

The End of Antibiotics?

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The Problem

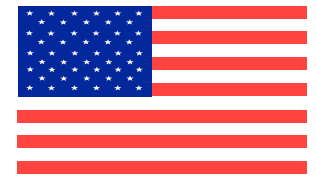


Antibiotic Resistance is a Global Clinical Disaster

More U.S. Deaths From MRSA Than AIDS

(CDC, Oct 2007 JAMA)

www.webmd.com



Superbug MRSA deaths up 1400% in a decade

Feb 2004

www.medicalnewstoday.com



Superbug infections climbing in Canadian hospitals

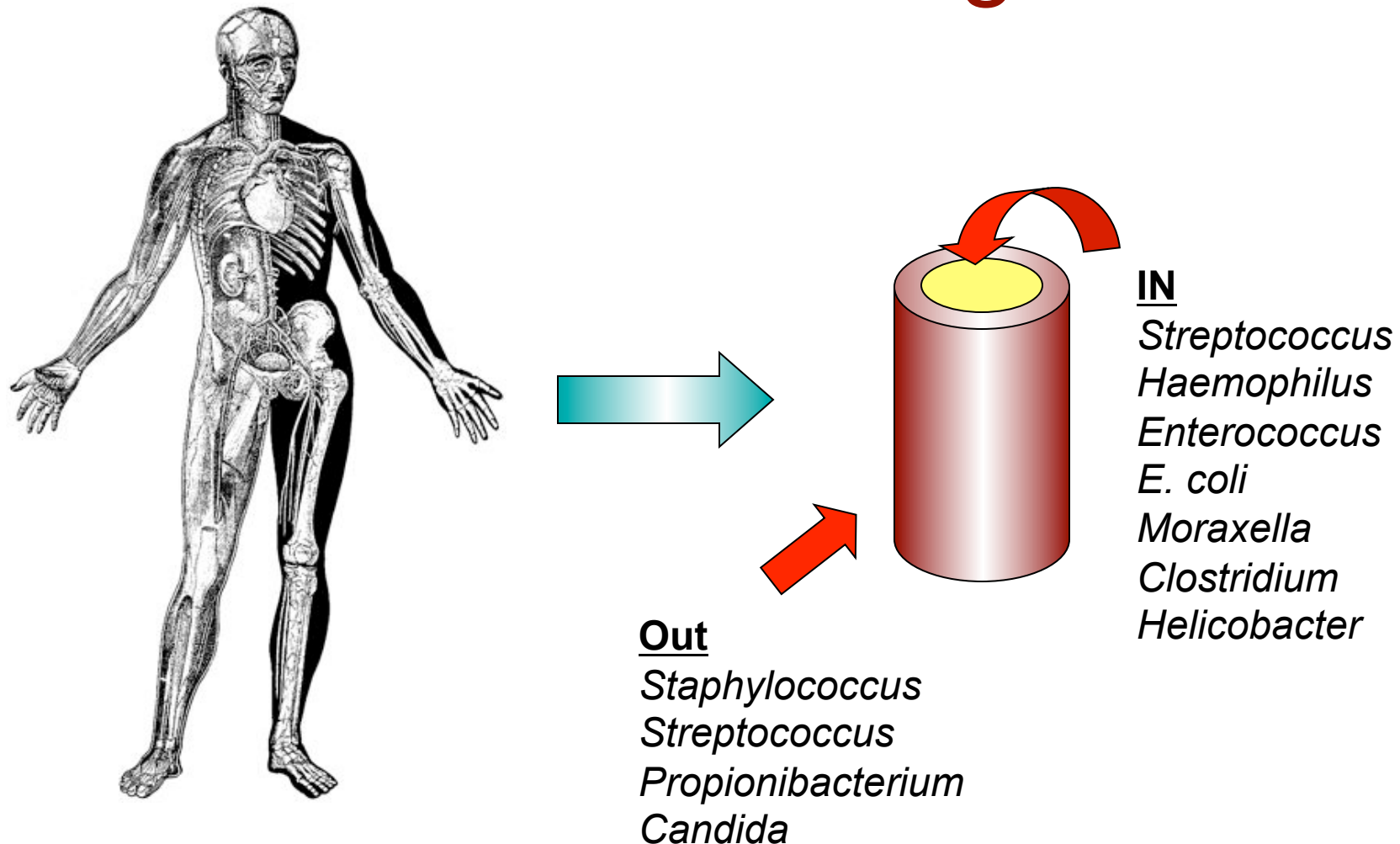
www.cbc.ca

March, 2008



Where does antibiotic
resistance come from?

Many Common Pathogens are Commensal and Drug Sensitive



Many Emerging Pathogens are Environmental and MDR

Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Acinetobacter baumannii
Burkholderia cepacia

Aeromonas hydrophila
Legionella pneumophila
Vibrio cholerae
Bacillus anthracis
Fungi





$\sim 5 \times 10^{30}$ prokaryotic cells

Many bacteria
produce
chemicals



Microbial Diversity in the Soil

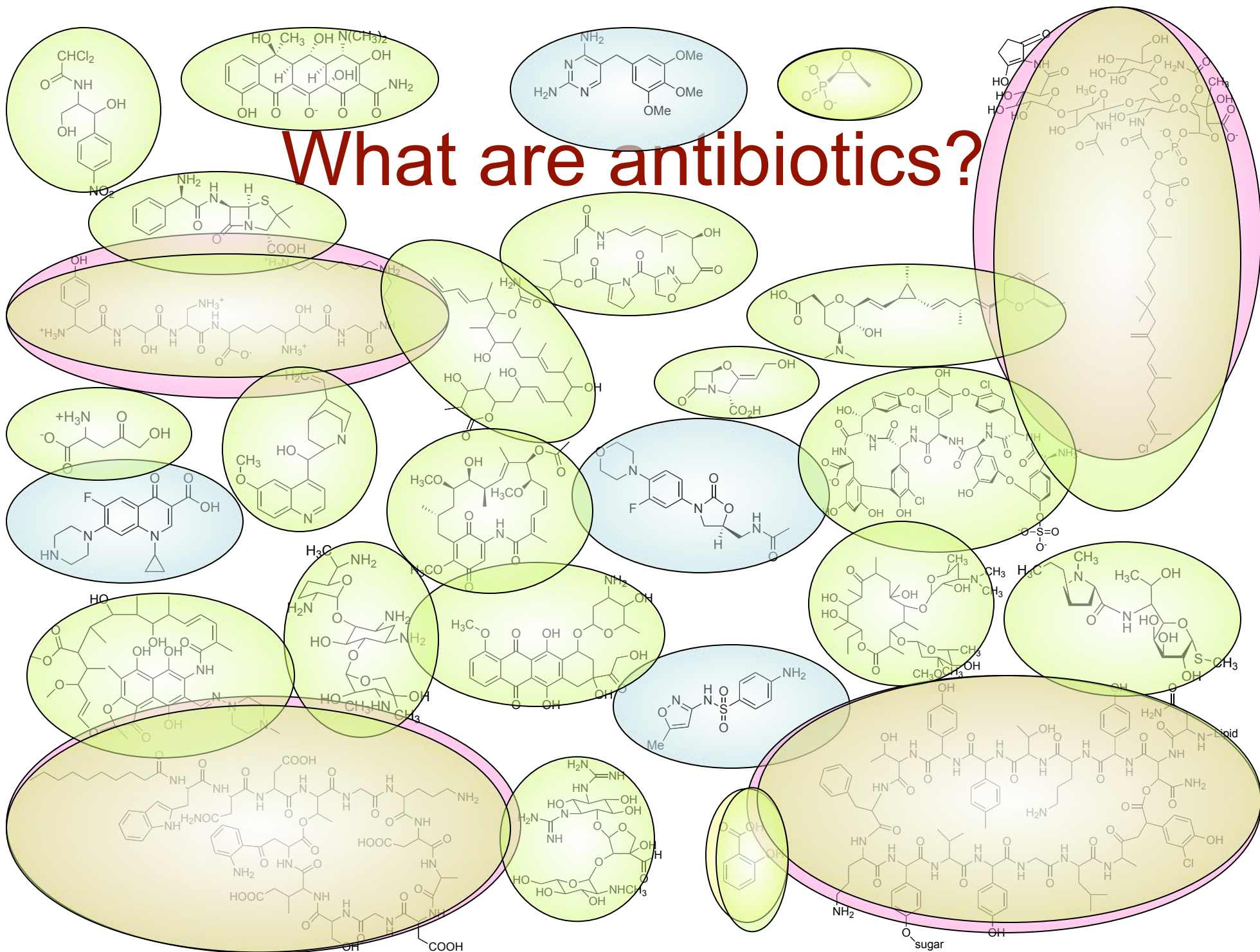
- 1 g soil holds 10^7 - 10^9 prokaryotes
- 4,000-10,000 species
(Schloss & Handelsman PLoS Comp Biol 2:e92)



