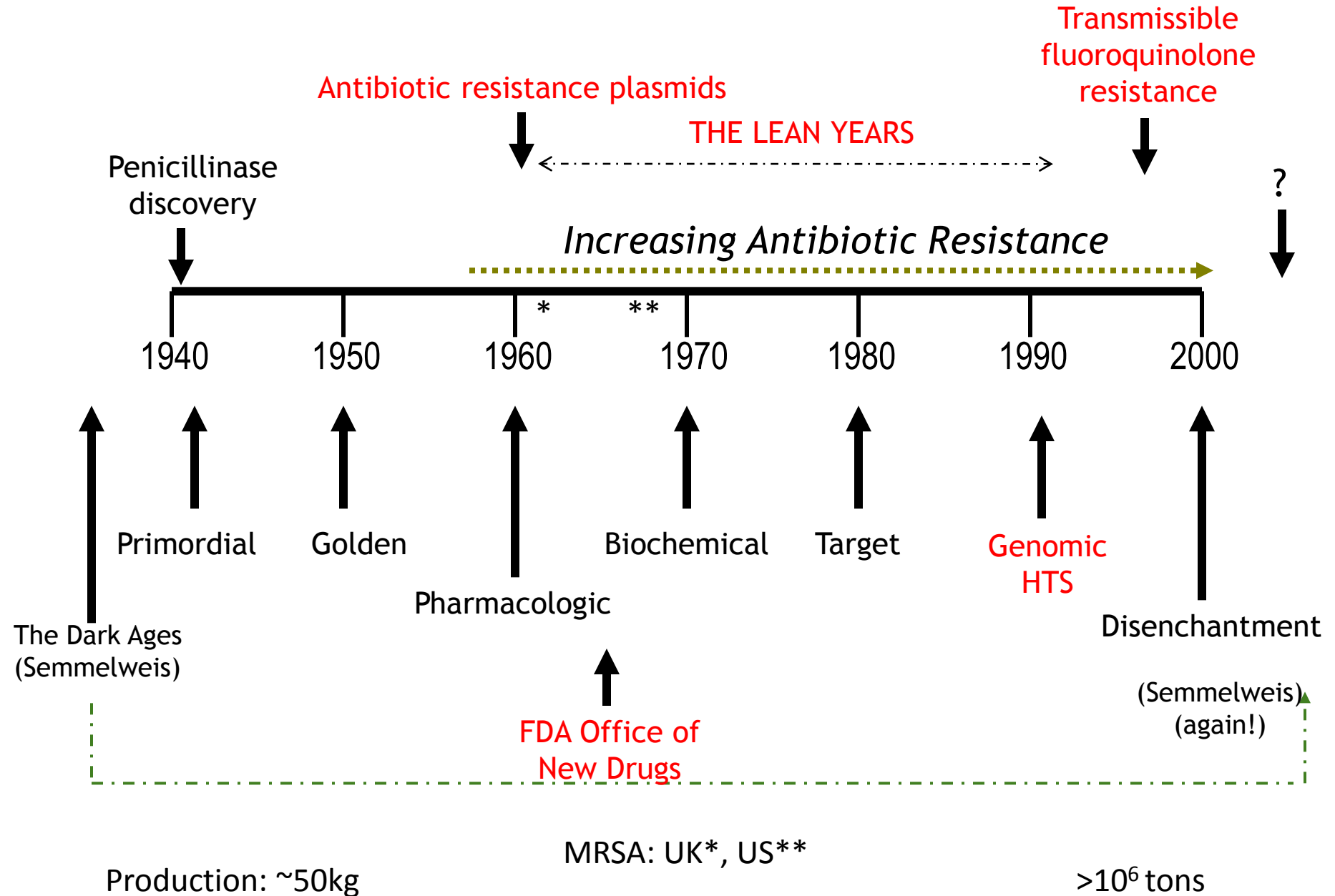


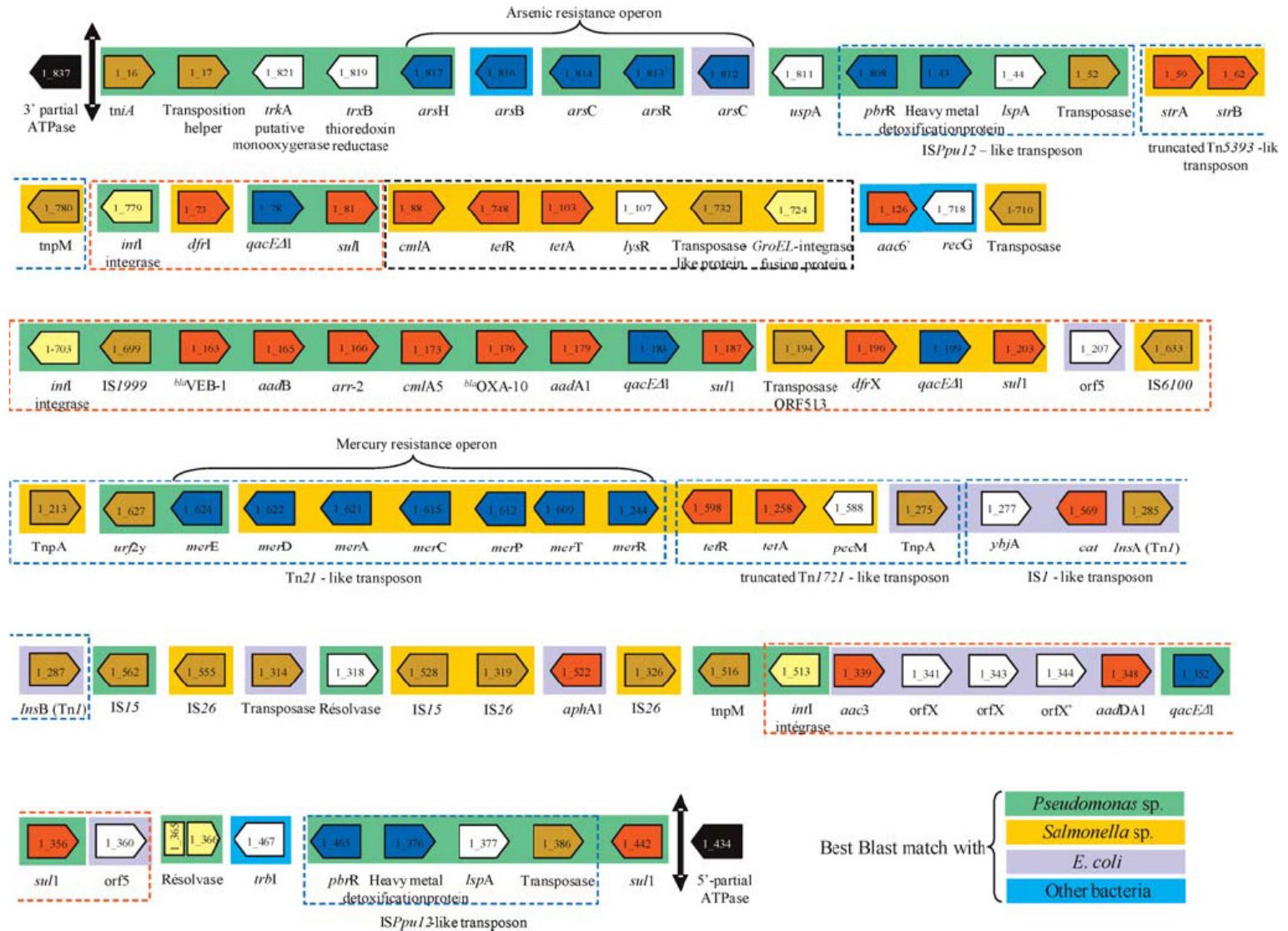
Harvesting the Molecular Wealth of Microbiomes



