Antimicrobial drug discovery: SAR optimization and QSAR

Guest speakers: Alastair Parkes & James Duffy

Moderator: Charles Mowbray

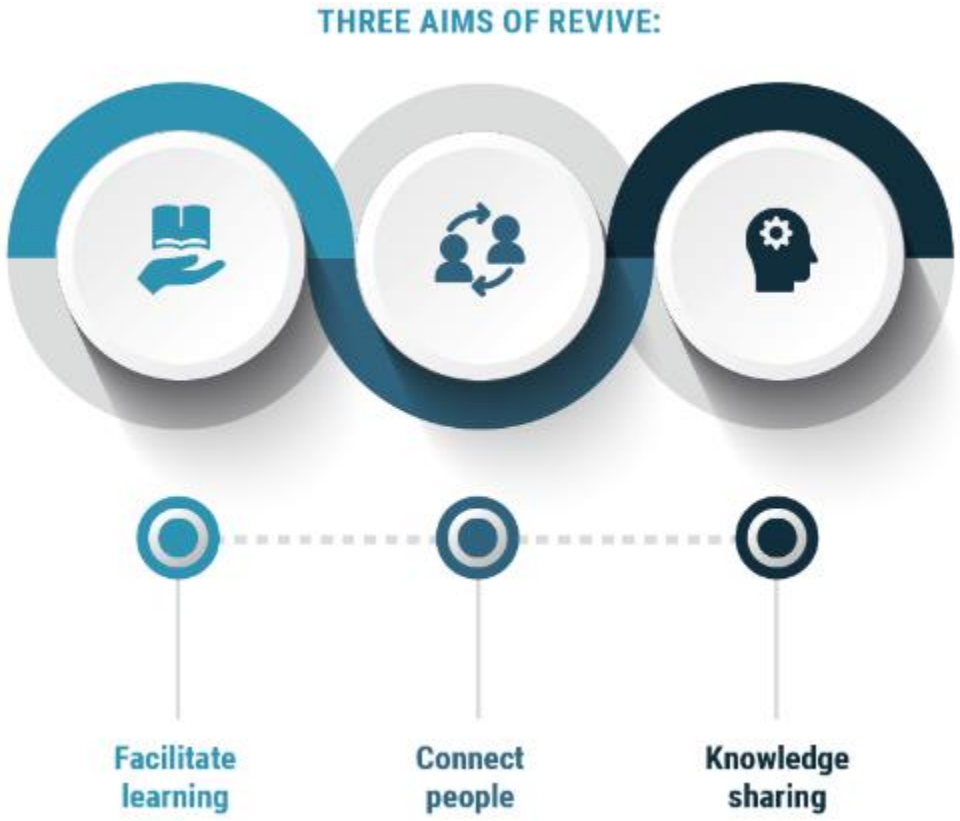
Host: Astrid Pentz-Murr (GARDP)

24 August 2023

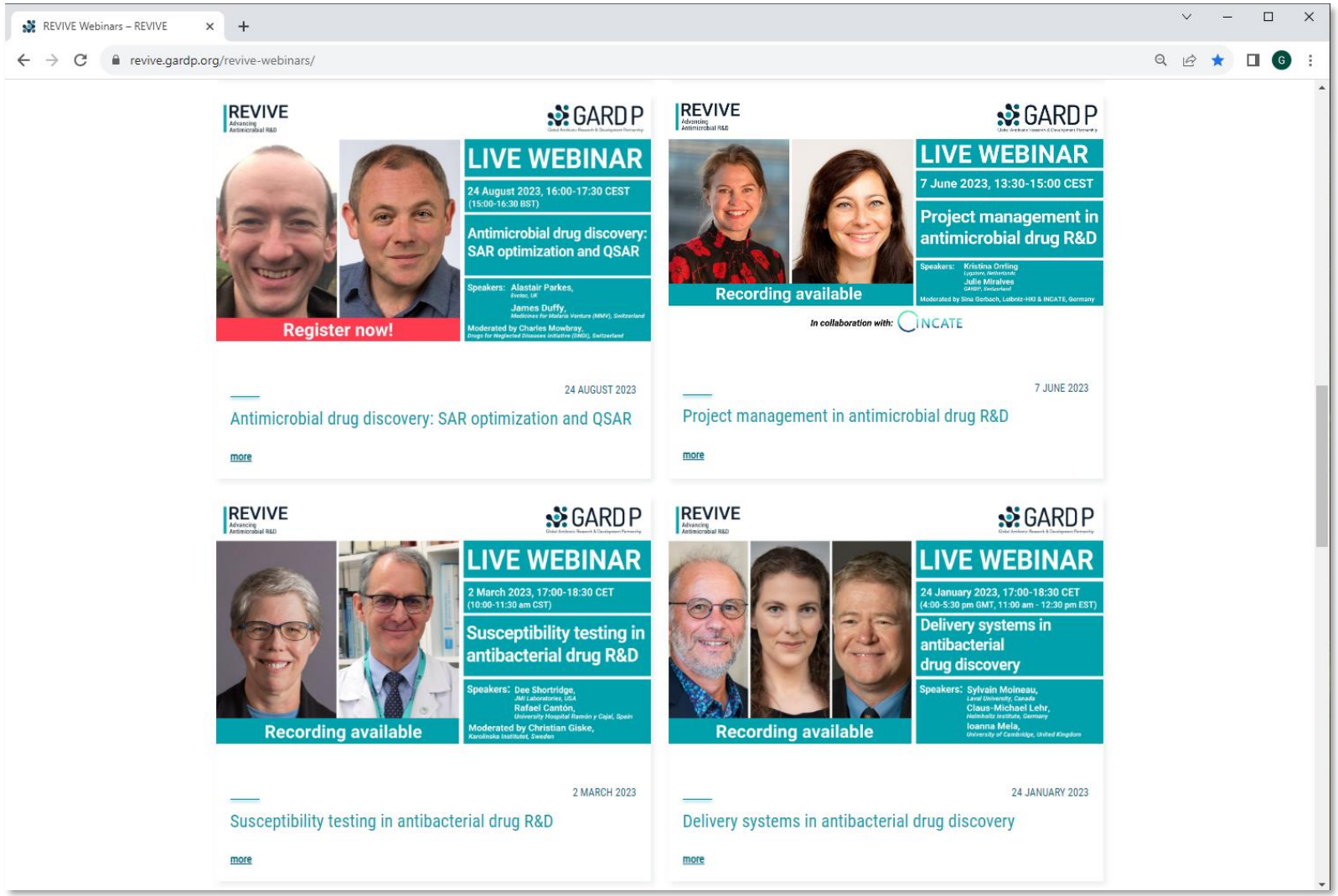
GARDP
Global Antibiotic Research & Development Partnership

REVIVE

Capture essential R&D technical knowledge and share expertise with the global community through the REVIVE website (revive.gardp.org).



Webinar recordings



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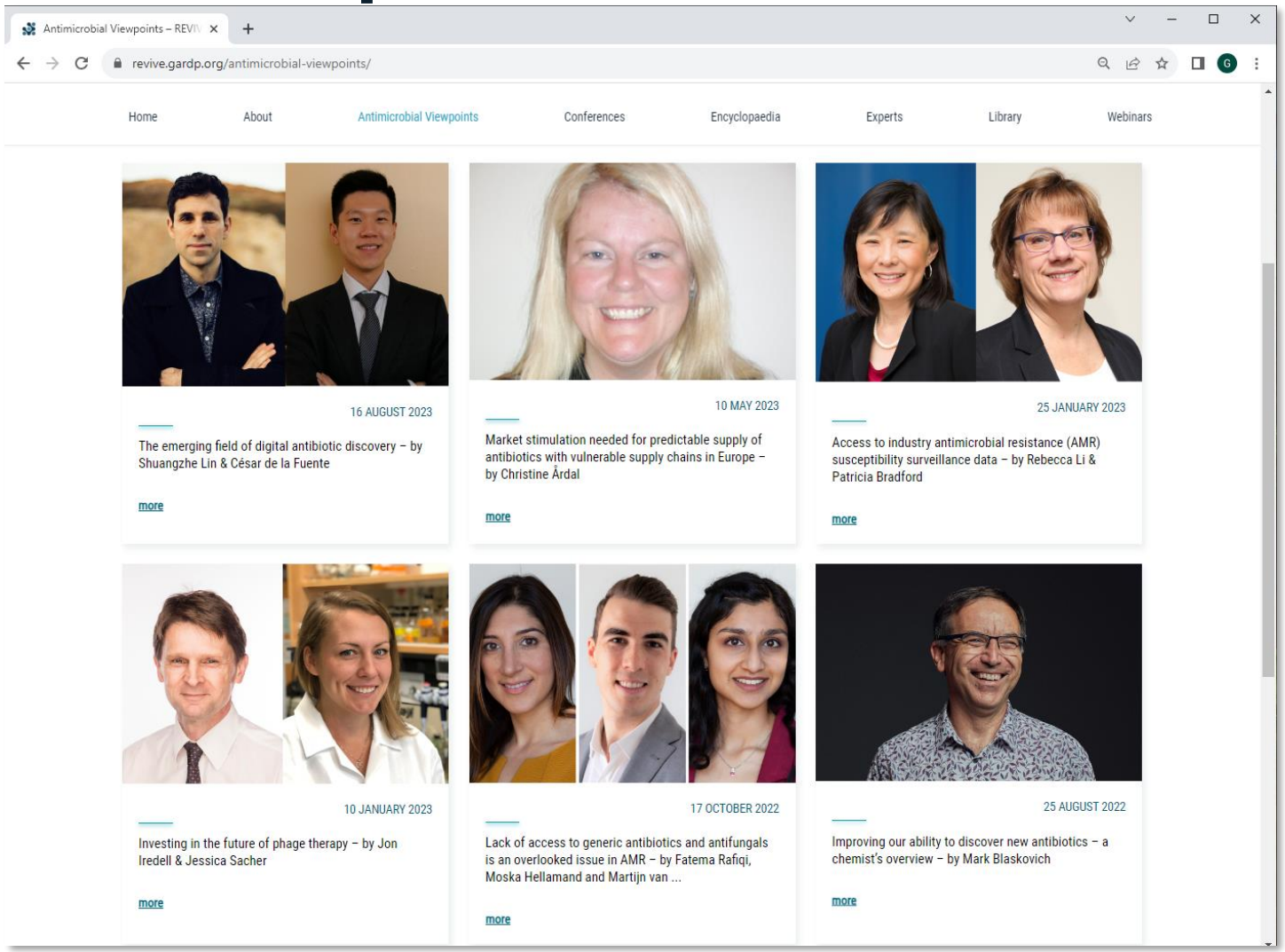
Antimicrobial Viewpoints



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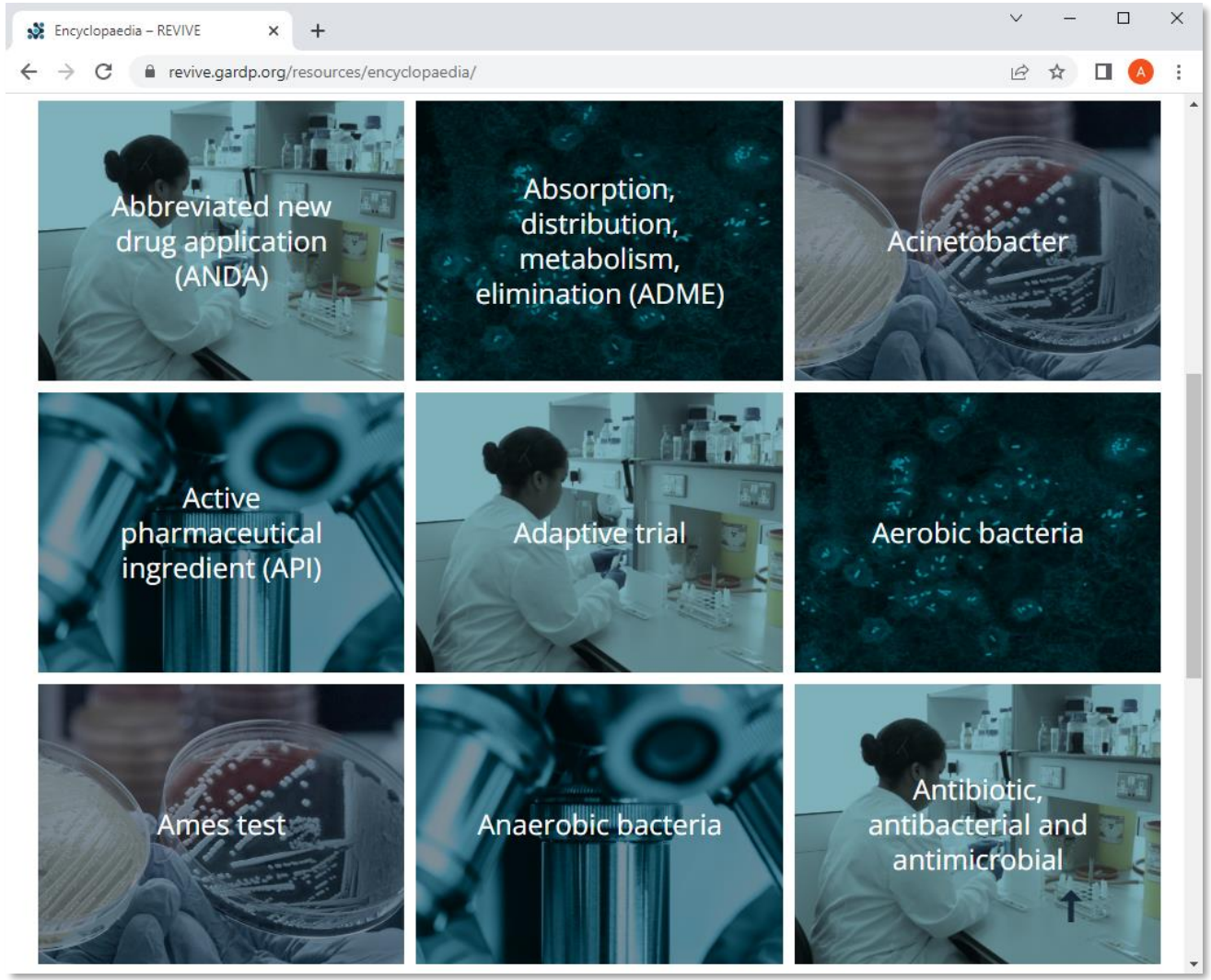
Antimicrobial Encyclopaedia



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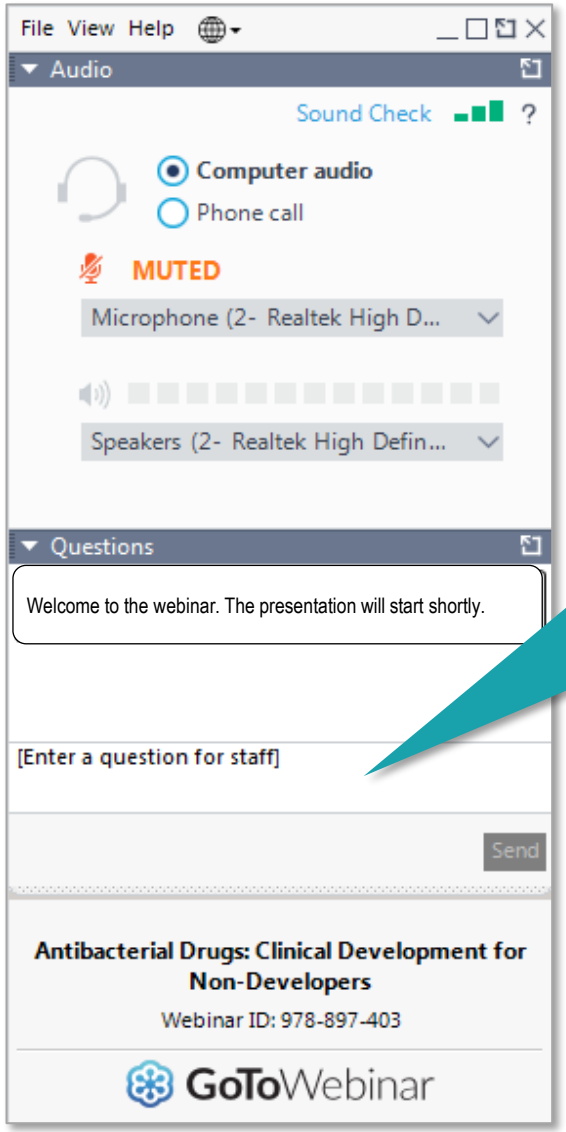
How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.



The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

Today’s speakers

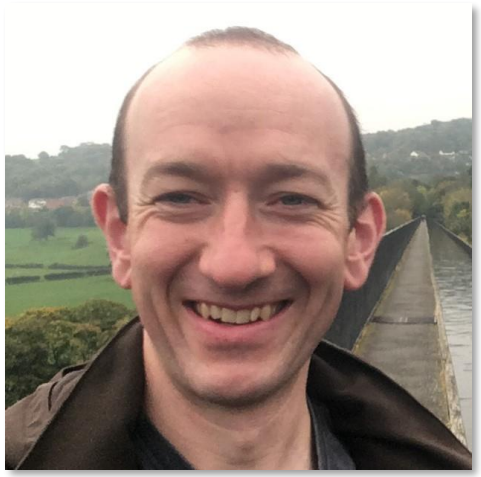
Antimicrobial drug discovery: SAR optimization and QSAR

Alastair Parkes
Vice-President, Medicinal Chemistry
Evotec (United Kingdom)

James Duffy
Senior Director, Drug Discovery
Medicines for Malaria Venture – MMV (Switzerland)

<u>Moderator:</u>
Charles Mowbray
Discovery Director
Drugs for Neglected Diseases initiative – DNDi (Switzerland)

Alastair Parkes



Alastair Parkes currently leads a medicinal chemistry department at Evotec, a global drug discovery and development company. Evotec's mission is to discover and develop highly effective therapeutics and make them globally available to the patients who need them.

He joined the company in 2006, working first on central nervous system drug discovery programmes and oncology projects, before focusing on antibacterial research since January 2014.

Alastair is a regular presenter at medicinal chemistry and antibacterial drug discovery conferences, sharing results from Evotec's antibacterial research programmes focused both on specific targets and also the development of new tools. He has been a regular speaker on antibacterial drug discovery at Oxford University's Centre for Doctoral Training in the UK, and has also published a number of papers in the field.

