Can anything be done to prevent antibiotic resistance development?

History, Mechanisms, Overuse, and Abuse

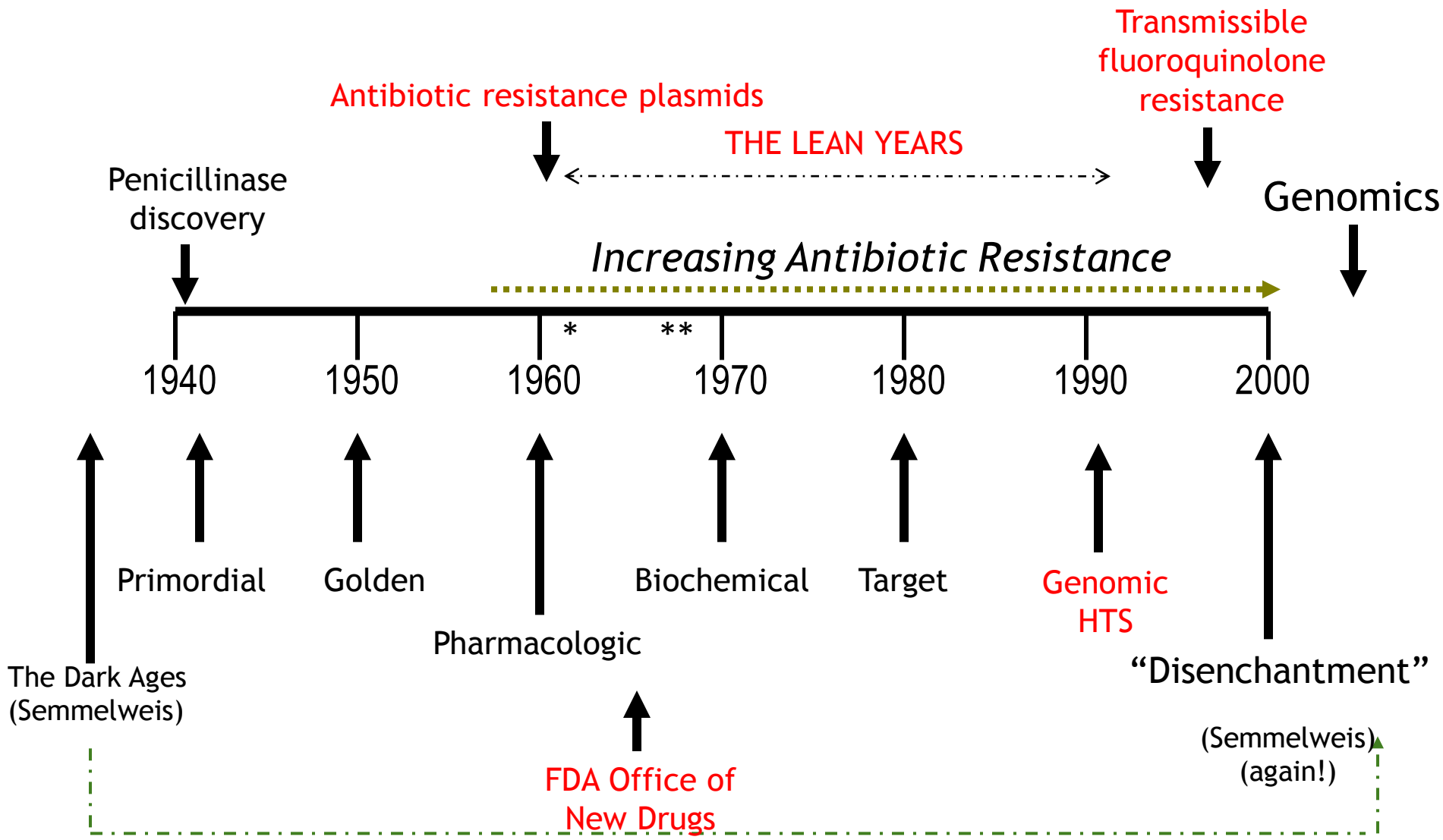
Antibiotics and antibiotic resistance: an inseparable combination?

Julian Davies

UBC,Vancouver

A brief history of antibiotic discovery

(The co-evolution of antibiotics and their cognate resistance)



MRSA: UK*, US**

Production: 50kg

>10^6 tons

Origins of R-factors (Japan)

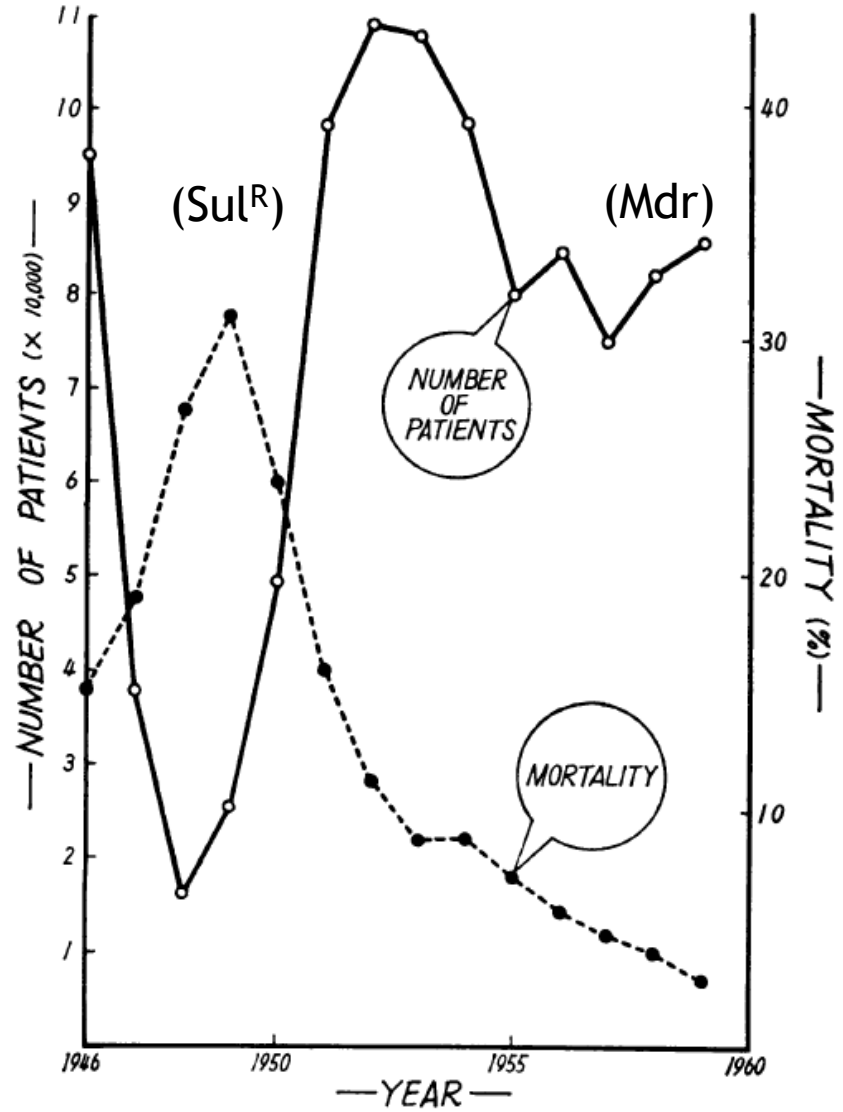
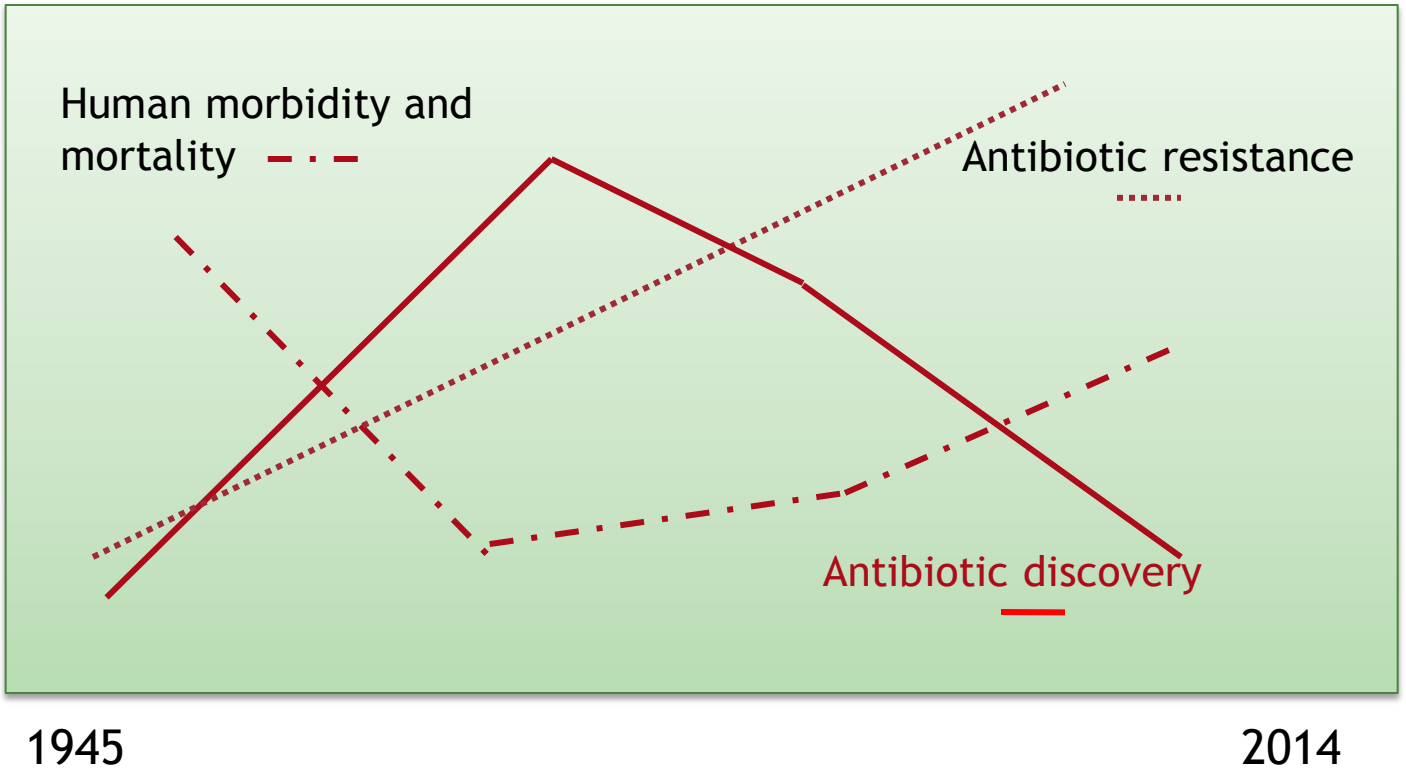


