



Cape Cod Morning, Edward Hopper, 1950

Finding hope in a hopeless time

How Predictive Modeling and Data Analytics shifts our perspective about antimicrobial discovery

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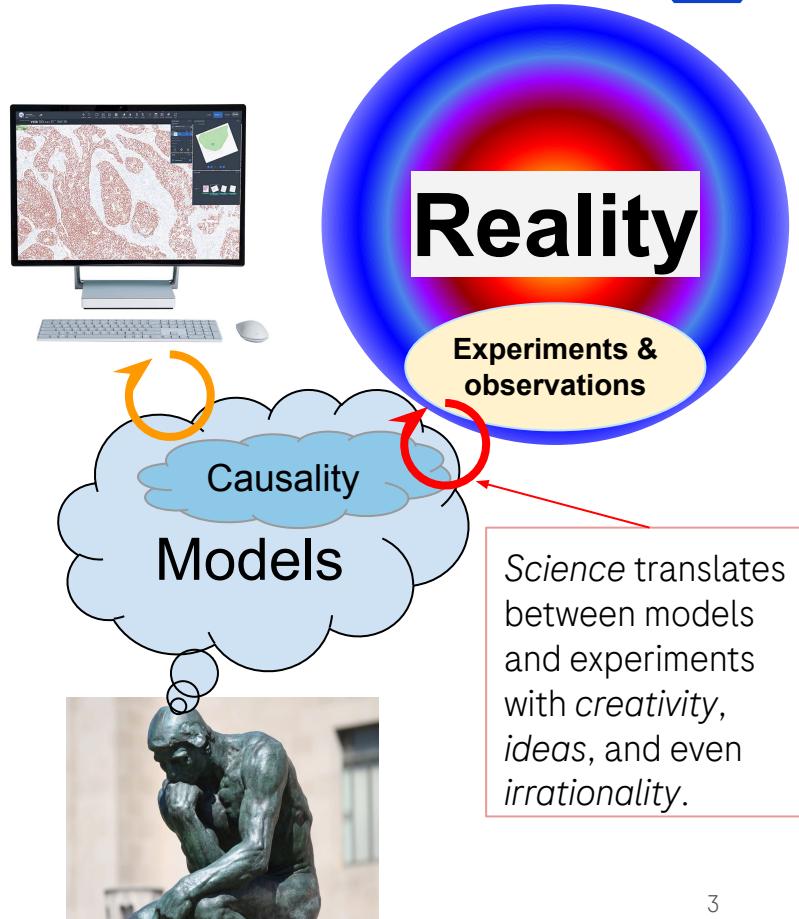
Pharmaceutical Sciences, Pharma Research and Early Development
Roche Innovation Center Basel
F. Hoffmann-La Roche Ltd

Outline

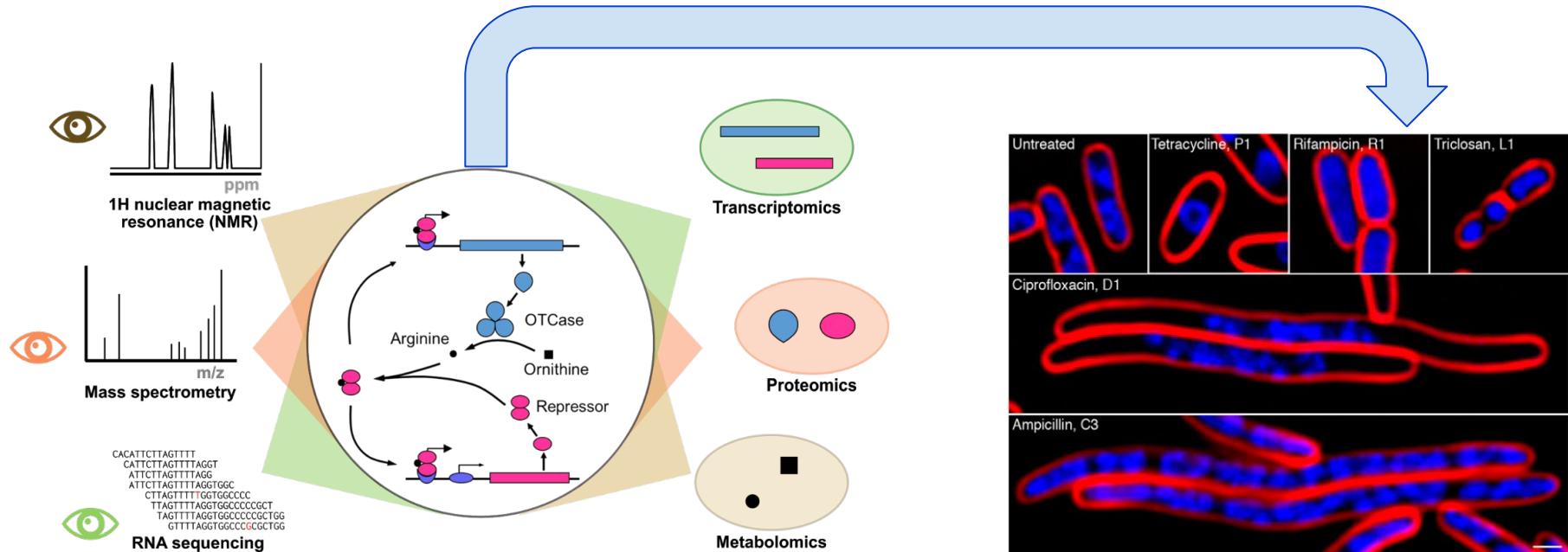
- Predictive Modeling and Data Analytics integrates knowledge, experiments, and machine intelligence to establish causality.
- Three case studies of PMDA in antimicrobial drug discovery:
 1. Imaging and machine learning for MoA;
 2. Molecular phenotyping for safety assessment;
 3. Single-cell sequencing for cellular heterogeneity;
- Challenges and prospects

Five hallmarks of predictive modeling in drug discovery

1. *Human intelligence*
2. *Machine intelligence*
3. *Experiments & observations*
4. *Models, including causality*
5. *Iterations*

