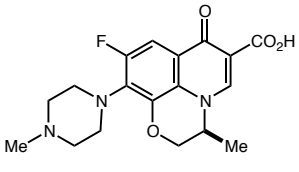
Nalidixic acid

- Nalidixic acid was the first synthetic quinolone antibiotic, formed as a byproduct during chloroquine (anti-malarial) manufacture in the early 1960s.

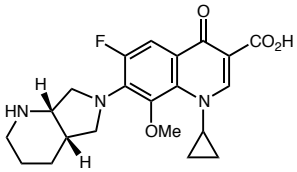


Ciprofloxacin

- Ciprofloxacin, or Cipro, is a second-generation fluoroquinolone, patented in 1983 by Bayer A. G. and receiving FDA approval in 1987. Fluorine substitution at the 6-position (common by this point) provides activity against both gram-negative as well as gram-positive bacteria. Sales were $242 million in 2008.



Levofloxacin

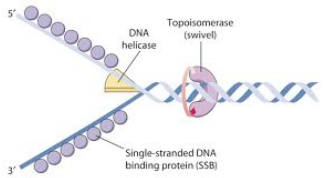


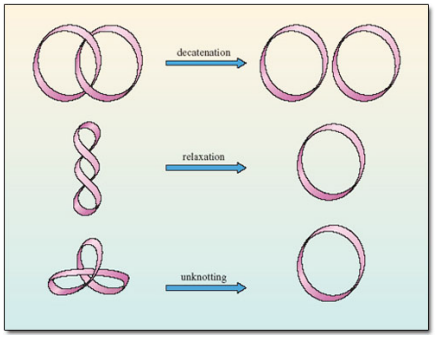
Moxifloxacin

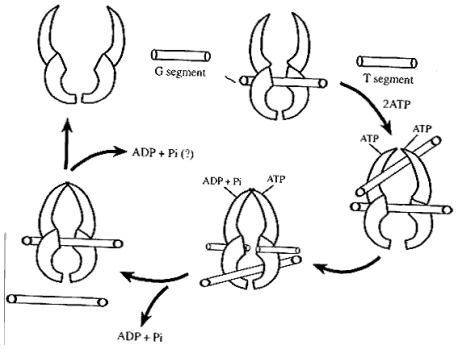
- Levofloxacin (Levaquin or Tavanic) and Moxifloxacin (Avelox or Avelon) are fourth-generation fluoroquinolones, generating $1,355 and $353 million in revenues in 2010, respectively.

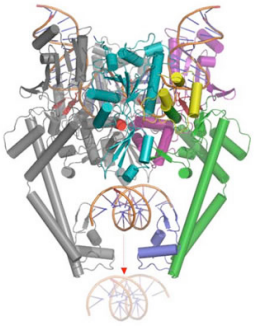
Emmerson, A. M.; Jones, A. M. *J. Antimicrob. Chemother.* **2003**, *51*, *Suppl. S1*, 13-20