An Estimate of Chemical Diversity in the Soil

- Alaskan soil sample is 5.8% Actinobacteria (Schloss & Handelsman PLoS Comp Biol 2:e92)
- 1/g of soil with 10,000 species holds 580 different species of Actinobacteria
- Genome sequences of soil Actinomycetes show potential to synthesize ~20 natural products
- 11,600 natural products/g of soil
- Many of these have antibiotic properties

What are antibiotics?



Why do organisms produce antibiotics?

- Protection
 - Rough neighborhoods
 - Selective advantage
- Communication
 - Intercellular
 - Intracellular
 - Are antibiotics really antibiotics?

Chemical Diversity in Natural Products Parallels Biological Diversity



Chemical Diversity is as Ancient as Biological Diversity



3.4 B year old stromatolite
Nature **441**:714

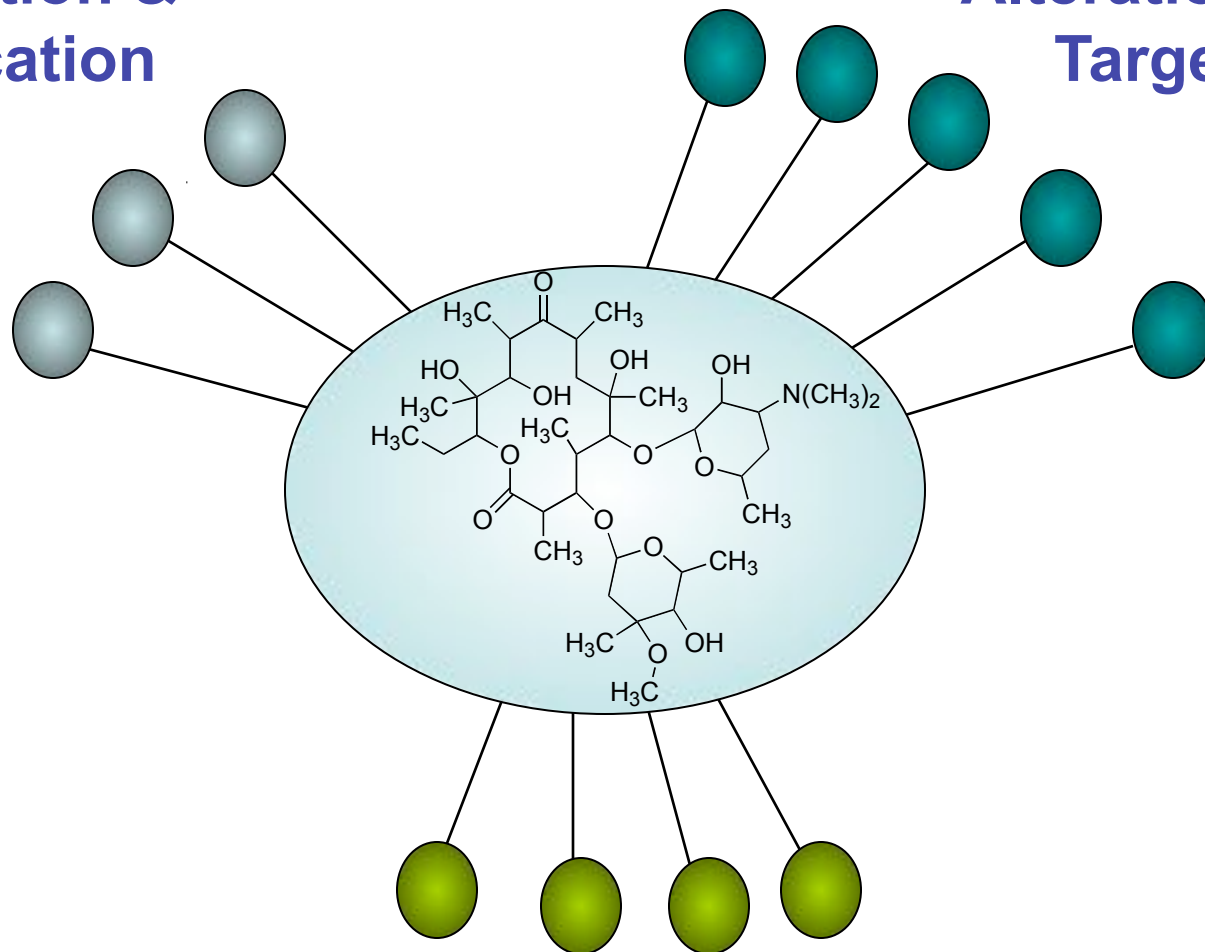


1st land plants emerge
475 M year ago
Nature **425**:282

Antibiotic Resistance: Another Level of Genetic Complexity

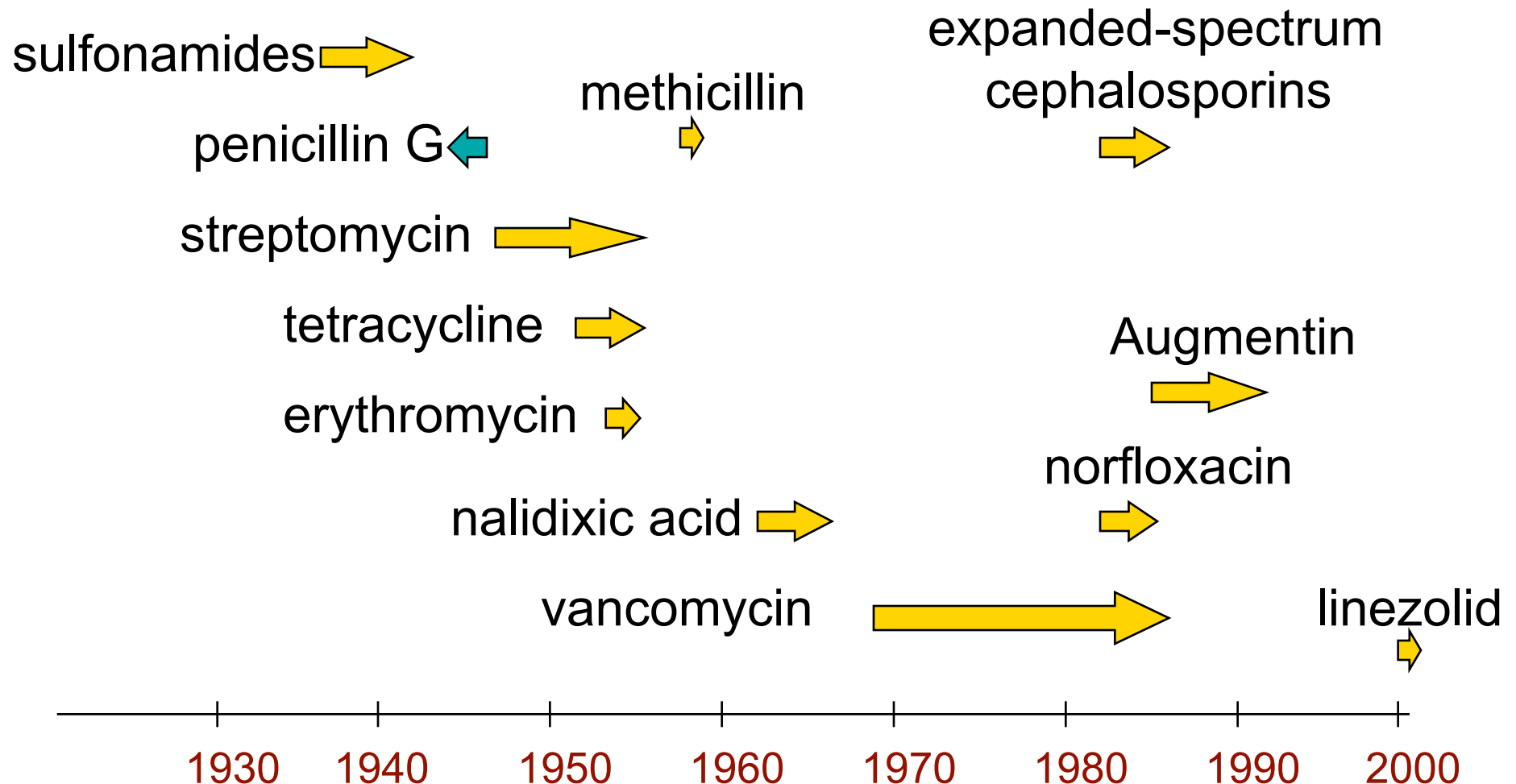