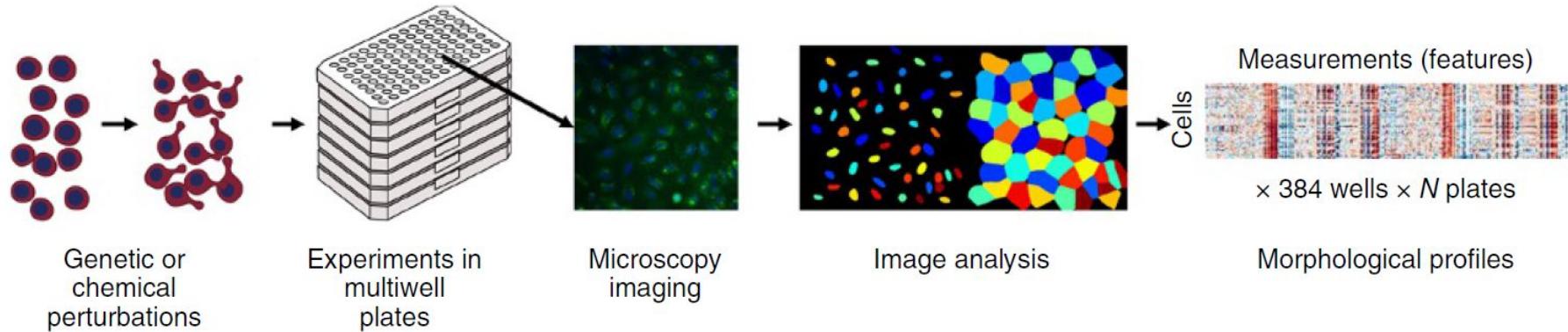
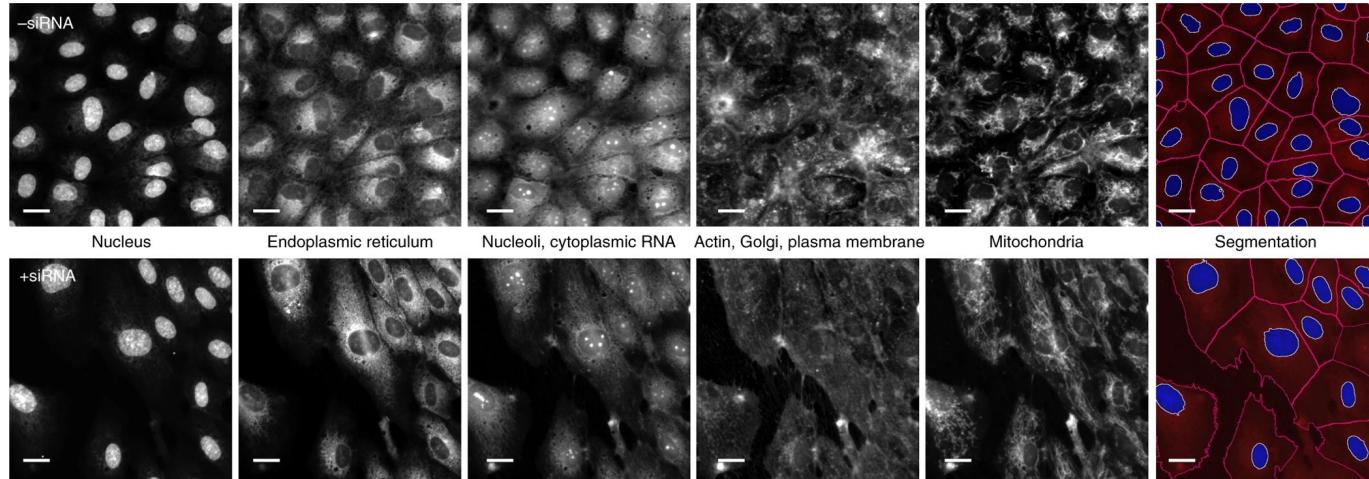


Omics and morphology offer rich biological information



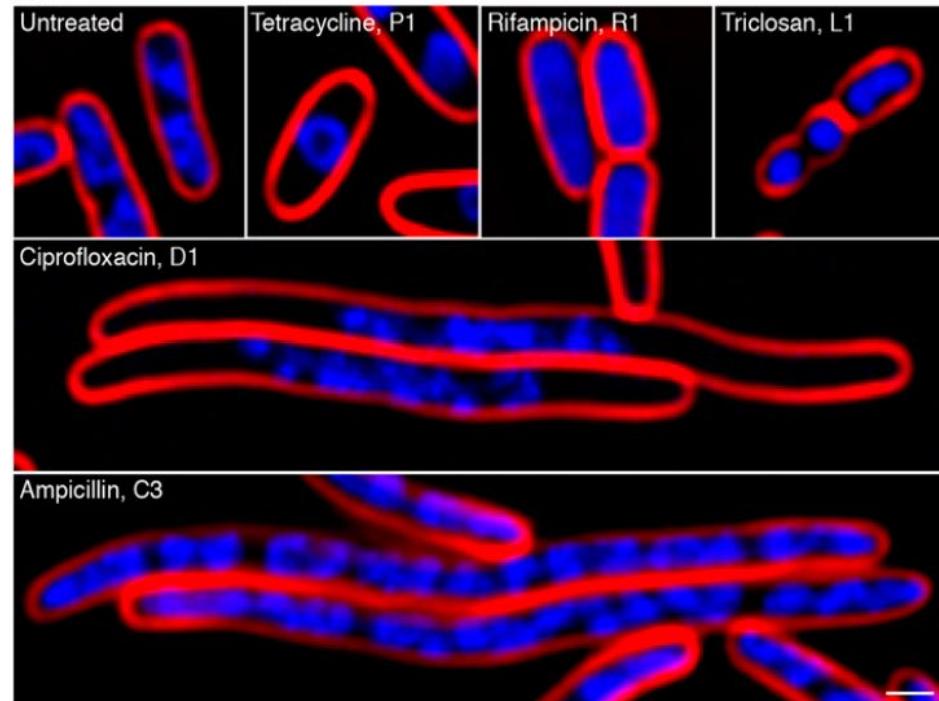
Cell identity and state represented as high-dimensional data

Imaging-based screening and machine learning empower phenotypic drug discovery

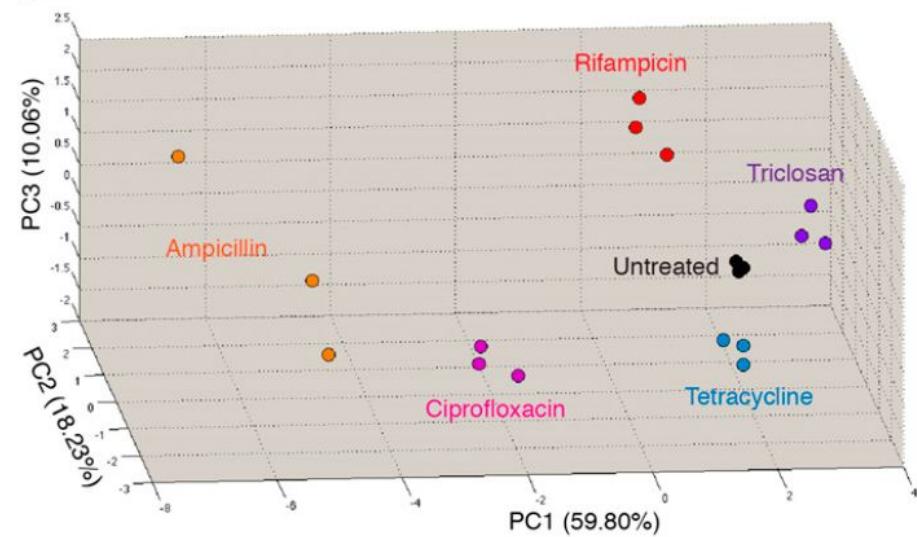


Bacterial cytological profiling identifies cellular pathways targeted by antibacterial molecules