DNA Replication and Repair Causes Supercoiling







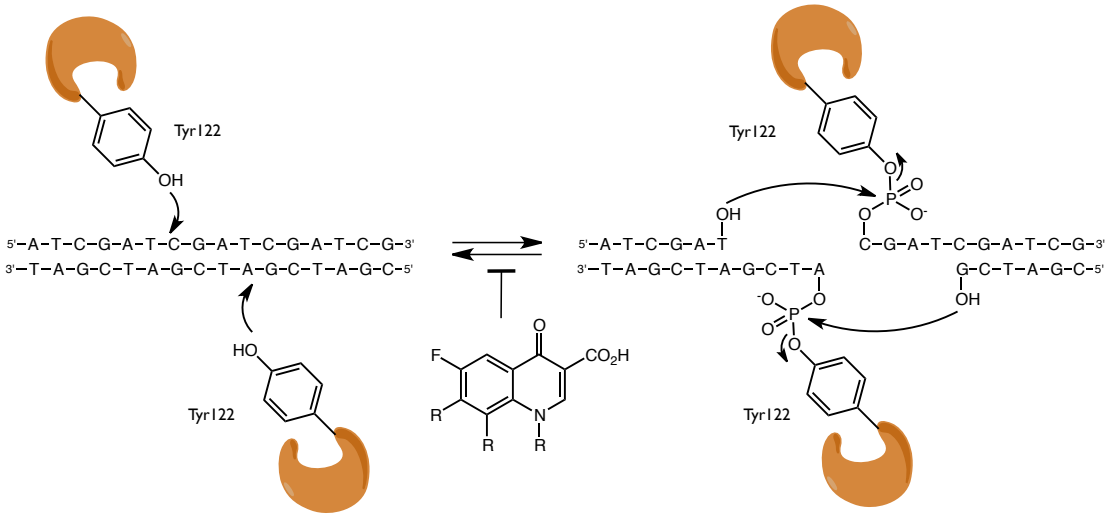


www.benthamscience.com/cmcaca/sample/cmcaca1-1/holden/f3-p7holden.gif

open.jorum.ac.uk/xmlui/bitstream/handle/123456789/956/Items/S377_1_013i.jpg

Quinolones Stabilize the DNA-Gyrase Covalent Intermediate

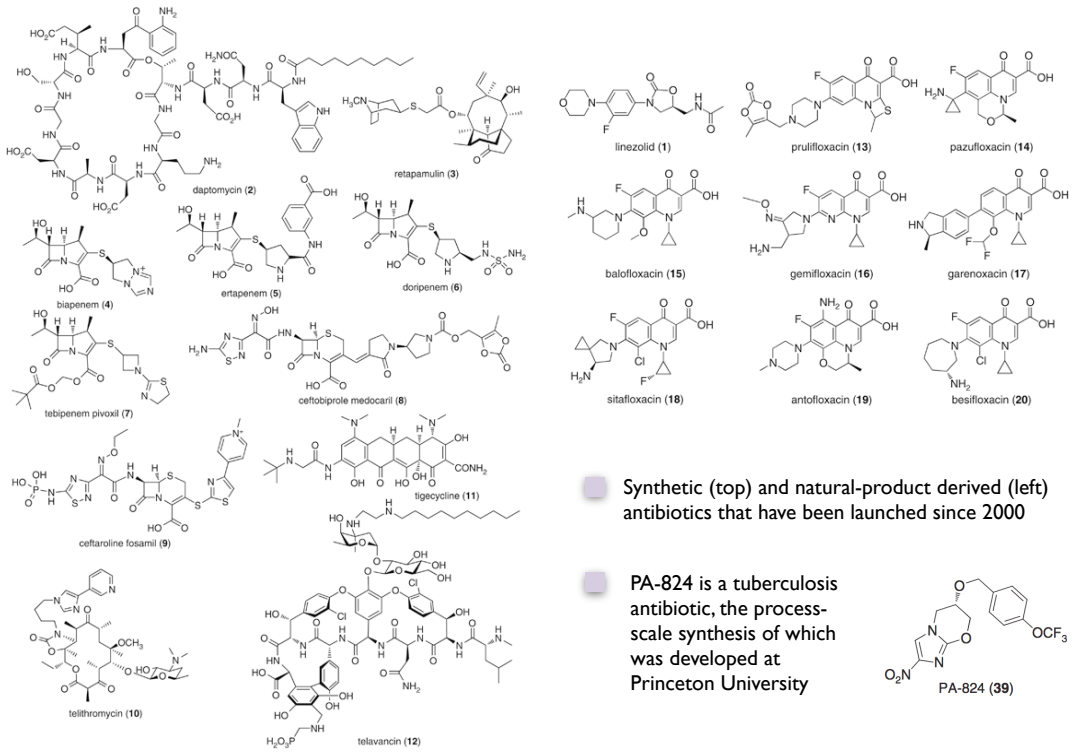
- Quinolones (and coumarins) cause accumulation of the doubly-cut covalent DNA-gyrase intermediate. The nature of the binding is uncertain (resistance hotspots on *gyrA* and *parC* subunits, may bind altered conformation of DNA)



Pan, X.-S.; Fisher, L. M. *J. Antimicrob. Agents Chemother.* **1997**, *41* (2), 471-474

Walsh, C. T. *Antibiotics: Actions, Origins, Resistance*, American Society for Microbiology Press, Washington DC, 2003 pp. 71-77