Inactivation & Modification

Alteration of Target

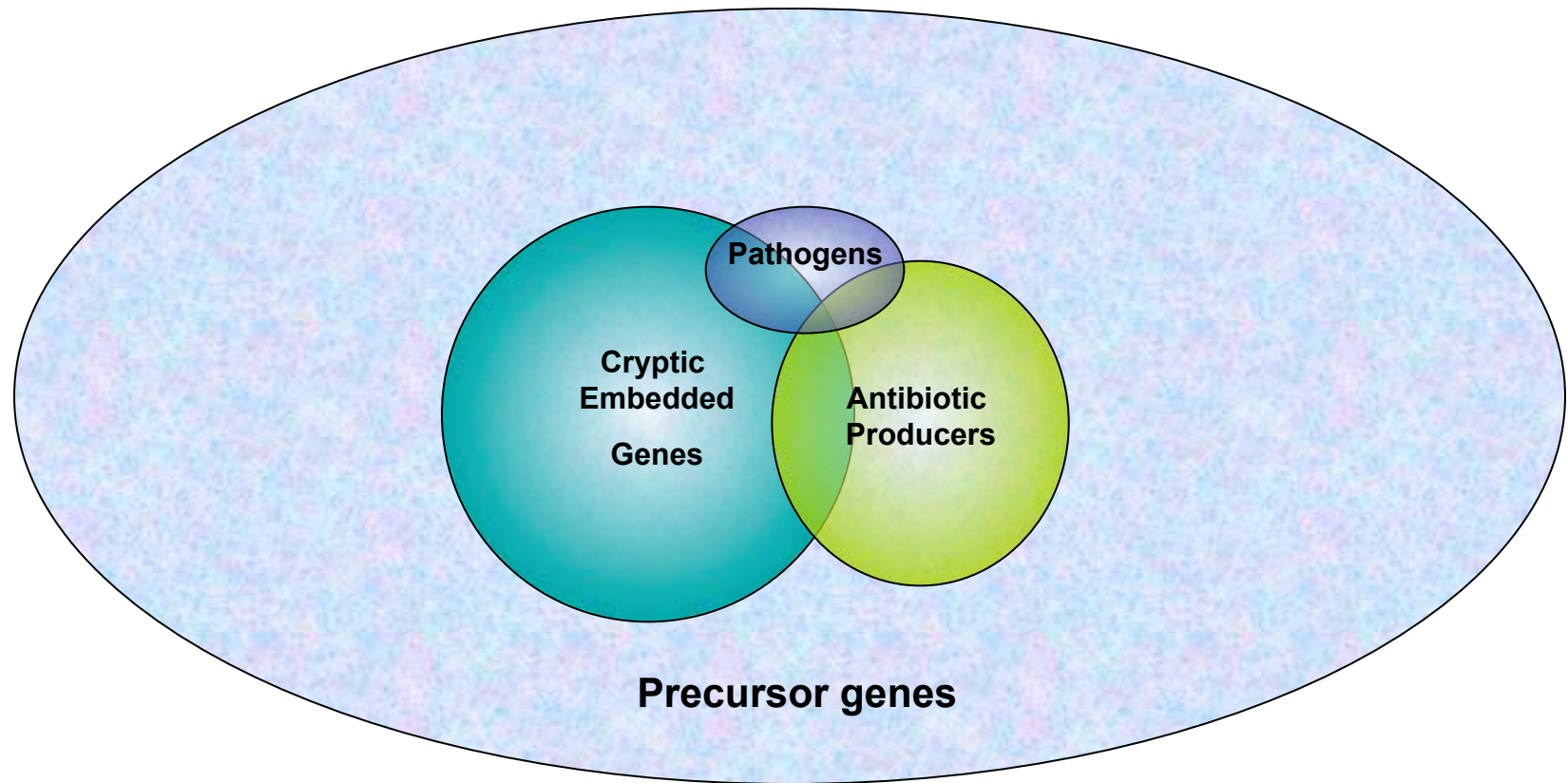


Efflux & Altered Uptake

Resistance Develops Rapidly



The Antibiotic Resistome



Microbial Diversity
+ Chemical Diversity
Genetic Diversity

A Systematic Search of Resistance Elements

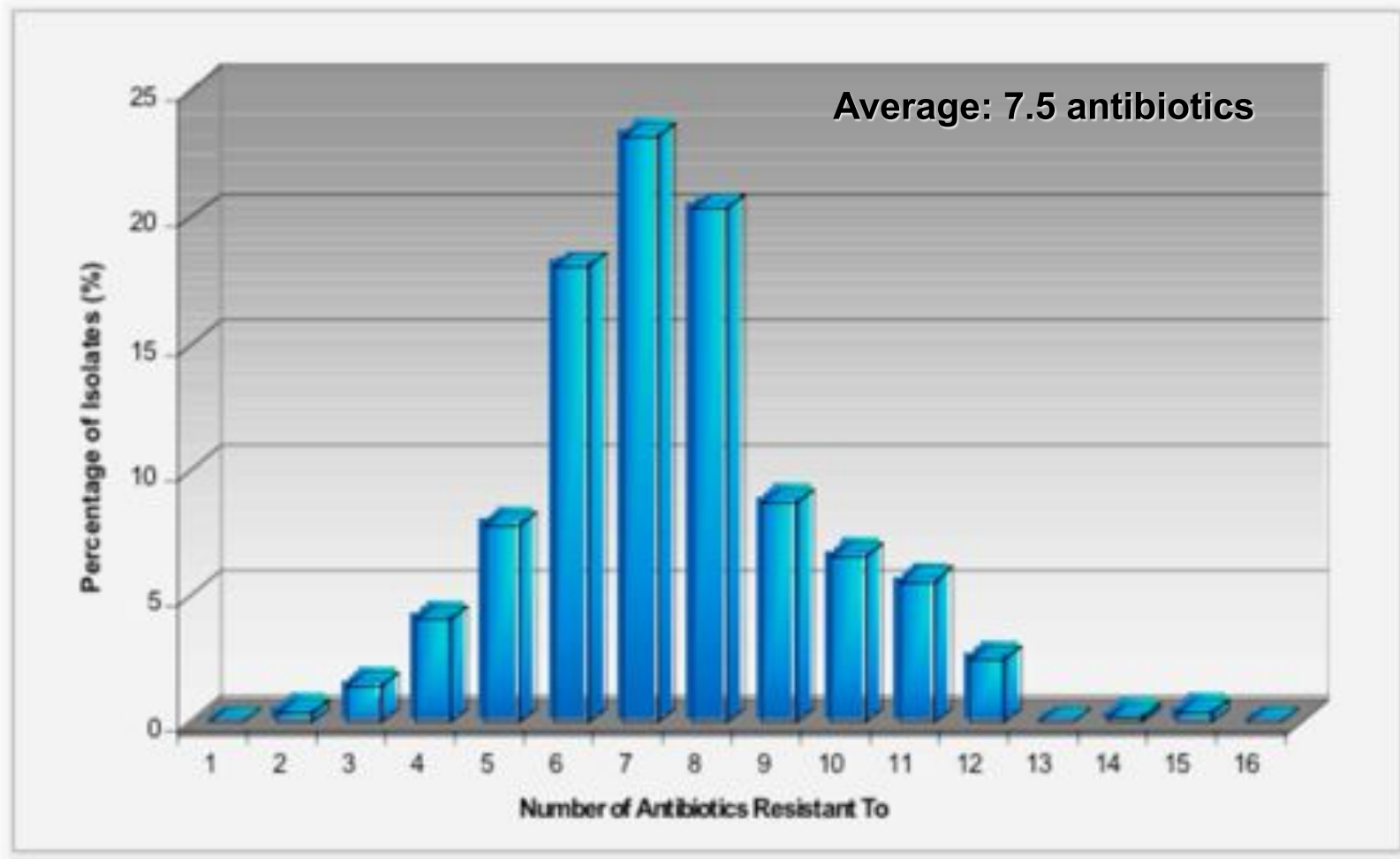
Soil bacteria

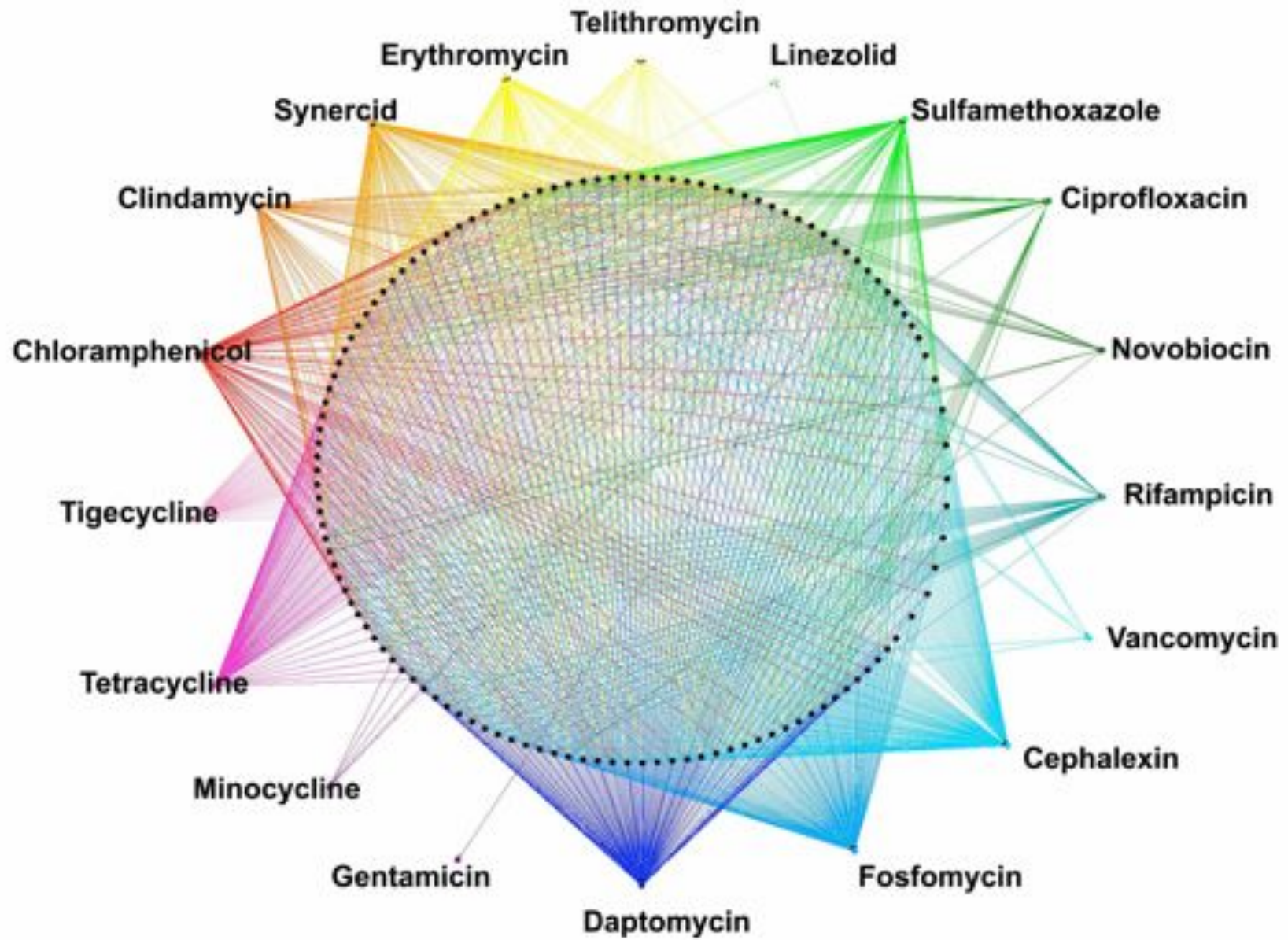
- genetically diverse
- natural product synthesis
- multiple resistance markers in *Streptomyces coelicolor*



