New approaches to address antibiotic resistance in animals
The co-evolution of antibiotics and their resistance

- Penicillinase discovery
- Antibiotic resistance plasmids
- THE LEAN YEARS
- Increasing Antibiotic Resistance
- Transmissible fluoroquinolone resistance

- Primordial
- Golden
- Pharmacologic
- Biochemical
- Target
- Genomic HTS
- Disenchantment

MRSA: UK*, US**

Production: 50kg...>10^6 tons
Evolution of β-lactamases
FIFTY YEARS OF MRSA!

Information provided by Karen Bush
The most expensive hydrolytic reaction in history!
Fifty years of “Industrial Research” on Antibiotics

Environmental
Doubling time: months
Aeration: low
Nutrients: variable
Carbohydrate: limited
Water: variable
Temperature: 0-40
pH: 2-10
Yield: μgrams

Production
Doubling time: hours
Aeration: high
*Nutrients: high and constant
Carbohydrate: high
Water: unlimited
Temperature: 25-30
pH: 6-7
Yield: grams

*Typical substrates for fermentation
Molasses (blackstrap)
Fish Meal (herring, anchovy)
Citrus pulp
Asparagus juice
Cottonseed oil
Malt extract
Beef extract
Bovine blood
Pork liver
Distillers solubles
Hydrolysed rabbit fur
We Live In A Microbial World

Microbial viruses on the Earth: $1 \times 10^{31}$
Microbes on the Earth: $5 \times 10^{30}$
Stars in the Universe: $7 \times 10^{21}$
Humans on the Earth: $6 \times 10^9$
Human genes in one person: $2.5 \times 10^4$
Human cells in one person: $1 \times 10^{13}$
Microbial genes in human gut: $3 \times 10^6$
Microbial cells in human gut: $1 \times 10^{14}$
Bubbles in one bottle of champagne: $1 \times 10^5$

We are less than 10% of what we think we are!
The “Revised” Central Dogma

DNA → RNA → Protein → Natural Products

Many independent functions

“Life would not exist without macromolecules alone.” Stuart Schreiber, 2005
The Parvome

Inter-Kingdom Signalling

MONERA

P. aeruginosa acyl homoserine lactones

Pseudomonas quinolone signal

Fungi

C. albicans Farnesol

D. pulchra halogenated furanone

ANIMALIA

epinephrine
norepinephrine
prostaglandin
retinoic acid
estrogen

ecdysteroid

PLANTAE

Auxin
Jasmonic Acid
Signaling Interactions between Cells in Nature  
(Communication, Cues, Competition, Cooperation)

Duan et al, 2009
Prospects for natural product drug discovery

• Bioactivity-based screens
• Combinatorial synthesis and biosynthesis
• Chemical library screening by “docking”
• Co-culturing producing strains: pathway activation
• Genomic identification of biosynthetic pathways
• Heterologous expression of pathways
• Drug combinations
• New approaches to vaccines
• A “new” look at plants and other sources
• Personalized treatments
Genomics and Drug Discovery
(A new paradigm)

Genome or Metagenome sequence

Bioinformatic scanning for biosynthetic gene clusters

Prediction of structure or molecule class

Virtual docking for target identification

Compound production by cluster expression in “designer” host
Analysis of molecular interactions in bacterial cell networks, using high-resolution MS with nanoDesi probe (Watrous et al 2012)

Streptomyces coelicolor A3(2)

Bacillus subtilis PY79
THE OTHER OPTION?