Before joining Evotec, Alastair was employed at the University of Manchester during his post-doctoral studies. He holds MChem and DPhil degrees in organic chemistry from the University of Oxford.

evotec

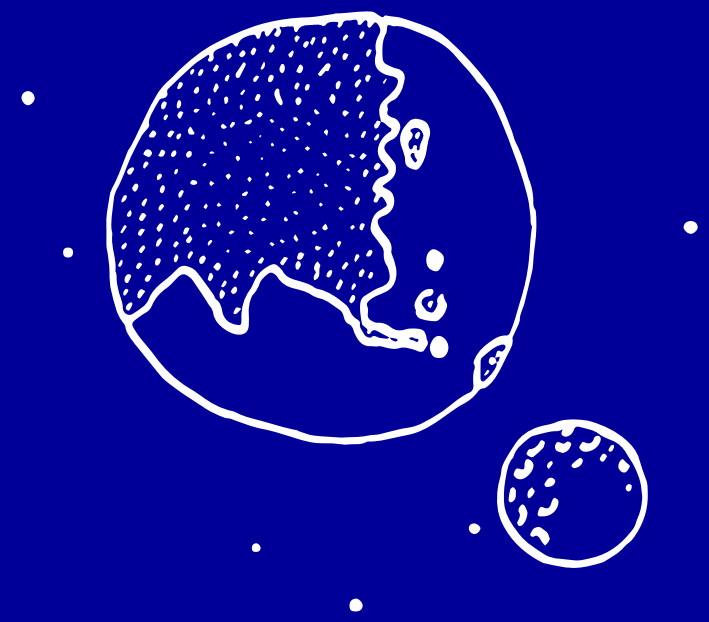
#RESEARCHNEVERSTOPS

SAR Optimisation in Antibacterial Drug Discovery

Alastair Parkes

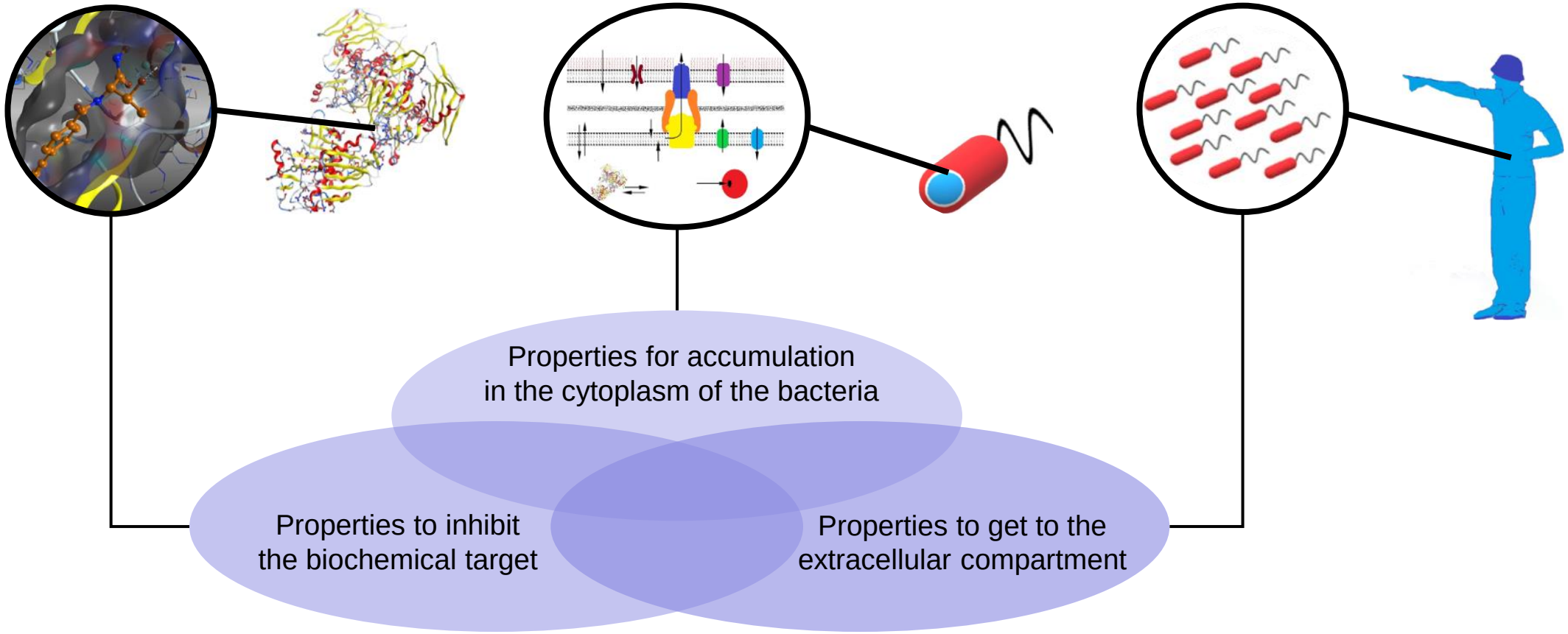
Agenda

1. The multiple challenges of antibacterial drug design
2. Addressing access to drug targets in bacteria
3. Designing for site of infection?
4. Case study
5. Conclusions



The multiparameter problem for antibiotics

Reaching the point where several property spaces overlap

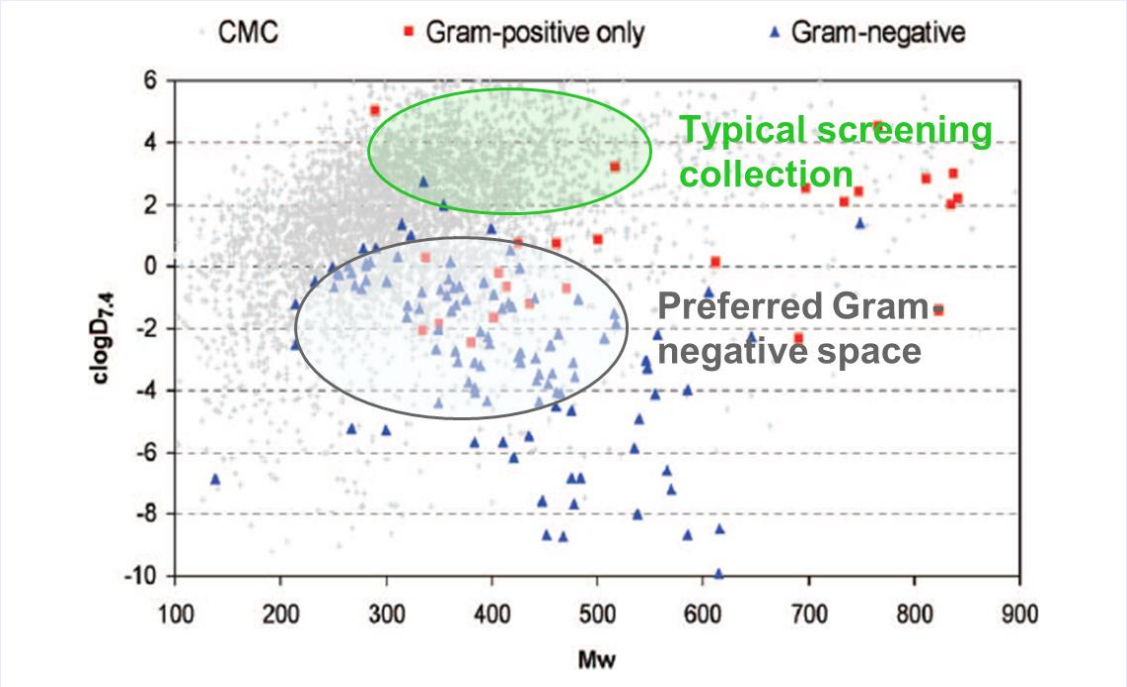


Expert Opinion on Drug Discovery, 15:9, 1005-1013, DOI: 10.1080/17460441.2020.1767065

Can we take a general approach to antibacterial design?

Analysis based on approved drugs suggests specific property space

Antibacterial drugs often occupy different physicochemical space from drugs targeting receptors in mammalian cells



The physicochemical space can vary significantly depending on the species of bacteria

AZ analysed 3,200 project compounds with whole cell activity (≤8µg/mL) and found that the average clogD varied between species[1)]

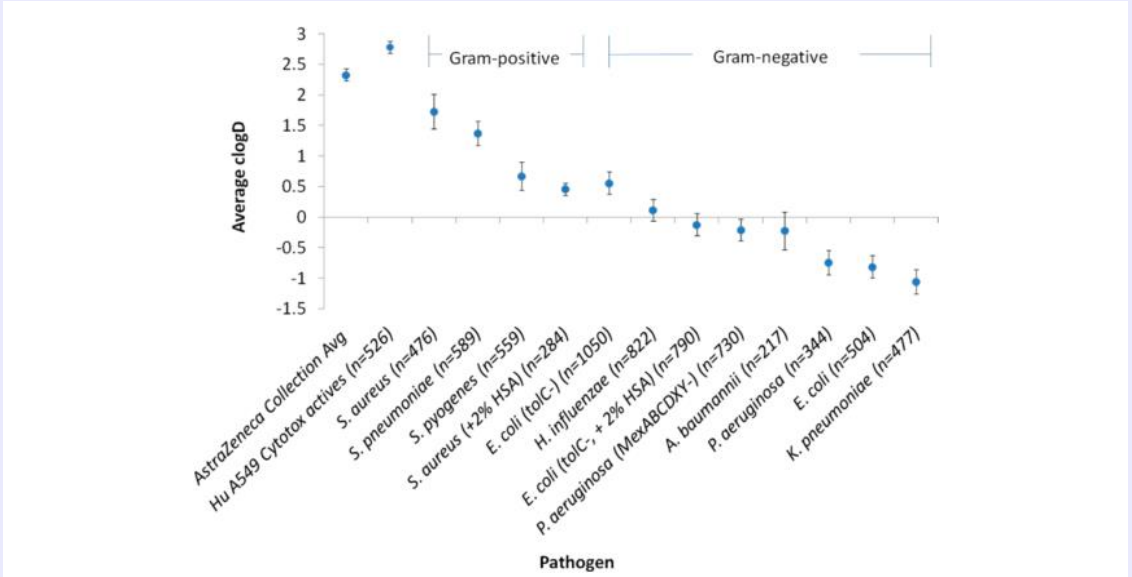


Image adapted from Moser et al. *J. Med. Chem*. 2008, **51(10)**, 2871-2878

[1)] Brown et al. *J. Med. Chem.* 2014, **57**, 10144-10161

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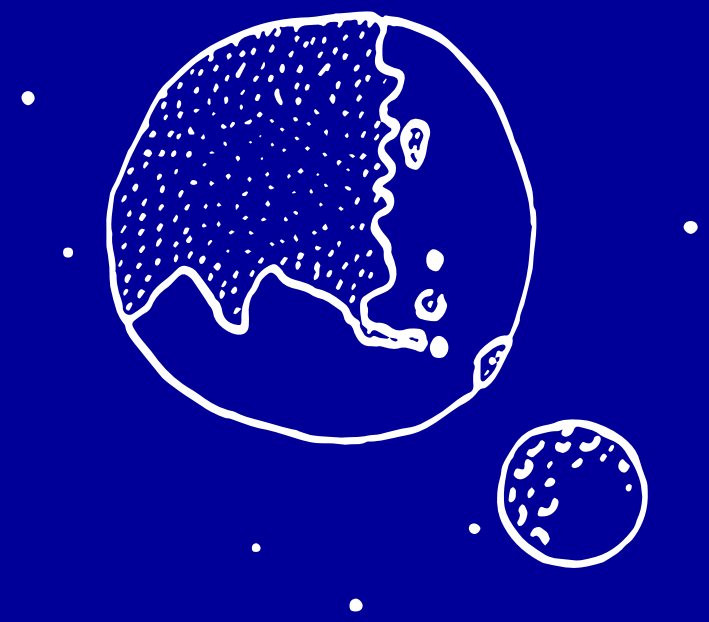

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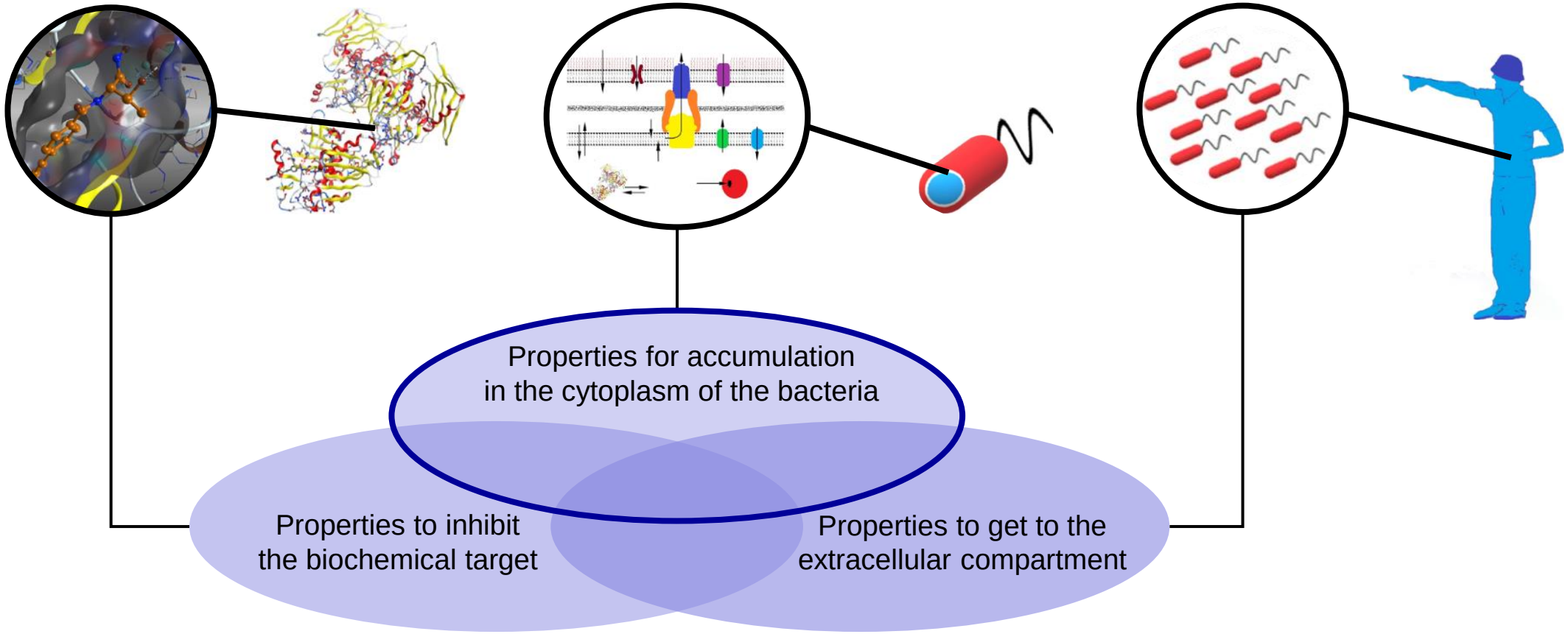
Reaching the point where several property spaces overlap



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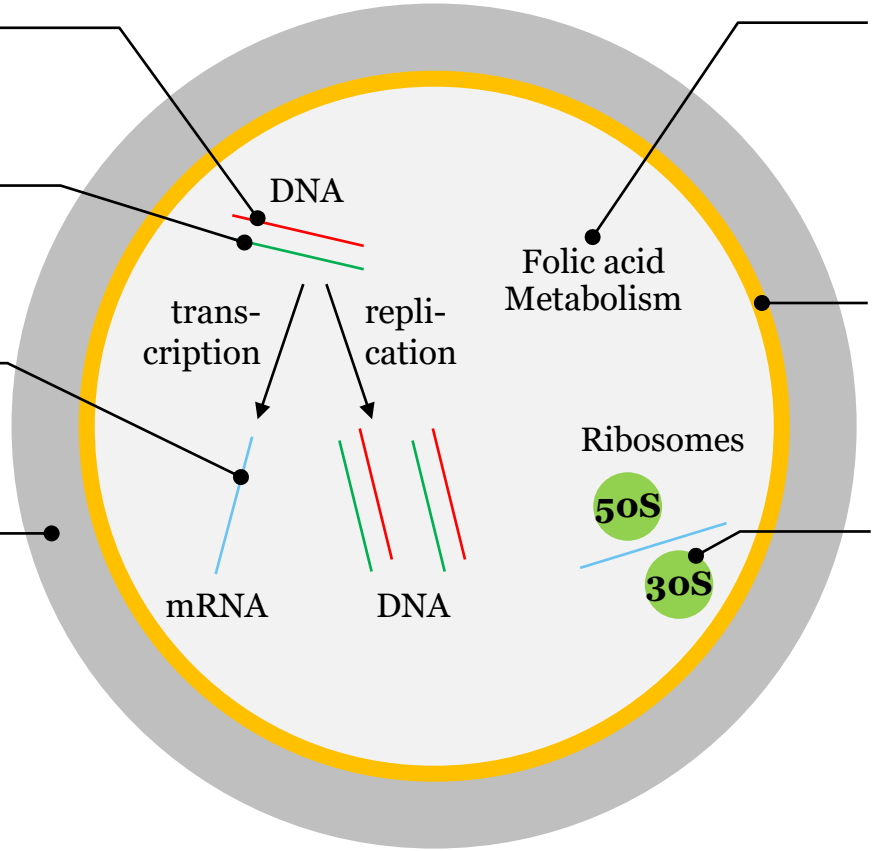
Why worry about bacterial penetration?