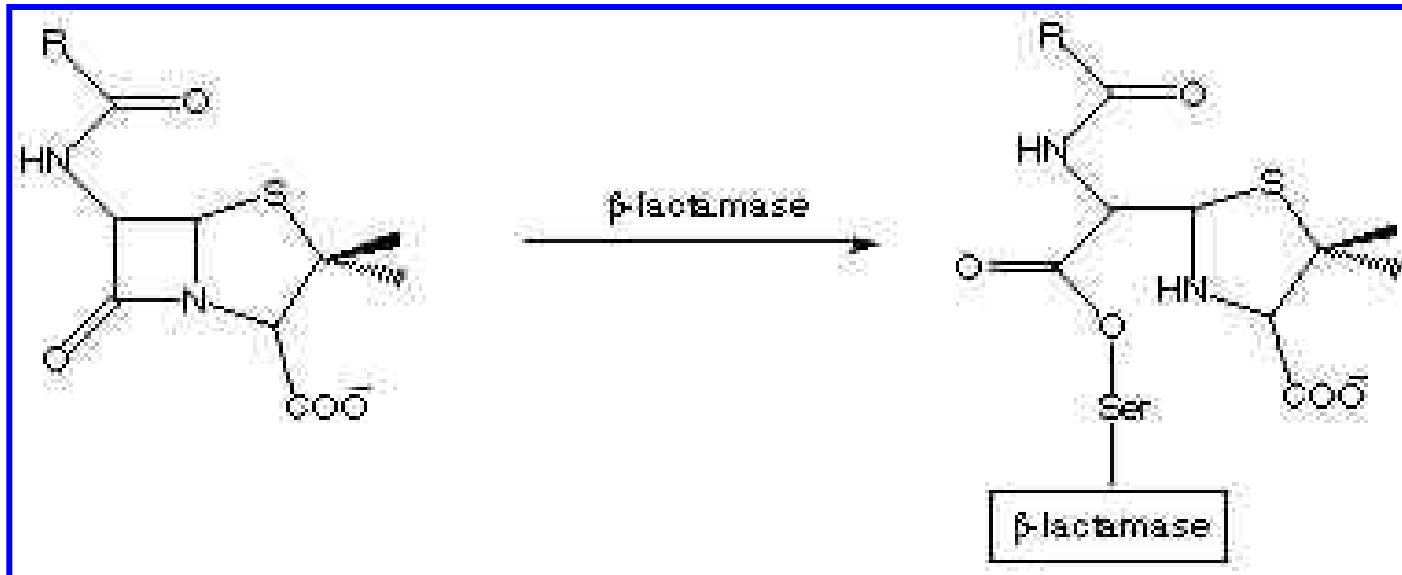
A brief history of antibiotics (co-evolution of antibiotics and their resistance)



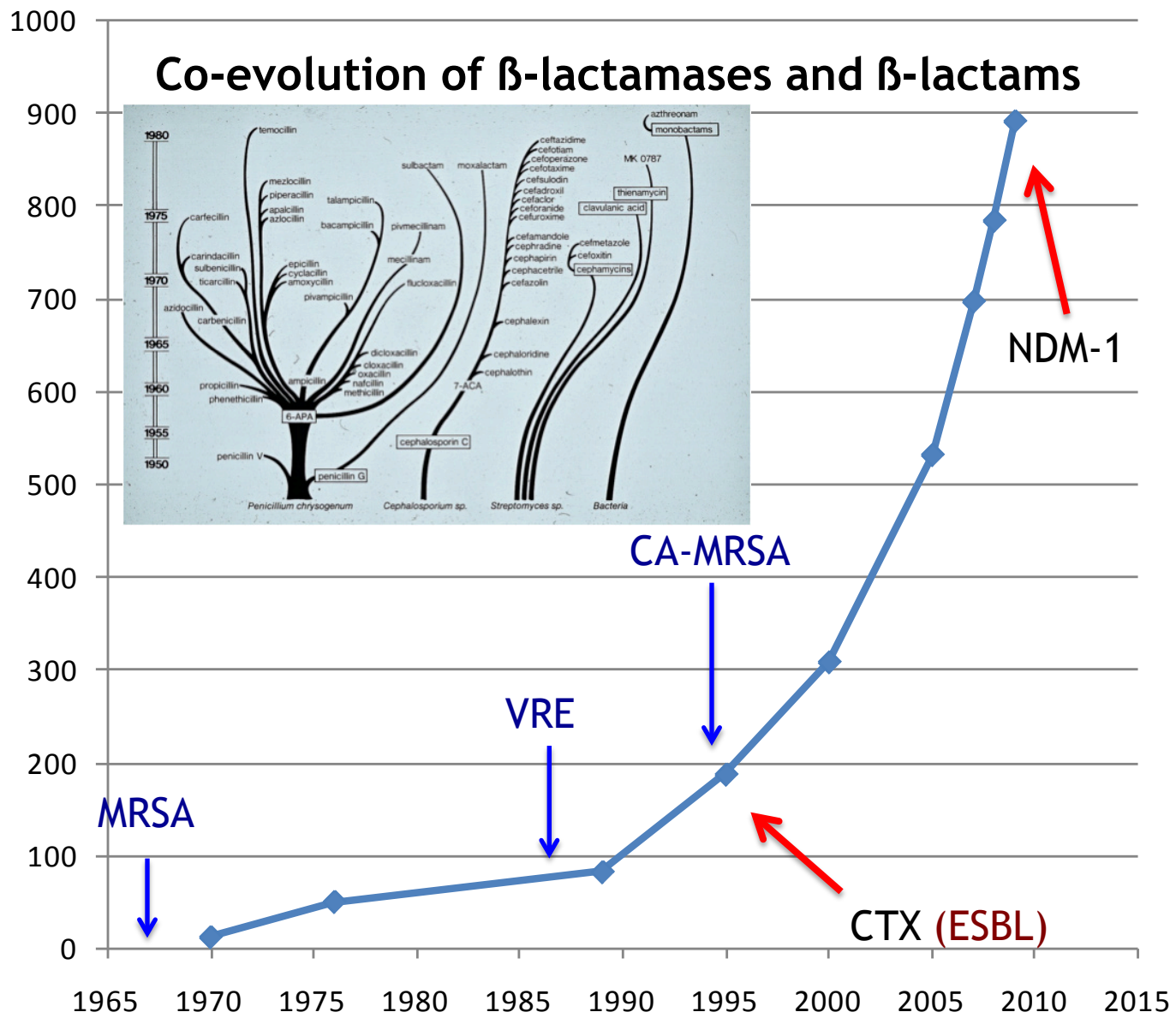
The 86kb resistance island of *Acinetobacter baumannii* AYE (88 ORFs, 45 resistance genes, 6 different antibiotic classes)