FIG. 1. *Statistics of bacillary dysentery in Japan between 1946 and 1959 (72).*

Watanabe,1963

Antibiotic Discovery, Resistance and Human Health

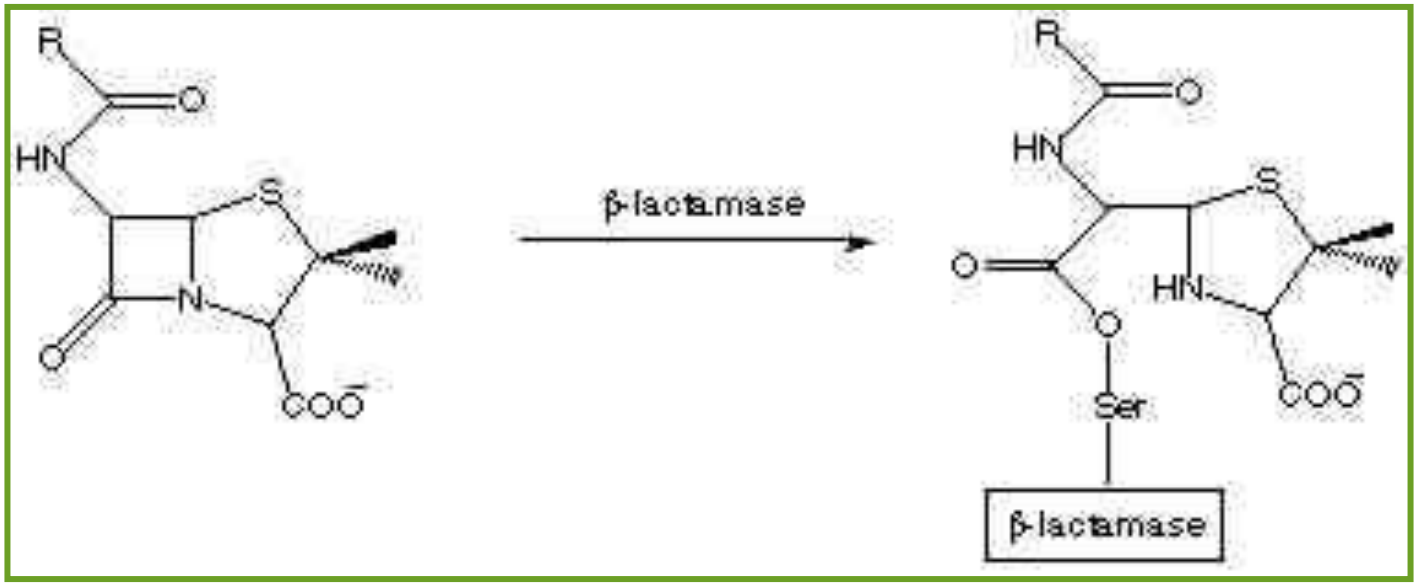


Biochemical Mechanisms of Antibiotic Resistance

Decreased influx*
Increased efflux*
Enzymatic inactivation of drug*
Sequestration*
Target modification*
Target by-pass*
Target repair
Target amplification*
Biofilm formation*
? Intracellular localisation in host

***ACQUIRED BY GENE TRANSFER.**

The most costly reaction in history!



Major classes of β-lactam antibiotics

Penicillin

Ampicillin, amoxicillin oxacillin, methicillin

Cephalosporin

Ceclor®, Keflex®, cefotaxime, ceftazidime

Carbapenem

Imipenem, meropenem ertapenem, doripenem

Oxapenam

Clavulanic acid

(**Augmentin® + Amox)**

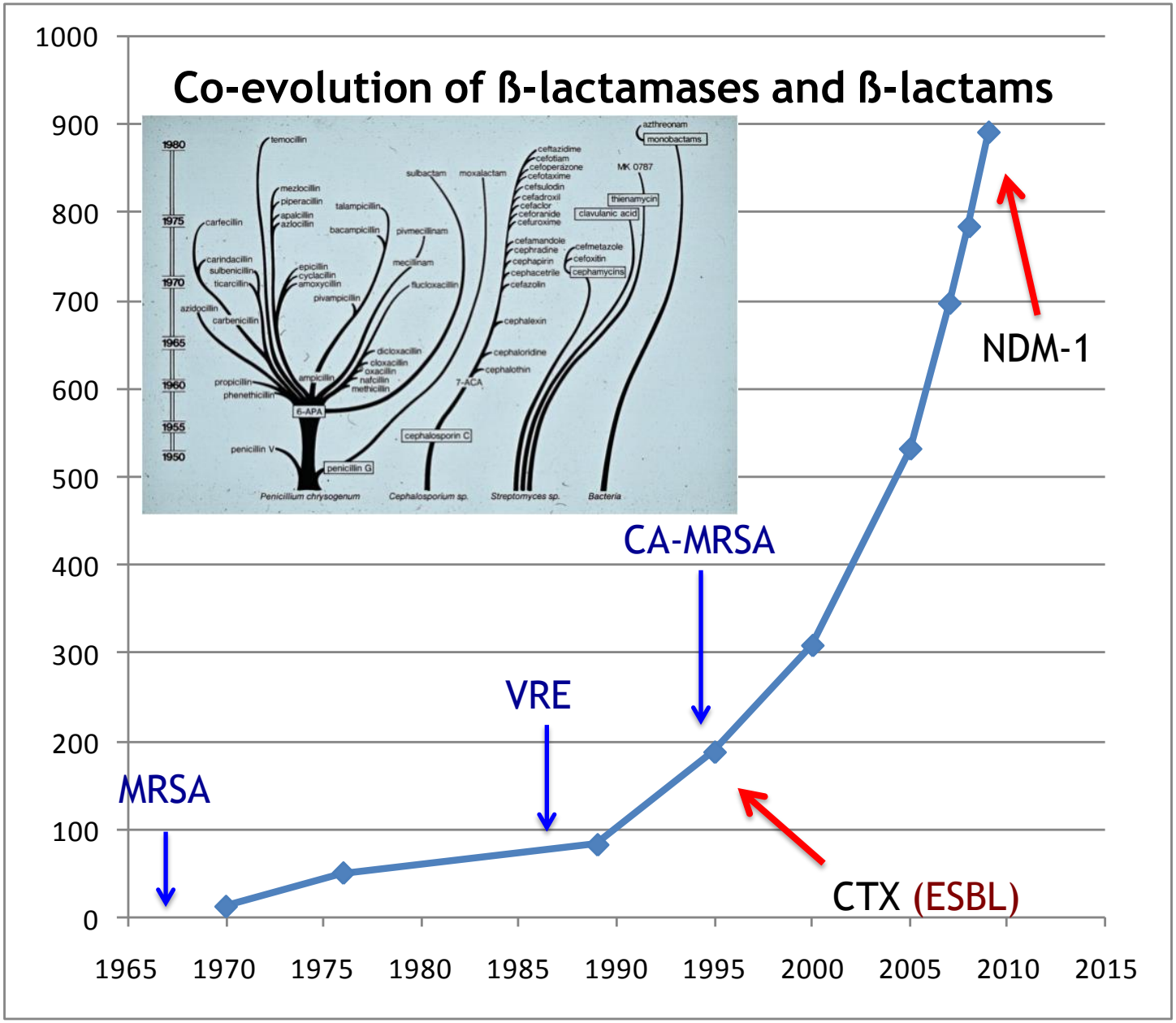
Penicillanic acid sulfone

Sulbactam

(Unasyn® + Amp)