A



B



P: Protein translation inhibitors

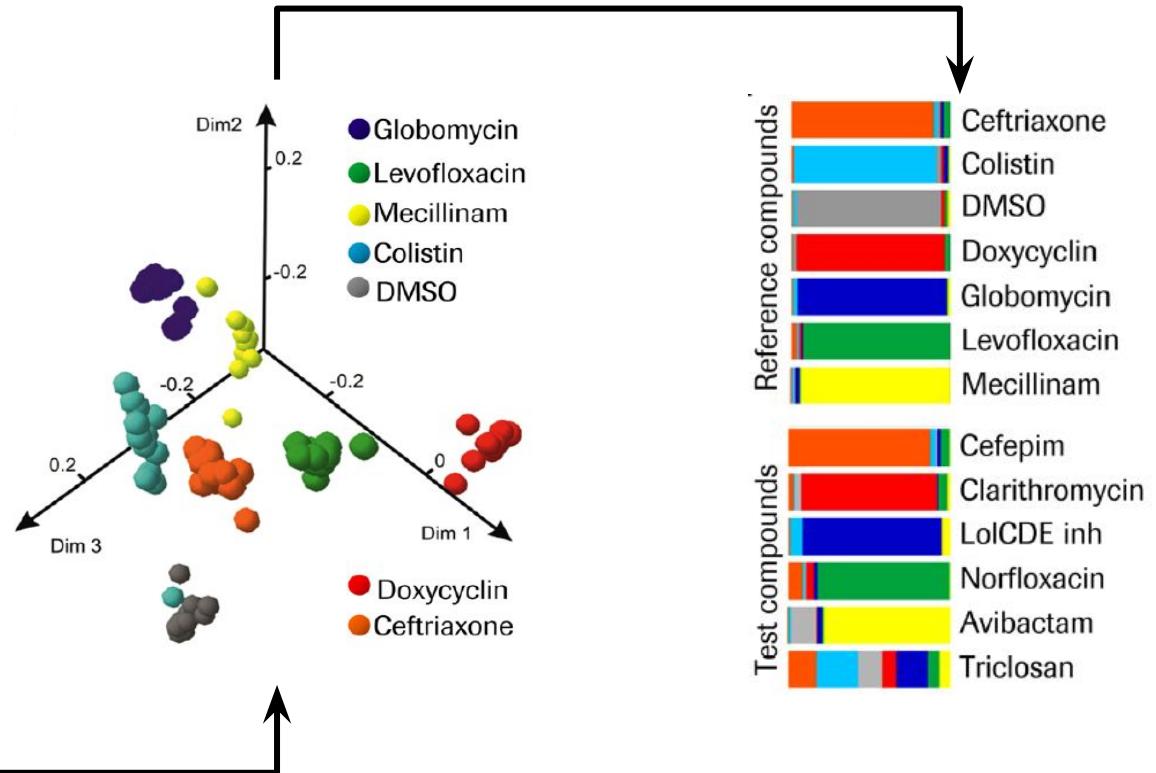
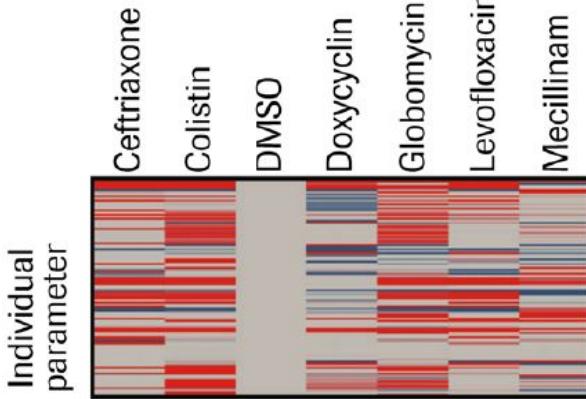
R: RNA transcription inhibitors

D: DNA replication inhibitors

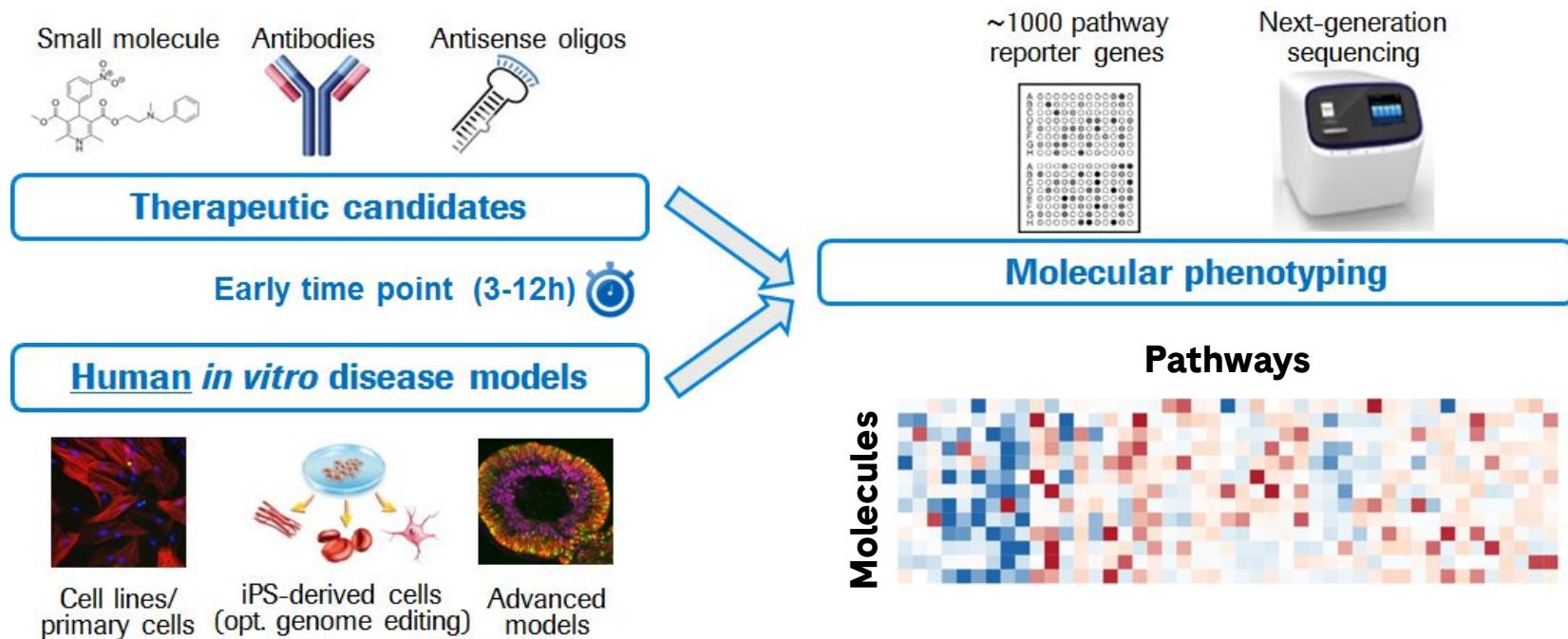
L: Lipid biosynthesis inhibitors

C: Cell-wall synthesis inhibitors (peptidoglycan)

