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The University Of Queensland AUSTRALIA | IMB
Institute for Molecular Bioscience

Community for Open Antimicrobial Drug Discovery

Open-access antimicrobial drug discovery

BIO 2016

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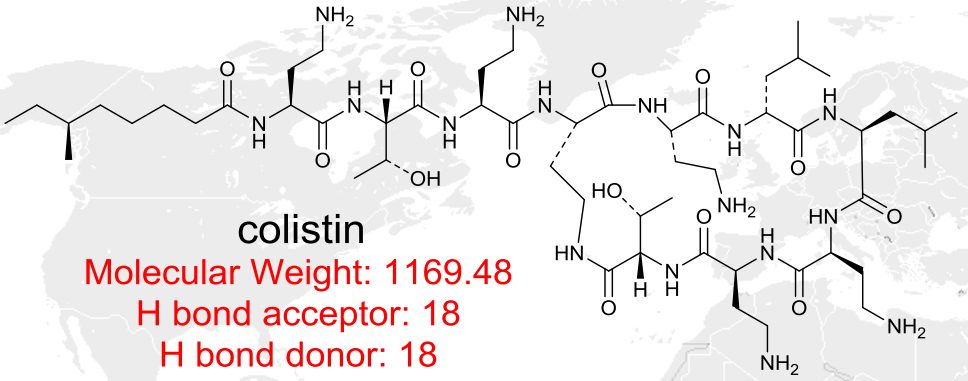
Institute for Molecular Bioscience
The University of Queensland

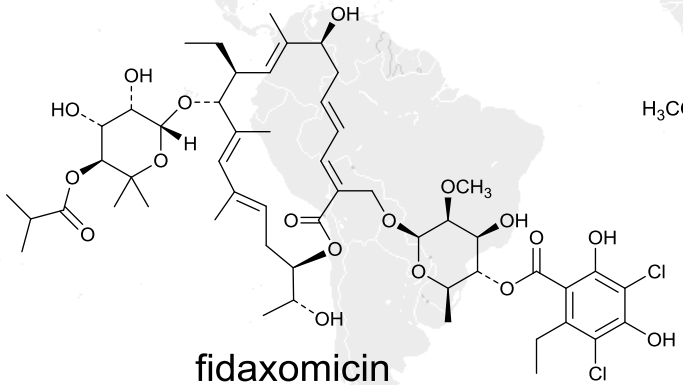
Antibiotics are not ‘drug-like’

Don’t obey the‘rules’

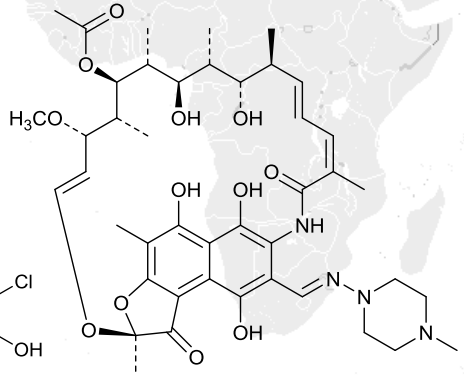
“Rule of Five”
Molecular Weight: <500
H bond acceptor: ≤10
H bond donor: ≤ 5
logP: ≤ 5



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

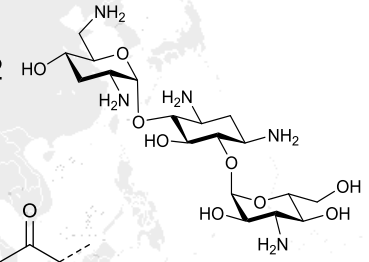


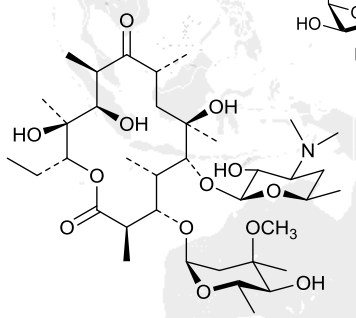
fidaxomicin
Molecular Weight: 1058.05
H bond acceptor: 18
H bond donor: 7
ALogP: 7.8



rifampicin
Molecular Weight: 822.95
H bond acceptor: 15
H bond donor: 6
ALogP: 3.3