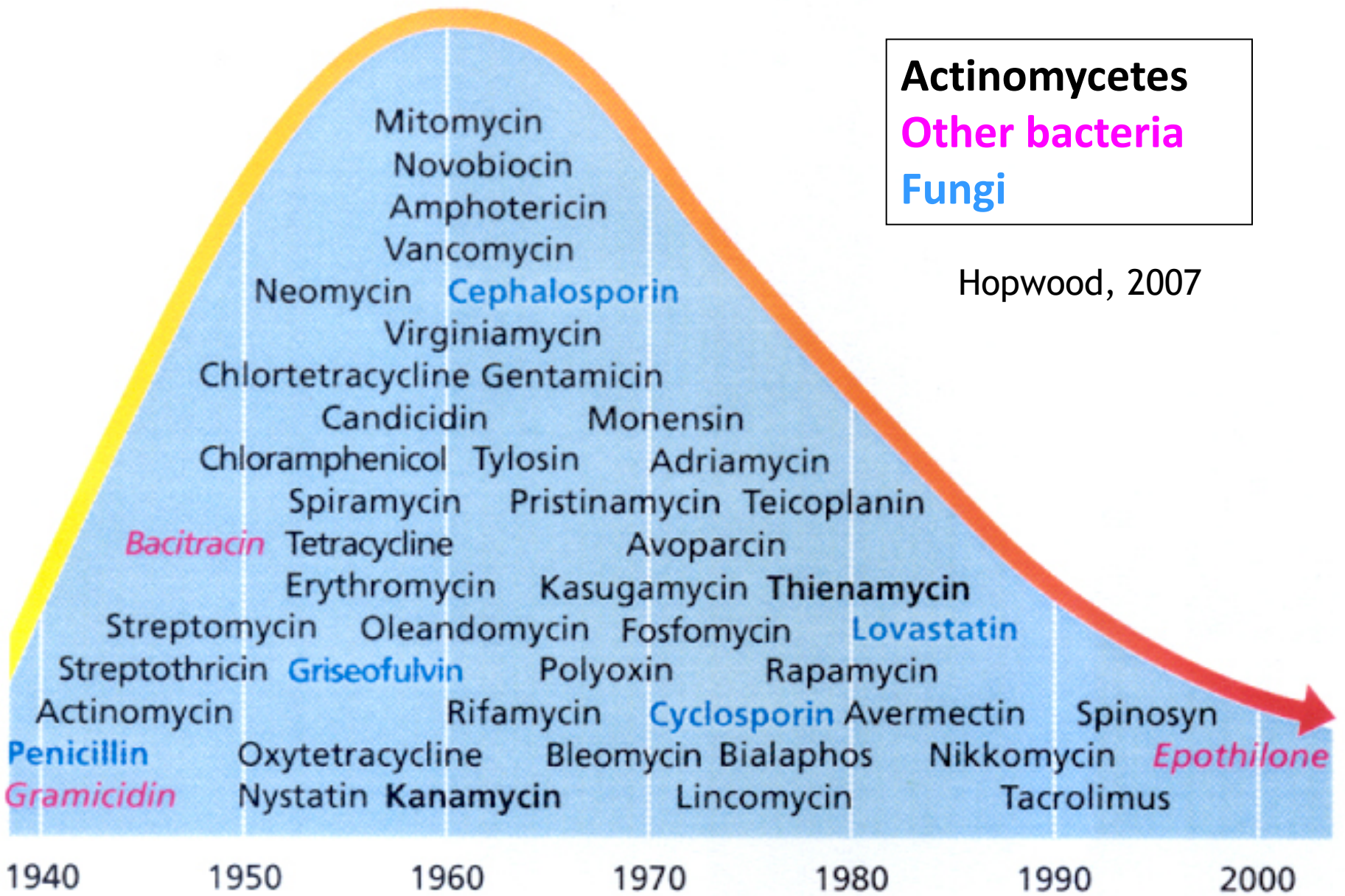


The most costly reaction in history!

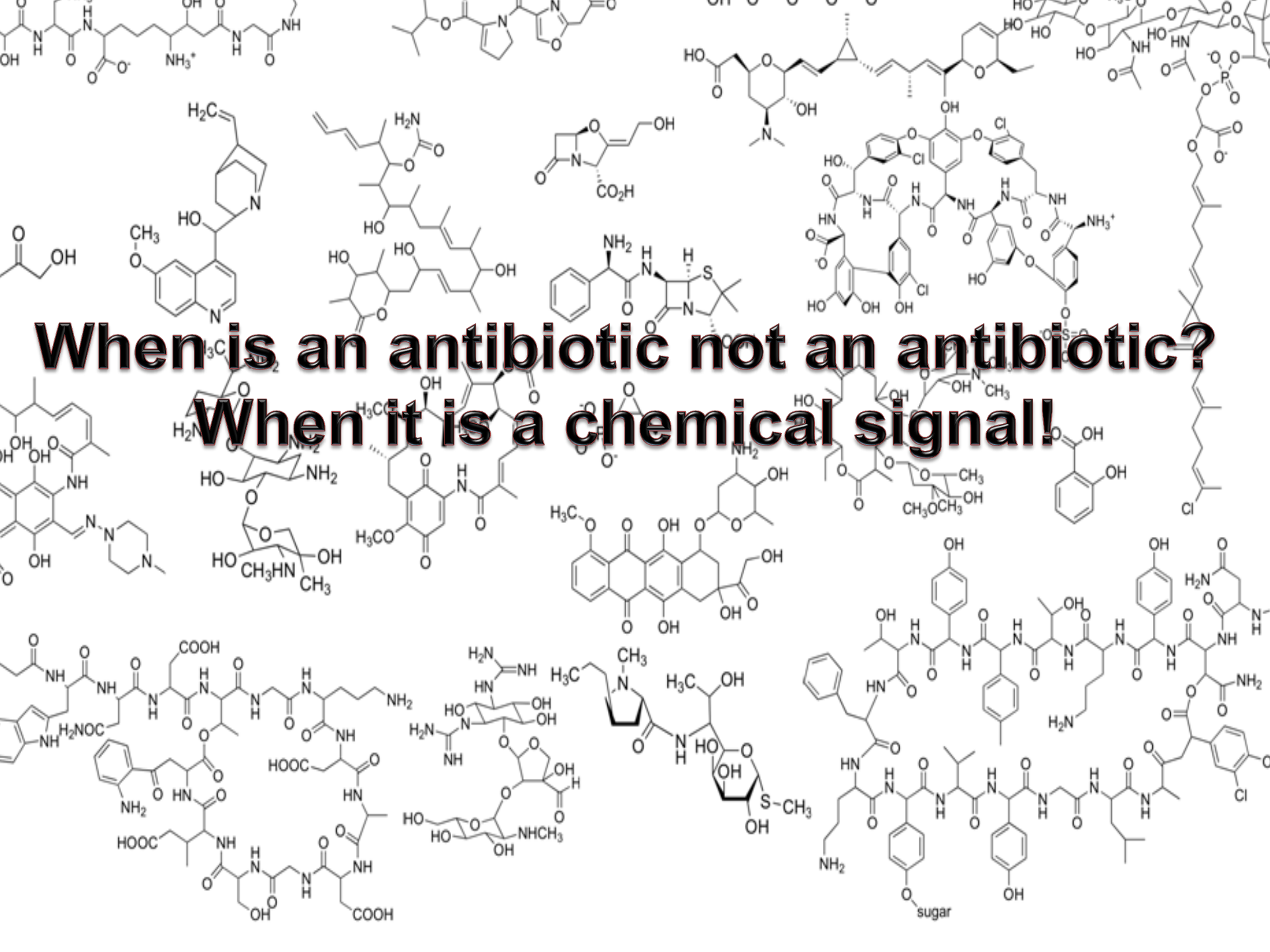


Co-evolution of β -lactamases and β -lactams





Diminishing returns in finding useful antibiotics



**When is an antibiotic not an antibiotic?
When it is a chemical signal!**

sugar

“At an appropriate concentration, any molecule is an antibiotic”



Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy. (*The dose makes the poison*)

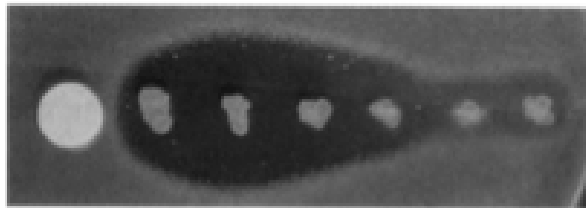
Auroleus Phillipus Theostratus Bombastus von Hohenheim
a.k.a Paracelsus (1493-1541)

Antibiotics are rare in nature but common in human medications (as poisons!)