Targets of commonly used antibiotics

Schematic representation of Gram-positive bacterial cell



DNA Gyrase
Quinolones

DNA synthesis
Metronidazole

RNA polymerase
Rifampicin

Cell wall synthesis and repair

Penicillins	Cephalosporins
Fosfomycin	Cycloserine
Vancomycin	Bacitracin
Monobactams/ carbapenems	Isoniazid

Metabolism
Sulfa drugs
Trimethoprim

Cell membrane
Polymixins (Colistin)

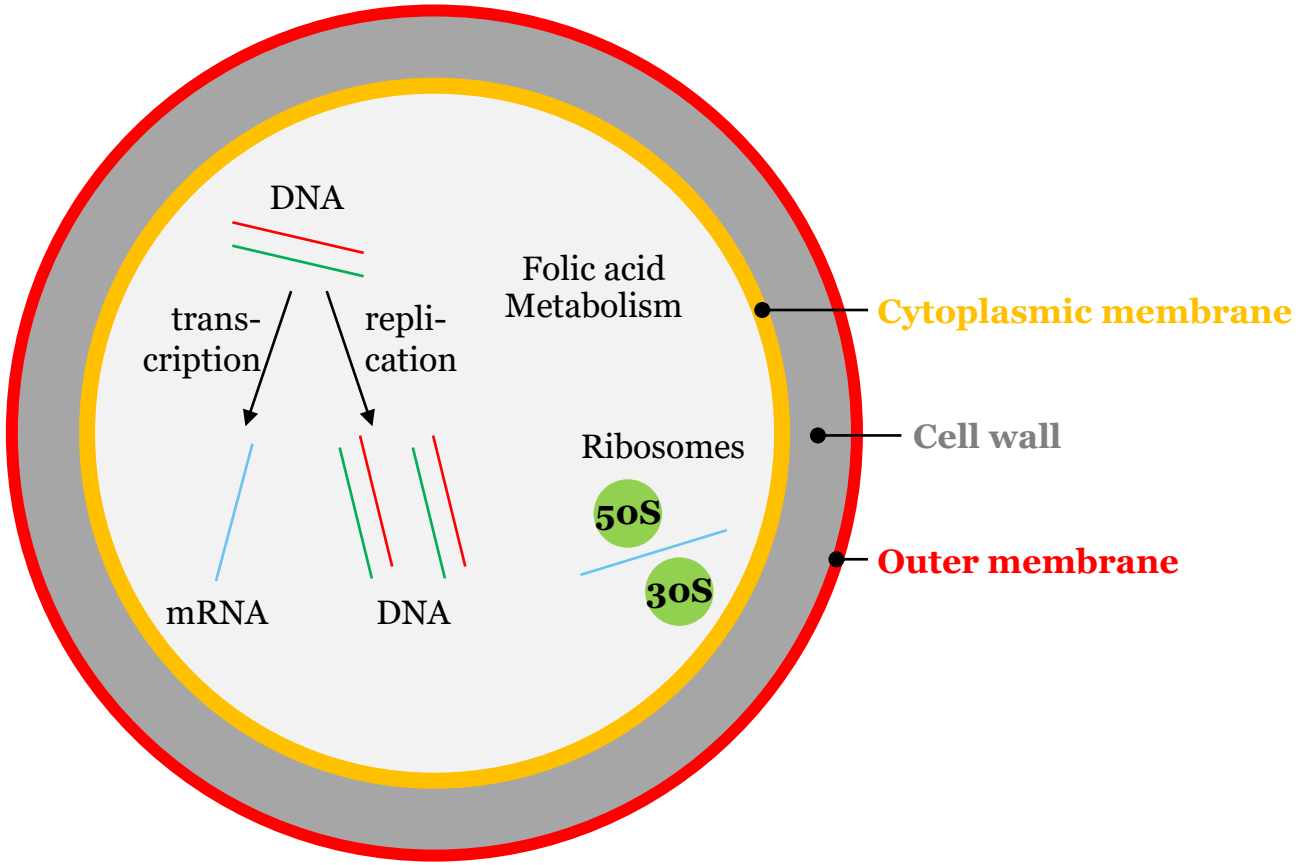
Protein synthesis

50S inhibitors	**30S inhibitors**
Chloramphenicol	Tetracyclines
Erythromycin	Aminoglycosides
Streptogramin	Gentamycin
Cindamycin	Streptomycin
50S and 30S	Linezolid

Focus on Gram-negative bacteria

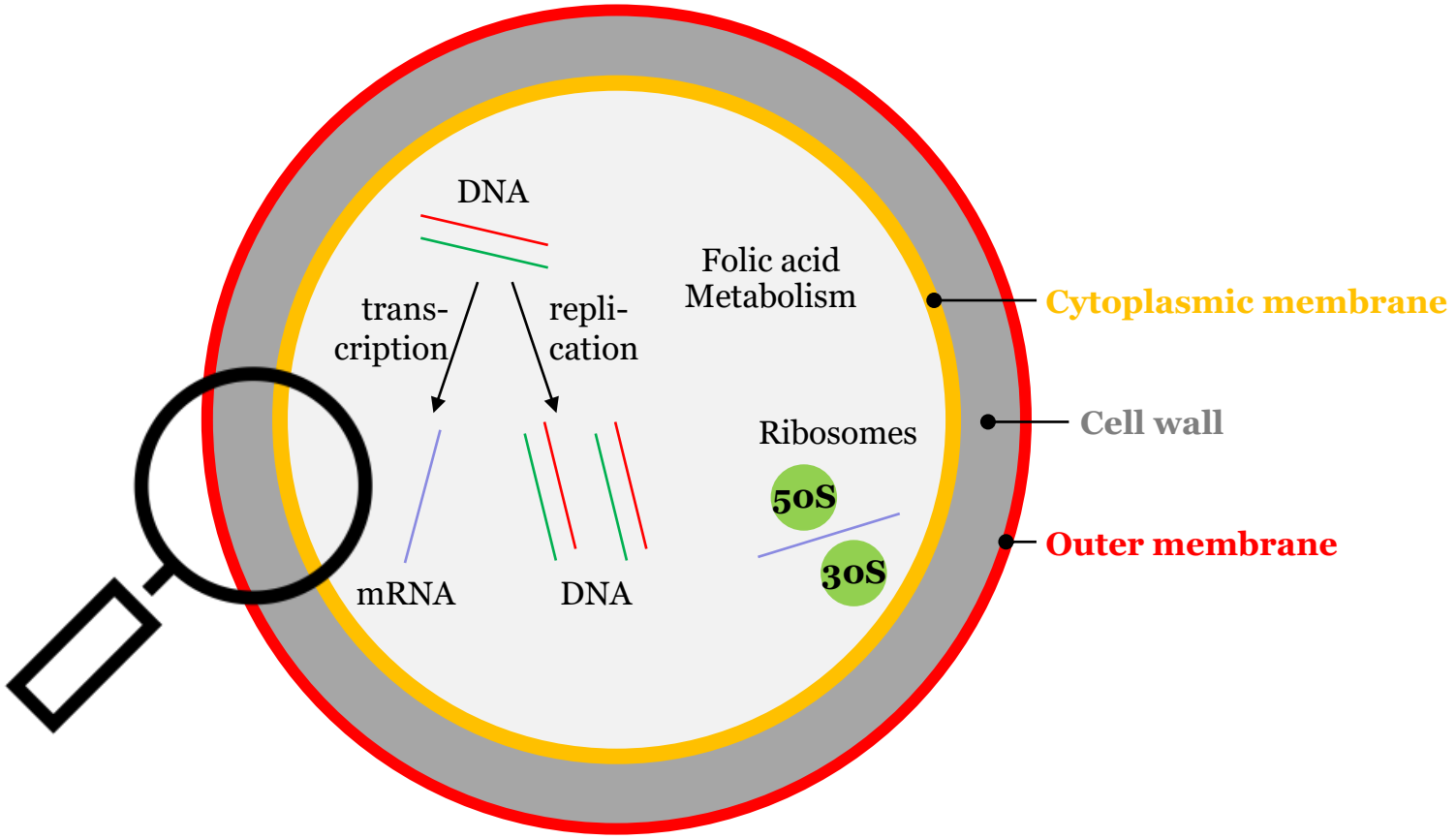
Targets of commonly used antibiotics

Major targets are all within the outer membrane



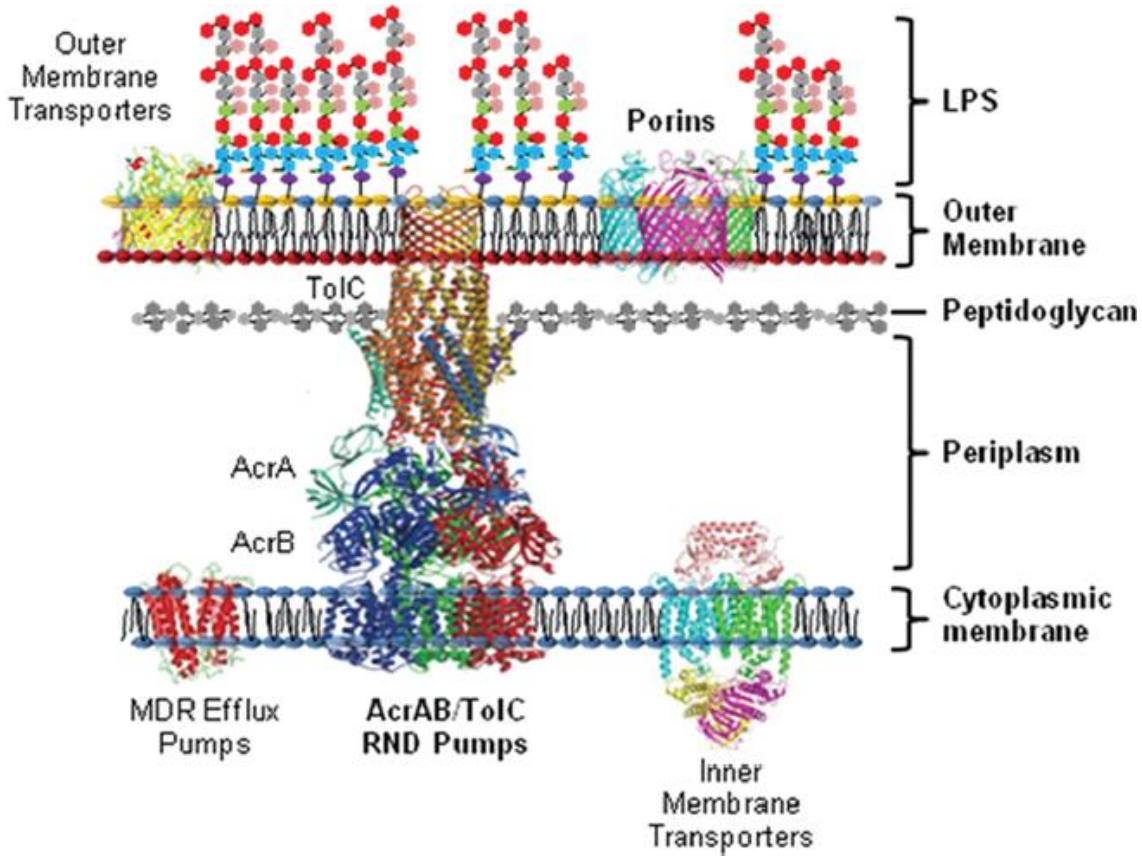
Focus on Gram-negative bacteria

The barrier(s) to entry

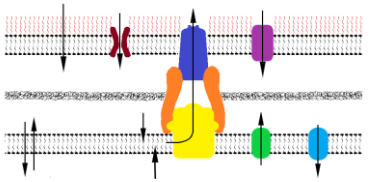


Why are Gram-negative bacteria so tough?

The Gram-negative cell envelope in more detail



J. Med. Chem. 2012, **55**, 2532-2537

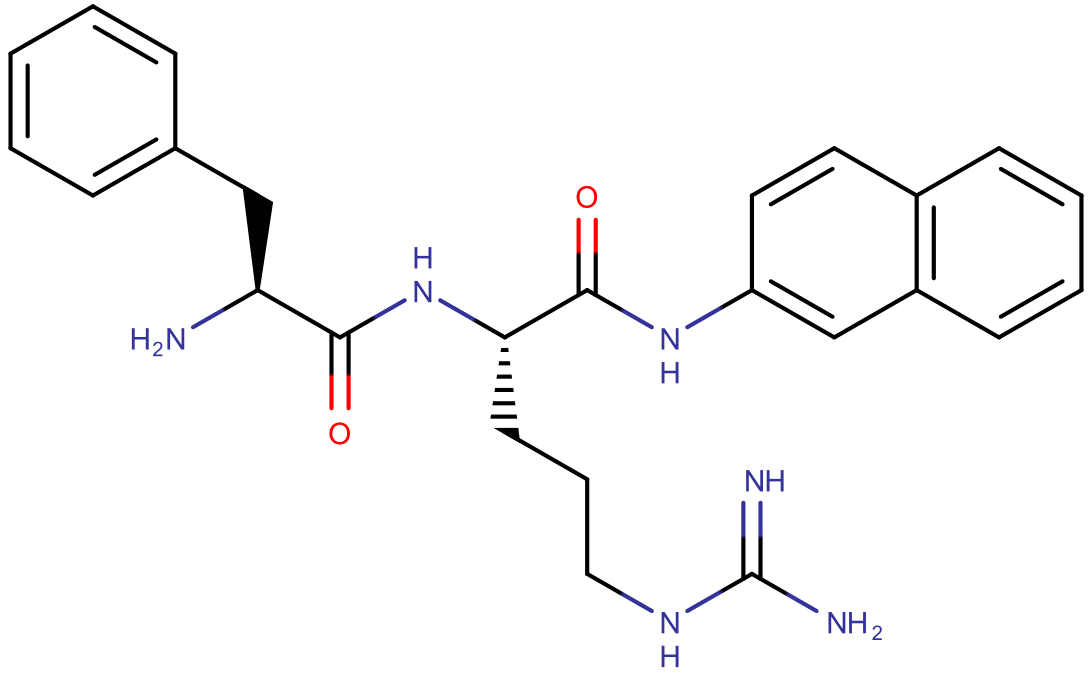


Efflux Pump Inhibitors

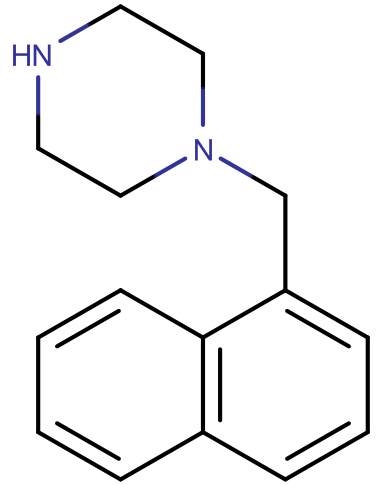
Blocking efflux pumps could potentiate known drugs in MDR strains

- Many compounds have been shown to inhibit efflux pumps and restore activity against resistant bacteria
- EPIs tend to have poor PK and toxicity to mammalian cells
- Demonstrated utility in determining efflux prevalence in clinical isolates

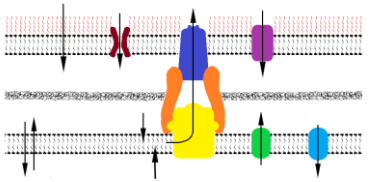
PAβN



NMP



[1] Pages et al. *TRENDS in Molecular Medicine*, 2005, **11**, 8, 382-389

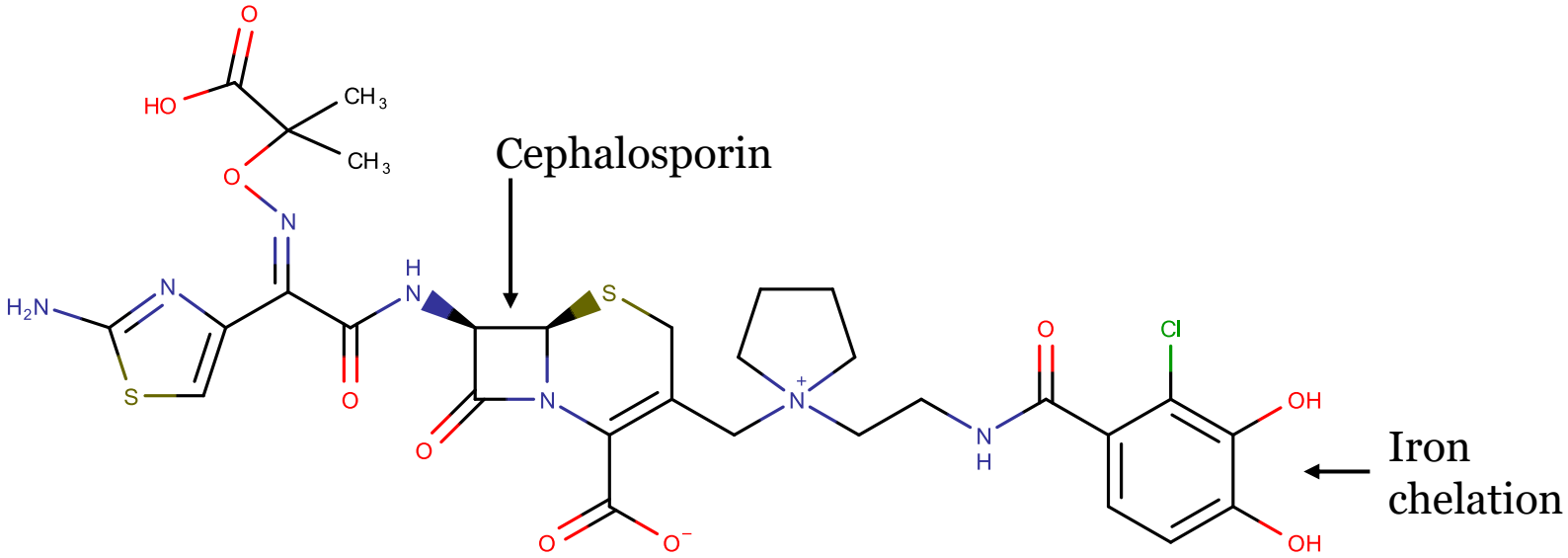


Siderophores – the Trojan Horse strategy

Utilise iron transport mechanisms to facilitate entry

- Bacteria require iron for many cellular processes and have mechanisms for its acquisition
- Siderophores are molecules able to coordinate iron, these are secreted and reabsorbed by bacteria using active transport
- The antibiotic-siderophore conjugate Cefiderocol was approved by the FDA in 2019 for treatment of multi-drug-resistant Gram-negative bacteria