Future Directions of Antibiotics Research - Molecules

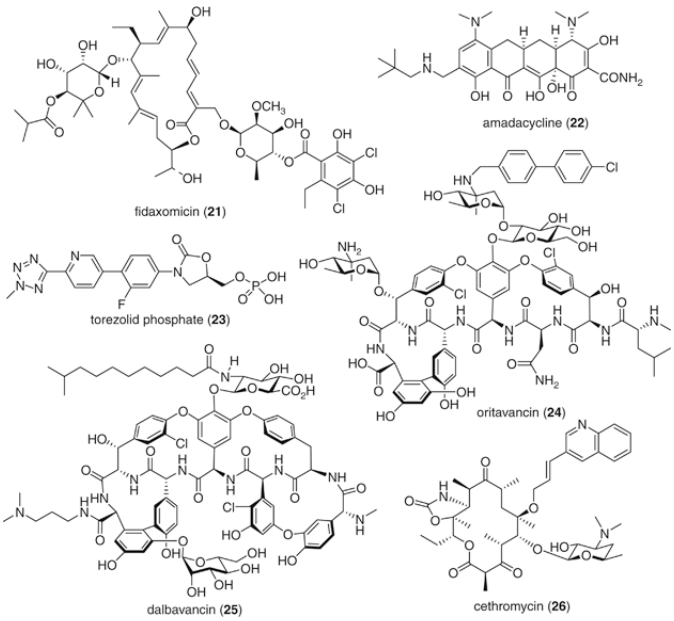


- Synthetic (top) and natural-product derived (left) antibiotics that have been launched since 2000
- PA-824 is a tuberculosis antibiotic, the process-scale synthesis of which was developed at Princeton University

Marsini, M. A.; Reider, P. J.; Sorensen, E. J. ***J. Org. Chem.*** **2010**, *75*, 7479-7482; Butler, M. S.; Cooper, M. A. *The Journal of Antibiotics* **2011**, *64*, 413-425

Future Directions of Antibiotics Research - Molecules

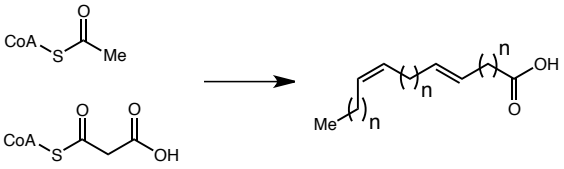
- Molecules currently in phase III clinical trials



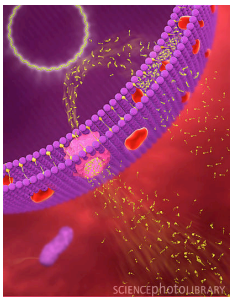
Butler, M. S.; Cooper, M. A. *The Journal of Antibiotics* **2011**, *64*, 413-425

Future Directions of Antibiotics Research - Targets

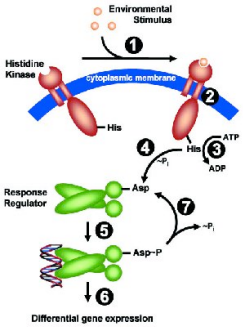
- **Fatty acid biosynthesis** - works well for antiseptics, unlikely to be applicable for antibacterials (environmental uptake).



- **Efflux blockers** - Target specific, not general.



- **Two-component signal transduction** - unique bacterial system to modify behavior based on external stimuli.



- **Quorum sensing**
- **Oxidative stress repair**

Walsh, C. T. *Antibiotics: Actions, Origins, Resistance*, American Society for Microbiology Press, Washington DC, 2003, chapter 15

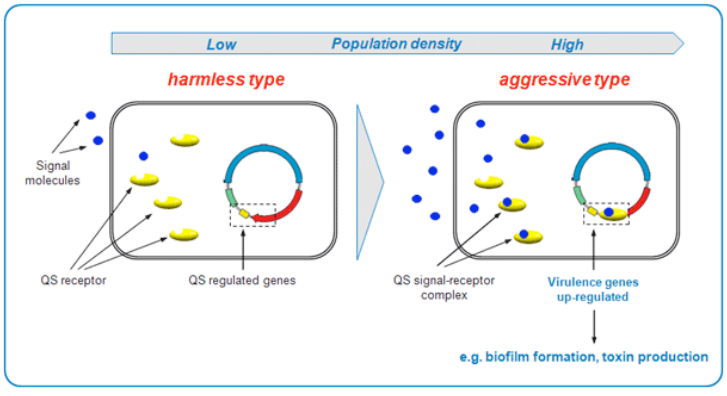
Quorum Sensing as a Novel Antibacterial Target

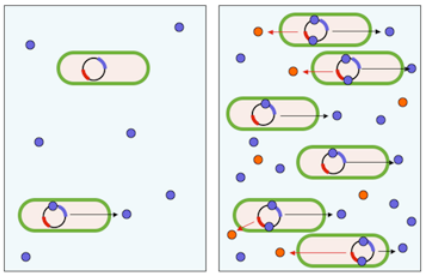
- Two strategies may be possible to use quorum sensing as an antibacterial strategy:

  Develop molecules that turn on QS-regulated genes early, allowing the immune response to eliminate the now-revealed intruder.