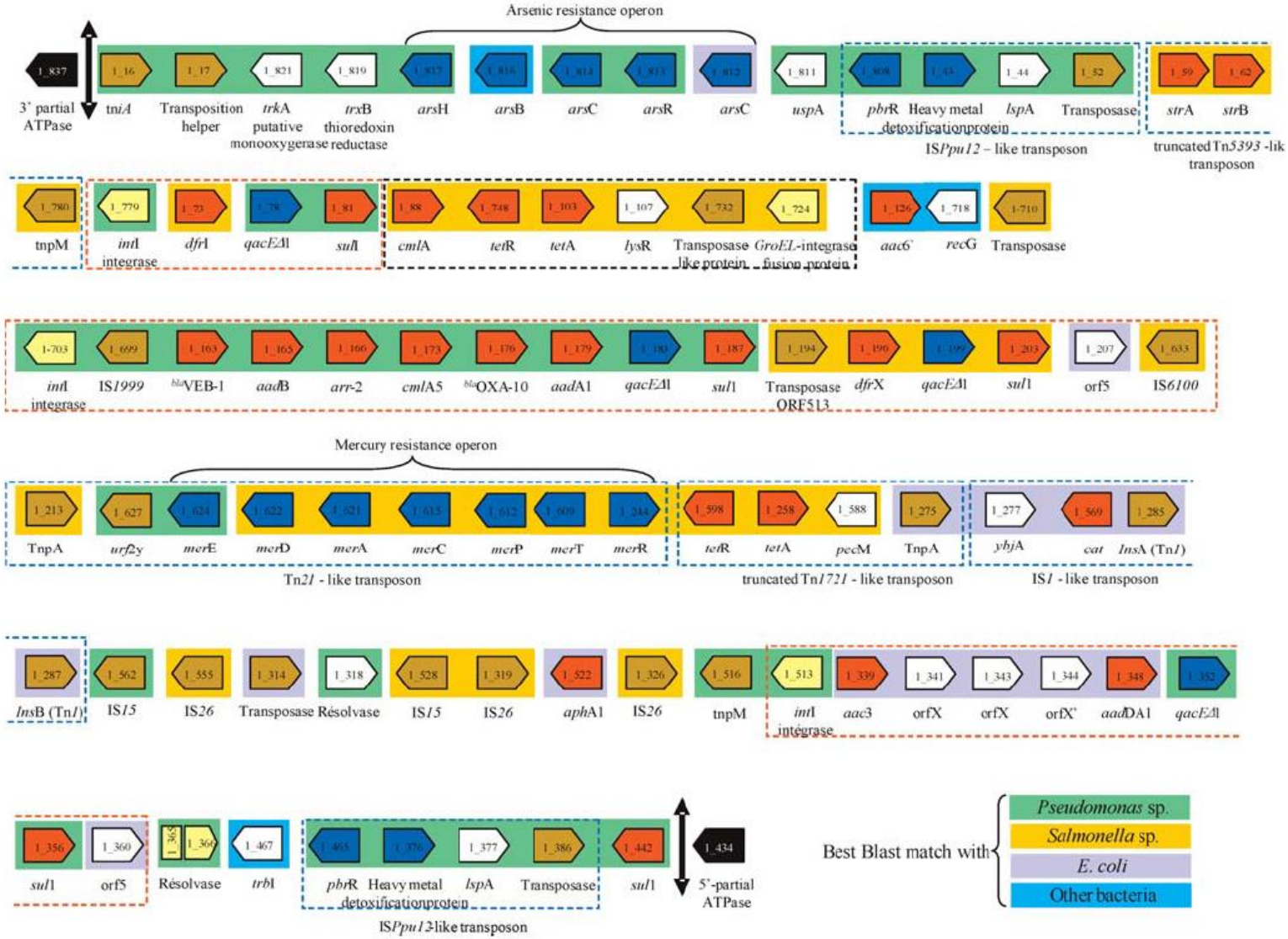
Monobactam

Aztreonam



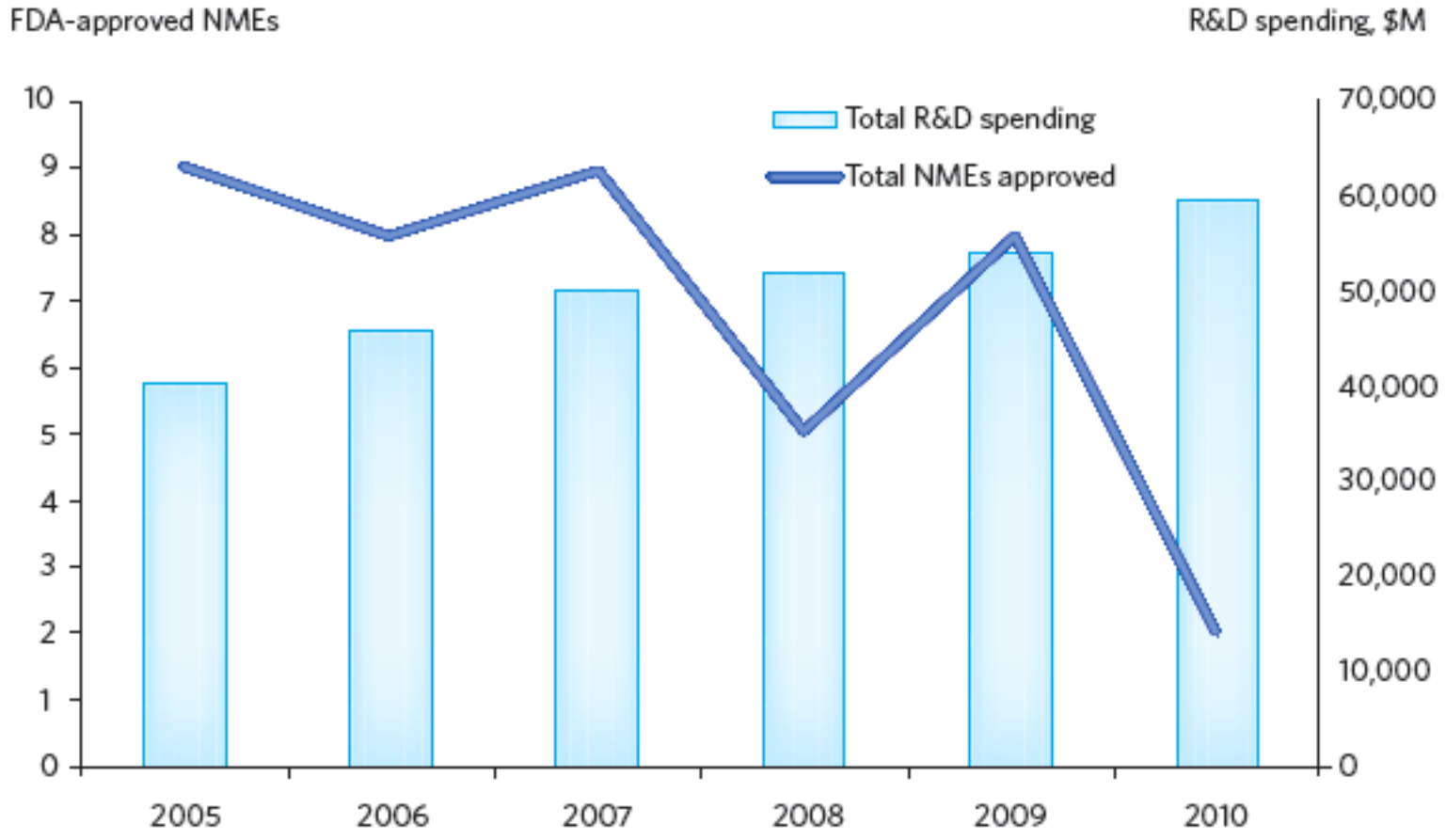
Information provided by Karen Bush

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