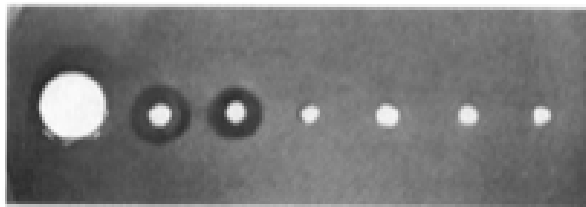
EXAMPLES OF INTER-CELL SIGNALLING BY “ANTIBIOTICS”



(Dietrich & Newman, et al, 2008)

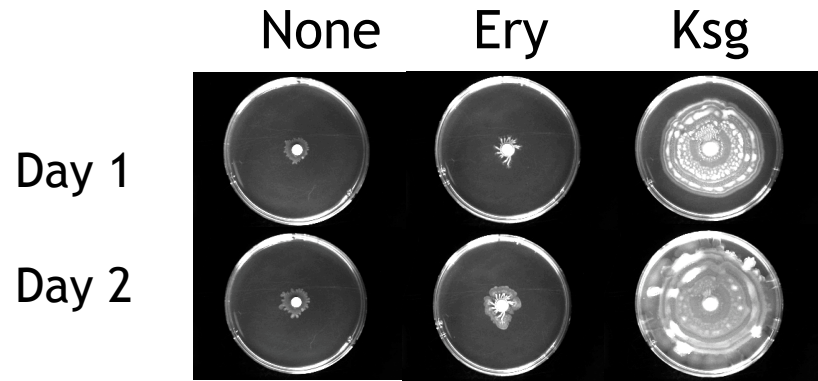


7 → 63



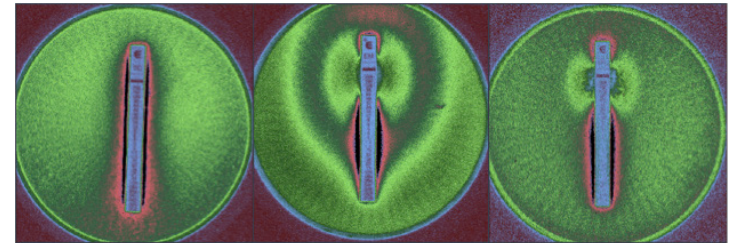
17 → 49

(Ueda, Beppu et al, 2002)

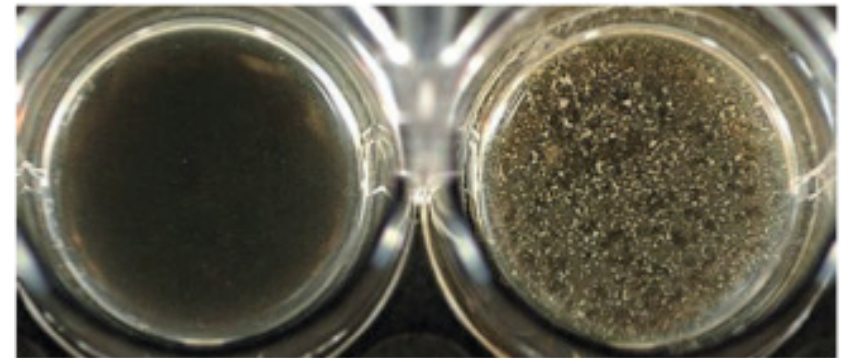


Day 1

Day 2

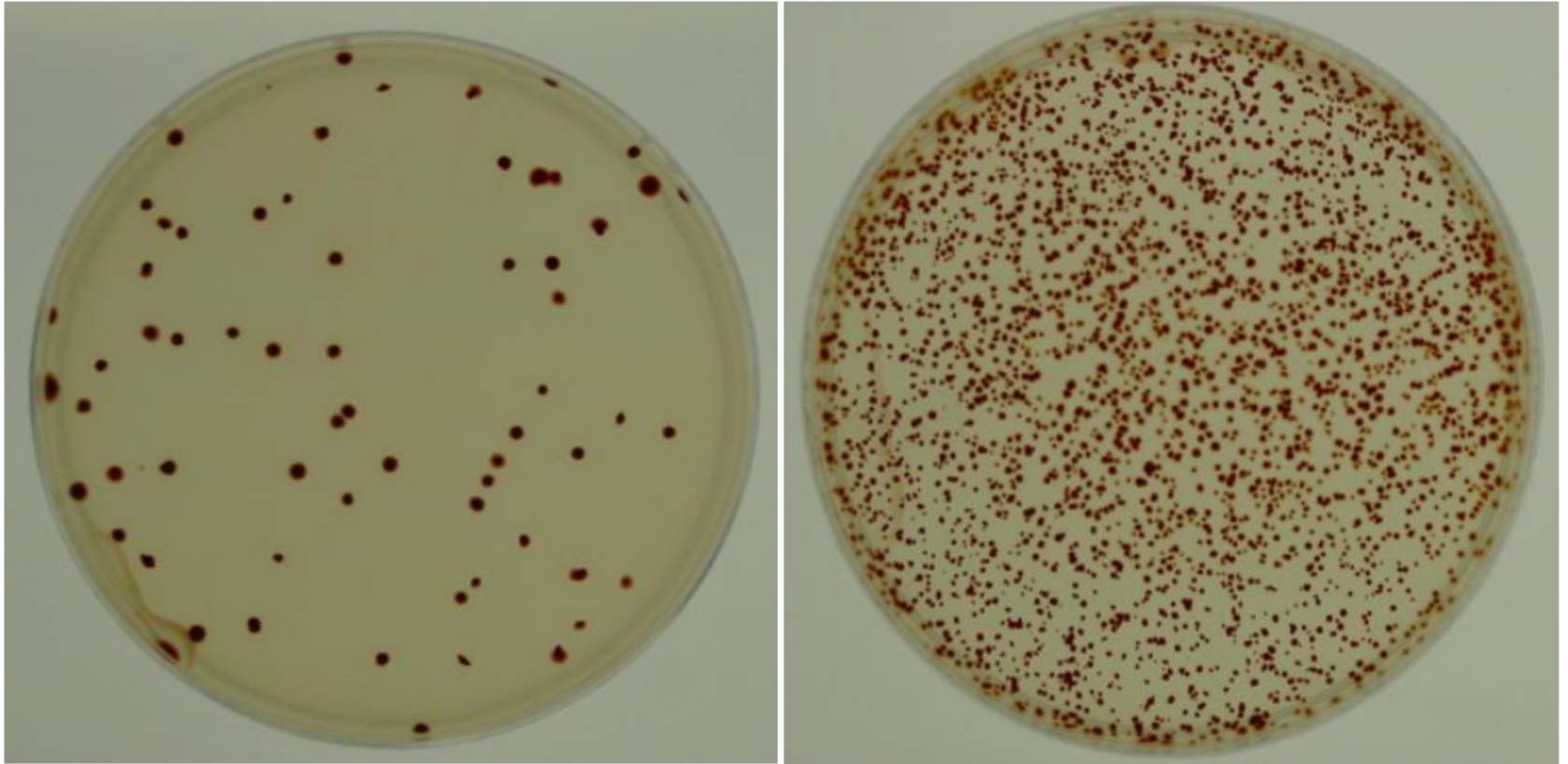


(Yamazaki, 2009)