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

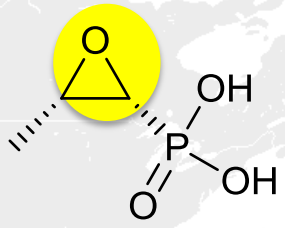




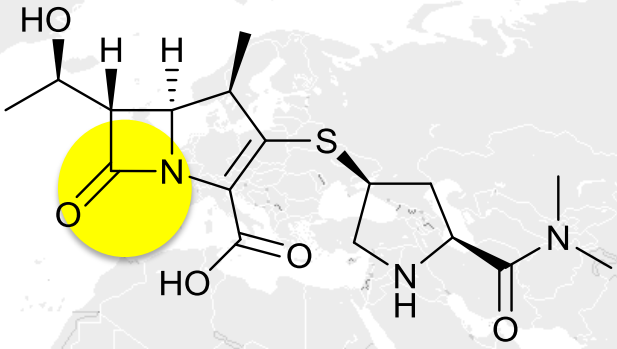
erythromycin
Molecular Weight: 733.94
H bond acceptor: 18
H bond donor: 7
ALogP: 7.7

Antibiotics are not ‘drug-like’

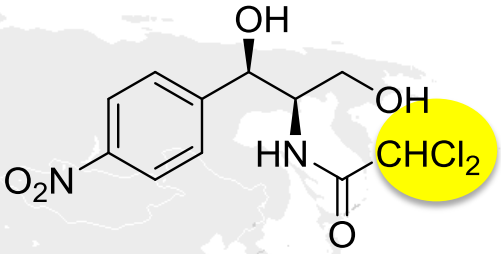
Often reactive



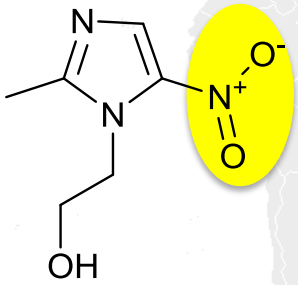
fosfomycin



