Open-access antimicrobial drug discovery

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Antibiotics are not ‘drug-like’

Don’t obey the ‘rules’

**“Rule of Five”**
- Molecular Weight: <500
- H bond acceptor: ≤10
- H bond donor: ≤5
- \( \log P \): ≤5

**Colistin**
- Molecular Weight: 1169.48
- H bond acceptor: 18
- H bond donor: 18
- ALogP: -7.1

**Tobramycin**
- Molecular Weight: 467.52
- H bond acceptor: 14
- H bond donor: 10
- ALogP: -6.9

**Fidaxomicin**
- Molecular Weight: 1058.05
- H bond acceptor: 18
- H bond donor: 7
- ALogP: 7.8

**Rifampicin**
- Molecular Weight: 822.95
- H bond acceptor: 15
- H bond donor: 6
- ALogP: 3.3

**Erythromycin**
- Molecular Weight: 733.94
- H bond acceptor: 18
- H bond donor: 7
- ALogP: 7.7
Antibiotics are not ‘drug-like’

Often reactive

- Fosfomycin
- Meropenem
- Chloramphenicol
- Metronidazole
- Mupirocin
Preferred property space for Gram-negative antibiotics

- Drugs (Approved)
- Gram-Pos (Approved)
- Gram-Neg (Approved)

Typical corporate archive
Pharma vs Academic

Biotech Company Library
Commercially-sourced diverse set

Typical Corporate Library

G-ve hit rate (MIC ≤ 32ug/mL)
0.008%

Published Academic Antibiotics
Where to find new antibiotics?

**Chemical Abstract Services**

- **80 Million** *Organic* Compounds  
  (no metal ion and MW < 1,500 Da)
- **29 Million** Anti-Bacterial like  
  (-10 < logD < 2; MW < 1,200 Da)
- **15.5 Million** Academic  
  (non commercial)

Diversity in vials in the labs of academic and biotech chemists? Not tested

ChEMBL only **14%** of 1.3 million tested against bacteria
How to enable antibiotic discovery?

How to access chemical diversity?

How to empower chemists around the world?

In the past we collaborated on an open access basis
Antibiotic R&D was collaborative

- **1945** tetracycline isolated from a actinomycete by Benjamin Duggar, a retired botany professor working in Lederle Laboratories in New York.

- **1947**, chloramphenicol recovered from an actinomycete by Gerald Langham, an agricultural geneticist working in Venezuela.

- **1951**, vancomycin isolated by E.C. Kornfield at Eli Lilly from soil samples collected in Borneo by his missionary friend William Conley, E.C. Kornfield

- **1952**, erythromycin isolated by Robert Bunch & James McQuire, biochemists at Eli Lilly from a streptomycete in a soil sample from the Philippines.
What is CO-ADD?

A global initiative to seek new chemical diversity to solve the antibiotic crisis

We seek diverse compounds from chemists from anywhere in the world

FREE screening against pathogenic microbes: 5 bacteria and 2 fungi
## CO-ADD Screening – 384 well

<table>
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<tr>
<th></th>
<th>Z’-Factor</th>
<th>Edge [%]</th>
<th>Growth [OD$_{600}$]</th>
<th>Growth [CV %]</th>
<th>Controls [CV %]</th>
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<td><strong>E. coli</strong></td>
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</tbody>
</table>

### S. aureus

![Heatmap of S. aureus](image)

### P. aeruginosa

![Heatmap of P. aeruginosa](image)
**CO-ADD Workflow**

1. **Primary Screen**
   - 32 ug/mL primary screen
   - MRSA, *E. coli*, *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *C. albicans*, *C. neoformans*, *E. coli* efflux pump & membrane mutants

2. **Hit Confirmation**
   - Minimum Inhibitory Concentration
   - Counter-screen for cytotoxicity, QC purity
   - Novelty score (from chemical fingerprint)

3. **Hit Validation**
   - Larger panel of bacteria inc. MDR clinical isolates
   - Effect of serum & lung surfactant
   - Plasma and microsomal stability, protein binding, haemolysis, membrane depolarisation.
   - Resynthesis and early SAR

4. **Up to you - Publish, Patent, Develop**
   - Public database of antimicrobial data after 2 years
CO-ADD – 1st year outreach

➢ 150 participating groups from 33 countries
➢ 100,000 received + 300,000 promised compounds
Status - since Feb 2015

106,000 compounds received

48,000 compounds screened

HIT RATES

Non-cytotoxic & MIC ≤ 16 ug/mL

- 0.21% for G+ve
- 0.12% for G-ve
- 0.39% for fungi

confirmed bacterial hits

confirmed fungal hits
Can we build a pipeline?

French National Chemical Bank (41 universities) → Antimicrobial screening → Hit-to-lead optimisation and clinical trials

African Network for Drug and Diagnostics Innovation (UN) → 43 Pan African Centres of Excellence → Antimicrobial screening
"CO-ADD provides exactly the sort of platform that synthetic chemists need to get high quality antibacterial screening"

Prof Mark Moloney, University of Oxford, UK

"CO-ADD has enabled us to explore the biological relevance of some of our synthetic molecules"

Prof Antonio Echavarren, Institute of Chemical Research of Catalonia, Spain

"CO-ADD fits perfectly with the mission of our national compound library to develop partnerships at the chemistry-biology interface"

Philippe Jauffret, CNRS Unit for the French National Chemical Library, France
Hang in there!

- Global survey of biotech and pharma companies
- <70 companies working in antibiotics research worldwide
  - Only 5 big Pharma
  - Average of 15 FTEs in discovery team
  - 2.5 drug candidates in pre-clinical R&D
  - 0 or 1 drug candidates in clinical trials.

Less than 1,000 antibiotics developers in industry on earth to tackle the challenge

We are an endangered ‘species’
Prof Dame Sally Davies, UK CMO

"Technologies such as this could hold the key to antimicrobial drug discovery in the future"