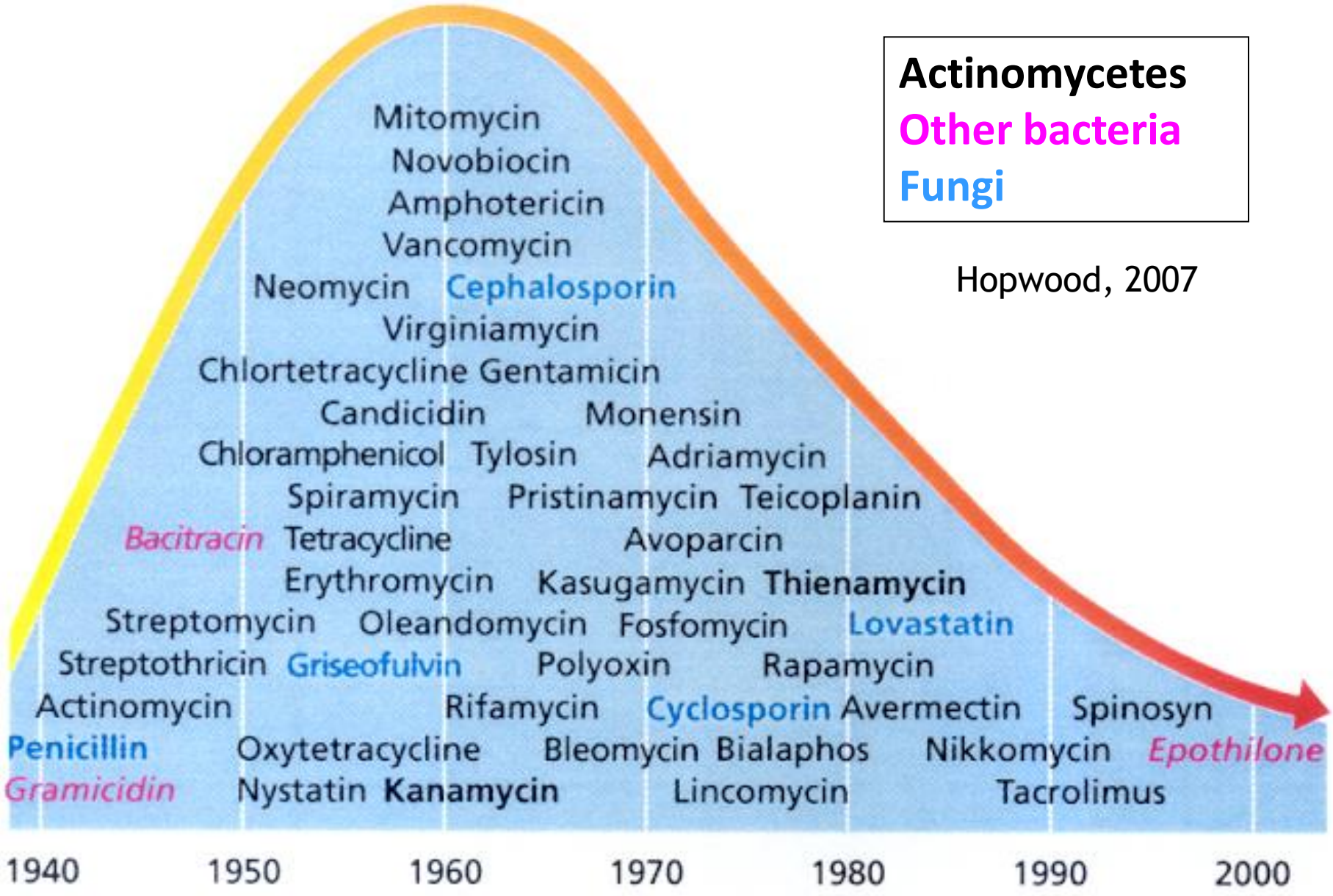


Fournier *et al.* (2006)[9]

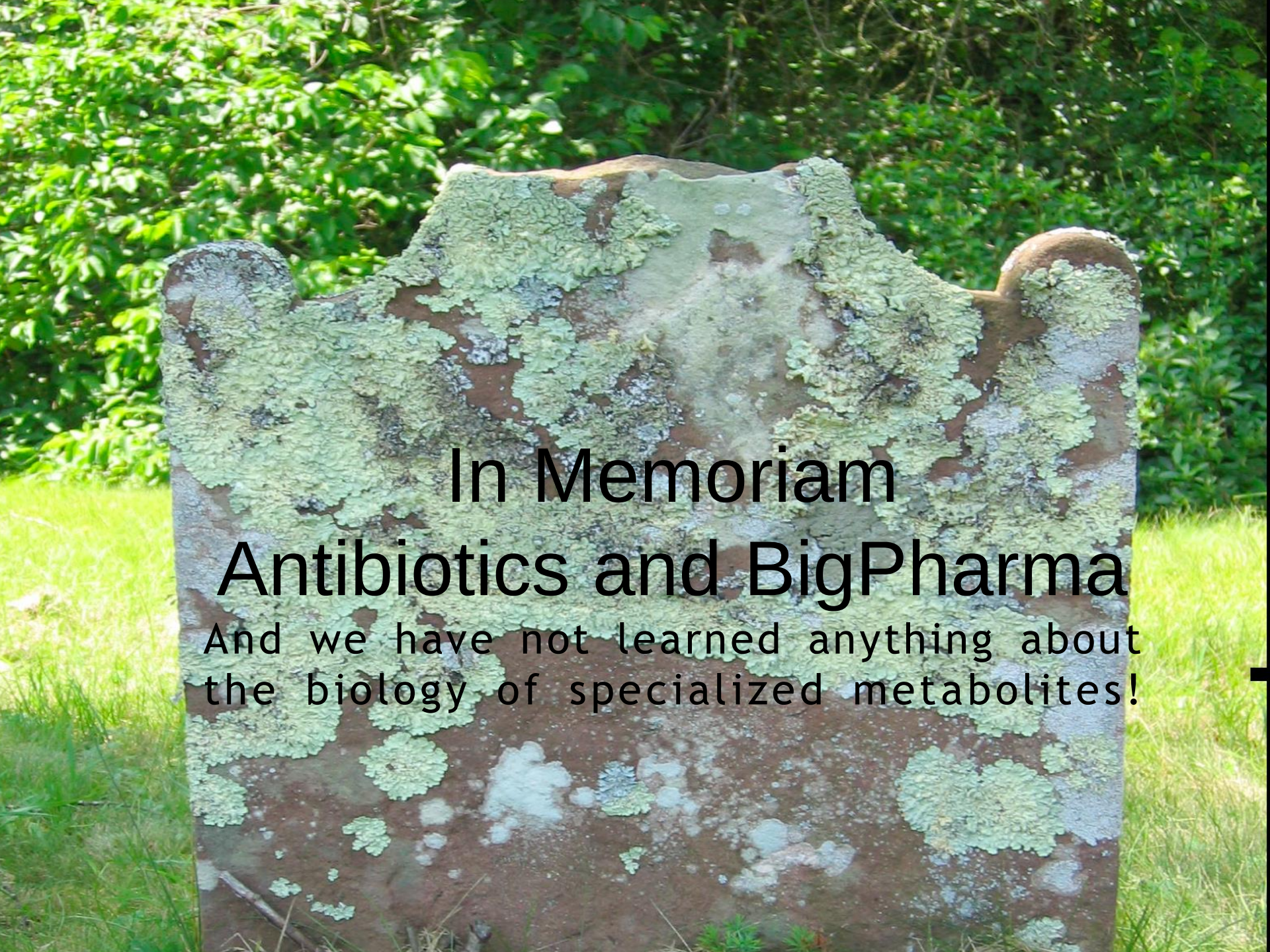
The Drastic Decline in Drug Discovery
How do we restore the Pharmaceutical industry?