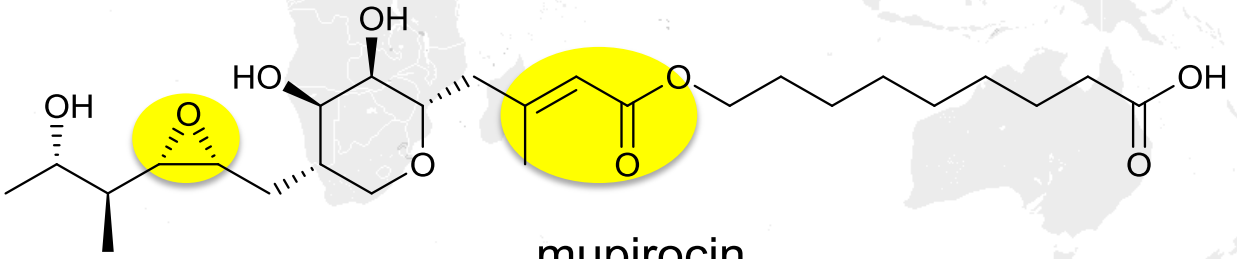
meropenem



chloramphenicol

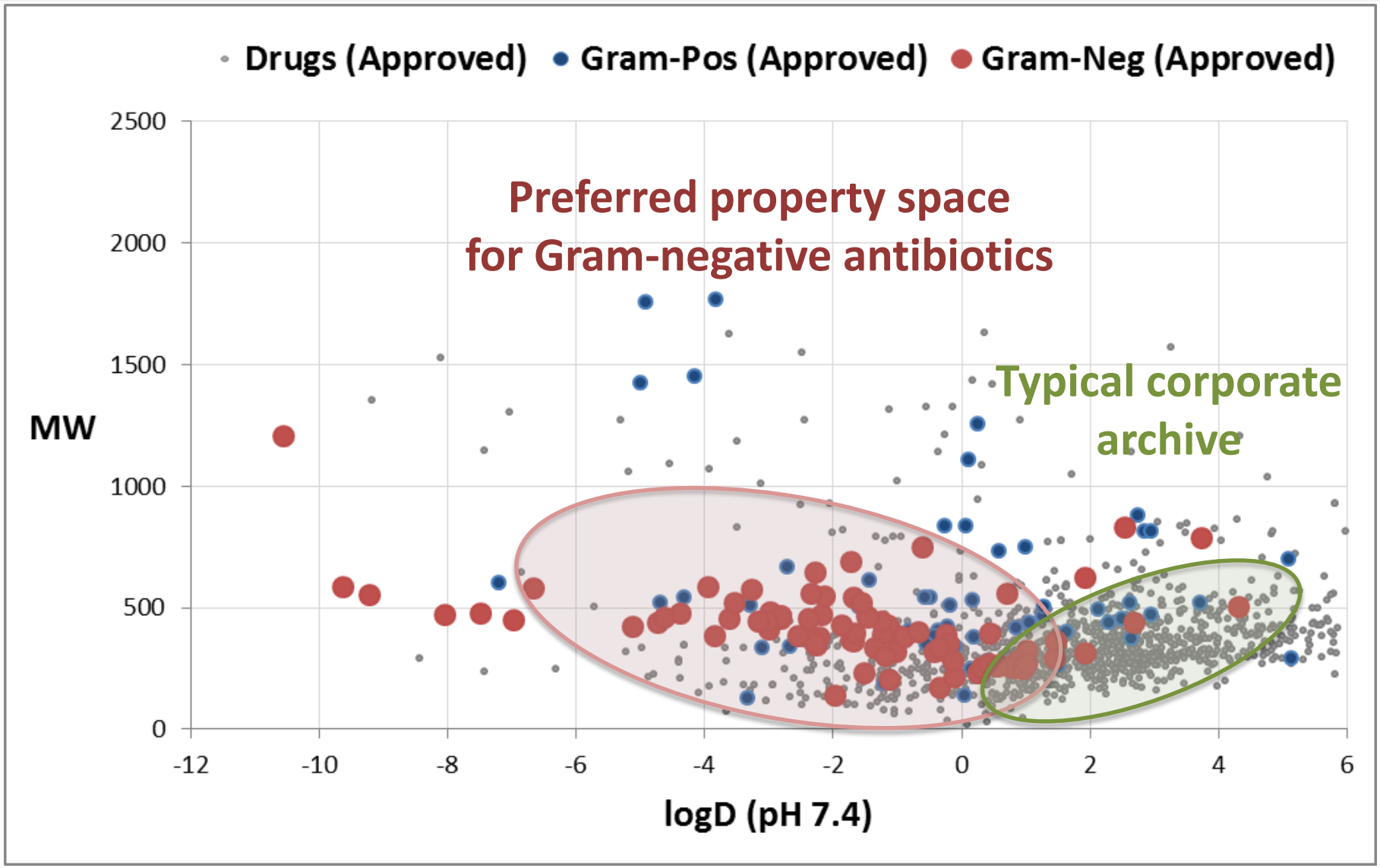


metronidazole

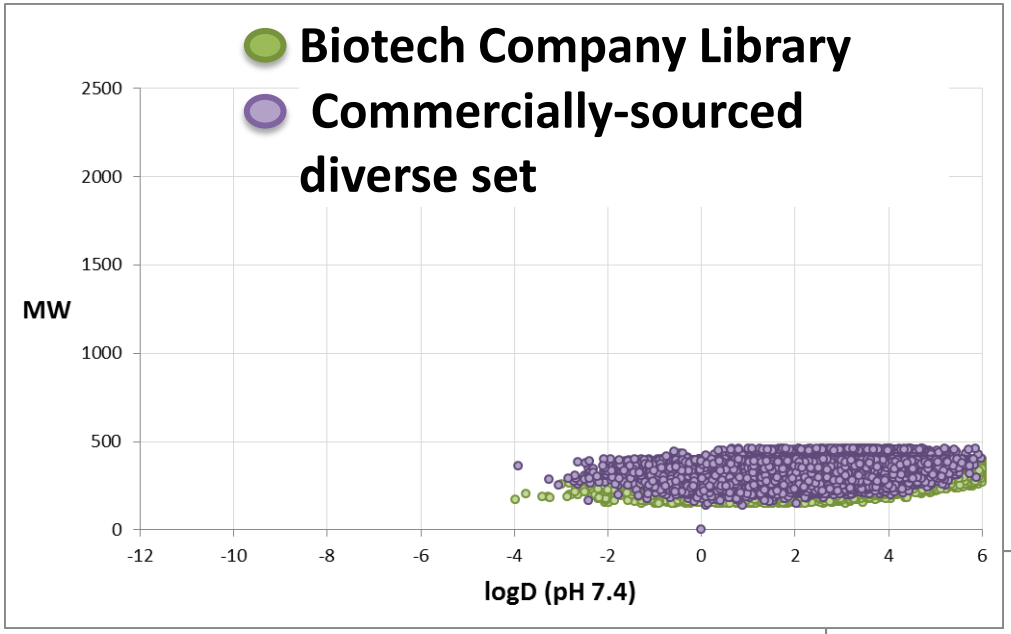


mupirocin

Chemical Space



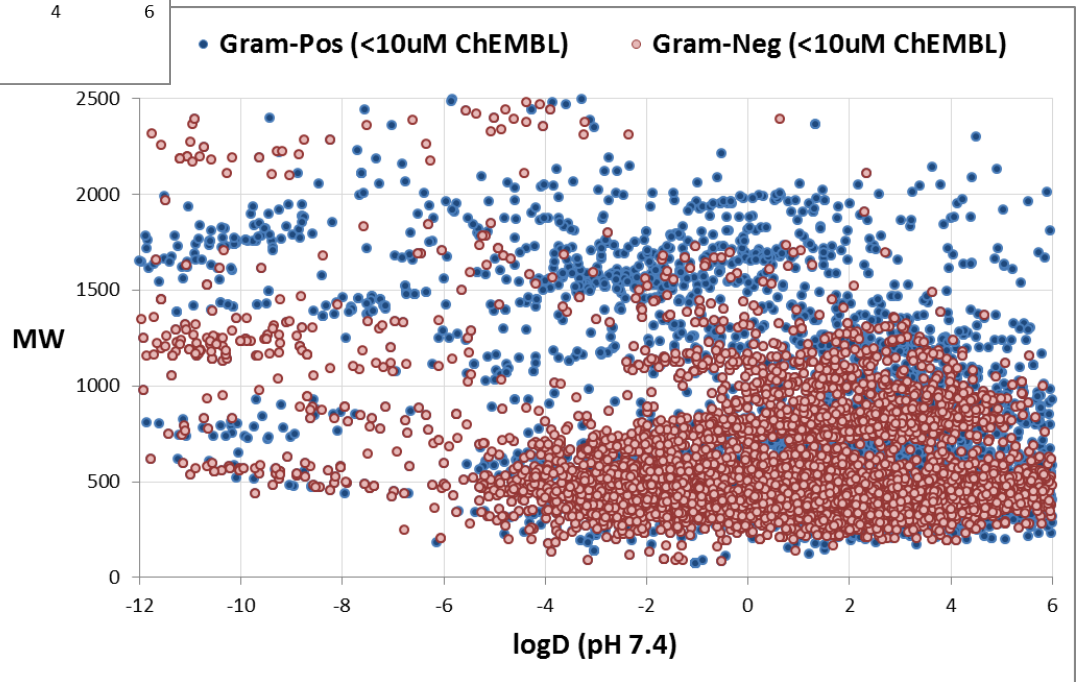
Pharma vs Academic



Typical Corporate Library

G-ve hit rate (MIC ≤ 32ug/mL) 0.008%

Published Academic Antibiotics