Morphology classifies compounds by MoA

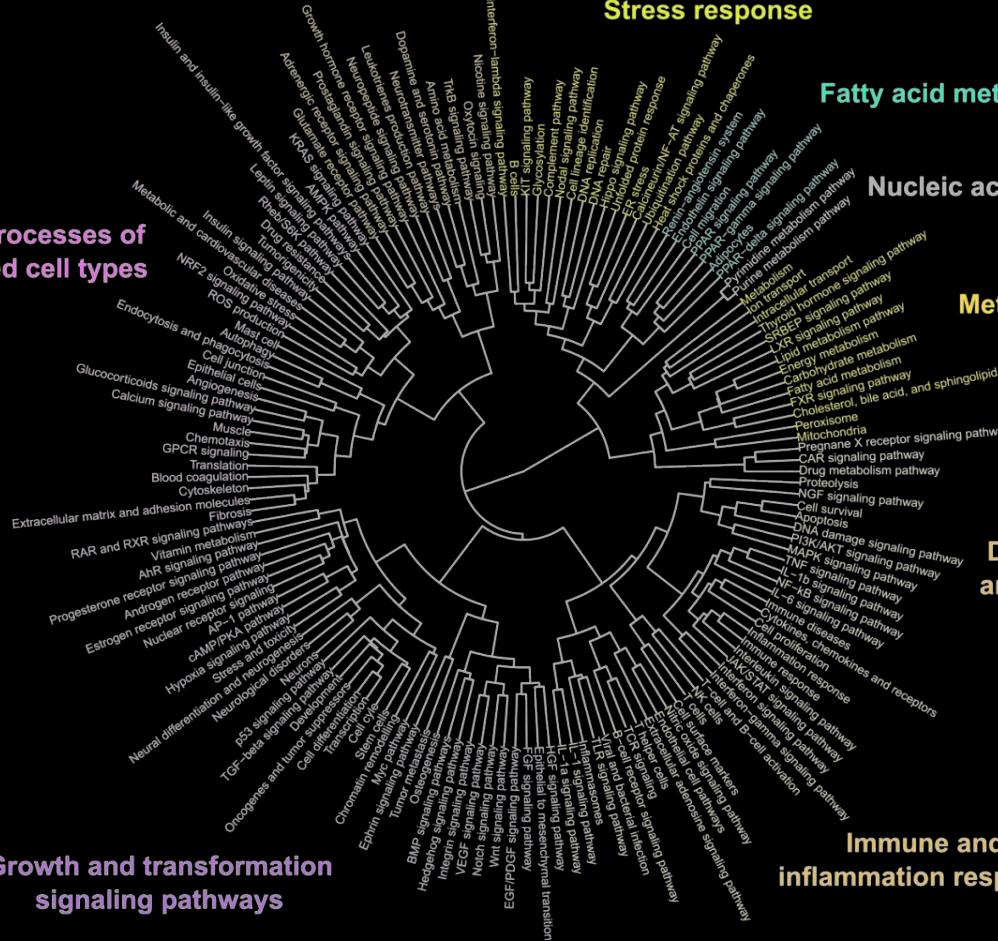


Molecular phenotyping reveals modulation of human pathway activities by compounds



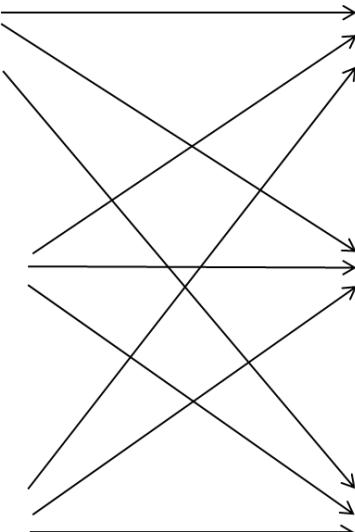
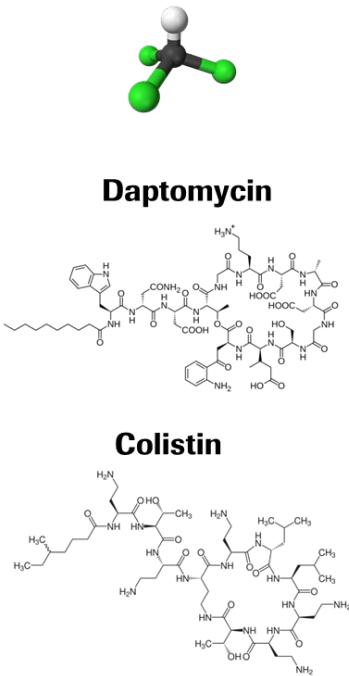
Hormone and neuropeptide signaling

Biological processes of differentiated cell types

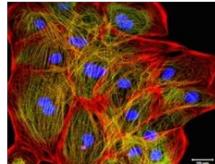


Three antibiotics profiled in three cell systems with molecular phenotyping for safety assessment

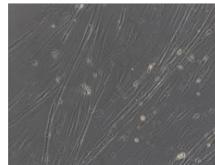
R0xyz



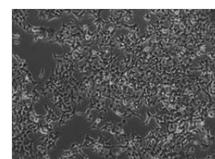
iPS-derived human cardiomyocytes



Primary human skeletal muscle cells



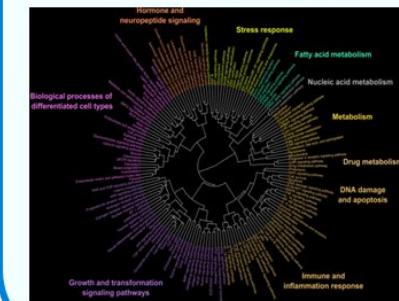
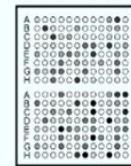
Human embryonic kidney cells



**6h treatment at
sub-cytotoxic concentration**

**Molecular
phenotyping**

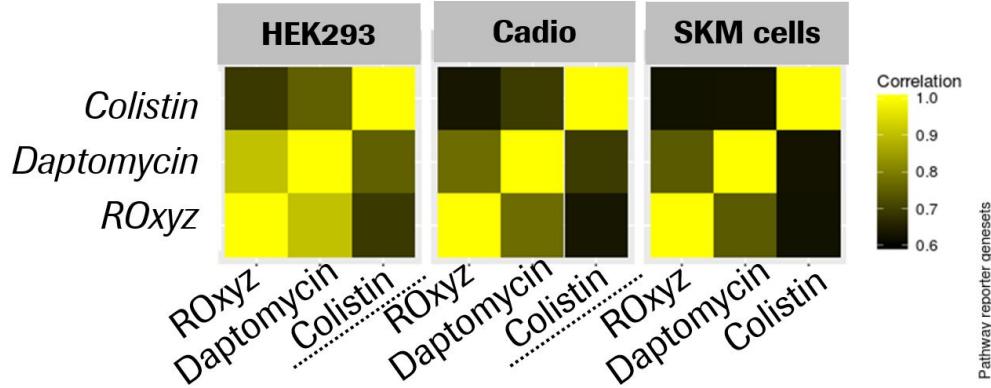
Pathway Reporter Genes



Roche compound is more similar with daptomycin than colistin, irrespective of cell type