  Develop antagonists that prevent QS-regulated genes from being turned on, preventing virulence.

Bonnie Bassler
Princeton University
check out TED talk!

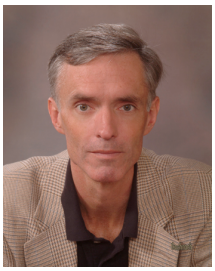




www.ted.com/talks/bonnie_bassler_on_how_bacteria_communicate.html http://upload.wikimedia.org/wikipedia/commons/c/cf/Quorum_sensing_diagram.png

http://www.advancedhealing.com/blog/wp-content/uploads/2009/12/Quorum_Sensing_Biofilm_Formation.gif

Quinolones Stabilize the DNA-Gyrase Covalent Intermediate

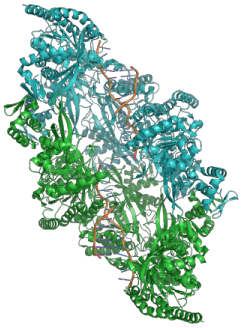


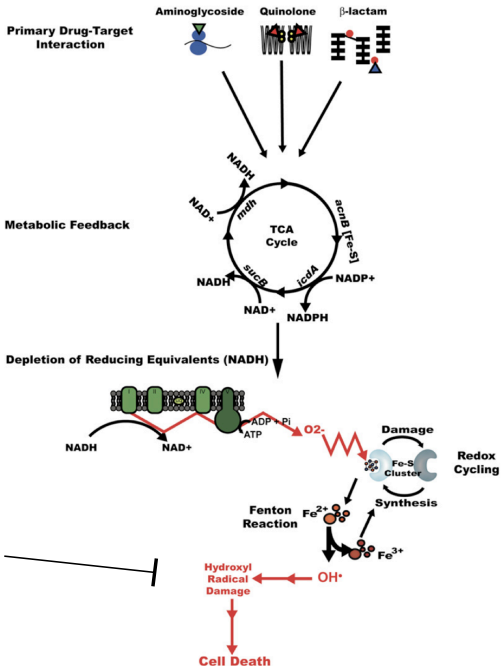
James J. Collins

Professor of biomedical engineering at Boston University

- Studies non-linear effects in systems biology
- In 2007, showed that all bactericidal antibiotics kill bacteria by a common mechanism, oxidative damage from hydroxyl radicals
- Suggests targeting *RecA* in order to potentiate current antibiotic therapies

- *RecA* - involved in DNA repair
- Inhibitors currently being developed by Scott Singleton, professor at UNC





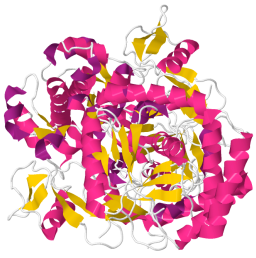
Wigle, T. J.; Singleton, S. F. *Bioorg. Med. Chem. Lett.* **17** (12): 3249–53.

Collins, J. J. *et. al. Cell.* **2007**, *130*, 797-810

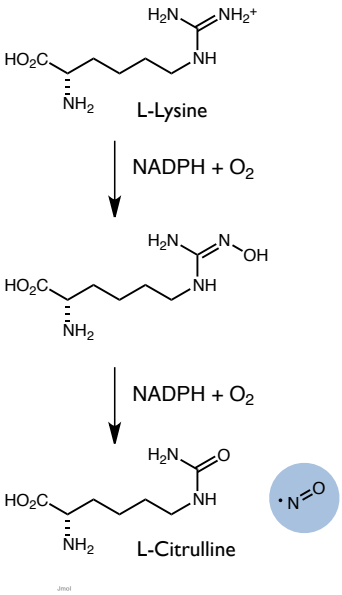
Nitric Oxide as Antibiotic Protection for Bacteria