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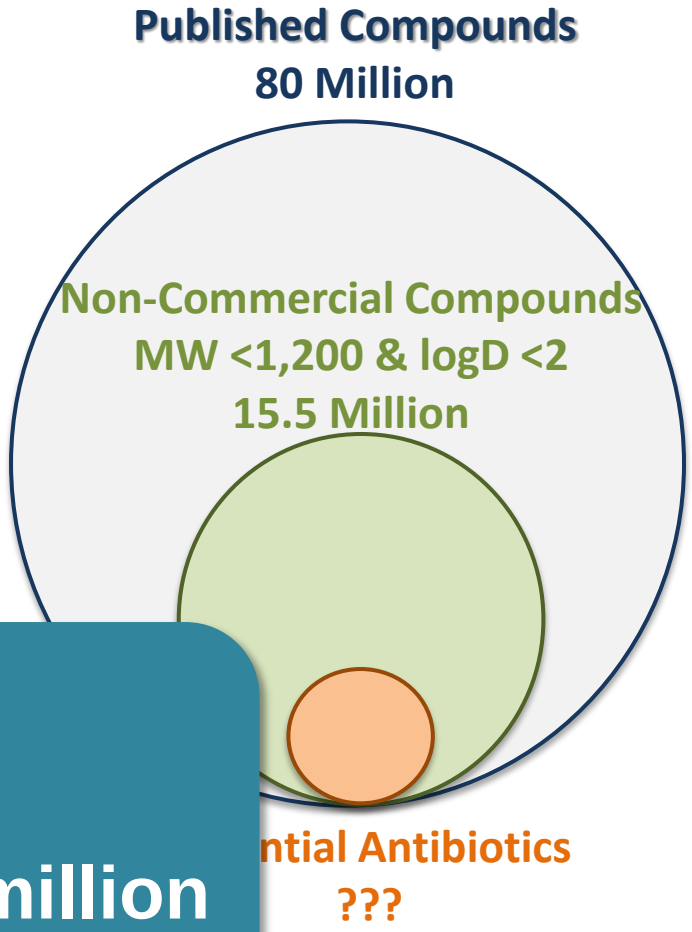
Where to find new antibiotics?

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
labs of aca
biotech c

Not tested
ChEMBL
only 14% of 1.3 million
tested against bacteria

How to enable antibiotic discovery?

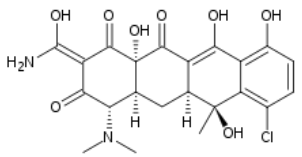
How to access chemical diversity?

How to empower chemists around the world?

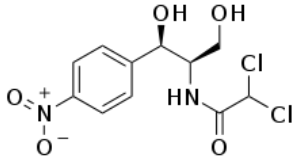
In the past we collaborated on an open access basis

Antibiotic R&D was collaborative

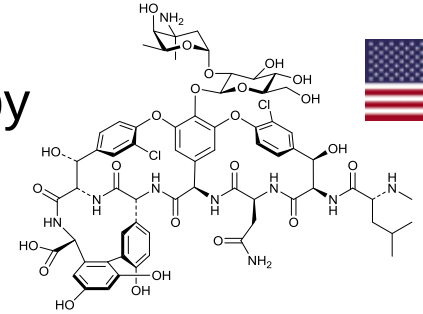
- **1945** tetracycline isolated from a actinomycete by Benjamin Duggar, a retired botany professor working in Lederle Laboratories in New York.