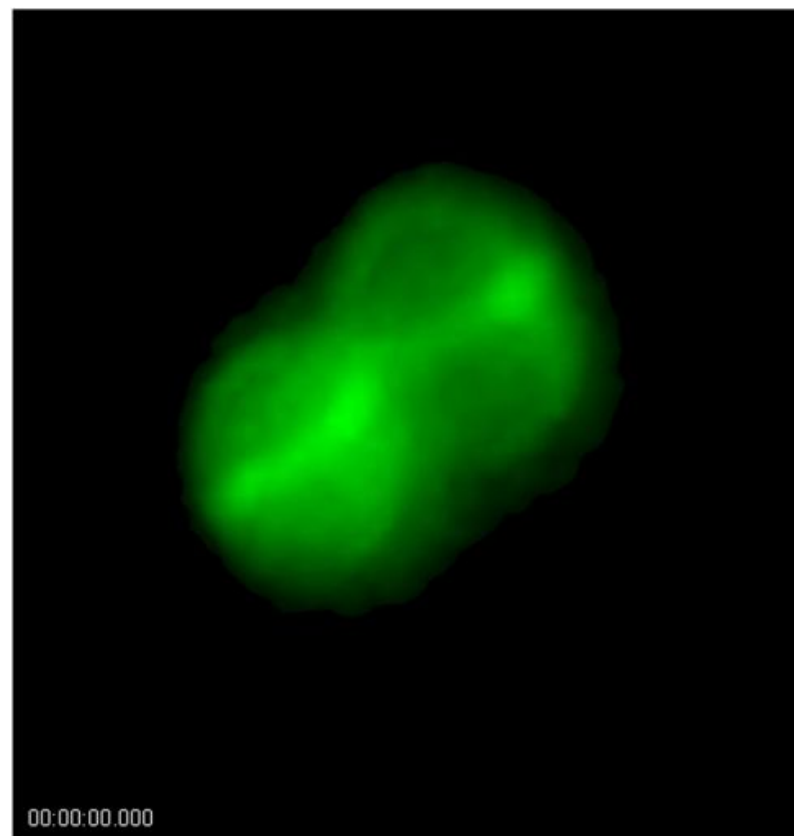
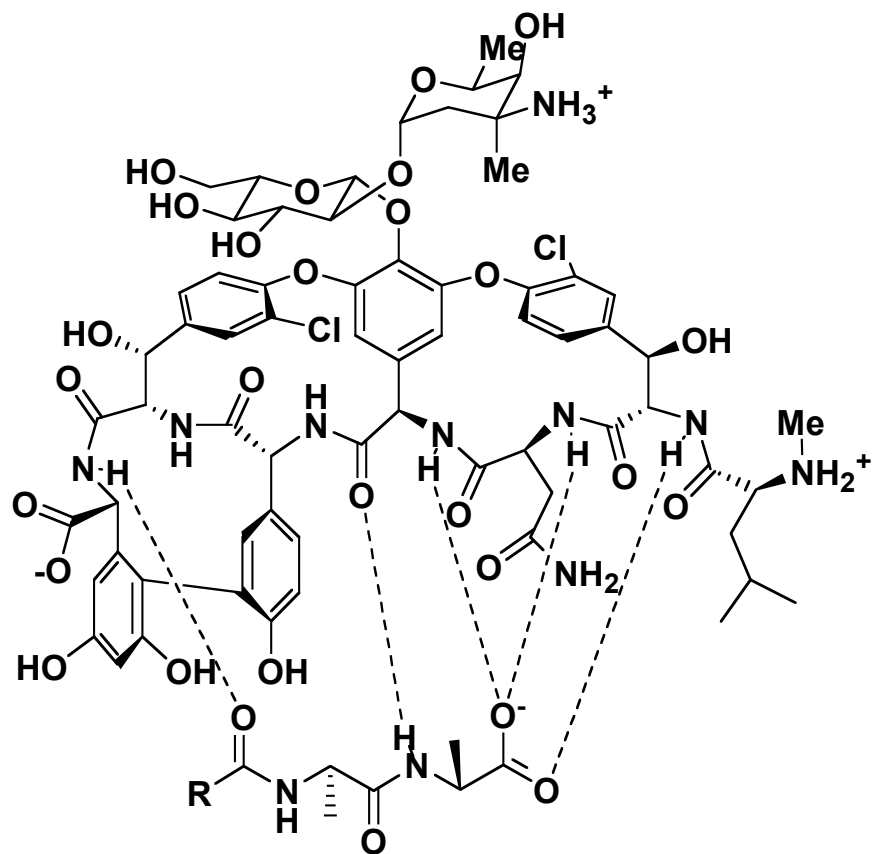
Resistance Profile of Soil Isolates

480 Isolates vs. 21 Antibiotics

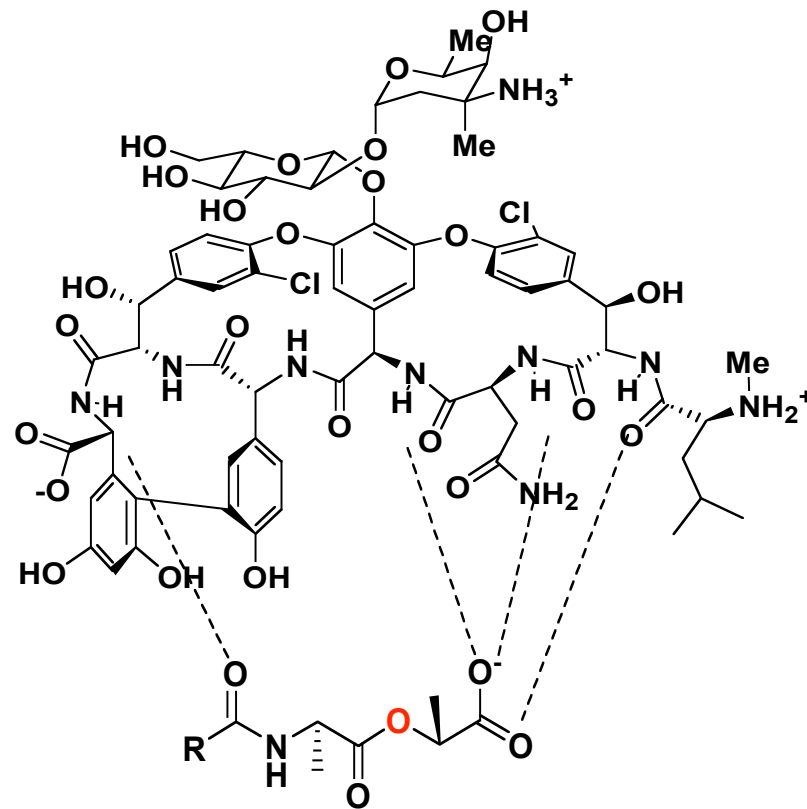
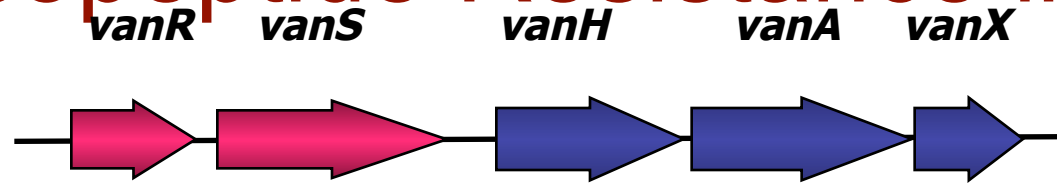