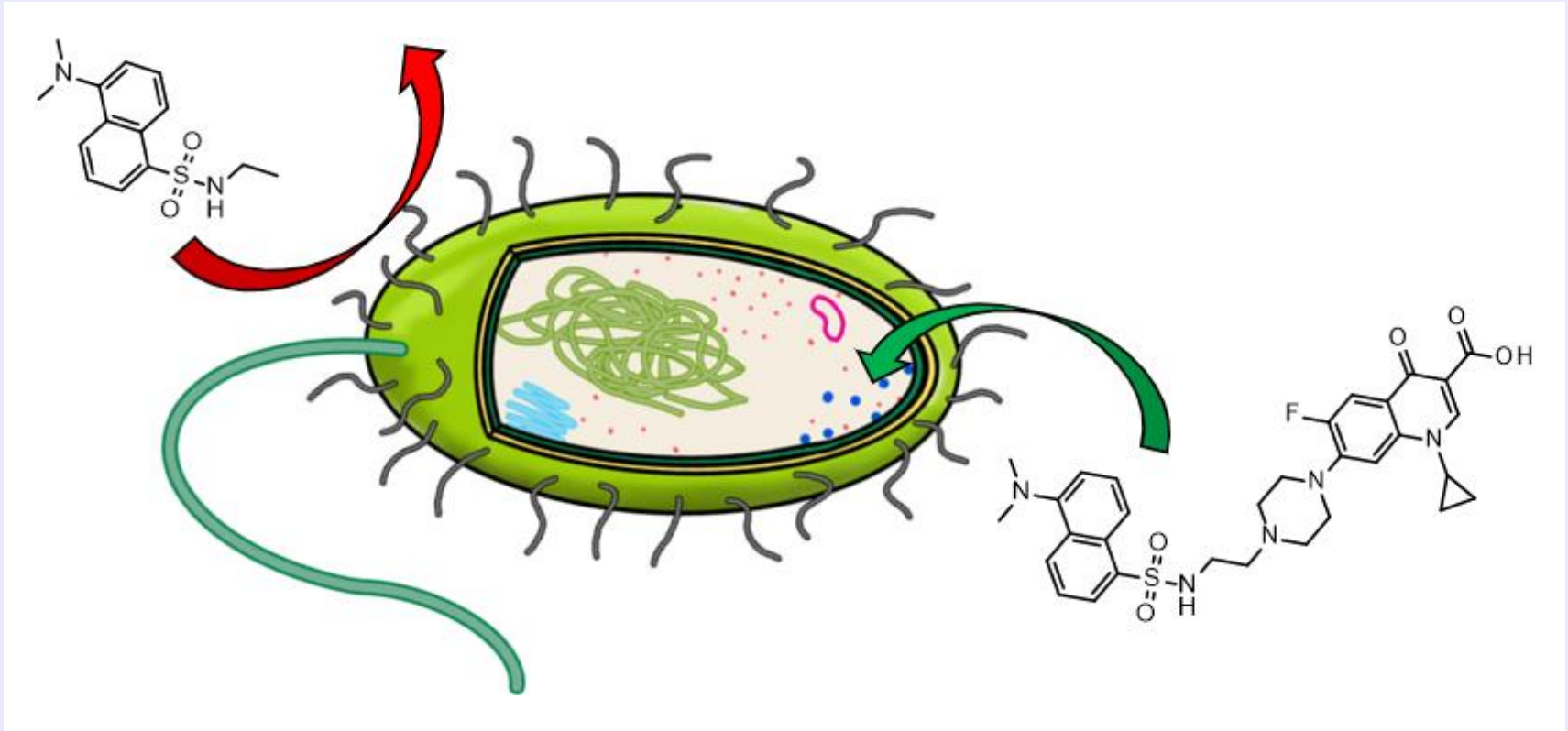
Cefiderocol



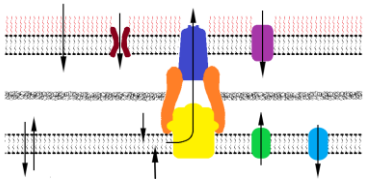
Hijacking other preferred entry routes for Gram-negatives?

Non-siderophore conjugates may enable penetration

- As part of a collaboration between Evotec and Harvard we were trying to broaden spectrum of a Gram-positive only series of molecules
- We developed a novel approach to enable compounds to access the cytoplasm of Gram-negative bacteria through conjugation with ciprofloxacin[1)]



[1)] Unpublished results, the image shows how conjugation to ciprofloxacin enabled a fluorophore to accumulate in bacteria

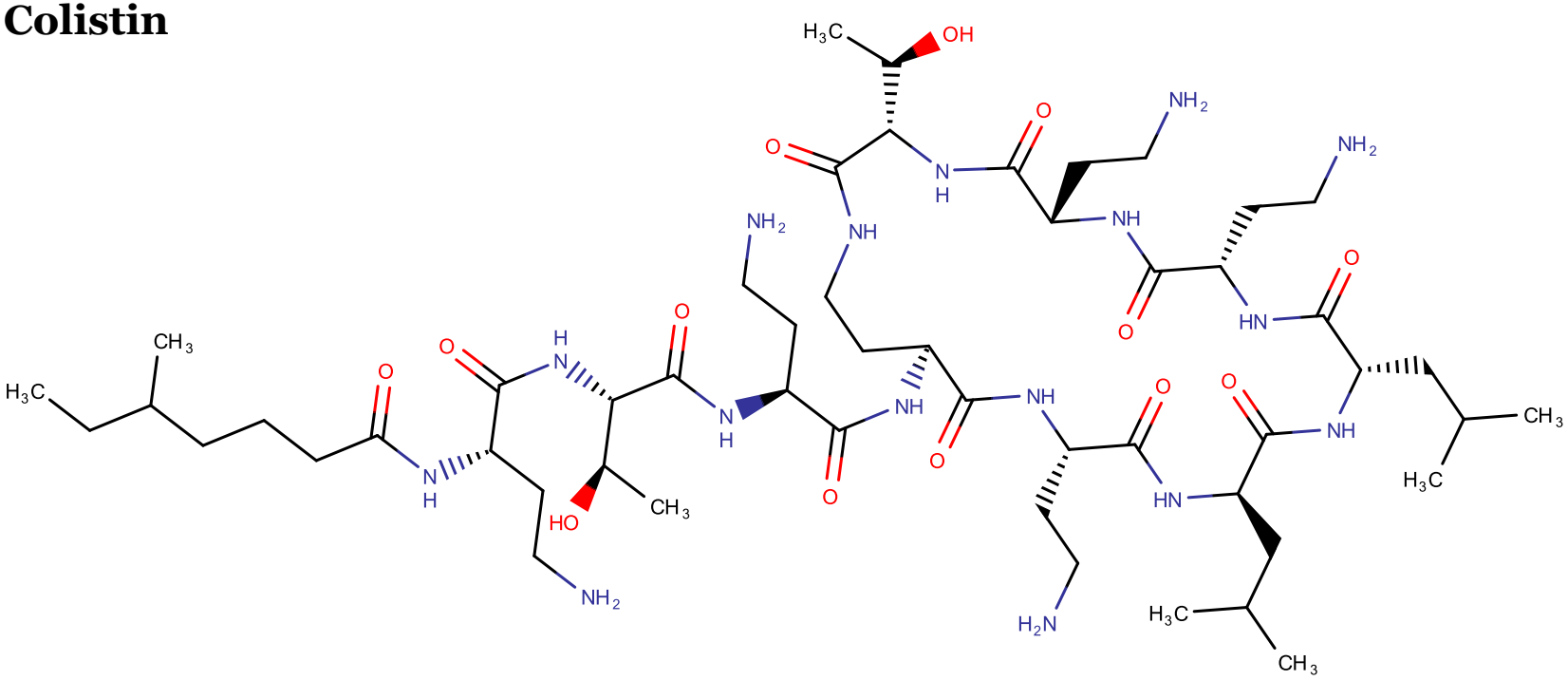


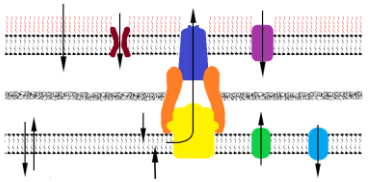
Permeabilisers

Compounds that disrupt bacterial membranes

- Polymixins, such as Colistin (sometimes known as the antibiotic of last resort) penetrate bacteria by interacting with both outer and inner membranes

Colistin



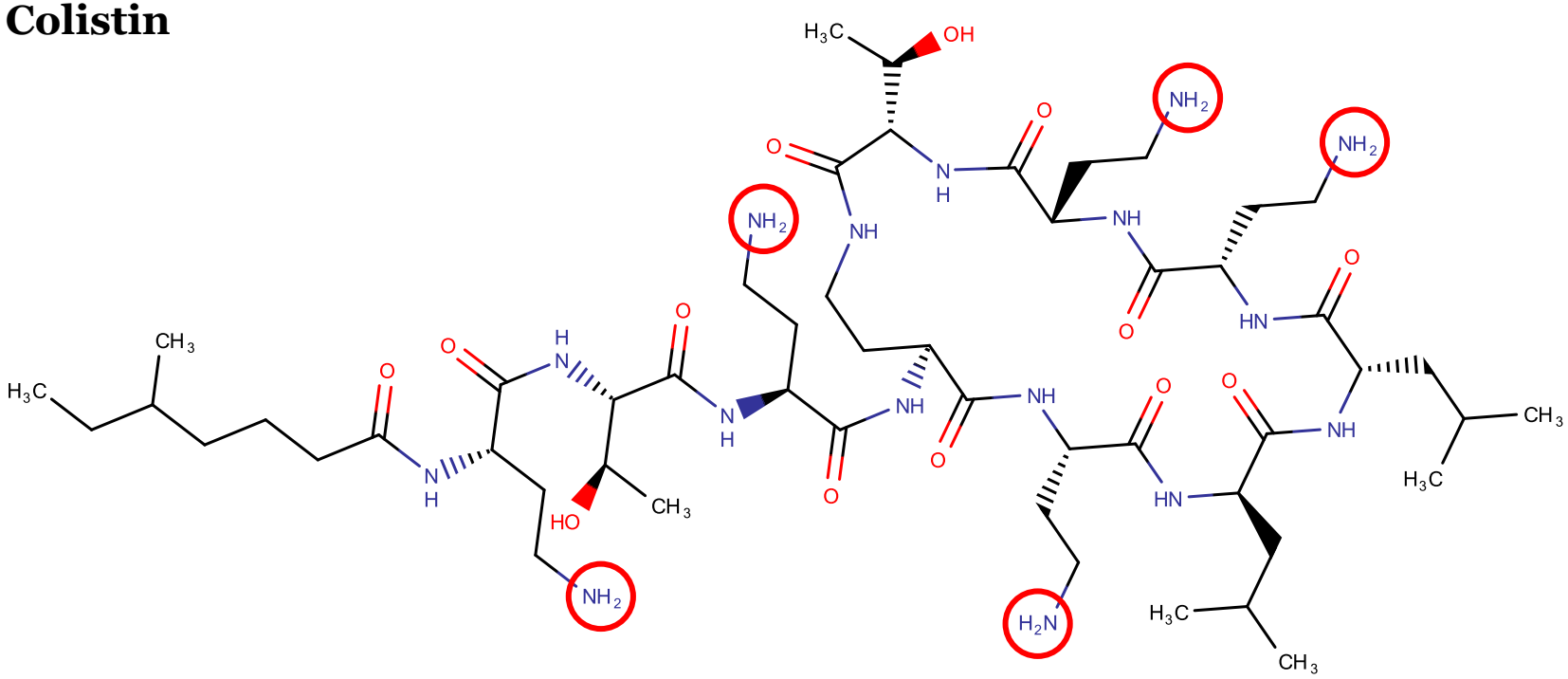


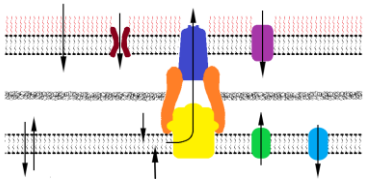
Permeabilisers

Compounds that disrupt bacterial membranes

- Polycationic nature enables disruption of the outer membrane through displacement of stabilizing metal ions in the lipopolysaccharide

Colistin



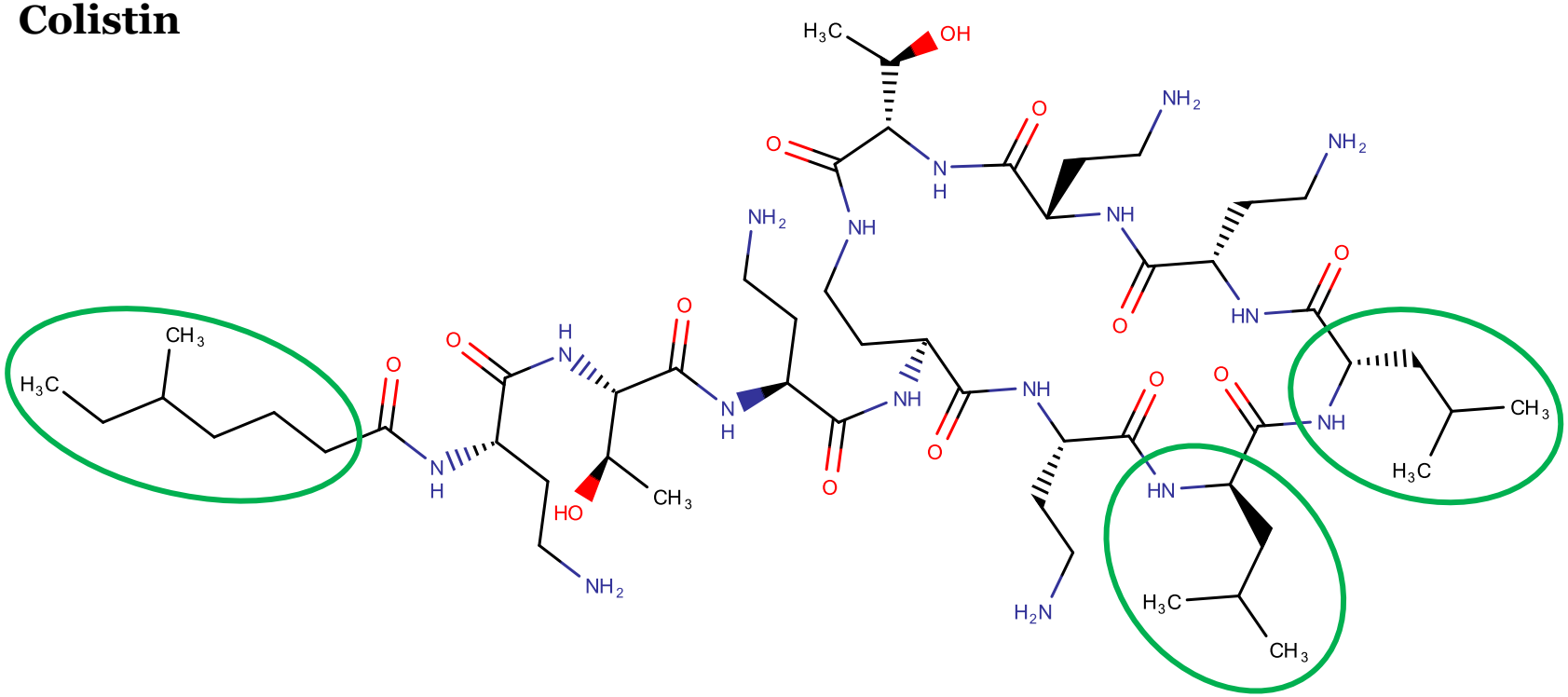


Permeabilisers

Compounds that disrupt bacterial membranes

- Lipophilic features enable polymixins to act as detergents to disrupt cytoplasmic membranes and other phospholipid bilayers
- Newer polymixins, with reduced toxicity but limited antibacterial activity, are being developed for co-dosing with known antibiotics as they retain the ability to permeabilise bacteria

Colistin



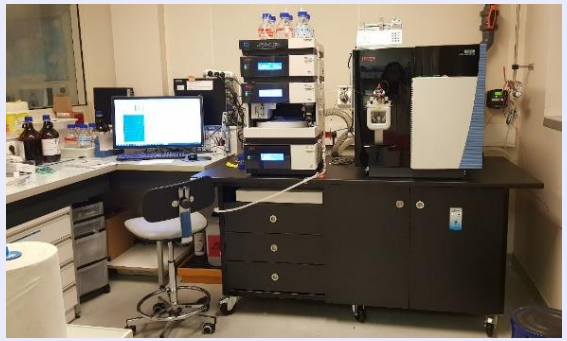
http://antibiotics-theperfectstorm.blogspot.com/2017/09/lets-kill-colistinpolymyxin.html

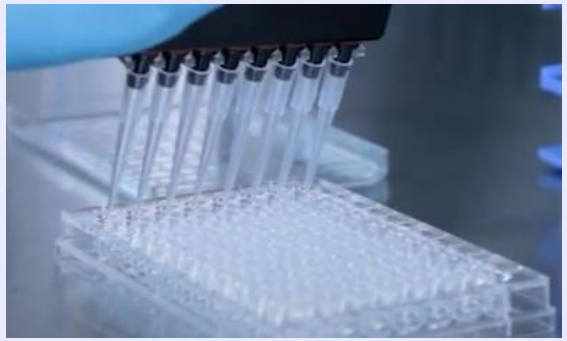
Compound quantification in bacteria

Tools to understand accumulation in cells and intracellular compartments

Whole-Cell Assay

- Determine the compound concentration in the whole cell
- Medium throughput (96-well plate assay)
- Applicable to different pathogens (*Ec, Kp, BCG, Mtb, …*)
- Applicable to different growth media
- Label-free mass spectrometry – based drug quantification

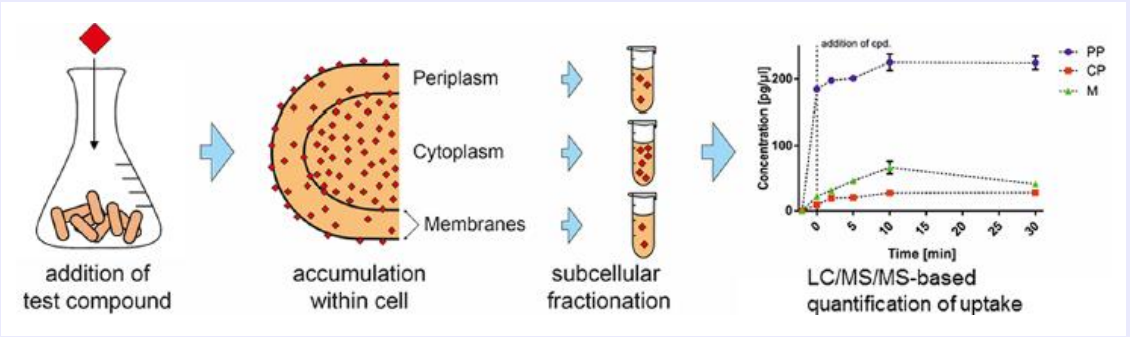




→ Correlate SAR and bacterial accumulation within a chemical series
→ Compare different chemical series, hits ranking