M.Bunnage, 2011



Diminishing returns in finding useful antibiotics

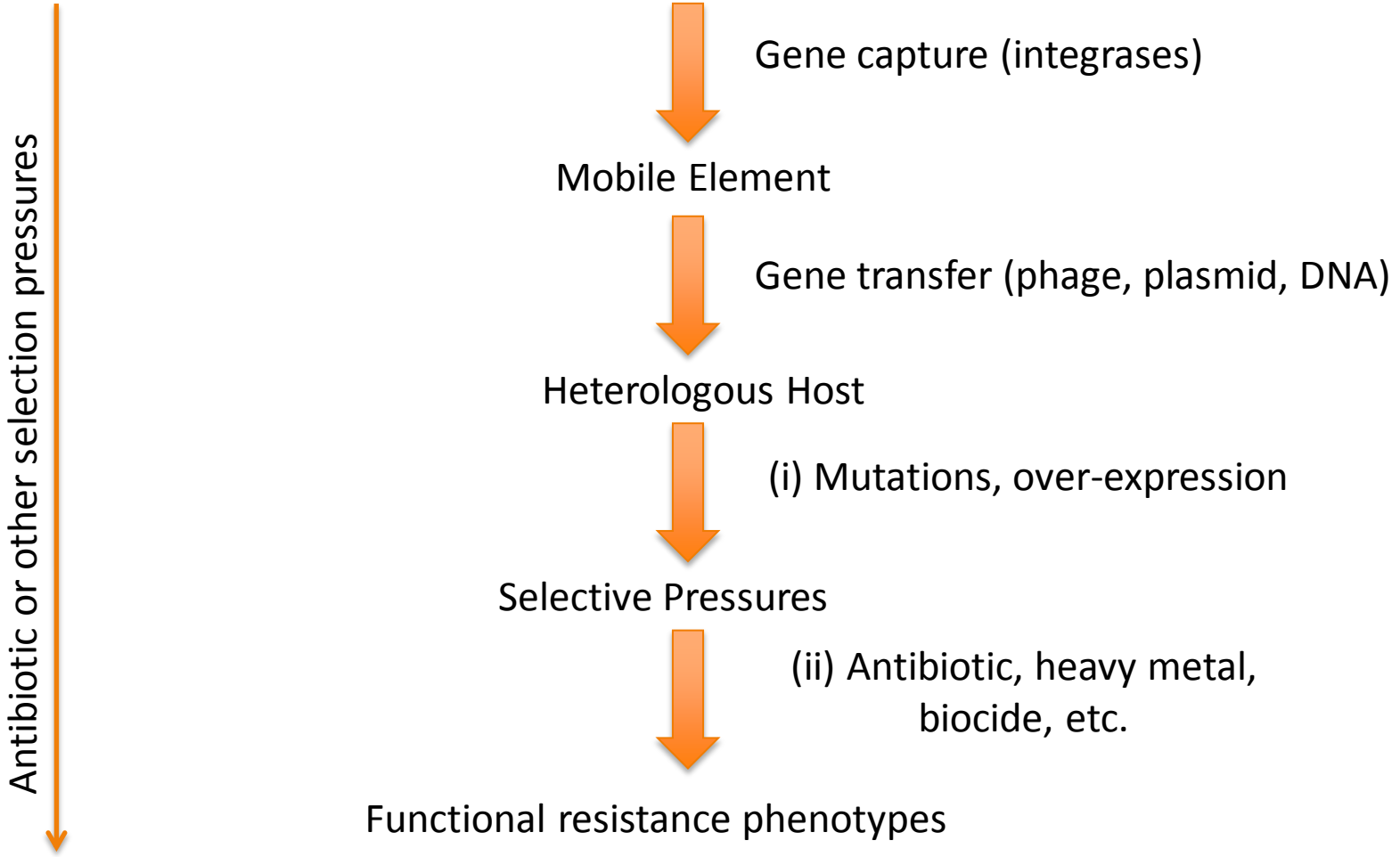

In Memoriam
Antibiotics and BigPharma
And we have not learned anything about the biology of specialized metabolites!

Overcoming antibiotic resistance: no single solution

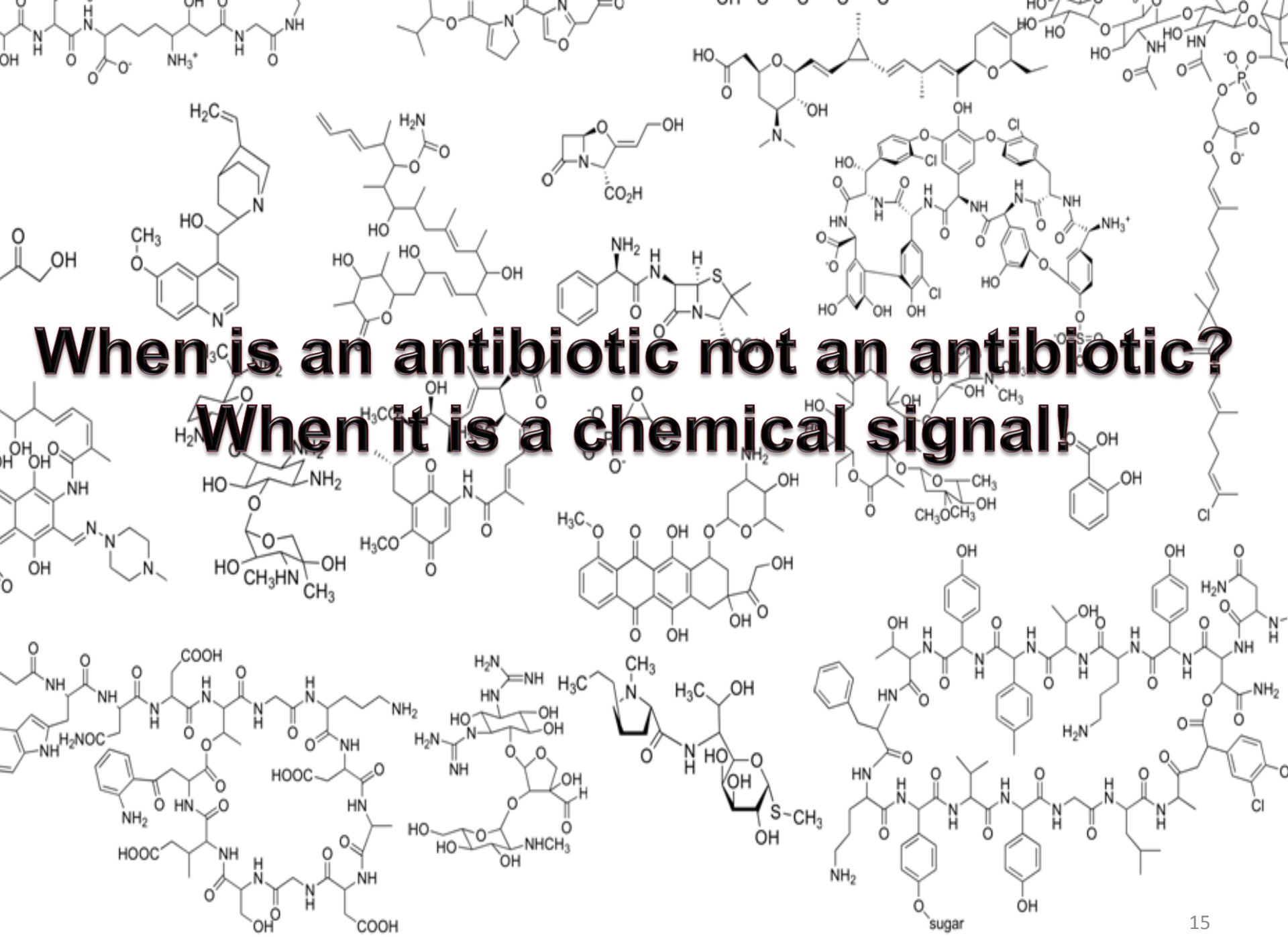
1. Novel antibiotics: harvesting the Parvome
2. “Revisiting” and remodeling old compounds
3. Defined, synergistic cocktails of antibiotics
4. Systems biology approaches to controlling resistance
5. Sequence-based rapid, accurate molecular diagnosis: “niche” treatments
6. Antibacterial vaccines
7. Phage therapy and combinations
8. Enhancing innate immunity
9. Microbiome transplants
9. Universal food and clean water standards
10. Strict control of antibiotic use

First of all: where do antibiotic resistance genes come from? Acquisition from clinical and environmental resistomes? How?

Genes for resistance or *quasi-resistance" (no/weak phenotype)



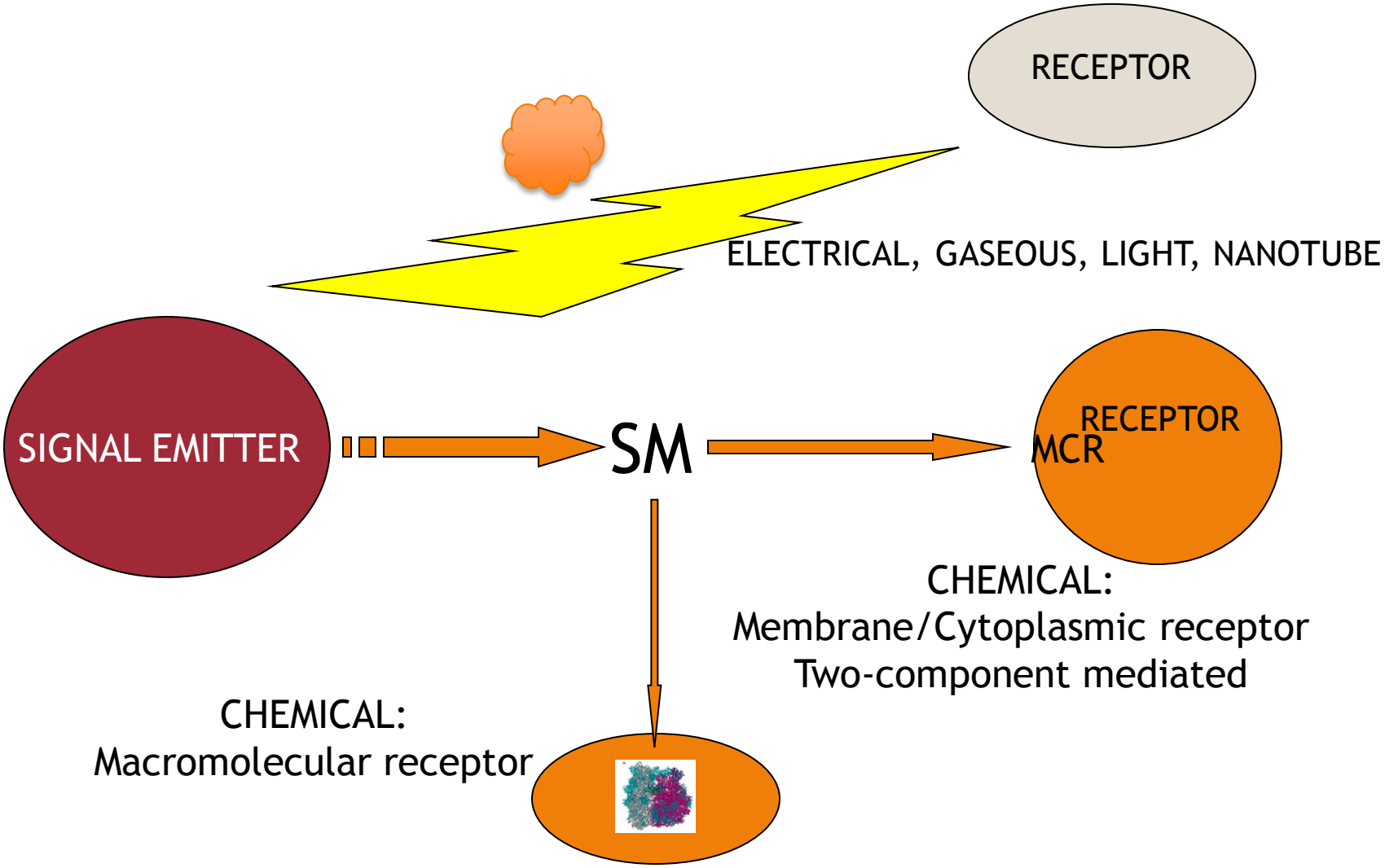
(*biosynthesis, degradation, signalling, metabolism, regulation)


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

Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.