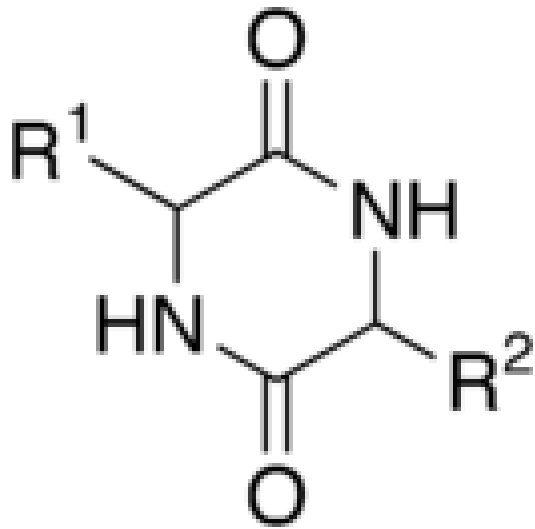
(Kolter et al, 2008)

ENHANCED TRANSFER OF *Rhodobacteriales* GENE TRANSFER AGENT BY subMIC COUMARIN ANTIBIOTICS



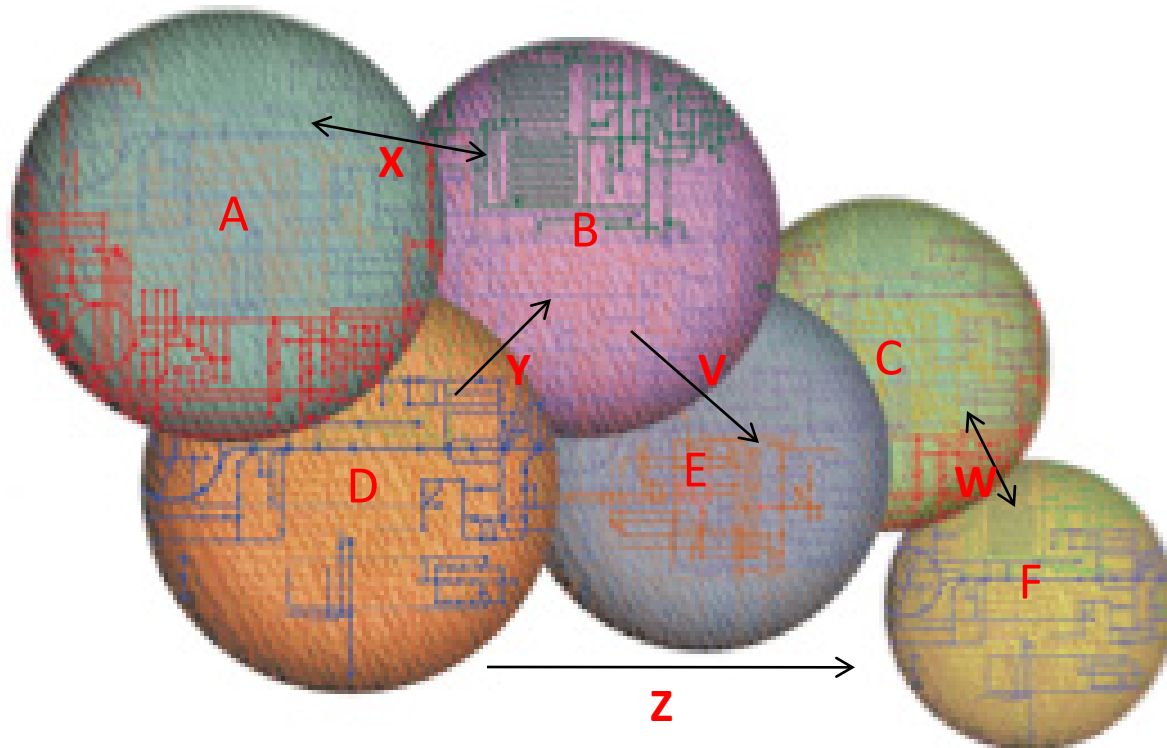
Rhodobacter capsulata DW5 X RC6
[Moens and Beatty, personal comm.]

***Bacillus* sp. produce many small molecules,
especially cyclic dipeptide effectors**



Antimicrobial
Antilarval
Cytotoxic
Neurotoxic
Anti-inflammatory
Growth promotion
Growth regulation
Siderophores
Enzyme activators/inhibitors
QS agonists/antagonists
Inhibition of biofilm formation

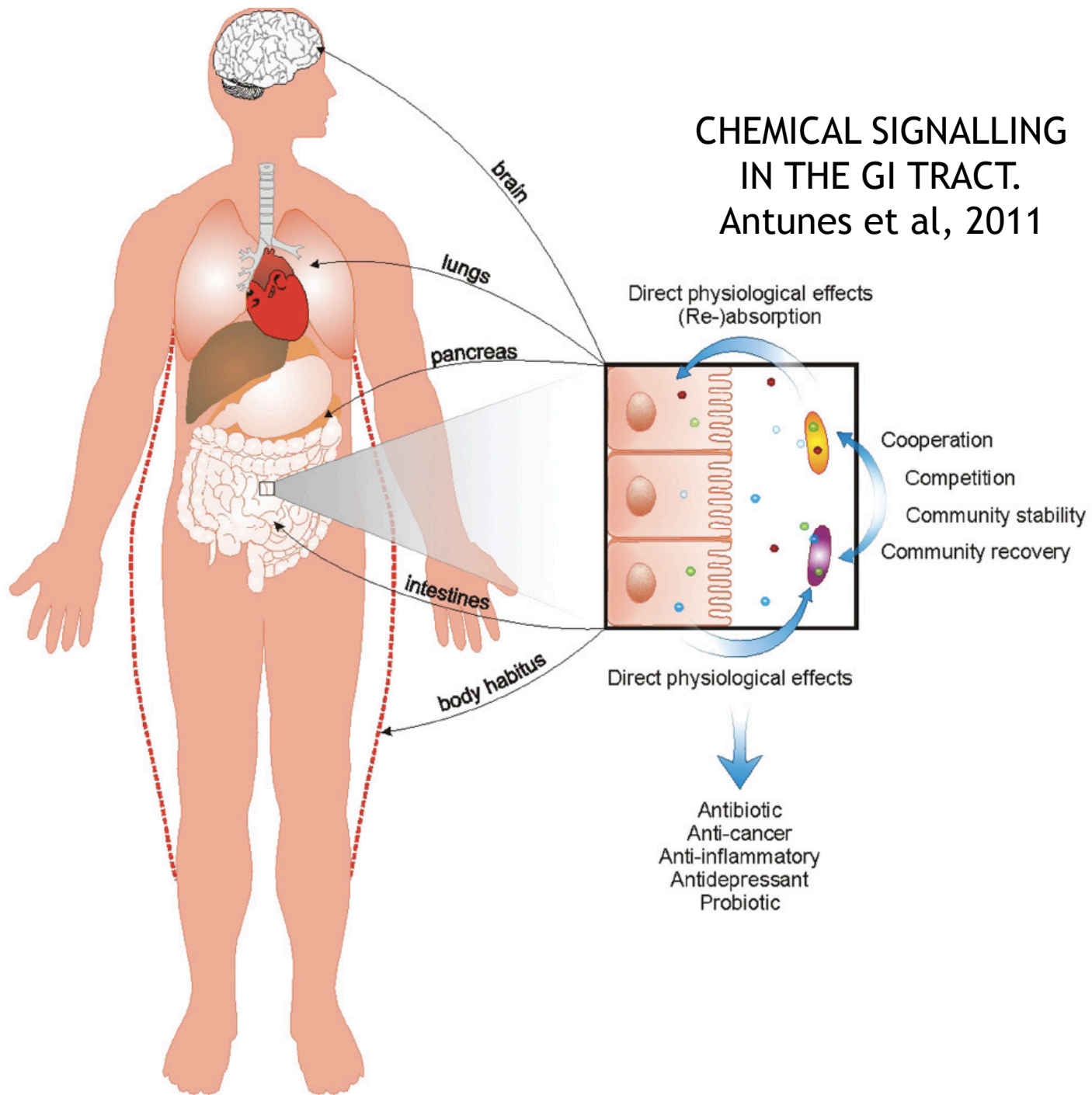
All microbial communities are distributed metabolic networks:
These are maintained by inter-specific signalling
and cross-feeding.