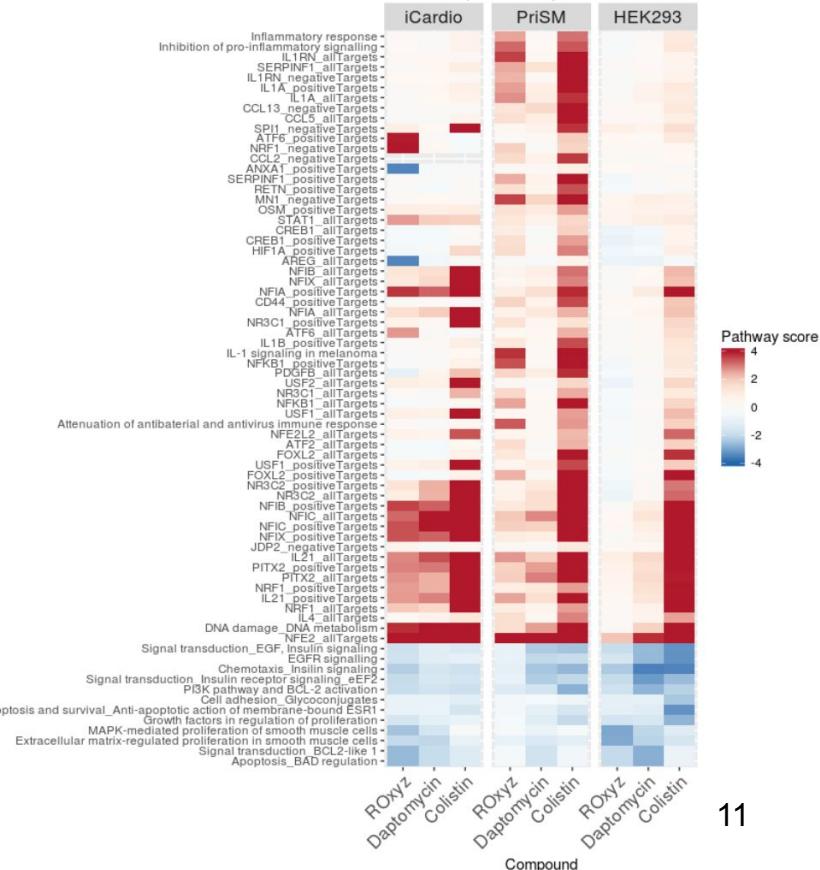


Similarity of differential expression profiles

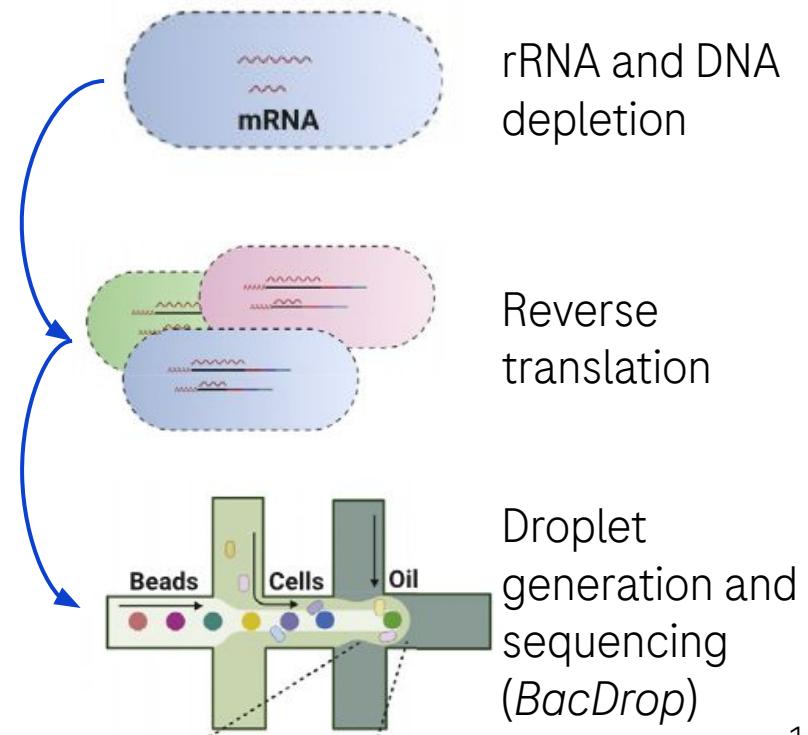
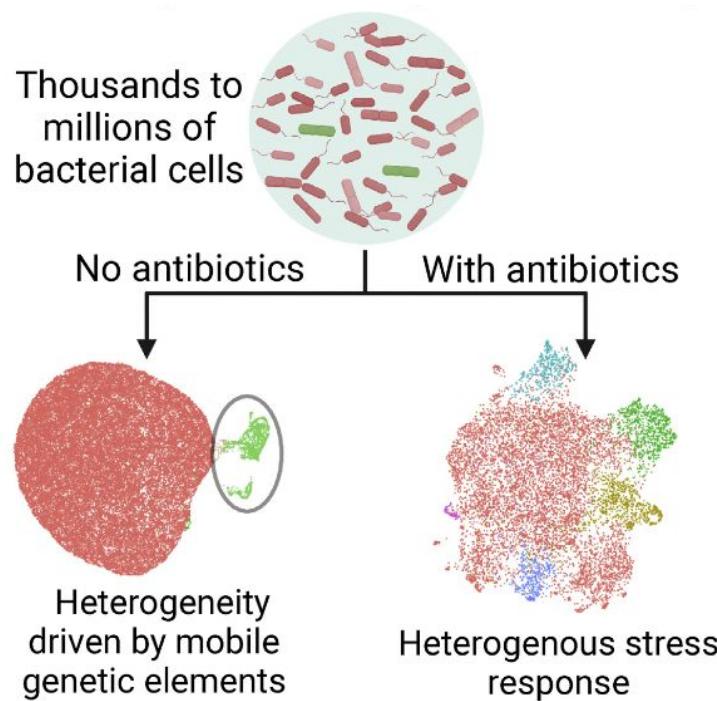


Roche compound shows molecular phenotypes more similar with daptomycin than with colistin, consistent with *in vivo* findings.