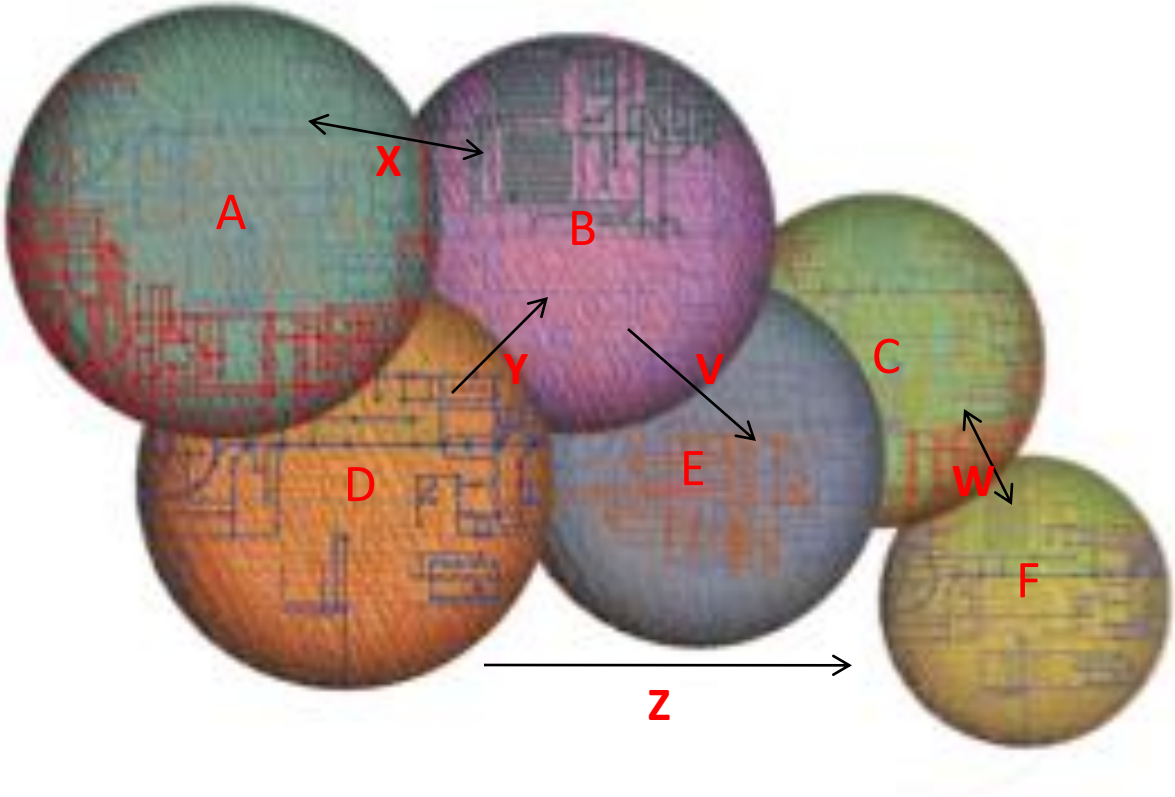
Auroleus Phillipus Theostratus Bombastus von Hohenheim a.k.a Paracelsus (1493-1541)

Natural signalling mechanisms



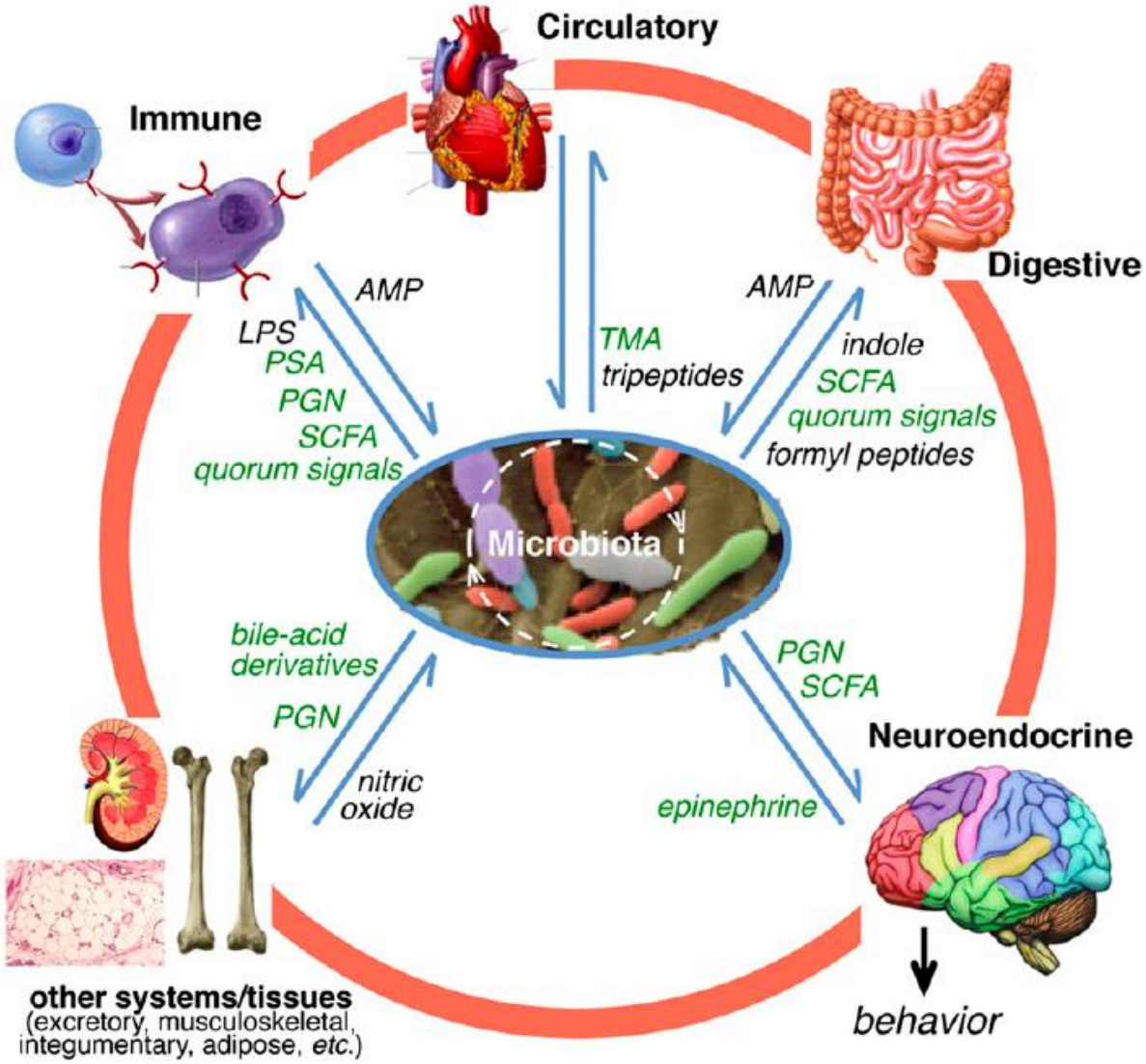
Signalling response ➡ specific transcription

The “NEW” understanding:
Cell communities consist of distributed metabolic networks