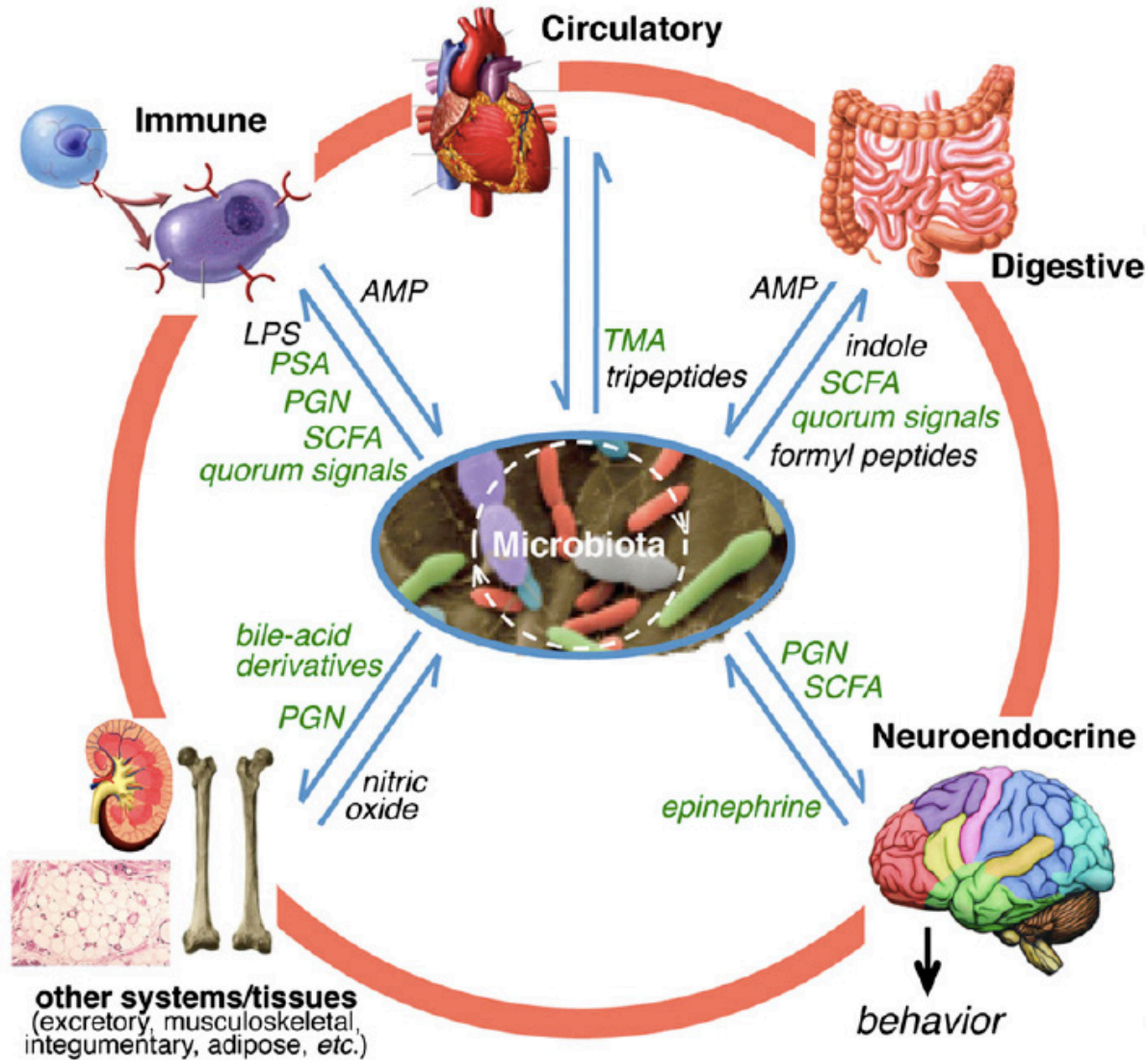
CHEMICAL CONNECTIONS/SIGNALS

CHEMICAL SIGNALLING IN THE GI TRACT.