Glycopeptide Antibiotics

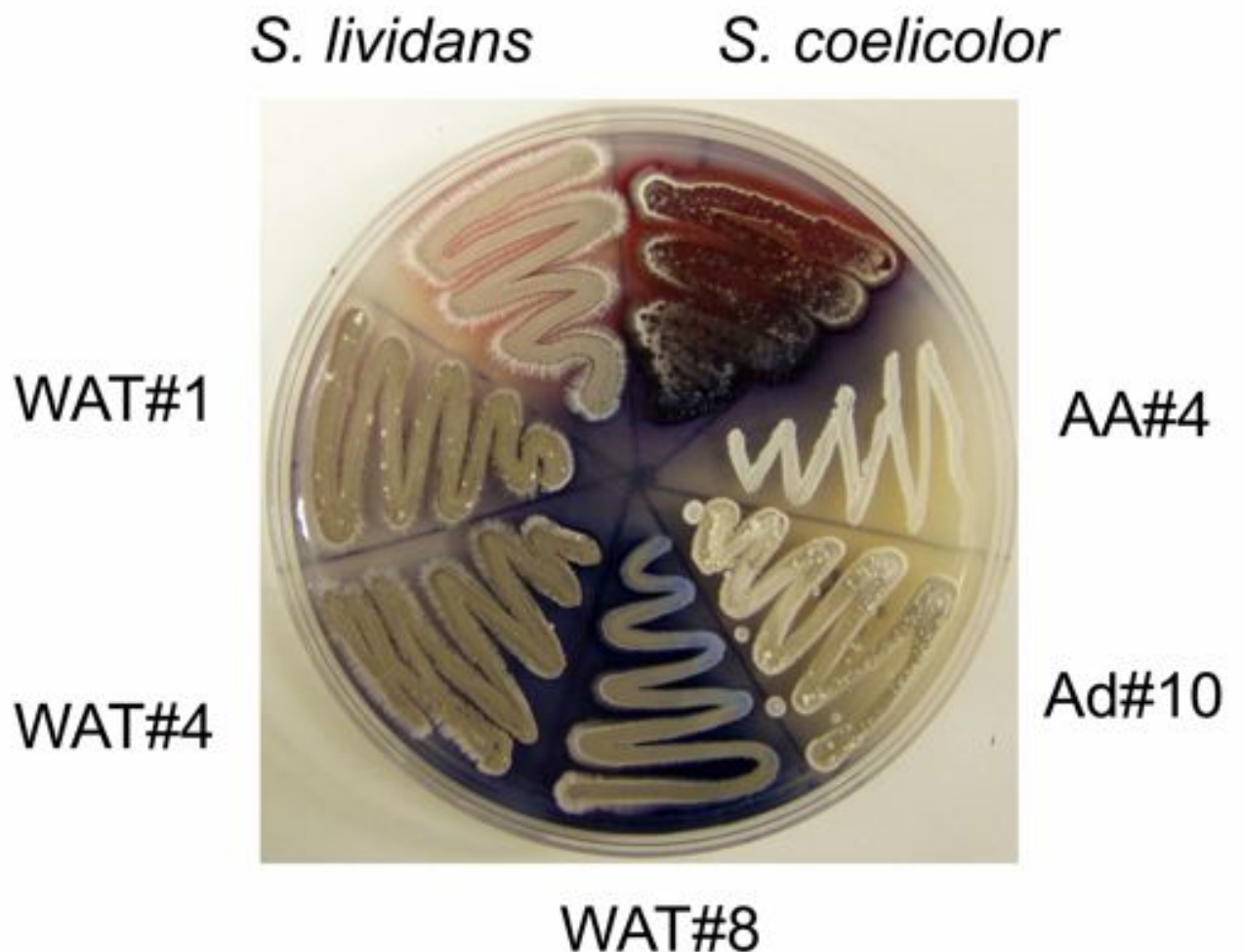


Glycopeptide Resistance in VRE



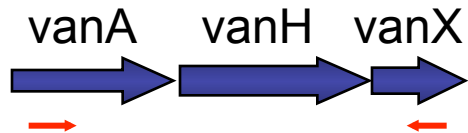
Vancomycin Resistant Isolates

- 5 of 500 isolates resistant to vancomycin
- MICs range from 128-256 $\mu\text{g/mL}$
- No inactivators

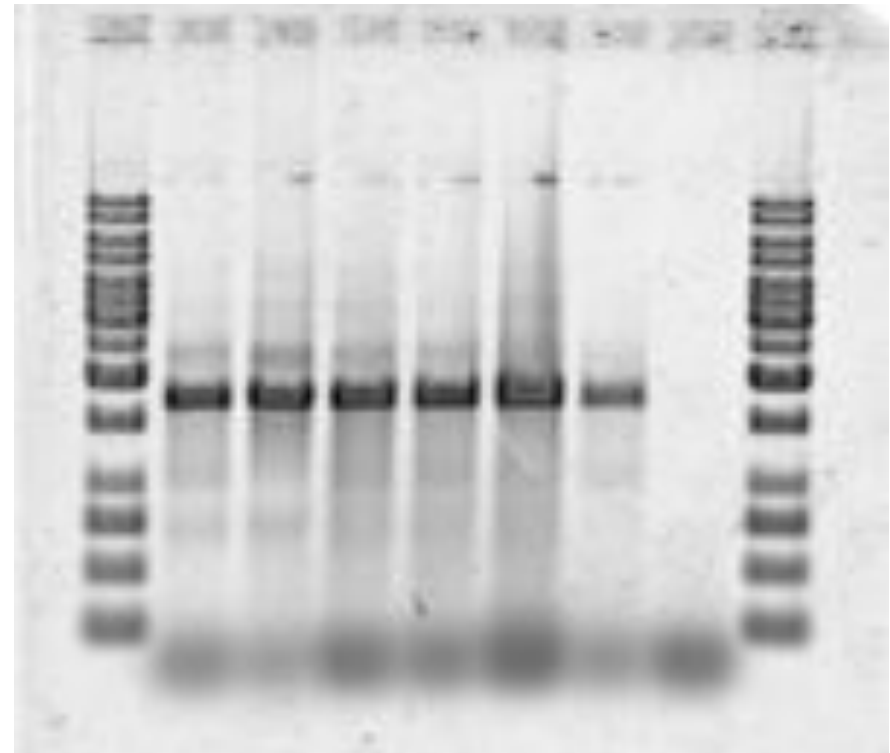


VanHAX Operon

- 4/5 resistant isolates have *vanHAX* operon



S. coelicolor
S. toyocaensis
WAT#1
WAT#4
WAT#8
Ad#10



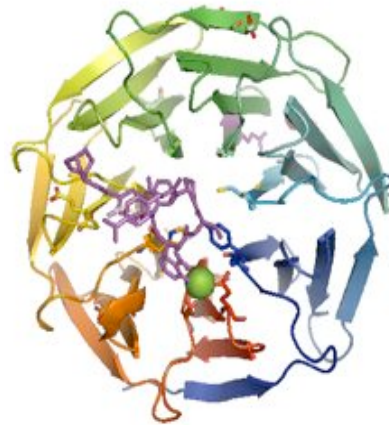
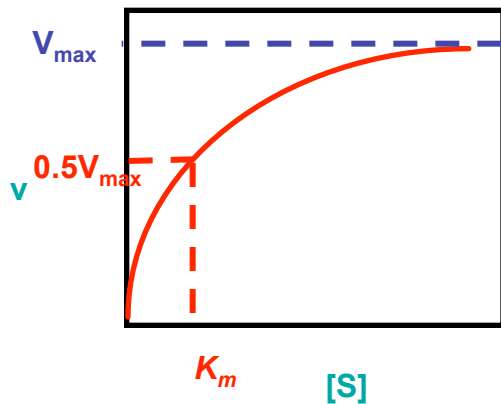


Some Solutions...