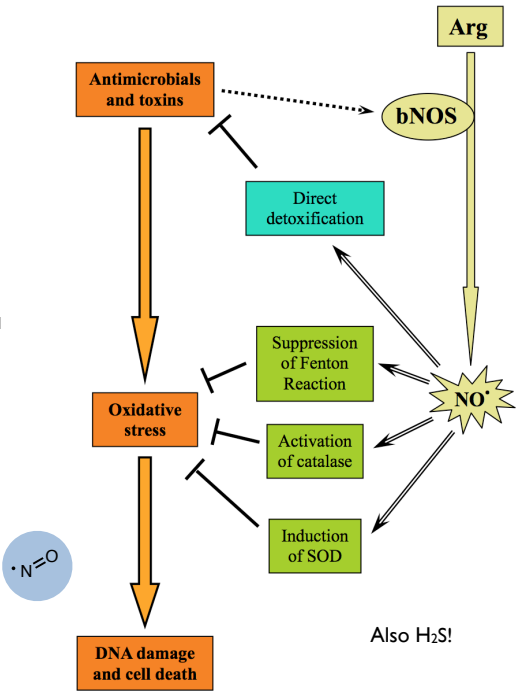
Evgeny Nudler

Professor of Biochemistry
NYU Langone Medical Center



Nitric Oxide Synthase





Nudler, E. A. *et. al. Science* **2009**, *325*, 1380-1384; Nudler, E. A. *et. al. Science* **2011**, *334*, 986-990

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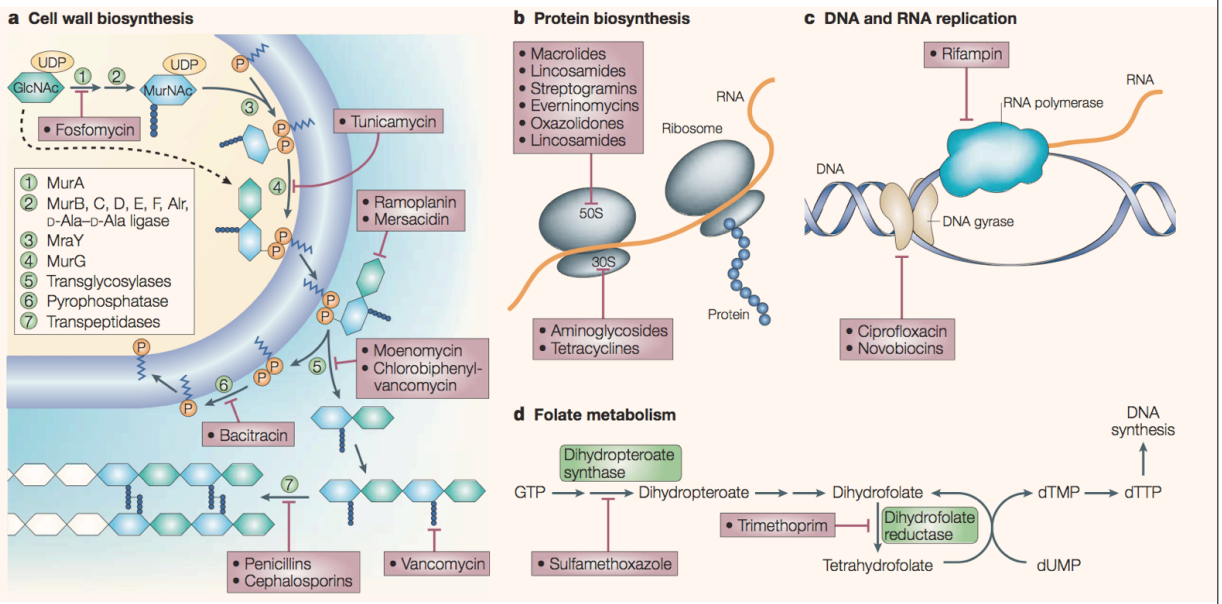
a Cell wall biosynthesis
UDP
GlcNAc
MurNAc
• Fosfomycin
• Tunicamycin
• Ramoplanin
• Mersacidin
• Moenomycin
• Chlorobiphenyl-vancomycin
• Bacitracin
• Penicillins
• Cephalosporins
• Vancomycin
1 MurA
2 MurB, C, D, E, F, Alr, D-Ala–D-Ala ligase
3 MraY
4 MurG
5 Transglycosylases
6 Pyrophosphatase
7 Transpeptidases
b Protein biosynthesis
• Macrolides
• Lincosamides
• Streptogramins
• Everninomycins
• Oxazolidones
• Lincosamides
RNA
Ribosome
50S
30S
Protein
• Aminoglycosides
• Tetracyclines
c DNA and RNA replication
• Rifampin
RNA
RNA polymerase
DNA
DNA gyrase
• Ciprofloxacin
• Novobiocins
d Folate metabolism
DNA synthesis
Dihydropteroate synthase
GTP
Dihydropteroate
Dihydrofolate
dTMP
dTTP
• Trimethoprim
Dihydrofolate reductase
• Sulfamethoxazole
Tetrahydrofolate
dUMP