CHEMICAL CONNECTIONS/SIGNALS

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

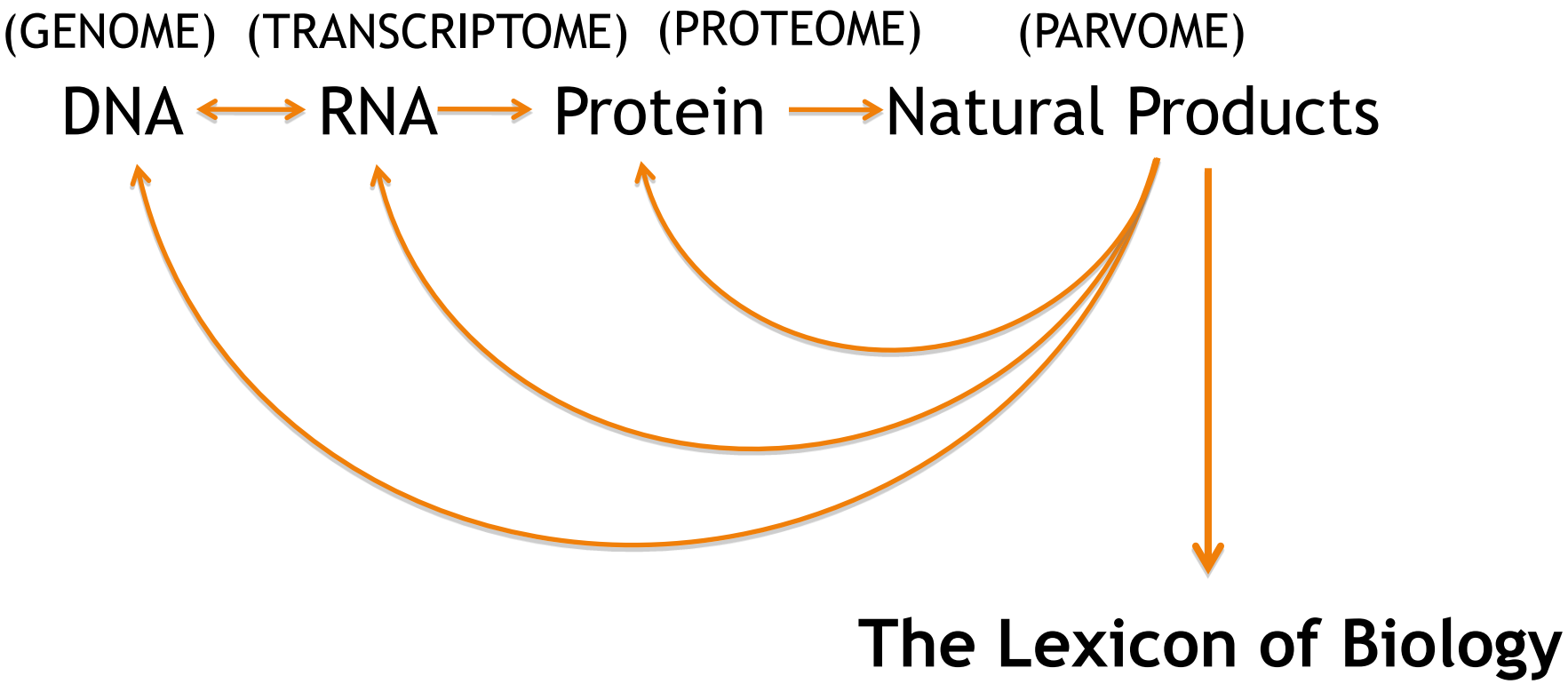


Microbial and cell phenotypes and interactions are controlled by exogenous chemical signals

Metabolic changes
Stress responses
Inhibitor susceptibility, resistance
Gene transfer, competence
Virulence
Pigmentation
Morphology, biofilms, swarming
Growth and multicellularity

Are antibiotics *naturally* antibiotics?

The "Revised" Central Dogma



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

Genomic-based Drug Discovery

Genome or Metagenomic sequences

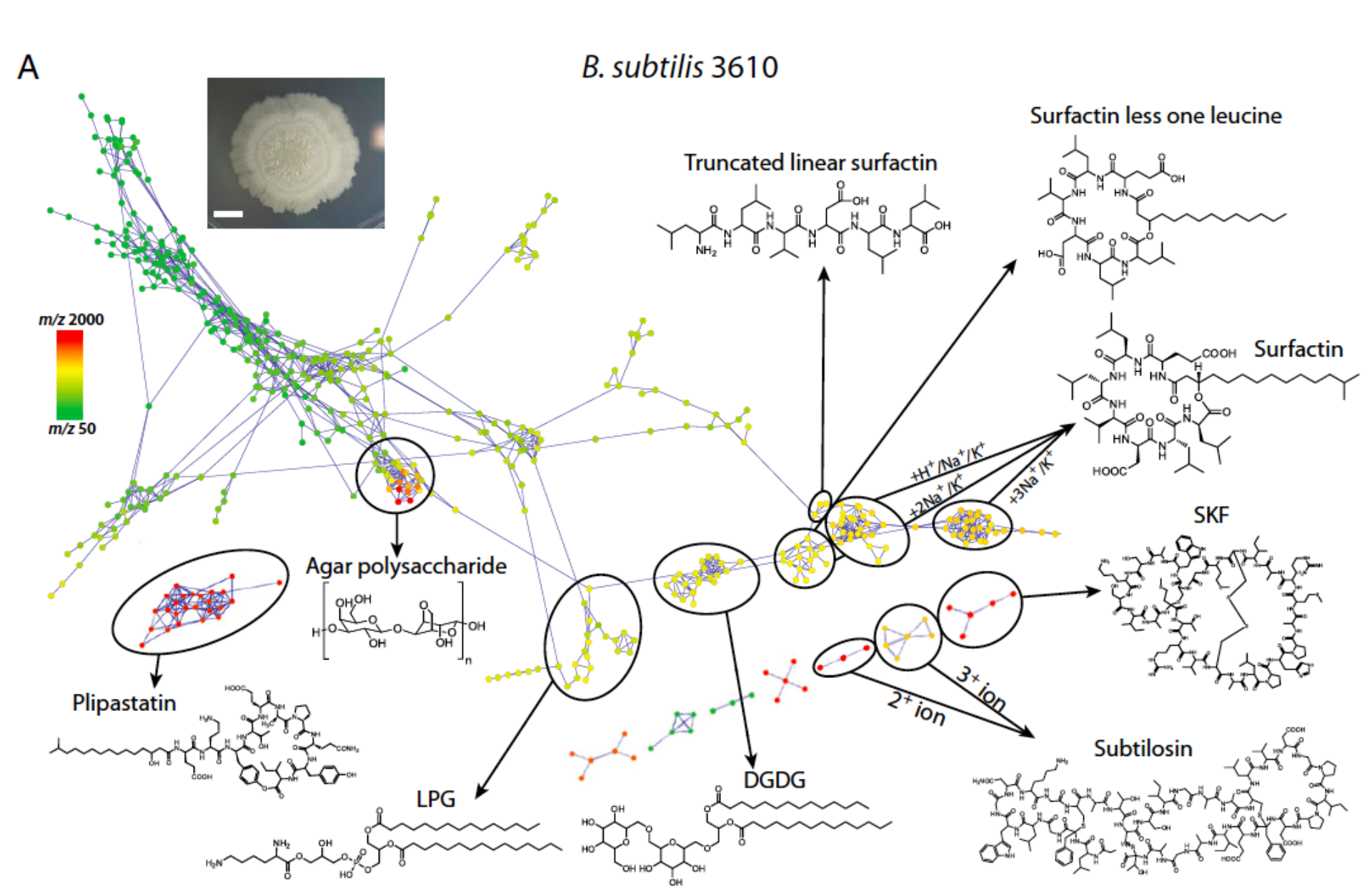
Bioinformatic scanning: amplicon mapping

Identification of related molecular classes

Cloning defined pathways

Over-production in “designer” expression host

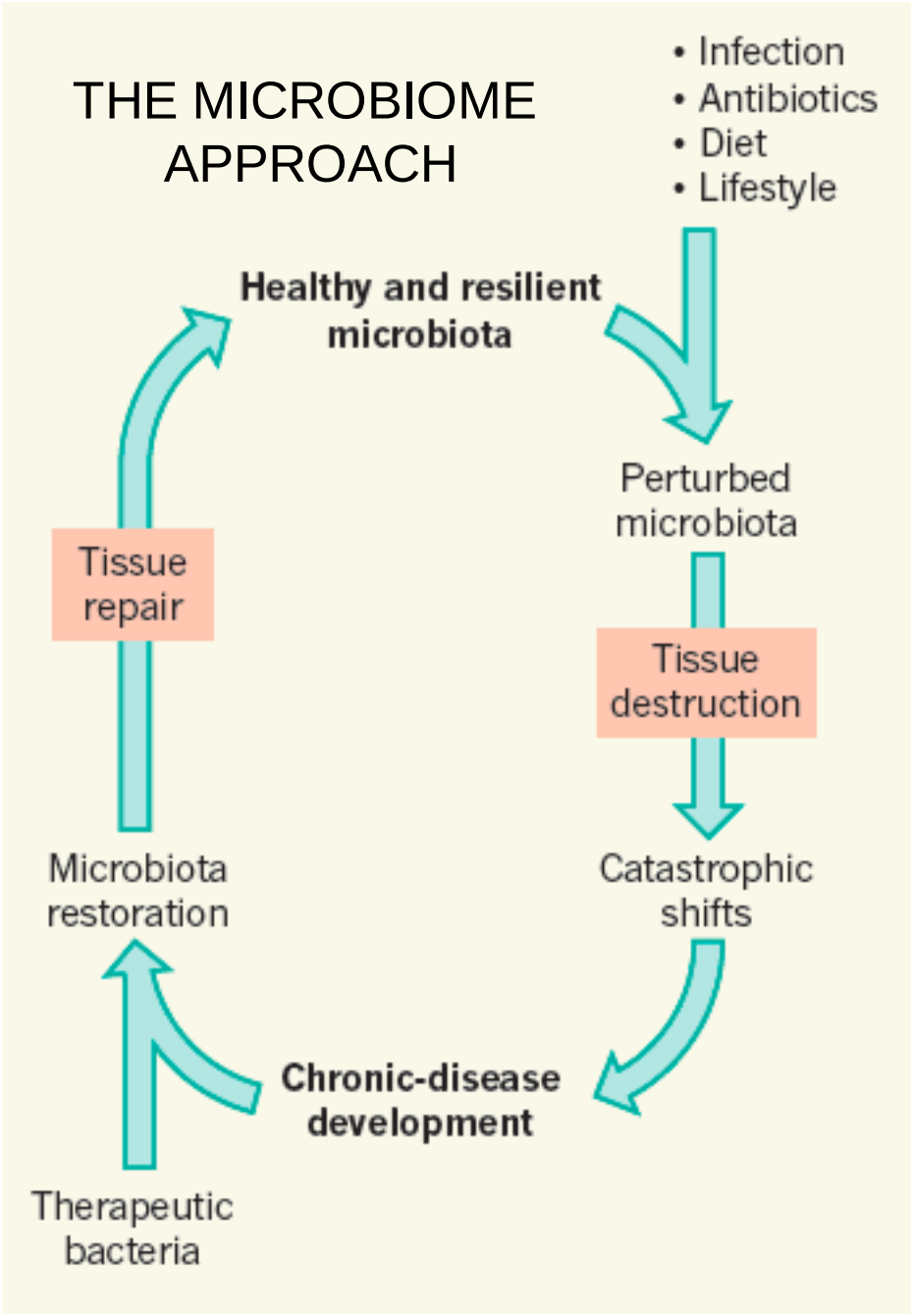
Novel molecules for testing:



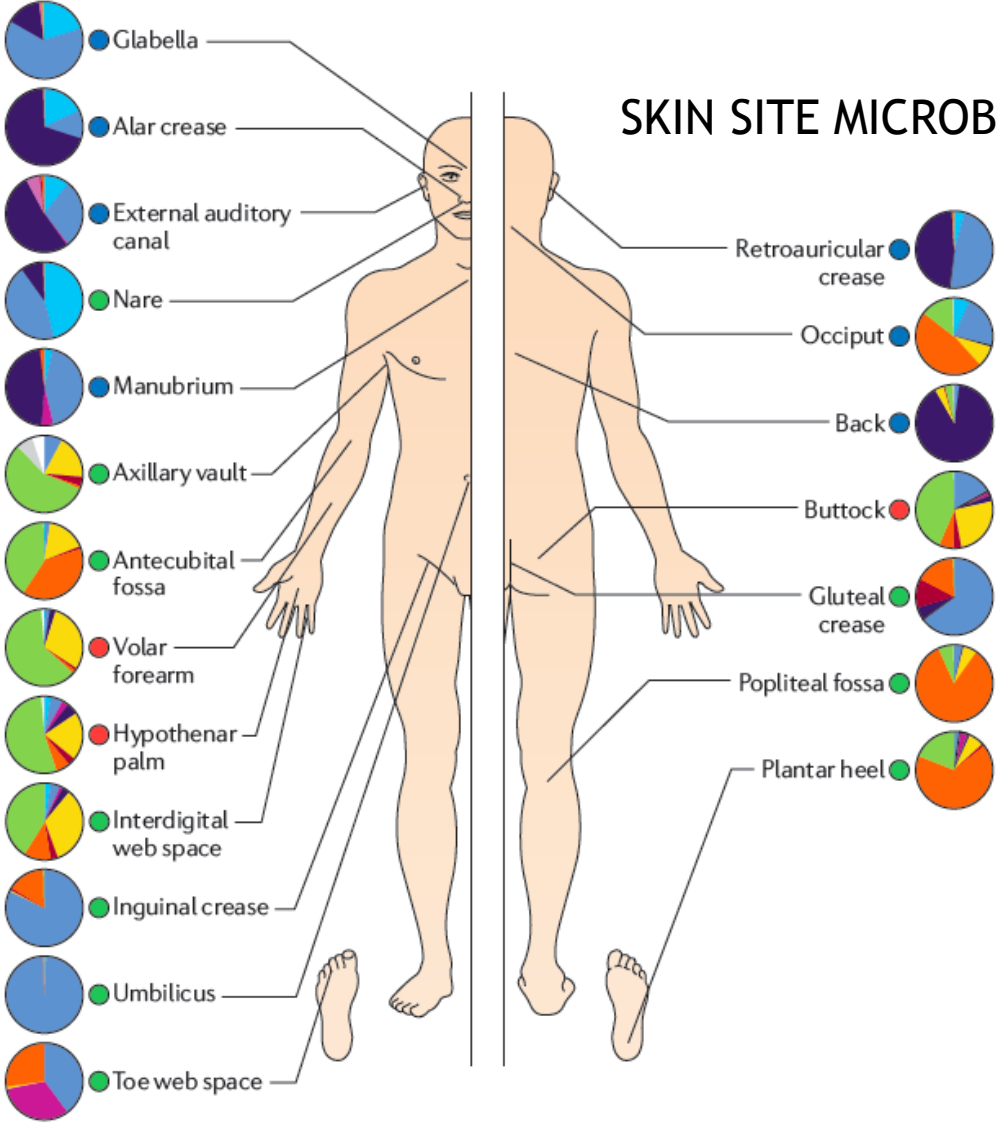
Finding novel metabolites *in situ* using Imaging Mass Spectrometry

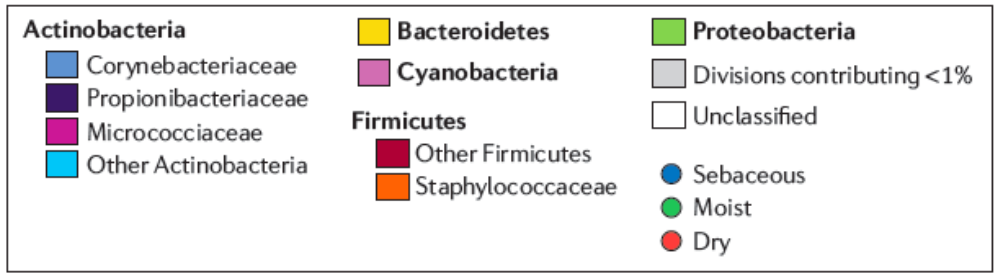
Watrous et al 2012

THE MICROBIOME APPROACH



SKIN SITE MICROBIOMES (Segre,2011)





OPPORTUNITIES FOR "DESIGNER" PROBIOTICS

SOME DISEASES ASSOCIATED WITH THE HUMAN MICROBIOME

Systemic Diseases	**Cancers**
Obesity	Esophageal adenocarcinoma
Type 1 diabetes	Colon cancer
Cardiovascular diseases	Colorectal cancer
	Cervical cancer
Digestive Tract Diseases	Liver cancer
Crohn's disease	Gastric cancer
Antibiotic-induced *C. difficile* infection	Oral squamous cell carcinoma
Necrotizing enterocolitis	Pancreatic cancer
Intestinal bowel disease	Colitis-associated cancer
Pediatric irritable bowel syndrome	
Ulcerative colitis	**Autoimmune Diseases**
Celiac disease	Multiple sclerosis
	Rheumatoid arthritis
Vaginal Diseases	Autoimmune uveitis
Bacterial vaginosis	Autism
	Asthma
Skin Diseases	Allergic diseases
Psoriasis	
Eczema	**Oral Diseases**
	Periodontal diseases

SOURCE: HMP #1

THE REVENGE OF THE SUPERBUGS

"In natural evolutionary competition,
there is no guarantee that we (humans)
will find ourselves the survivors"

JOSHUA LEDERBERG

"The microbe always has the last word"

LOUIS PASTEUR

"It is not the strongest of species that survive,
nor the most intelligent,
but the ones most responsive to change"

CHARLES DARWIN

Will this succeed? Locally? Nationally? Worldwide?

WASH YOUR HANDS!

(BUT DON'T USE TRICLOSAN)

Recommendations of the Banbury Conference 2011

- Research Priorities:, development of new antimicrobials, identify resistance sources, emergence, interception, “point of care” analyses, rapid action, world-wide surveillance, origins (persistors?).
- Public education, public health, clean water and good sanitation-for-all, quality-of-life objectives: resuscitate old antibiotics: global efforts in finding and tracking outbreaks: stricter control of antibiotic use: alternatives such as vaccines, phage, antibodies: use of new diagnostic/predictive medicine: international/collaborative interventions.
- Set achievable goals

Antibiotic classes (and their targets)

(1947) Aminoglycosides (protein synthesis)*
(1957) Rifampicin (RNA synthesis)
(1940) ß-lactams (cell wall synthesis)*
(1948) Chloramphenicol (protein synthesis)*
(1979) Fluoroquinolones (DNA synthesis)*
(1957) Macrolides (protein synthesis)*
(1962) Lincosamides (protein synthesis)*
(1947) Polymyxins (membrane function)
(1949) Tetracyclines (protein synthesis)*
(1969) Fosfomycin (cell wall synthesis)
(1987) Daptomycin (cytoplasmic membrane)
(1953) Vancomycin (peptidoglycan synthesis)*
(1951) Mutilins (protein synthesis)*

* Indicates significant use in animals