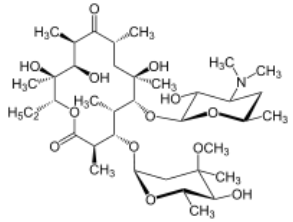
- **1947**, chloramphenicol recovered from an actinomycete by Gerald Langham, an agricultural geneticist working in Venezuela.



- **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

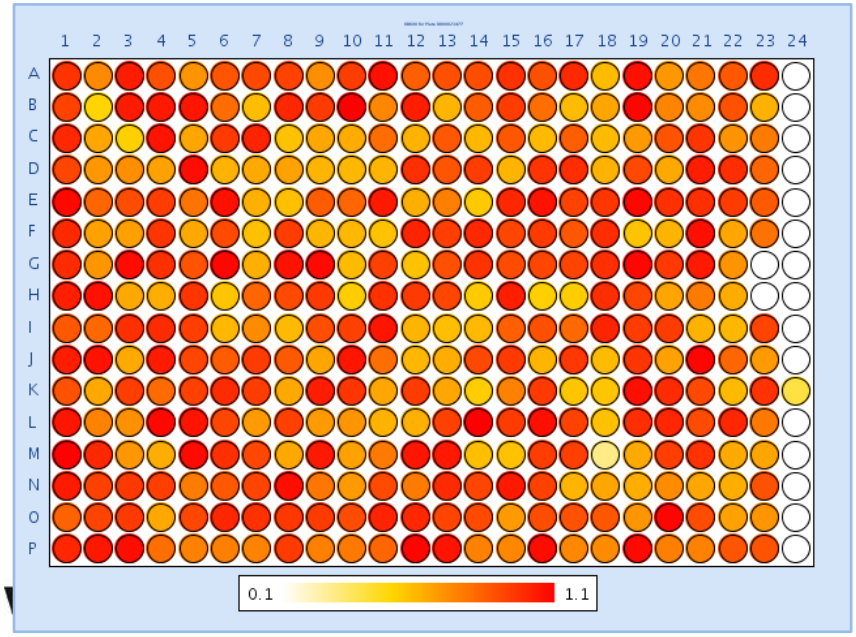
We seek diverse compounds from chemists from anywhere in the world