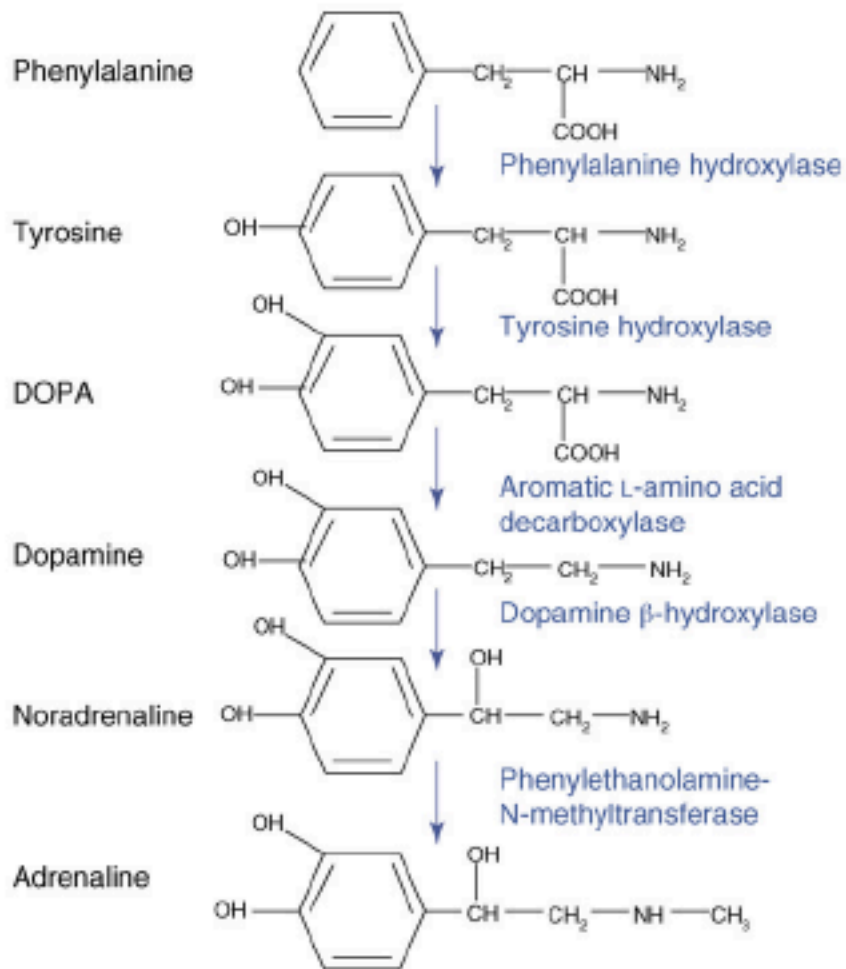
Antunes et al, 2011



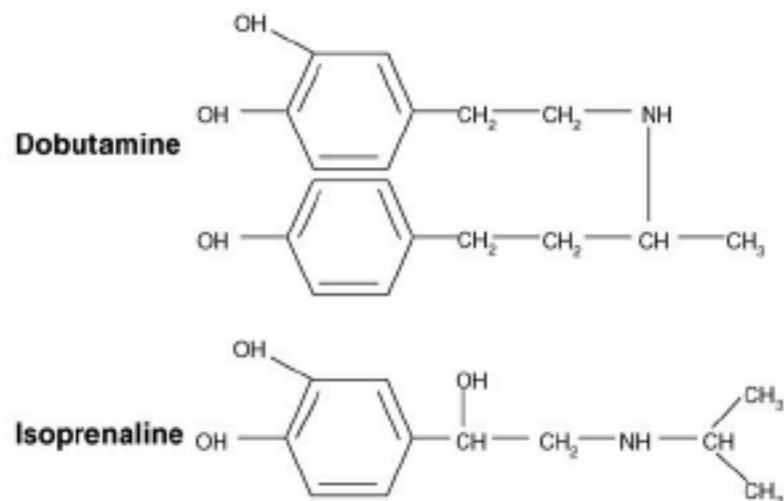
Chemical signalling; animals and their microbiota (McFall-Ngai et al, 2013)



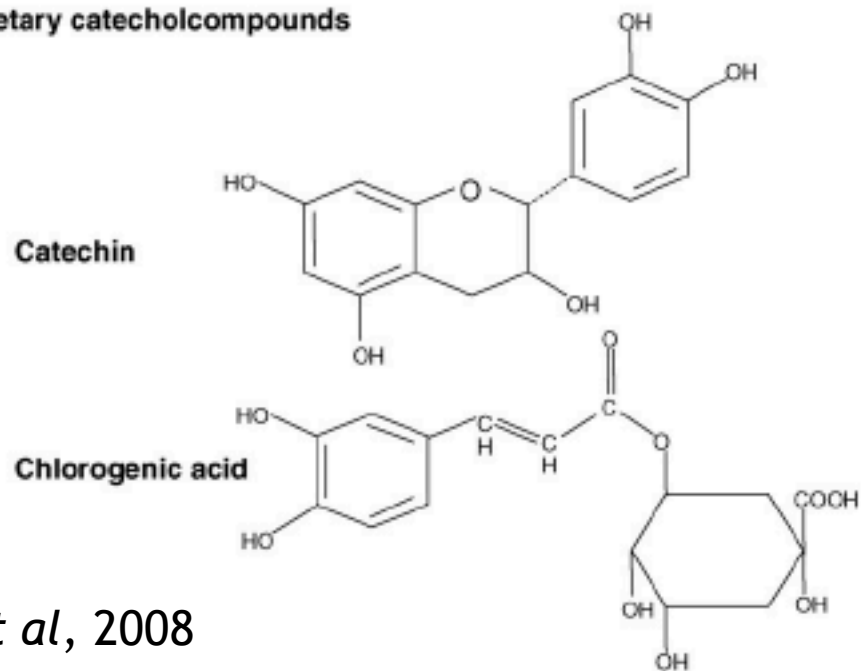
(a) Catecholamine biosynthetic pathway



(b) Synthetic catecholamine inotropes



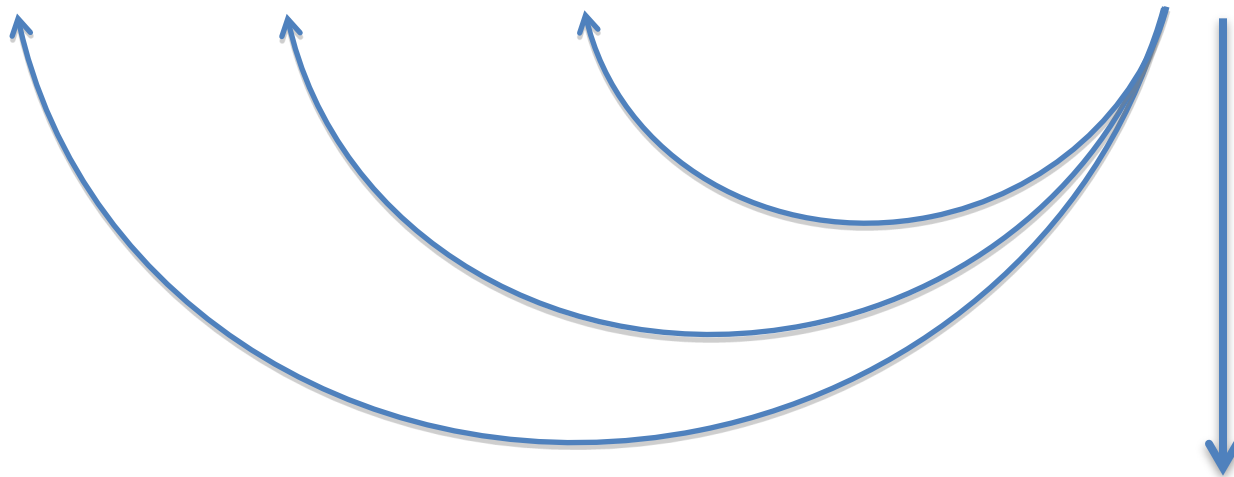
(c) Dietary catechol compounds



MICROBIAL ENDOCRINOLOGY. Freestone *et al*, 2008

The “Revised” Central Dogma

(GENOME) (TRANSCRIPTOME) (PROTEOME) (PARVOME)
DNA ↔ RNA → Protein → Natural Products



The Lexicon of Biology

“Life would not exist with macromolecules alone” (Stuart Schreiber, 2005)