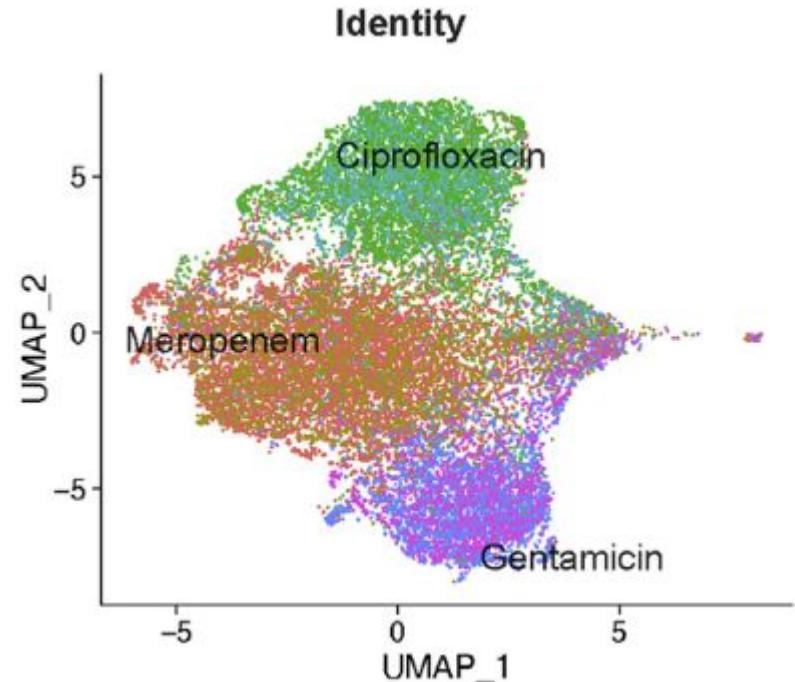
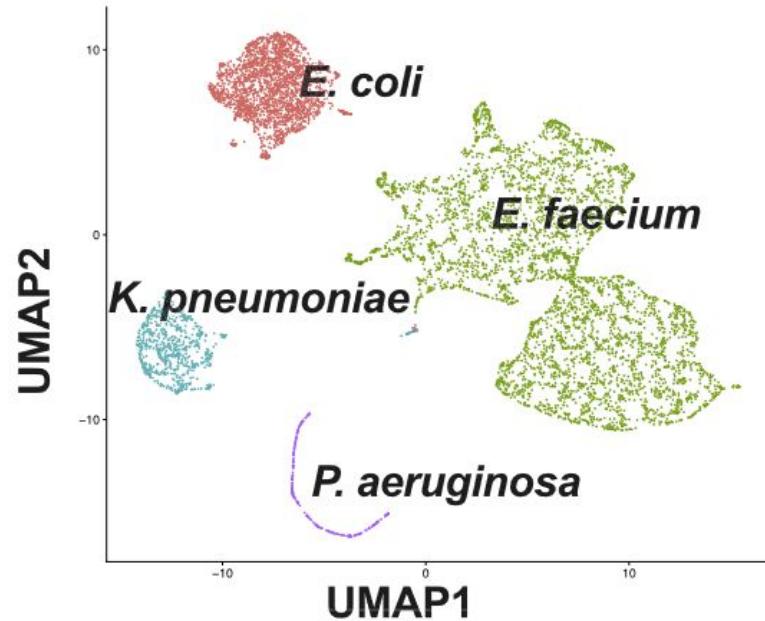
Pathway regulation



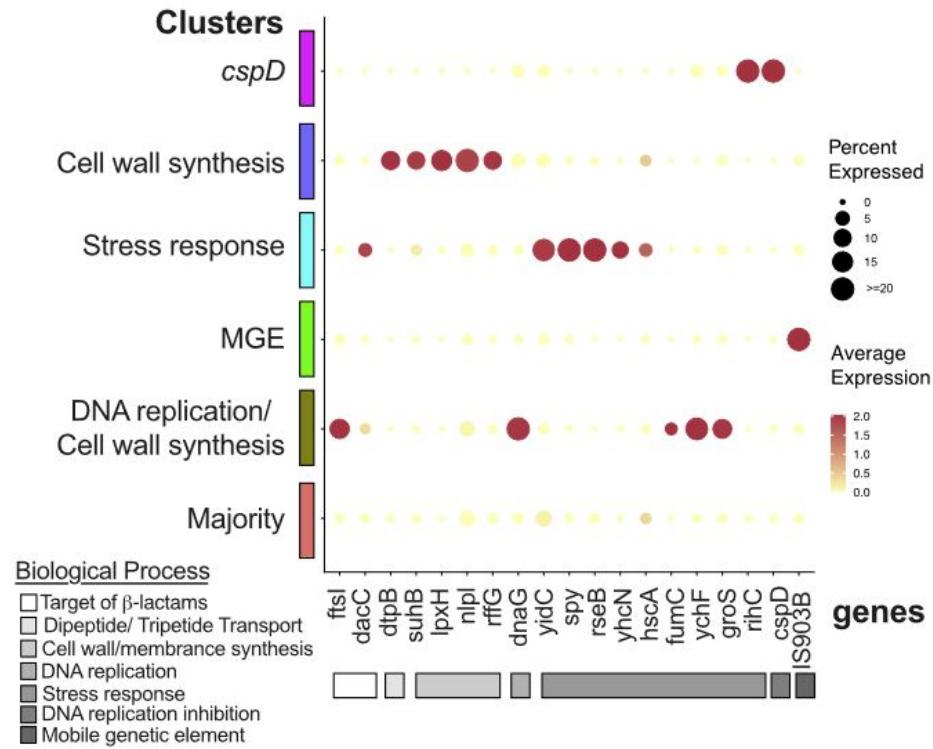
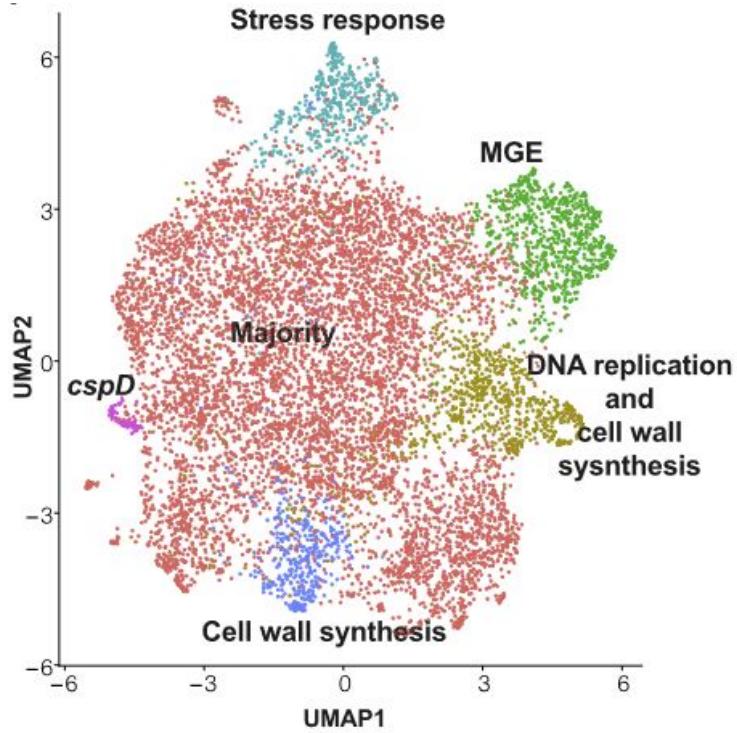
Single-cell RNA-seq reveals cellular heterogeneity of response to antimicrobial drug treatment