Subcellular Fractionation Assay

- Determine the compound concentration in the different cell compartments
- Low throughput
- Proof of concept done on *E. coli*
- **Assay development started on *A. baumannii***
- Label-free mass spectrometry – based drug quantification



→ Variable level of activity between different strains/mutants of the same species (MoA and MoR)

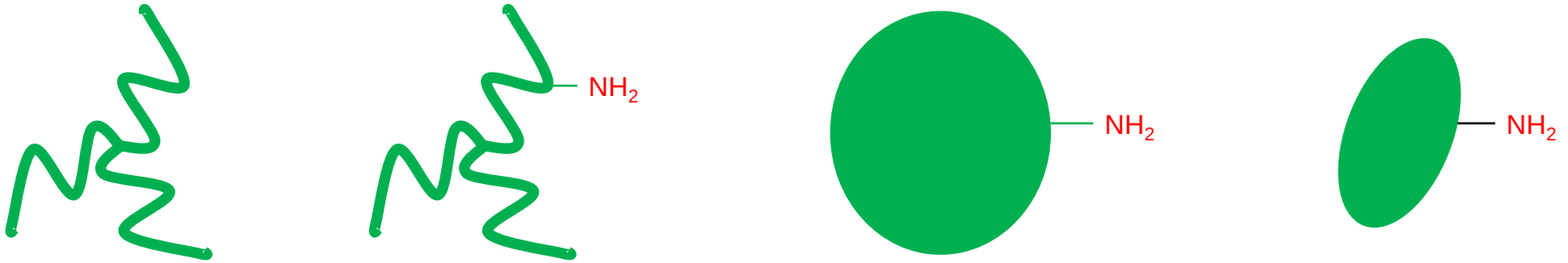
Understand drug permeability into bacteria to support rational design of novel drug candidates

H. Prochnowb *et al.*, Analytical Chem., 2019

Utilising accumulation data to derive predictive rules for *E. coli*

A seminal paper in 2017 provided some guidelines

- Measured accumulation in *E. coli* using MS analysis of cell material & supernatant for 180 diverse compounds
- Findings from this set of compounds
  - Positively charged compounds are more likely to accumulate than either neutral or negative compounds irrespective of clogD
  - Of the positively charged compounds that accumulate primary amines represent the majority
  - Of the compounds containing primary amines rigid amphiphilic compounds and those with low globularity are most likely to accumulate in *E. coli*



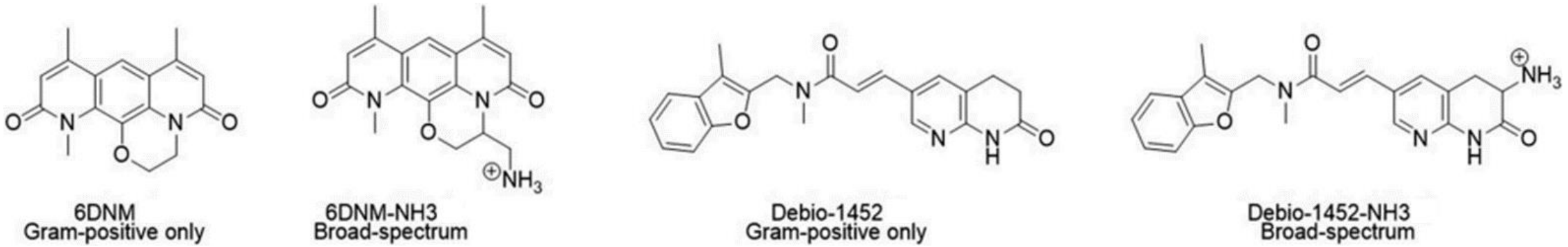
Richter, Hergenrother et al. *Nature* 2017; **304**, 505, 299-316

clogD – calculated distribution constant between octanol and buffered water (usually at pH 7.4)

Applying eNTRyway rules

Broadening spectrum by applying guidelines derived from accumulation data

- The Hergenrother group went on to share a web-based application eNTRyway[1)] designed to be a simple tool to help predict accumulation in Gram-negative bacteria
- Addition of primary amines to two Gram-positive only antibacterial compounds meeting the rigidity and low globularity criteria resulted in broad spectrum agents[2)]



1) Entryway (entry-way.org)
2) Nat Microbiol. 2020;5:67-75

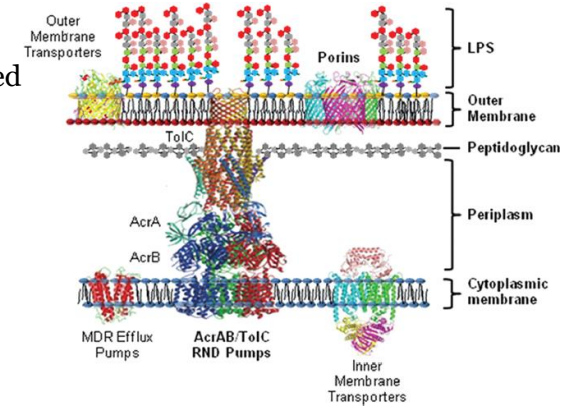
How about accumulation in other Gram-negatives

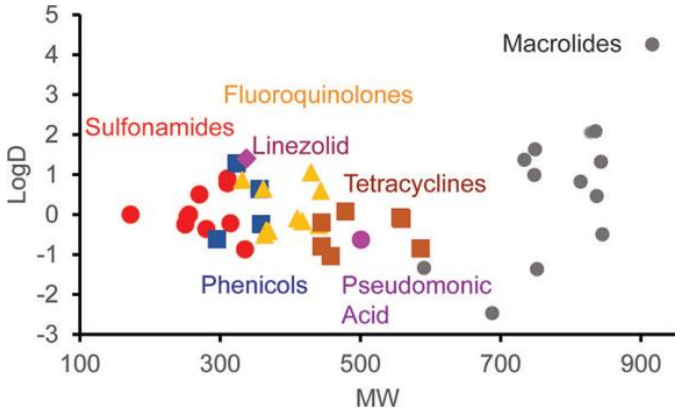
How do different classes of antibiotics penetrate cell envelopes

- Using wild type, hyperporinated (reducing the outer-membrane barrier), efflux-knockout, and combined hyperporinated and efflux knockout strains of *E. coli*, *P. aeruginosa* and *A. baumanii* Zgurskaya and co-workers examined the diversity of Gram-negative permeability barriers
  - Both MIC values and accumulation assays were utilised to assess permeation & efflux of a diverse panel of 47 antibiotics

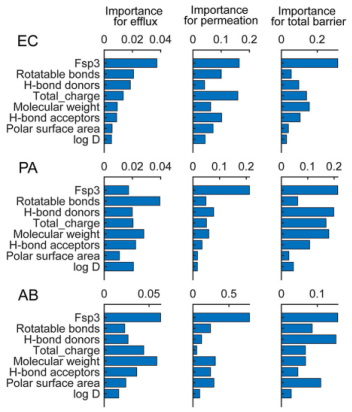
Hyperporinated to increase penetration

Efflux pumps removed to prevent expulsion





Antibiotics chosen cover diverse chem-ical space



Producing multi-species models is very challenging

- The rates of accumulation of various antibiotics vary significantly between Gram-negative species:
  - different LPS, different porins, different efflux pumps

Zgurskaya et al. Antimicrobial Agents and Chemotherapy 2022; 10.1128/aac.01377-22
Cell envelope schematic from *J. Med. Chem.* 2012, **55**, 2532-2537

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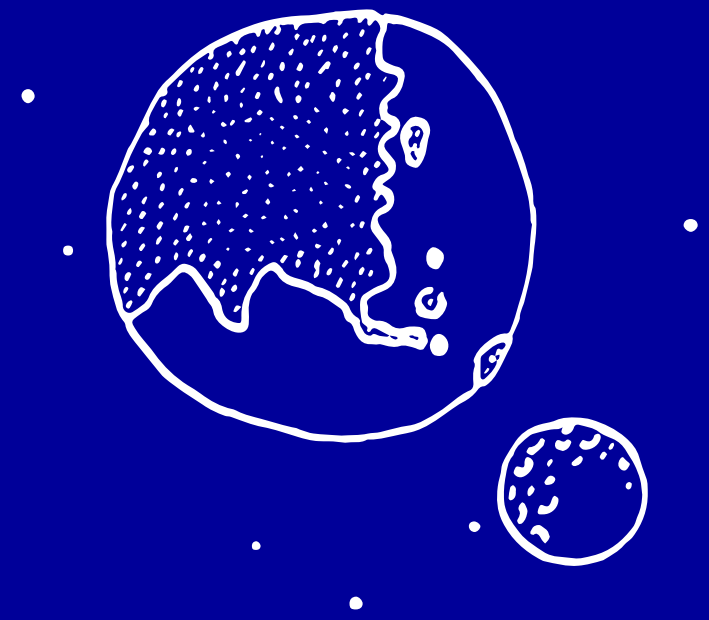
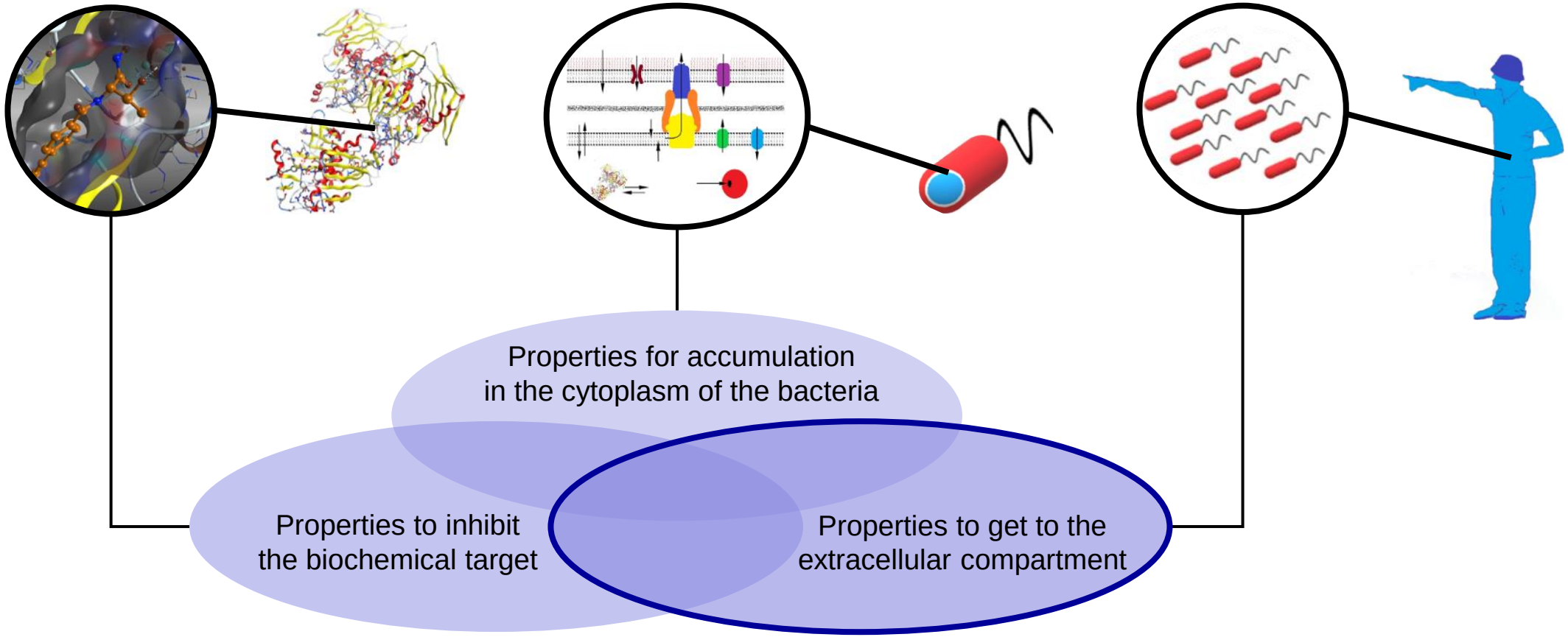


The multiparameter problem for antibiotics

Designing for site of infection



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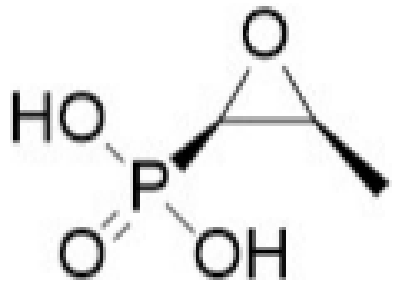
Designing for site of infection

Focus on urinary tract infections

- Measuring tissue concentrations can be important, but designing for accumulation in specific tissues is difficult
- For UTI focusing on renal clearance can deliver drugs to the site of infection
  – aim for small hydrophilic molecules with minimal plasma protein binding
  e.g. Fosfomycin (a key drug for UTI, inc. bladder infections)
- How can we apply this in a drug discovery project?

Fosfomycin



Designing for renal clearance for Urinary Tract Infections

Selecting compounds to test in a UTI model

- A series of compounds were optimised addressing a cytoplasmic target
- Designing for renal clearance resulted in weaker activity:

Compound	Target IC_{50} (nM)	MIC[1] *(E. coli)*	Measured LogD (7.4)	Molecular Weight
A	5	0.5	2.9	500
B	108	8	-0.6	450
		Compound B is:	more hydrophilic	smaller

But does more of the compound reach the urine?

[1] MIC – minimum inhibitory concentration, in µg/mL

Designing for renal clearance for Urinary Tract Infections

Selecting compounds to test in a UTI model

- A series of compounds were optimised addressing a cytoplasmic target
- Designing for renal clearance resulted in weaker activity
- How does this affect PK?

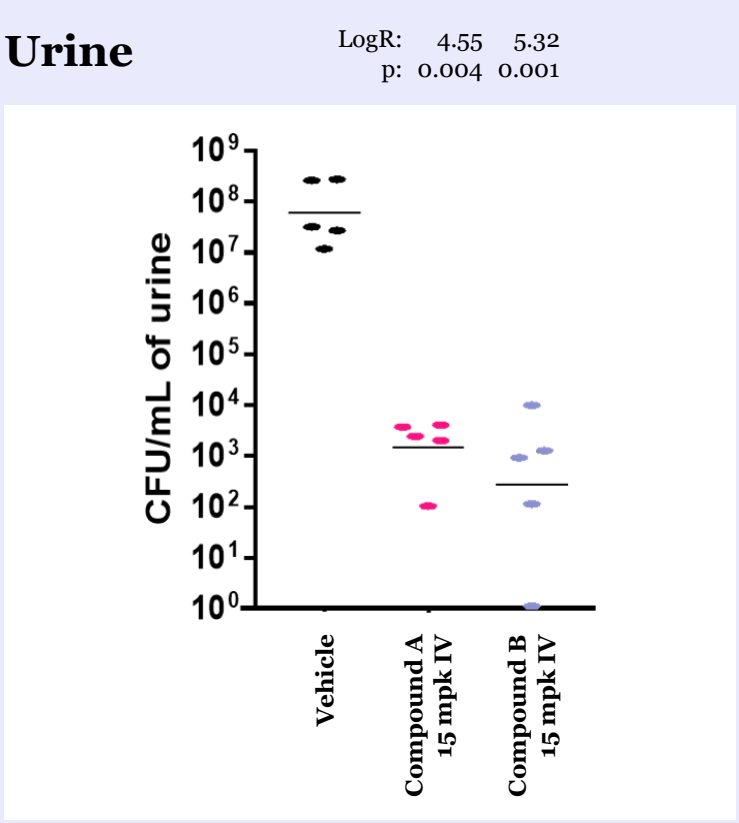
Compound	Target IC_{50} (nM)	MIC *(E. coli)*	Measured LogD (7.4)	Molecular Weight
A	5	0.5	2.9	500
B	108	8	-0.6	450

PK Dose	1 mg/kg IV				10 mg/kg IV
Compound	AUC 0-∞ (µg.hr/mL)	C_{max} (µg/mL)	Blood CL (ml/min/kg)	V_D (L/kg)	% of dose in urine
A	0.3	0.3	94	4.5	**0.8**
B	3.5	8	5	0.8	**26**

Designing for renal clearance for Urinary Tract Infections

Selecting compounds to test in a UTI model

Urine



- A series of compounds were optimised addressing a cytoplasmic target
- Two compounds had very different *in vitro* properties
- How does this affect clearance of bacteria in a mouse UTI model?