IMPORTANT, BUT INCONCEIVABLE
NUMBERS

4×10^{11} Stars in the Milky Way

1×10^{24} Stars in the Universe

1×10^{30} Bioactive molecules in the Parvome

Genomic-based (intelligent?) Drug Discovery

Genome or Metagenomic sequences



Bioinformatic scanning: amplicon mapping



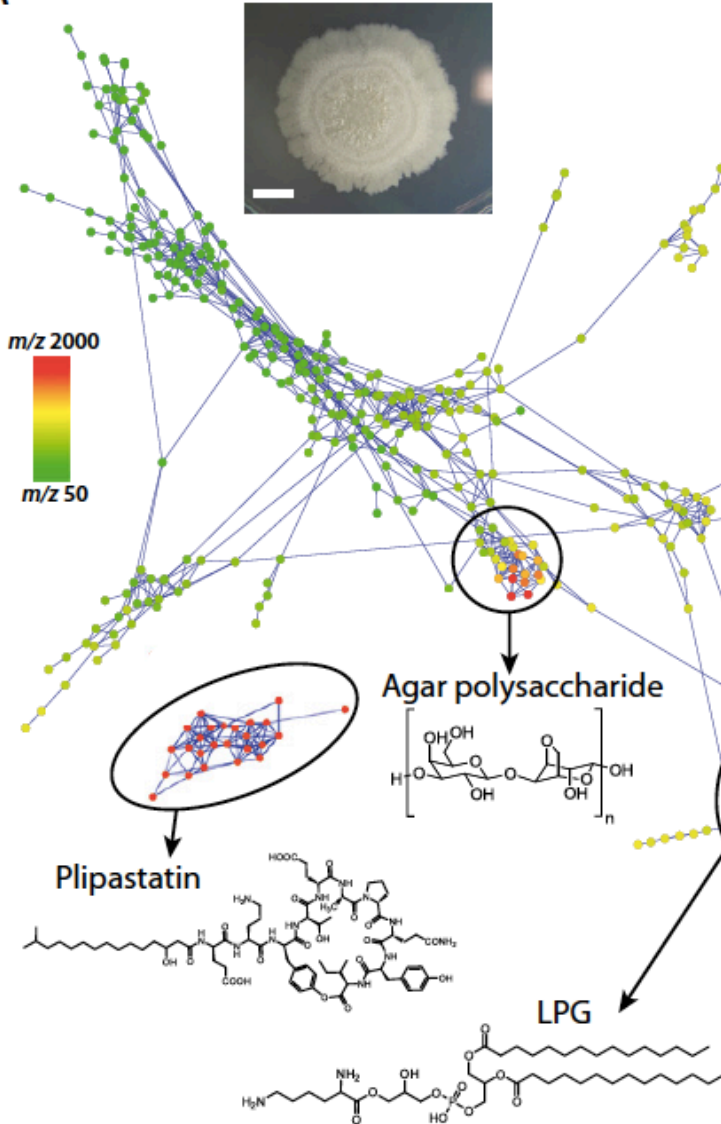
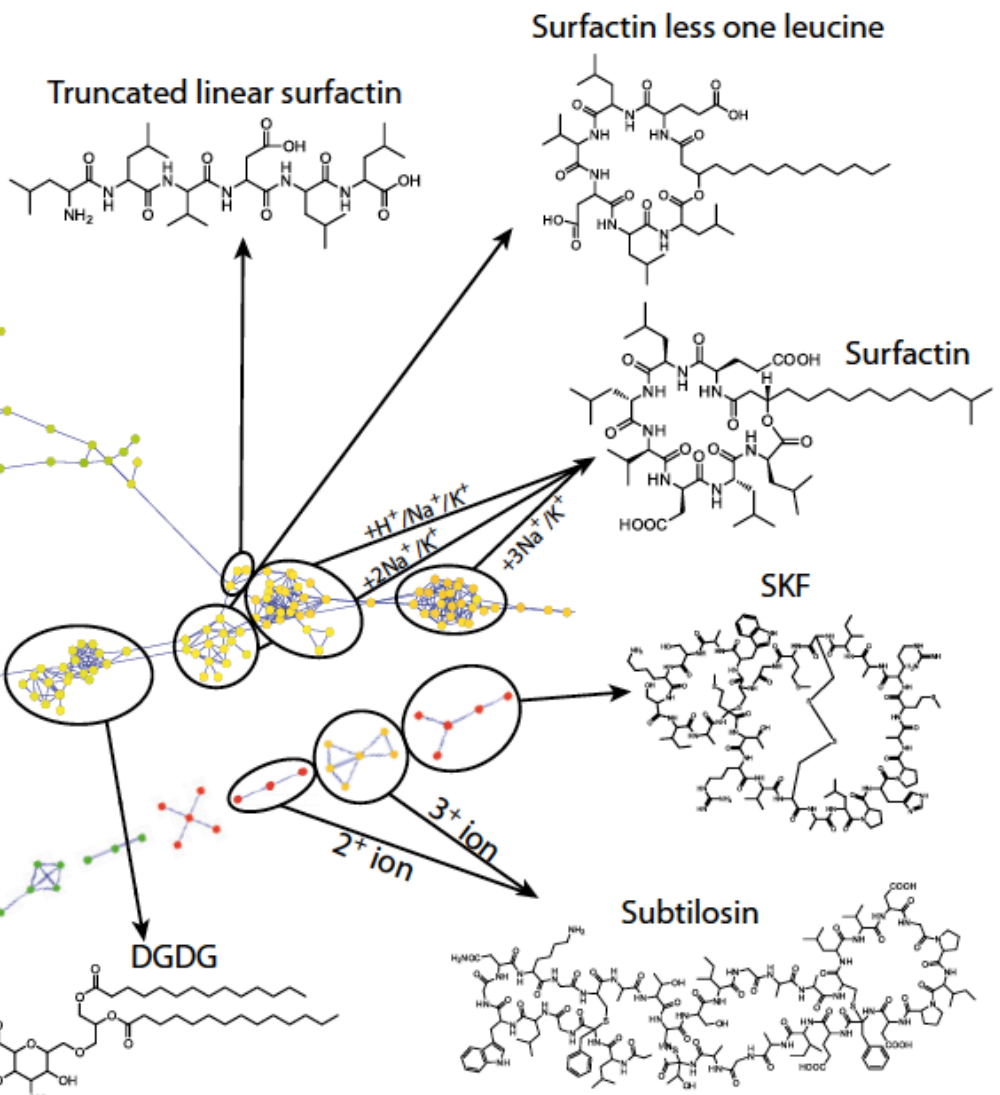
Identification of related molecular classes



Virtual docking with target databases

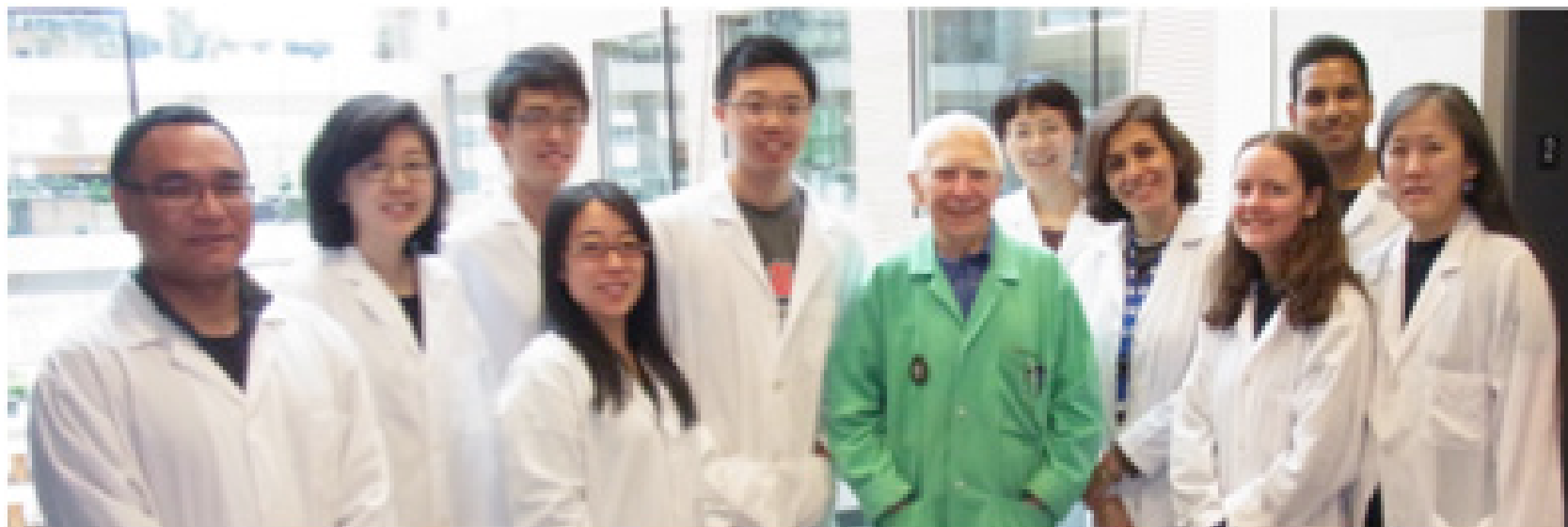


Over-production in engineered expression host

A**B. subtilis 3610**

Tracking and chemical identification of metabolites *in situ* using Imaging Mass Spectrometry

Watrous et al 2012



JED LAB
April 2013

Gaps and Challenges

- (1) State-of-the-art mass spectrometry and software essential but costly
- (2) Isolation of active compounds requires skilled hands and expensive software
- (3) The Human Microbiome Project is far from finished!

WASH YOUR HANDS!