BacDrop recovers bacterial species and reveals effects of antibiotics treatment



Meropenem treatment induced heterogeneous responses



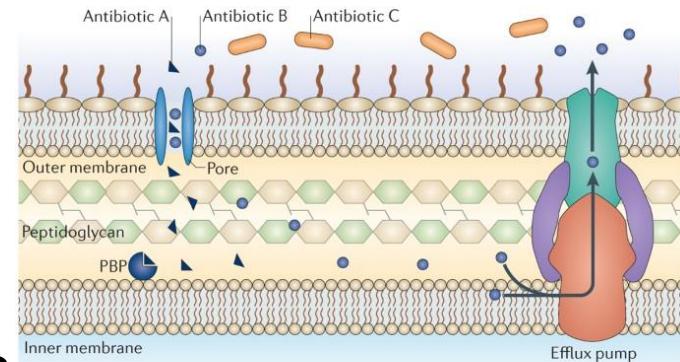
Challenges and prospects

- **Fighting Gram-negative bugs**
 - New chemistry to penetrate Gram-negative cell walls;
 - Learning from failures is as important as from successes.
- **(Molecular) phenotypic drug discovery**
 - Dissecting pharmacology from toxicology;
 - Preclinical models with high predictivity for clinical outcome;
- **Acting against resistance from day 0**
 - Omics-enhanced resistance detection and understanding;
 - Precompetitive knowledge sharing is essential.

Doing now what patients need next

What's X?

- X is protected by magical walls.
- Few secret passages connect inside of X with outside.
- X constantly changes its internals.
- Relatively little is known how to destroy X.
- In fact, X has never been completely extinct.

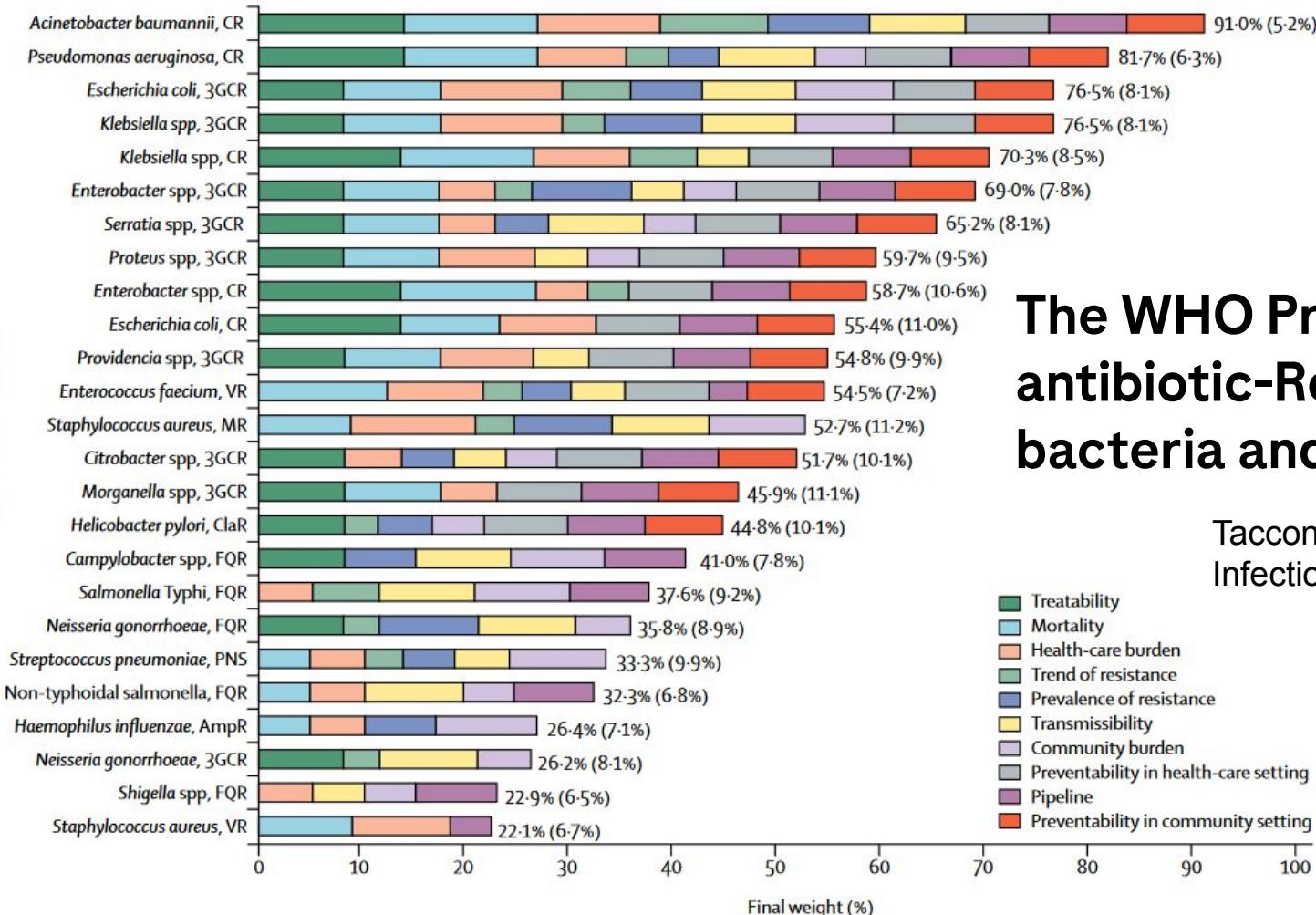


Hogwarts? Multiresistant bacteria?

The WHO Priority list of antibiotic-Resistant bacteria and tuberculosis

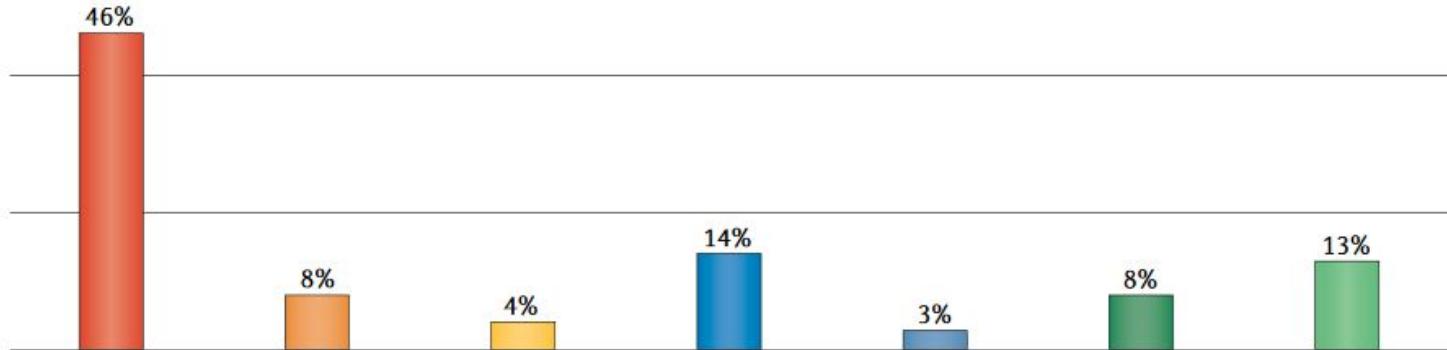
Tacconelli *et al.*, The Lancet Infectious Diseases, 2018