Compound	Target IC_{50} (nM)	MIC (*E. coli*)	Measured LogD (7.4)	Molecular Weight
A	5	0.5	2.9	500
B	108	8	-0.6	450

PK Dose	1 mg /kg IV				10 mg/kg IV
Compound	AUC 0-∞ (µg.hr/mL)	C_{max} (µg/mL)	Blood CL (ml/min/kg)	V_D (L/kg)	% of dose in urine
A	0.3	0.3	94	4.5	**0.8**
B	3.5	8	5	0.8	**26**

LogR = Log reduction from vehicle control
NS – not significant

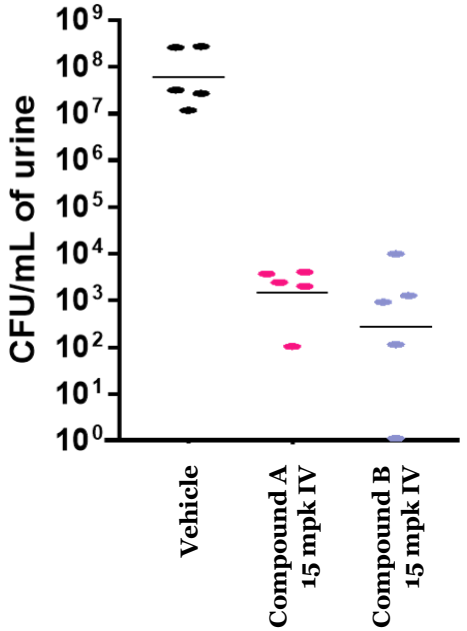
CFU – colony forming units
mpk – milligrams per kilogram

Designing for renal clearance for Urinary Tract Infections

It’s the balance of properties that matters

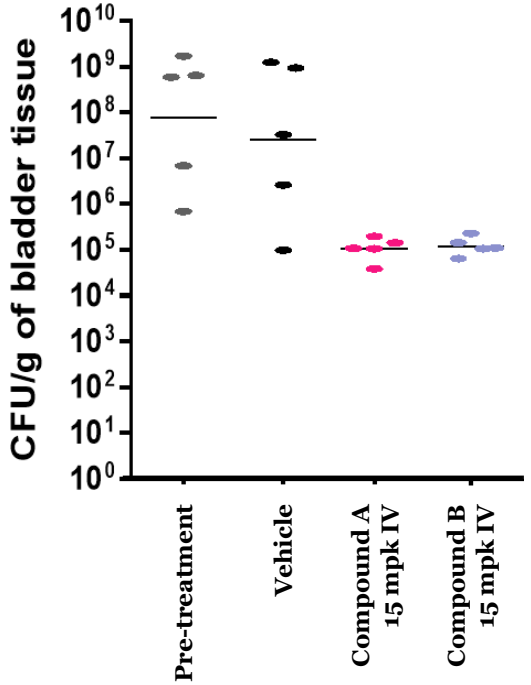
Urine

LogR: 4.55 5.32
p: 0.004 0.001



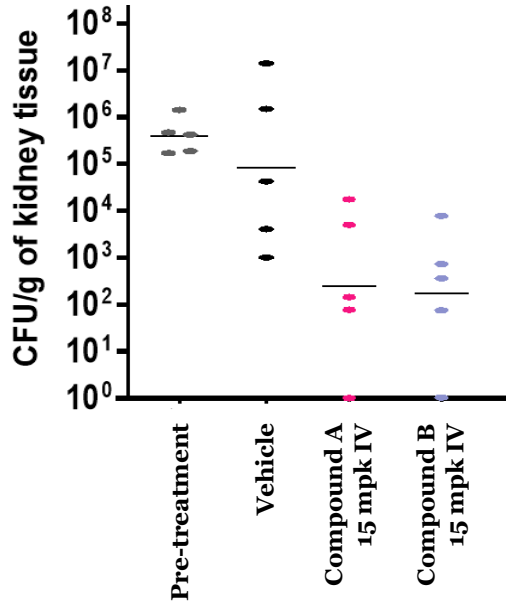
Bladder

LogR: 2.38 2.31
p: 0.049 NS



Kidney

LogR: 2.53 2.71
p: 0.014 0.016



LogR = Log reduction from vehicle control
NS – not significant

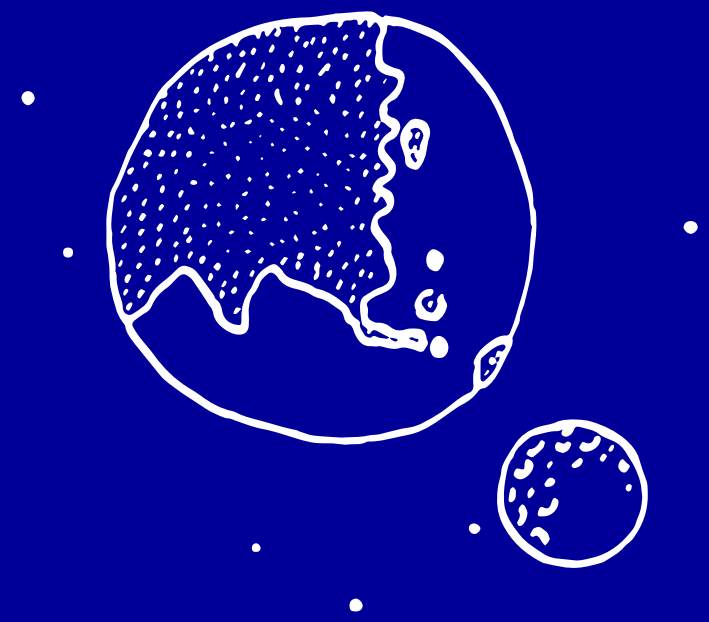
CFU – colony forming units
mpk – milligrams per kilogram

Conclusions for targeting the right extracellular compartment

- Designing for accumulation in most tissues is difficult, and so optimising for unbound plasma exposure is often the most sensible strategy
- Designing for renal clearance is possible and for UTIs achieving high levels of renal clearance can result in enhanced efficacy in *in vivo* models of infection

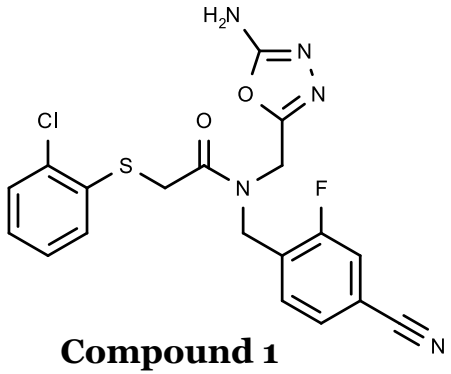
Agenda

1. The multiple challenges of antibacterial drug design
2. Addressing access to drug targets in bacteria
3. Designing for site of infection?
4. Case study
5. Conclusions

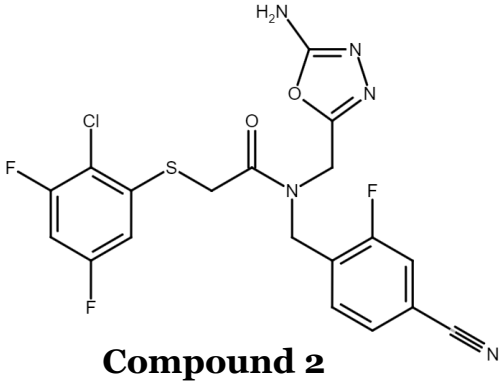


Case study – LpxA inhibitors for *P. aeruginosa*

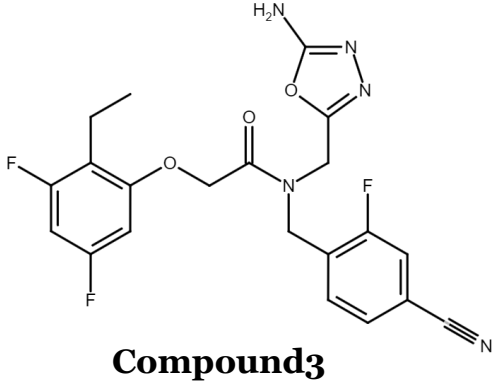
Data guided optimisation of biochemical potency, antibacterial activity and exposure



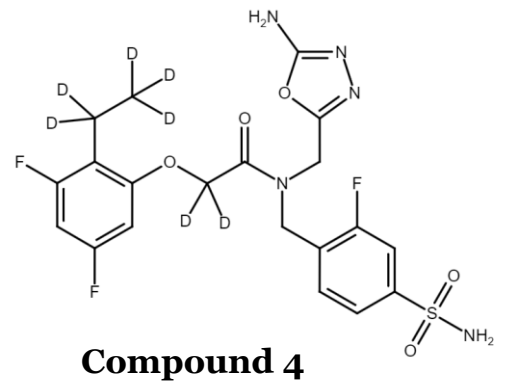
Compound 1
PaLpxA IC_{50} 20 nM
PAO1 MIC 64 µg/mL
in vitro $t_{1/2}$ < 3 mins[1]



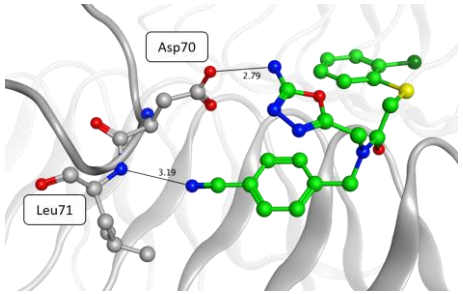
Compound 2
PaLpxA IC_{50} 3 nM
PAO1 MIC 8 µg/mL
LESB58 MIC 4 µg/mL
in vitro $t_{1/2}$ < 3 mins[1]



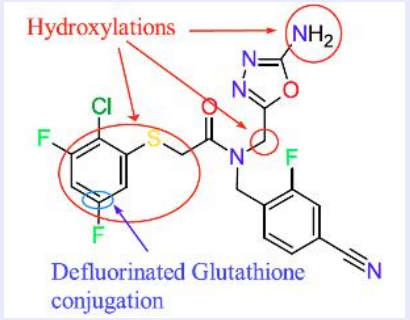
Compound3
PaLpxA IC_{50} 3 nM
PAO1 MIC 8 µg/mL
LESB58 MIC 4 µg/mL
in vitro $t_{1/2}$ 6 mins[1]

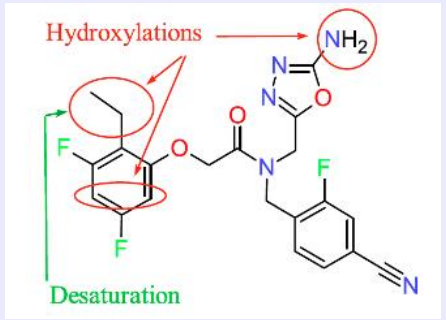


Compound 4
PaLpxA IC_{50} 3 nM
PAO1 MIC 32 µg/mL
LESB58 MIC 4 µg/mL
in vitro $t_{1/2}$ 71 mins[1]

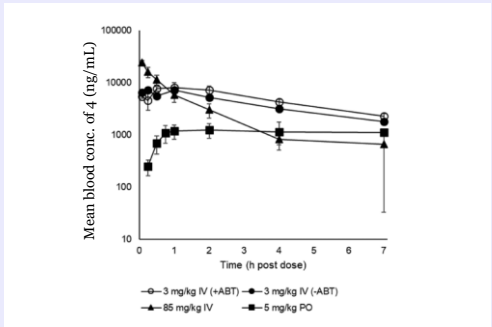


Crystal structures





In vitro MetID studies

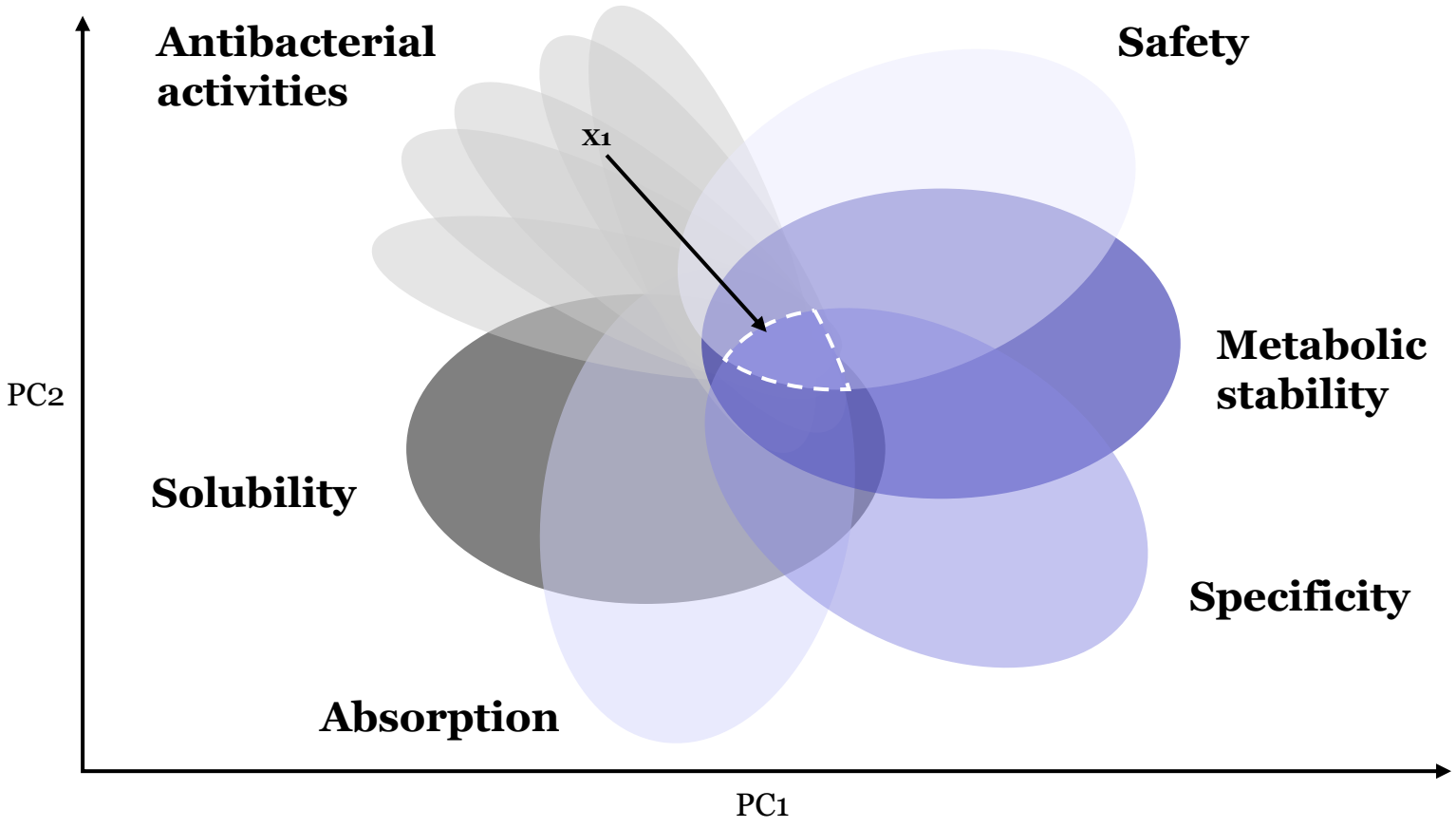


In vivo pharmacokinetics

[1]Half life in mouse microsomes

Journal of Medicinal Chemistry 2021, 64, 19, 14377-14425

Strategies and predictive models to aid antibacterial drug design



- Some guidelines and strategies exist for design of compounds to penetrate *E. coli*
  - Permeabilisers or efflux pump inhibitors
  - Conjugate molecules
  - eNTRYway rules
- Data gathering and proper curation can enable construction of predictive models
  - But due to the diversity of bacteria we have no general solutions
- Once we have multiple models for bacteria the challenge is to combine with multi-parameter optimisation required for all drug discovery

Acknowledgements

- Evotec: David Corbett, Peter Warn, Michelle Southey, Adele Faulkner, Shelley Parrott, Emily Trimby, Stephanie Sandiford, Alain Dorali, Martin Arthuis, Beth Williamson, Swapna Vaddi, Ian Yule, Sebastien Coyne, Anthony Dickie, Ole Andersen, Daniel Stein, Olivier Barbeau, Angelo Sanzone, Pia Thommes, John Barker, Ricky Cain, Christel Compper, Magali Dejob, Alain Dorali, Donnya Etheridge, Sian Evans, Elise Gadouleau, Tim Gorman, Denes Haase, Maisie Holbrow-Wilshaw, Thomas Krulle, Xianfu Li, Chris Lumley, Barbara Mertins, Spencer Napier, Rajesh Odedra, Kostas Papadopoulos, Vas Roumpelakis, Kate Spear, Jennifer Williams, Michael Zahn
- Harvard: Prof. Dan Kahne, Veerasak Srisuknimit
- Forge: David Puerta, Min Teng, Kostantin Taganov, Baskar Nammalwar
- X-Biotix: Dominic Ryan, Boudewijn DeJonge

evotec

#RESEARCHNEVERSTOPS

Dr Alastair Parkes
VP, Medicinal Chemistry

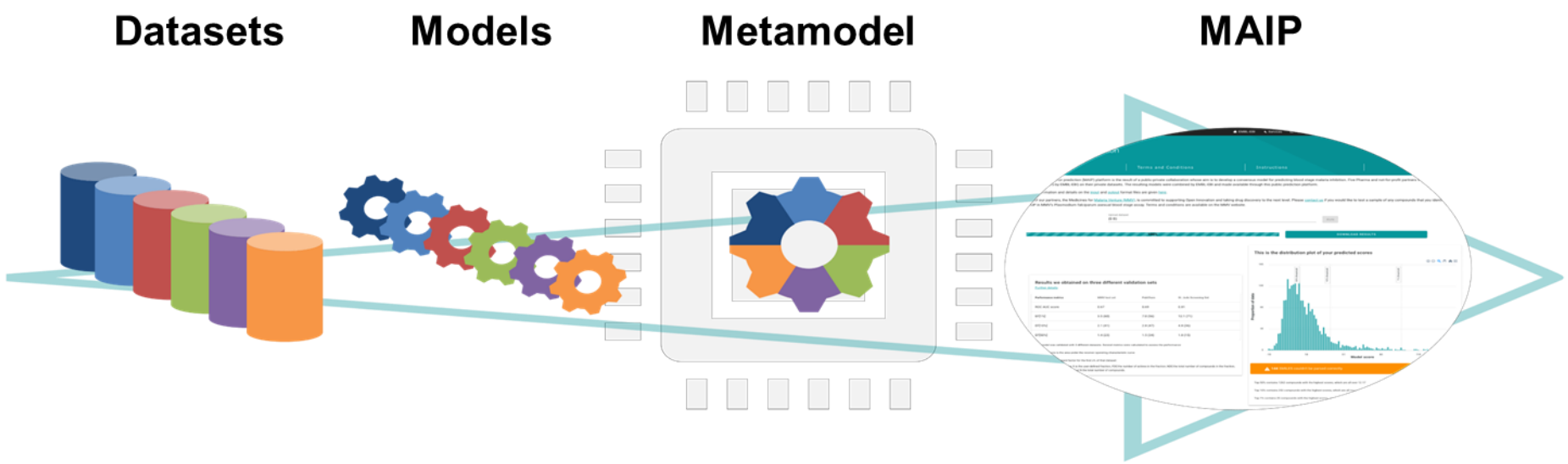
Alastair.Parkes@evotec.com

James Duffy

James Duffy is a Senior Director of Drug Discovery at Medicines for Malaria Venture (MMV) with 25 years' experience working in drug discovery.

He has a special interest in malaria and other infectious diseases that disproportionately affect vulnerable populations in the global south. Working at MMV, he is part of the efforts to reduce the burden of malaria in disease-endemic countries by discovering, developing and delivering new, effective and affordable antimalarial drugs. His current role is to provide scientific input and strategic leadership to multidisciplinary collaborations with academic, biotechnology and pharmaceutical partners engaged in malaria drug discovery projects.