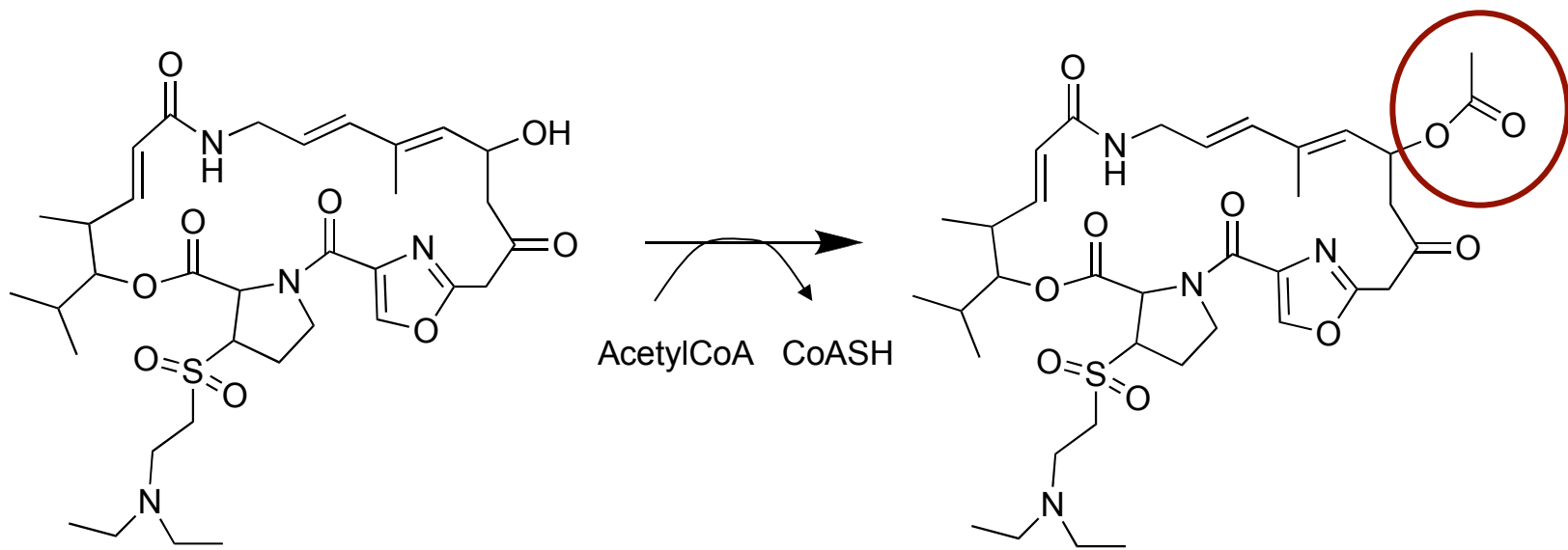
- Find new antibiotics
- Use molecular understanding of resistance to rescue 'old' antibiotics and repurpose discarded ones
- Leverage 'systems biology'
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Genomic Enzymology of Antibiotic Resistance Provides a Pathway to Solutions

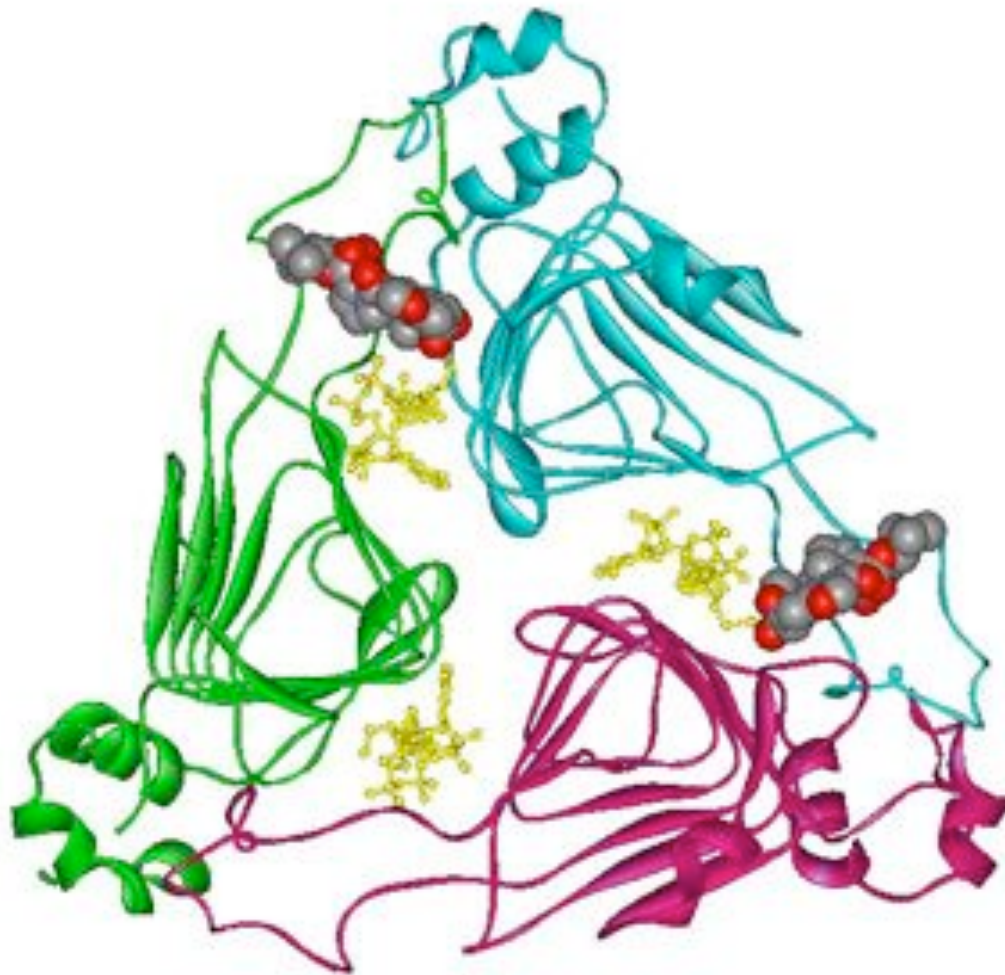
Characterize Enzymes + Determine 3D Structure + Identify Homologues = Solutions