Antibiotic-resistant bacteria



- Treatability
- Mortality
- Health-care burden
- Trend of resistance
- Prevalence of resistance
- Transmissibility
- Community burden
- Preventability in health-care setting
- Pipeline
- Preventability in community setting

**407 preclinical antibiotic projects from
314 institutions (81% small and medium-sized enterprises)**



Direct-acting small molecules

- ~70% new and ~20% old targets
- ~50% targeting Gram-negative bacteria

Potentiators

- β -Lactamase or efflux pump inhibitors
- Expanding spectrum
- Enhancing or restoring activity
- Protectors

Repurposed drugs

- FDA-approved drugs

Antibodies and vaccines

- Against select pathogens

Immuno-modulators

- Support pathogen elimination

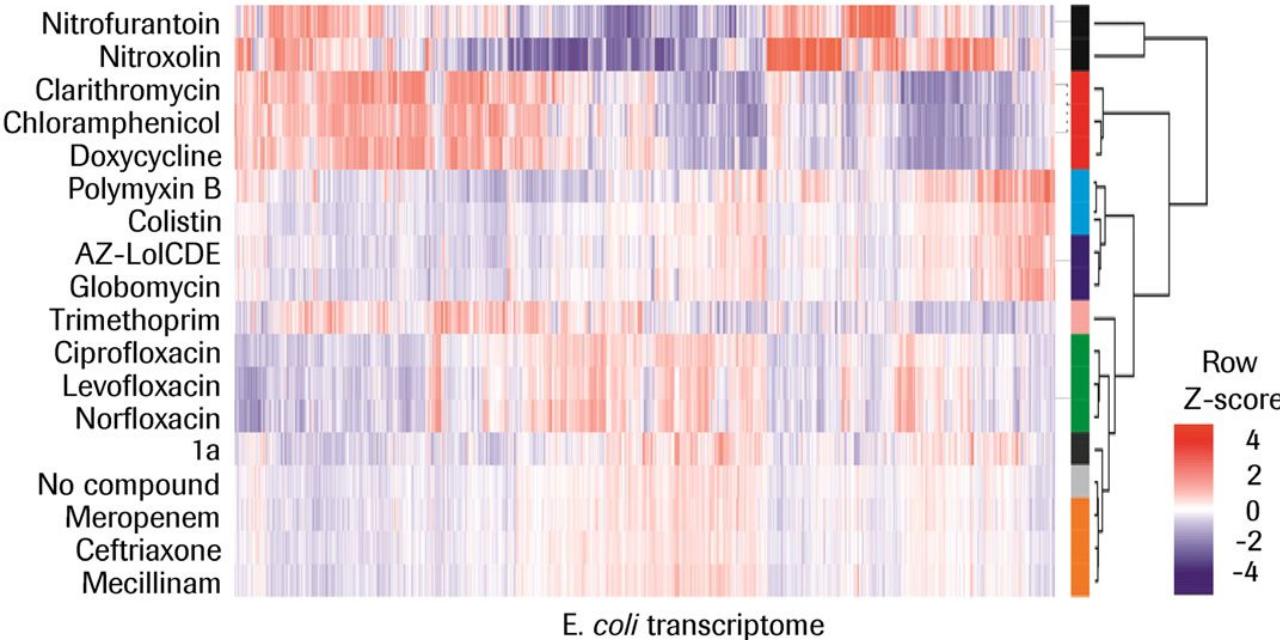
Antivirulence approaches

- Adjunctive
- Targeting different virulence factors and strategies
- Against select pathogens

Phages and microbiota

- Phages against select pathogens
- Endolysins
- Modulators of microbiota (mostly gut)

Morphology and gene expression offer complementary information

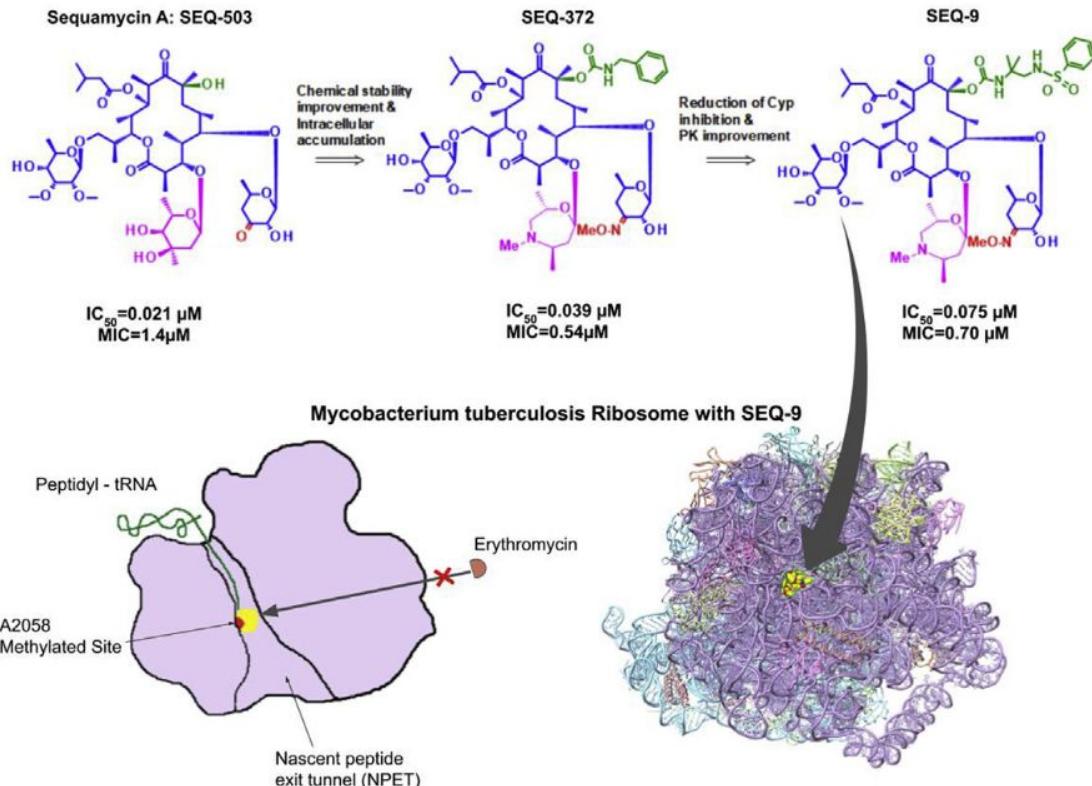


Pathway and network analysis

Alternative assays

Pathway-
Phenotype associations

CryoEM reveals molecular interactions of antimicrobials



- Structure-based optimization of SEQ-9, a sequanamycin derivative.
- Sequanamycins overcome Mtb macrolide resistance.
- SEQ-9 adjusts its binding mode to the resistant Mtb ribosome.
- SEQ-9 kills Mtb in vitro and is efficacious in mouse models of TB.

Prospects



- New experimental approaches, empowered by computational methods, shift our perspective of antimicrobial drug discovery.
- Make the new wet-lab and *in silico* approaches available to researchers is indispensable to overcome the challenges of AMR.

Copyright, sources, and references

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