James obtained his PhD from the University of Sussex (Brighton, UK) and prior to MMV he worked at BioFocus (Cambridge, UK) where he was a co-inventor of the FDA approved HDAC inhibitor Belinostat.



Experimental validation of the MAlaria Inhibitor Prediction (MAIP) platform

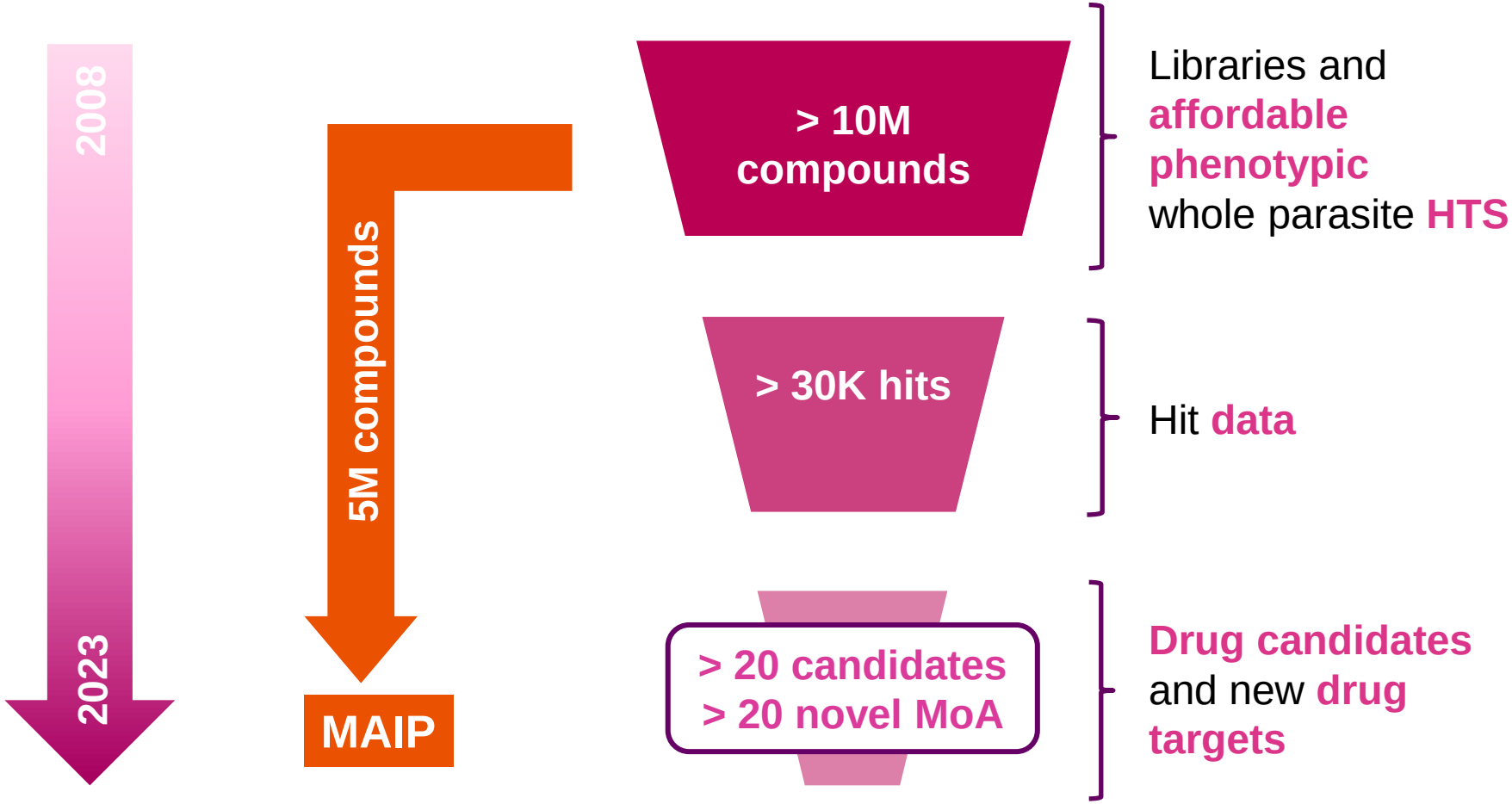
James Duffy, Senior Director Drug Discovery

GARDP, Geneva, 24 August 2023

Defeating Malaria Together

MMV
Medicines for Malaria Venture

Asexual blood stage phenotypic HTS | 15 Years of Hit Gen.



Screening partners

Rottman, M. *et al. Science,* **325**, 1175-80 (2010)
Gamo, F. J. *et al. Nature,* 2010, **465**, 305-10 (2010)
Guiguemde, W. A. *et al. Nature,* **465**, 311-15 (2010)

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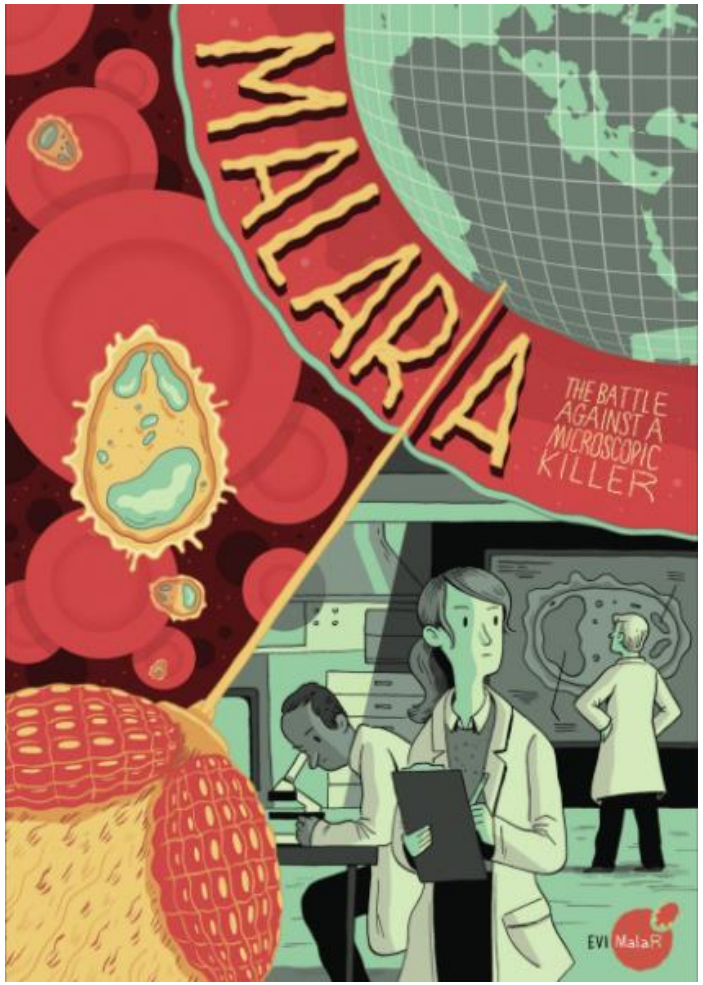
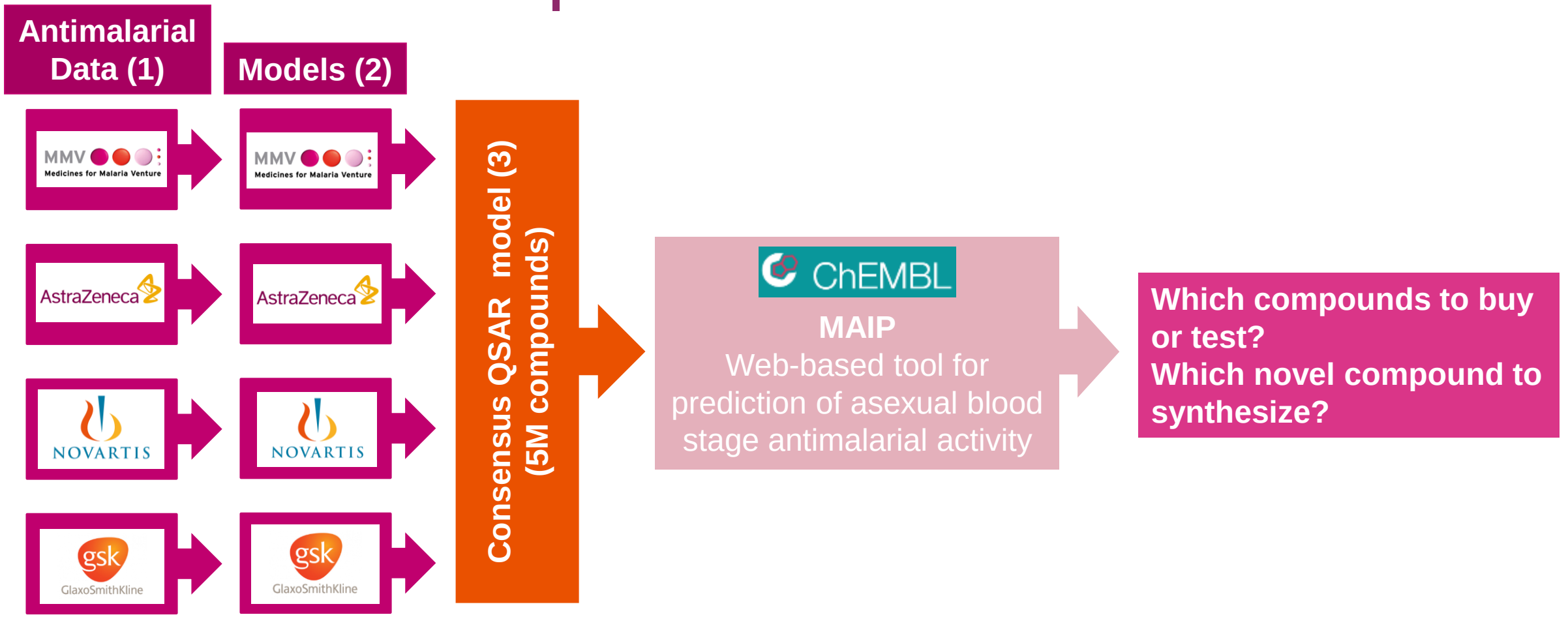
MAIP | Motivation and potential uses



- Clear need for **accessible**, **affordable** and **user-friendly computational tools** to support infectious and neglected tropical disease drug discovery (https://www.mmv.org/our-work/research-and-development)
- Maximize the **impact** of compound testing through **enrichment** (using the model) towards a greater proportion of potential actives
  - Organizations/institutions with **large screening collections** who are willing to test (blinded) subsets in the whole cell asexual blood stage HT assays
  - Organizations who are designing and acquiring **new** (antimalarial) **libraries** (especially those with limited compound acquisition budget)
  - Groups with access to **novel compounds**
- Potential application of the approach (open access consensus model) for use in other **NTD drug discovery projects**

MMV Medicines for Malaria Venture

MAIP | Construction of model



1. Data defined by descriptors
= 'fingerprints' of molecular structure
= calculated properties (MW, LogP, etc.)
= dependent variable (active/inactive)

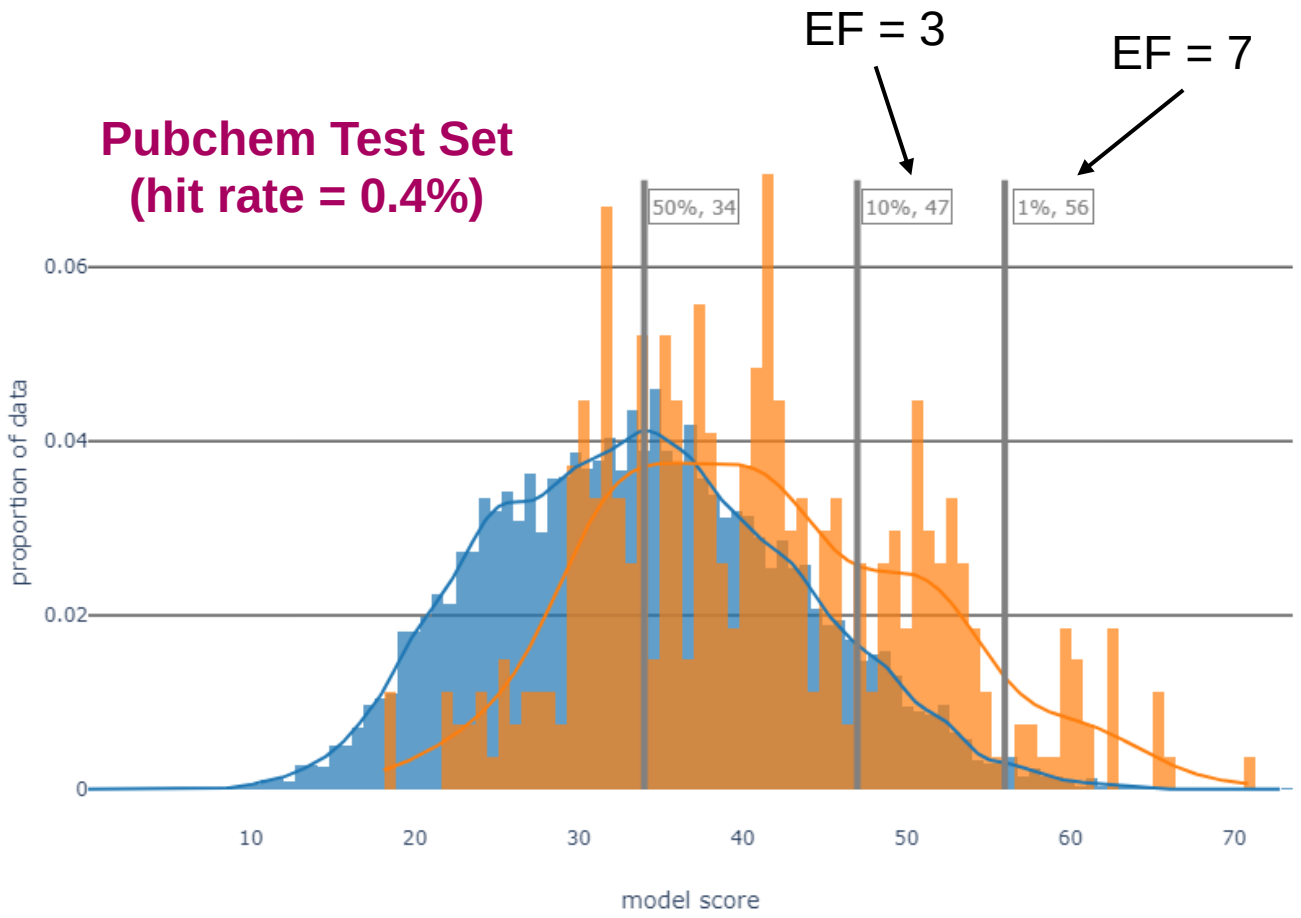
2. Model selected by data owner
= Naïve Bayes, Multilinear Regression, Neural Networks, Random Forests etc.

3.Consensus model
= max score
= mean score
= **metamodel**

Bosc, N., *et al*., *J. Cheminform.*,***13***, 13 (2021)

MMV Medicines for Malaria Venture

MAIP | Use of tool (example)

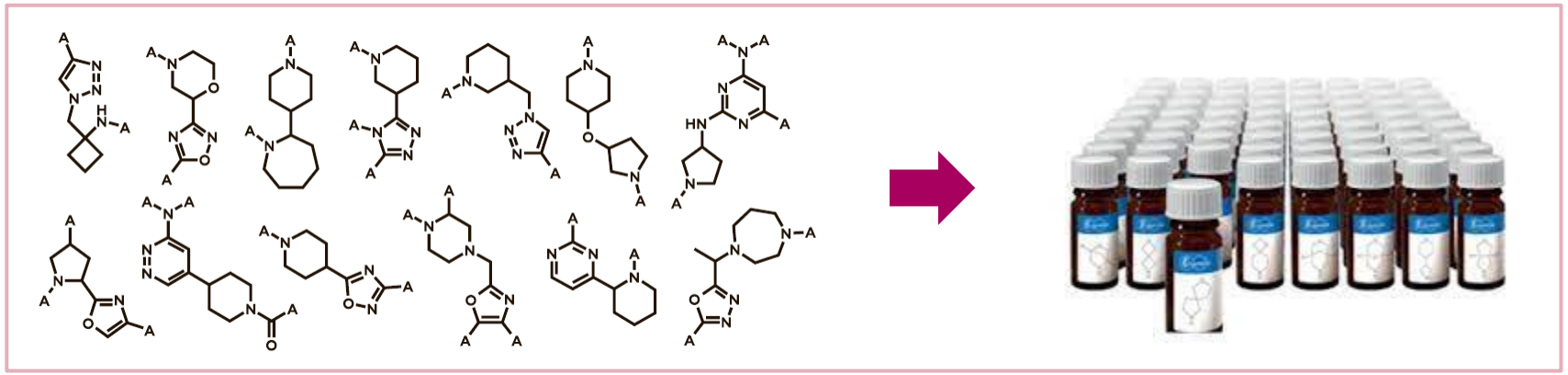


- Distribution of model scores for the active (orange) and inactive (blue) compounds
- Grey lines illustrate the fractions of compounds used to calculate the enrichment factor (EF)
- EF = hit rate (the proportion of active compounds) within a defined sorted fraction divided by the total hit rate

- MAIP (**https://www.ebi.ac.uk/chembl/maip/**) generates a score for each compound in uploaded file
- Based on test sets, prioritize scores above **40-50** for **good enrichment**

MMV Hit Generation | Library design

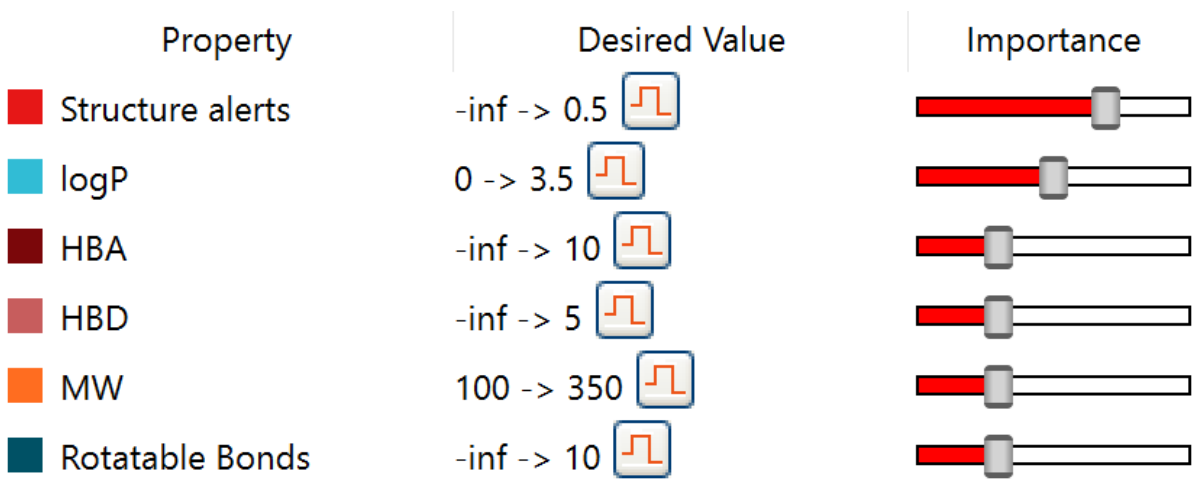
MMV libraries are designed as a sets of **diverse**, **novel**, and **high-quality** compounds

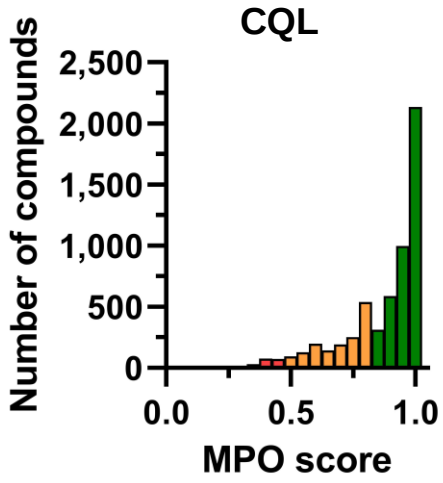


Feature	Ideal Criteria
Diversity	EMBL-EBI ‘reduced graphs’ & frameworks protocol to identify unique scaffolds Only centroids or singletons (Stardrop clustering sim. > 0.7)
Novelty	No compounds in MMV in-house database, malaria subsets of ChEMBL[1] and SureChEMBL No ‘malaria drug fragments’ (MMV in-house list)
Quality	Balanced calculated physicochemical property profile with potential for further development No compounds with a structure alert[2] Predicted malaria active (MAIP)
Balanced profile	MMV Library Design MPO score > 0.8

1. https://chembl.gitbook.io/chembl-ntd/
2. Brenk, R., *et al*. *ChemMedChem*, **3**, 435–444 (2008).