FREE screening against pathogenic microbes: 5 bacteria and 2 fungi

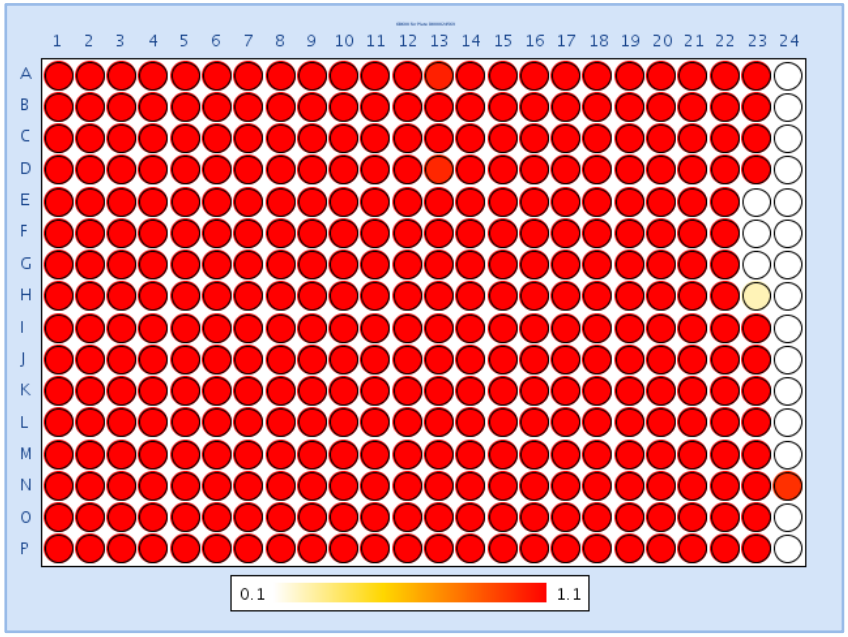
CO-ADD Screening – 384 well

	Z'-Factor	Edge [%]	Growth [OD_{600}]	Growth [CV %]	Controls [CV %]
E. coli ATCC 25922	0.94	2.26	1.164	11.8	4.54
P. aeruginosa ATCC 27853	0.87	2.25	1.161	9.5	12.1
S. aureus ATCC 43300	0.52	9.21	0.854	20.4	13.2

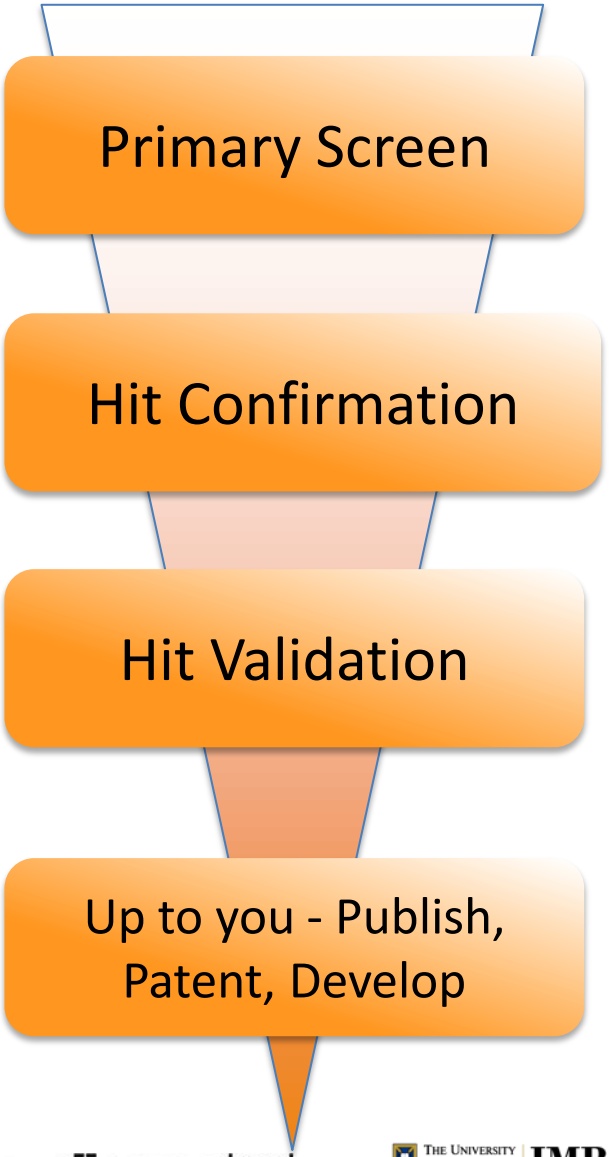
S. aureus



P. aeruginosa



CO-ADD Workflow



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

- Minimum Inhibitory Concentration
- Counter-screen for cytotoxicity, QC purity
- Novelty score (from chemical fingerprint)

- 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

- 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 re

48,000 compounds

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?

Australia - Europe - USA

French National Chemical Bank
(41 universities)

Antimicrobial screening

Hit-to-lead optimisation
and clinical trials

Australia - Africa

African Network for
Drug and Diagnostics
Innovation (UN)

43 Pan African
Centres of Excellence

Antimicrobial screening

User feedback

"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’

CO-ADD Community for Open Antimicrobial Drug Discovery

www.co-add.org

Prof Dame Sally Davies , UK CMO

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

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