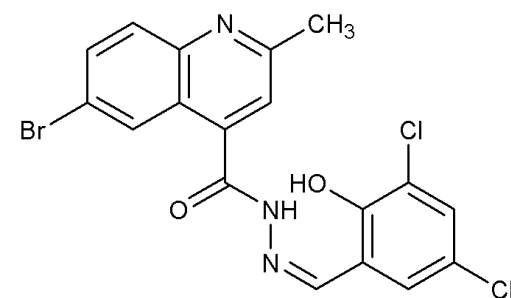
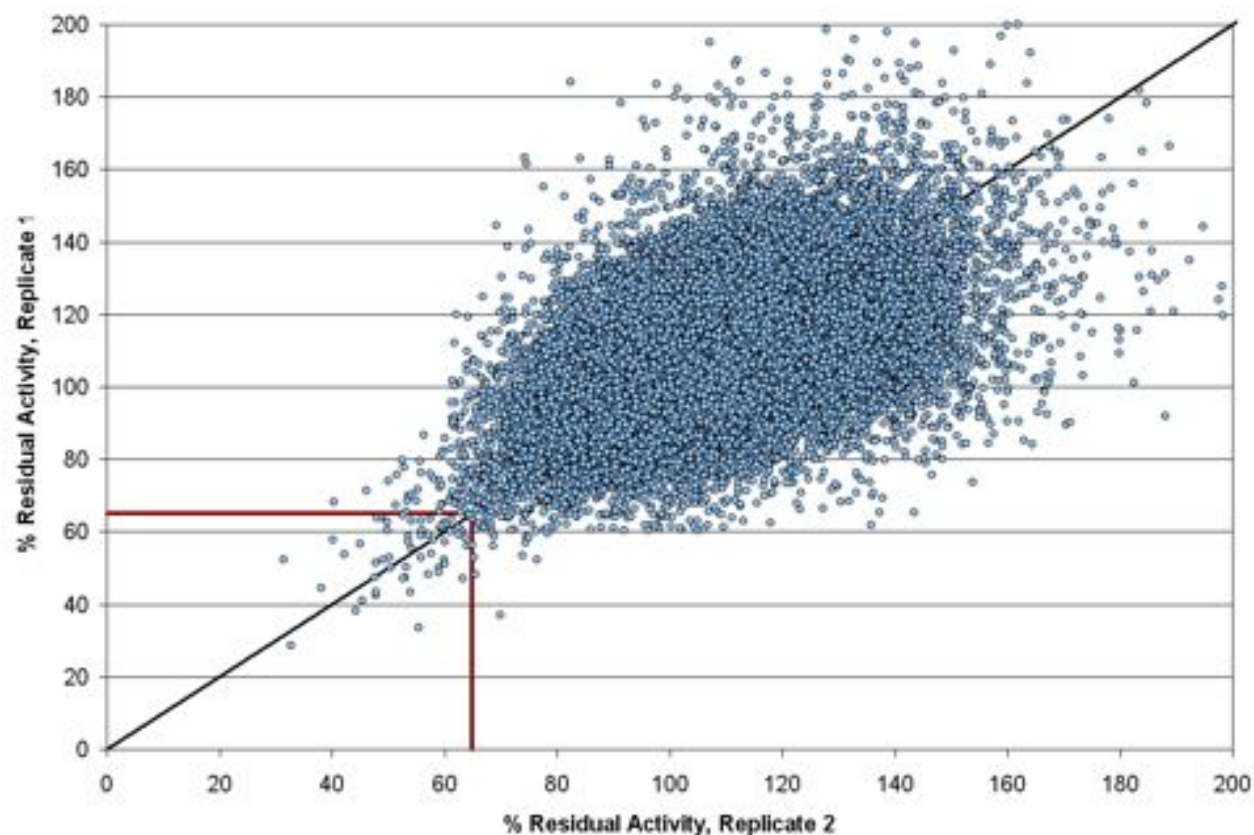
Vat, a streptogramin acetyltransferase



VatD: A Trimeric Hexapeptide Repeat Protein

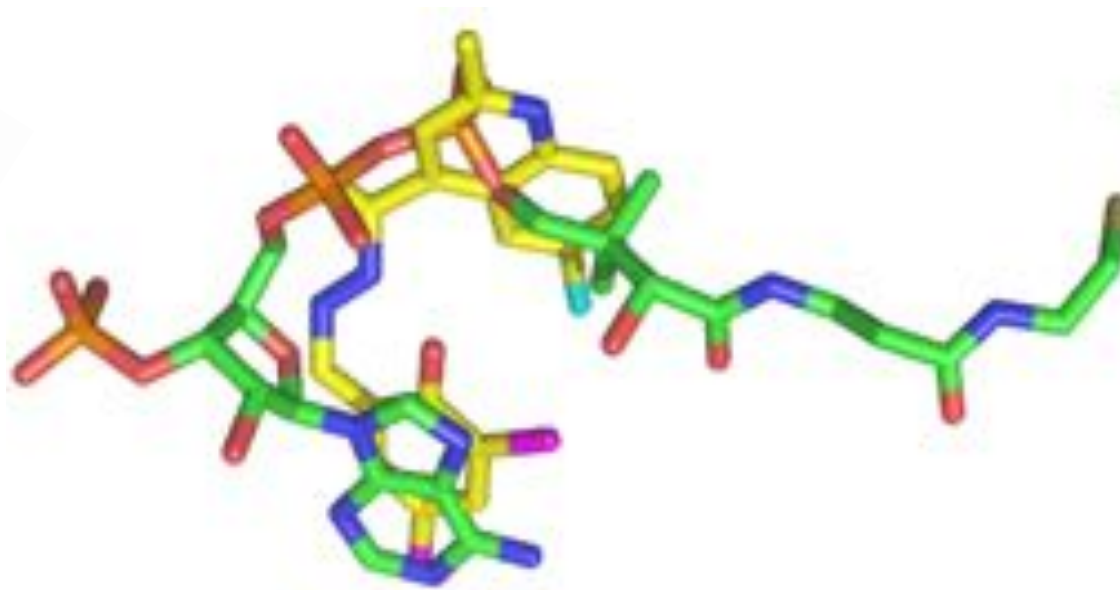
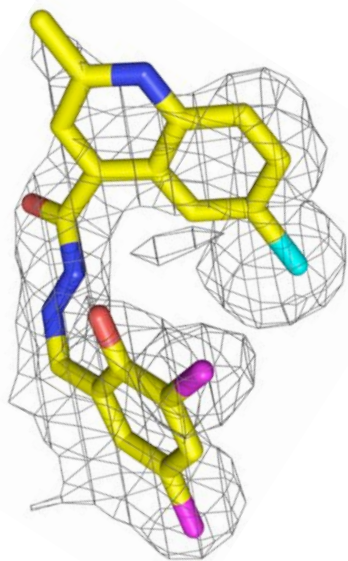


HT Screening Uncovers an Inhibitor of Vat



BTB01807

3D-Structure offers Clues for Improved Activity



BTB01807 Blocks Drug Resistance

Compound	MIC ($\mu\text{g/mL}$)
Pristinamycin IIA	512
BTB01807	>128
Pristinamycin IIA + BTB01807 (32 $\mu\text{g/mL}$)	256 (FIC 0.5)

Summary

- The antibiotic Resistome is broad and ancient
- Solutions to the problem require understanding of molecular mechanisms
- Lots of room to be optimistic for antibiotics