MMV Hit Generation | Library design MPO profile



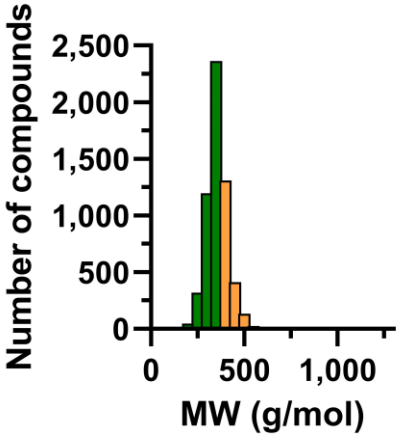


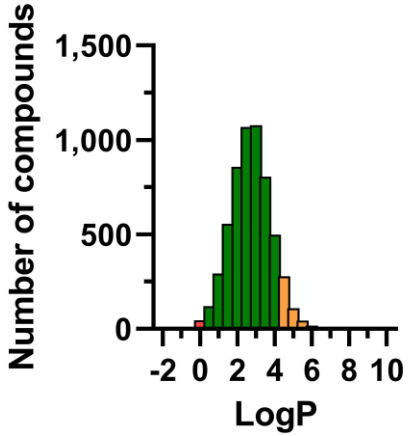
Use of weighted MPO scoring profile in library design:

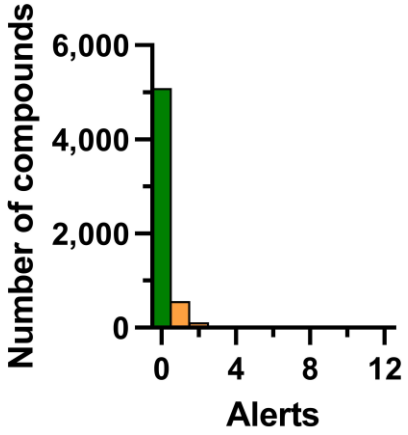
- Design focus is to achieve a **balanced profile** (*vs.* imposing strict cut-offs)
- Max. **MPO score** for a compound with **'ideal' properties = 1**
- **Properties** selected to be **complementary** (avoid placing too much importance on one property)
- MMV MPO scoring profiles available on Optibrium website (https://optibrium.com/downloads/mmv-antimalarial-scoring-profile/)

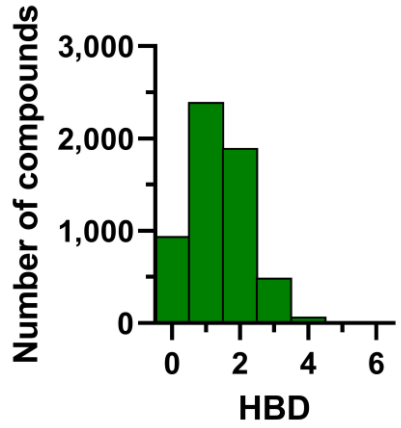
Yusof, I. *et al. Drug Discovery Today*, **18**, 659–666 (2013)

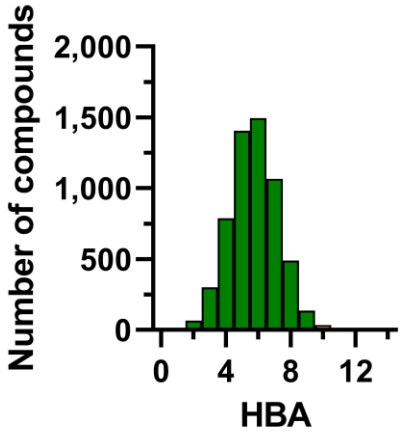
MMV Hit Generation | ChEMBL QSAR Library (CQL)

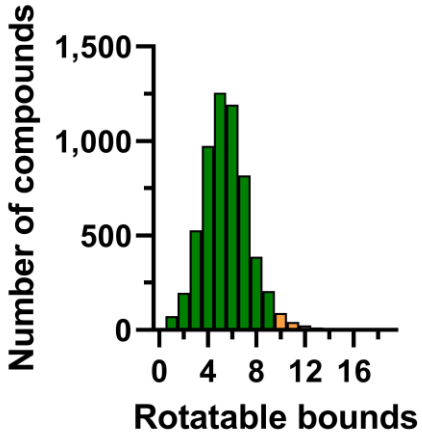


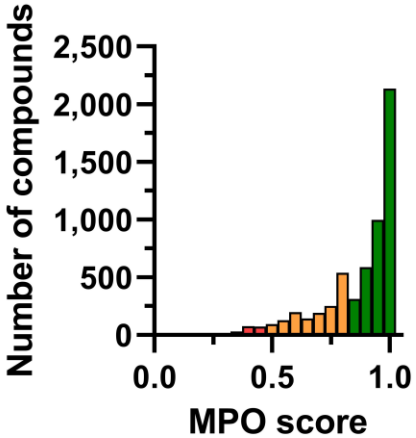


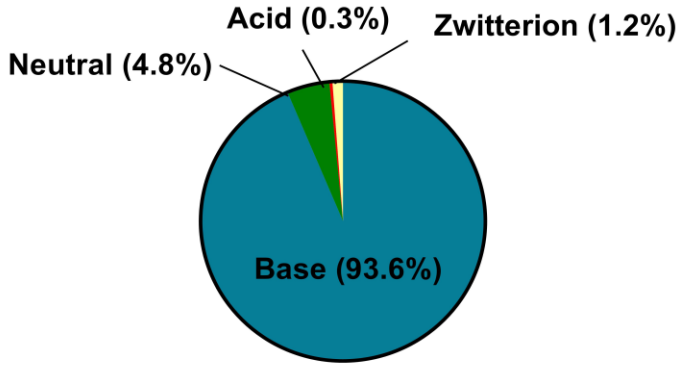








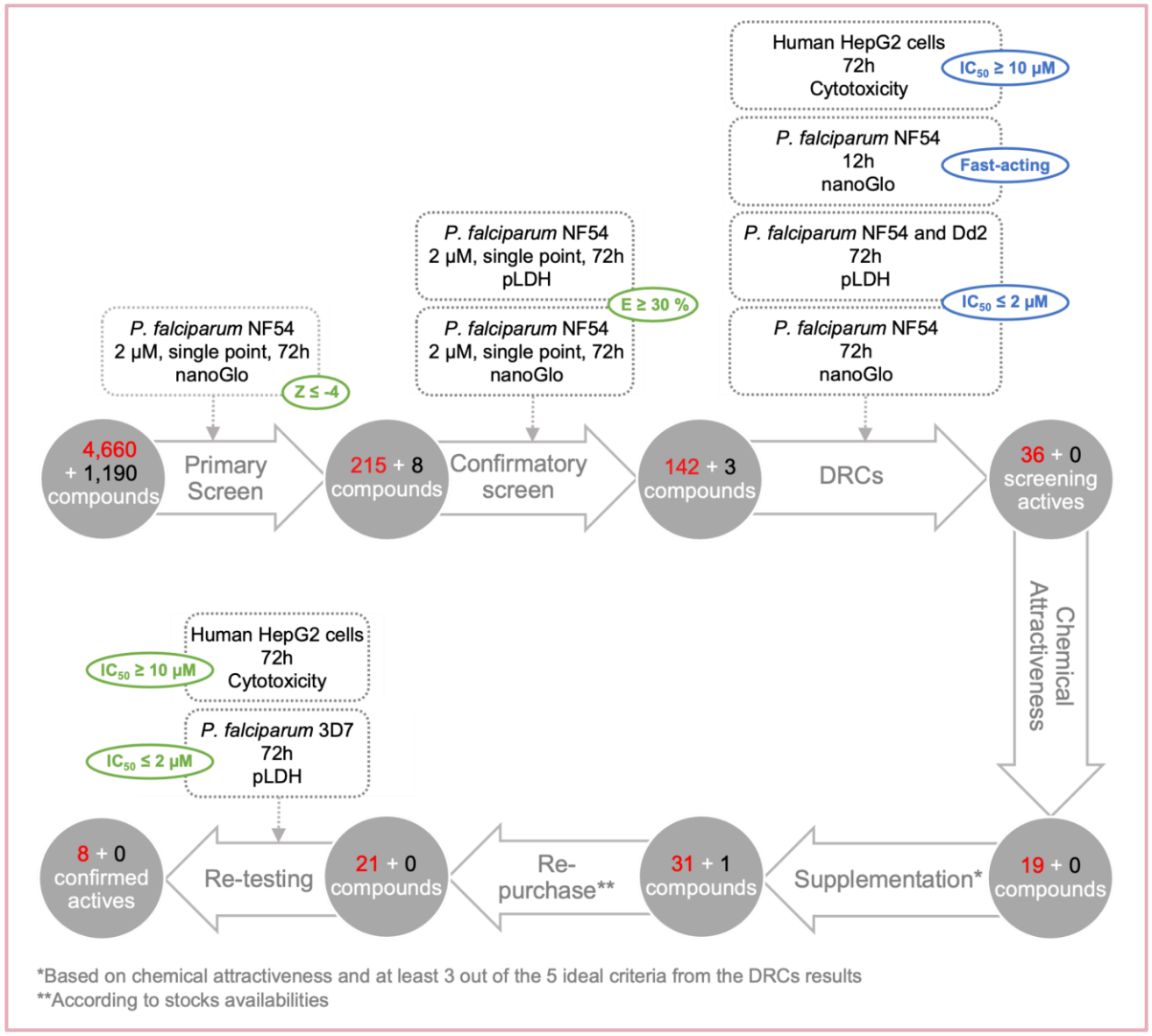




- Compounds in CQL have calc. physicochemical properties associated with **high quality chemical hits**
- MPO criteria not met for all compounds and some high scoring (MAIP) compounds selected with MPO < 0.8 (generally containing ≥ 1 structural alerts)

MMV
Medicines for Malaria Venture

MMV Hit Generation | Screening cascade (CQL *vs*. random)



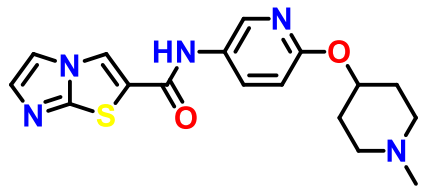
*Based on chemical attractiveness and at least 3 out of the 5 ideal criteria from the DRCs results
**According to stocks availabilities

- MMV have developed a **comprehensive primary screening** and **hit triage cascade**
  - Strict selection criteria are depicted in green, and ideal ones in blue
  - Predicted actives (CQL) = red
  - Randomly selected (control) = black
  - Key activity data generated at 2 test centers
- **CQL** has significantly **higher hit rates** than libraries designed without MAIP (e.g. HGL1)
  - **CQL** = **3%** screening actives
  - **HGL1** = **0.1%** screening actives
- 8 Confirmed Actives
  - **MAIP** score = **51-62**
  - **MPO** score **> 0.8** (7 of 8 compounds)
  - **Novel** antimalarial **hits** (ChEMBL)

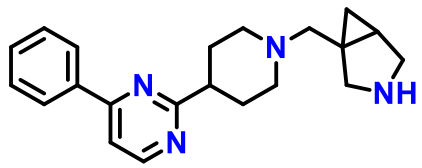
Bosc, N., *et al*., *(2023). Manuscript submitted for publication*

pivotpark screeningcentre | TCG Lifesciences | Chembiotek | MMV Medicines for Malaria Venture

MMV Hit Generation | Confirmed Actives



MMV1797331



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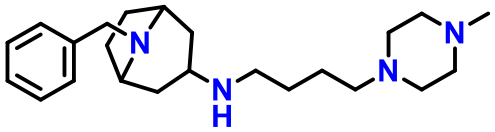

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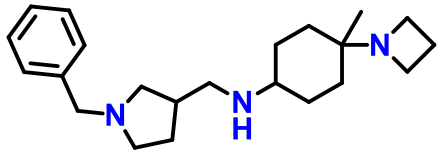

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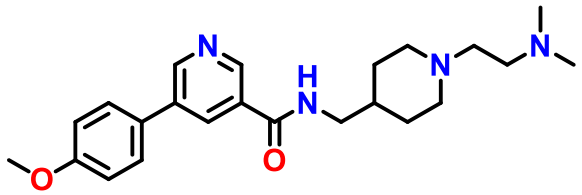
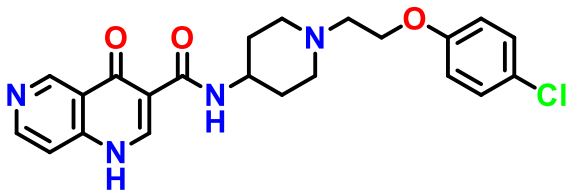
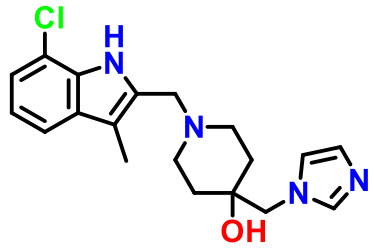


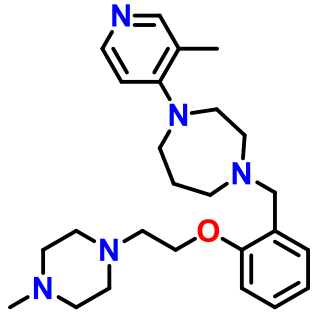
MMV1799348



MMV1798946



MMV1801316



MMV1802771

MMV ID	MMV MPO	MW	LogP	3D7 LDH (72h) IC50 (µM)	Dd2 LDH (72h) IC50 (µM)	HepG2 (72h) IC50 (µM)
MMV1797331	0.21	357	2.0	1.9	2.0	21.6
MMV1797658	0.36	335	3.2	0.78	1.5	22.1
MMV1797951	0.14	371	3.1	1.0	0.98	13.8
MMV1798925	0.28	342	3.4	1.1	1.5	19.1
MMV1798946	0.26	427	2.5	0.75	2.0	> 25
MMV1799348	0.35	397	2.8	1.1	2.7	> 25
MMV1801316	0.23	359	3.6	1.5	3.6	> 25
MMV1802771	0.29	424	3.0	0.81	1.1	20.0

MMV ID	LogD pH 7.4	Kin. Sol. (µM)	HLM CLint (µL/min/mg)	Rat Heps CLint (µL/min/10^6 cells)
MMV1797331	1.0	200	3.7	1.9
MMV1797658	0.5	200	3.5	7.2
MMV1797951	-0.2	200	8.3	1.4
MMV1798925	0.3	173	3.5	7.2
MMV1798946	2.9	170	14	2
MMV1799348	1.2	198	3.5	1.2
MMV1801316	2.8	86	24.1	2.7
MMV1802771	1.0	100	11	2.6

MMV MPO = MMV Screening Active MPO score

MMV Medicines for Malaria Venture

MMV Support | Compound testing

Please **contact us (maip@mmv.org)** if you would like to test a sample of any compounds that you identify using **MAIP** in MMV's *Plasmodium falciparum* asexual blood stage assay.

- 'Requestor' must be able to supply sample (e.g. 1 mg)
- Compound must be 'novel' (not in MMV or public database)
- MMV will test the compound at no cost to requestor and share results
- 'Requestor' owns the data

MMV
Medicines for Malaria Venture

MAIP | Project Team

MAIP model build

Nicolas Bosc (EMBL-EBI)
Eloy Félix (EMBL-EBI)
Ricardo Arcila (EMBL-EBI)
David Mendez (EMBL-EBI)
Martin Saunders (GSK)
Darren Green (GSK)
Jason Ochoada (SJCRH)
Anang Shelat (SJCRH)
Eric Martin (Novartis)
Preeti Iyer (AZ)
Ola Engkvist(AZ)
Andreas Verras (ex-MSD)
James Duffy (MMV)
Jeremy Burrows (MMV)
Rich Elliot (BMGF)
Mark Gardner (AMG)
Andrew Leach (EMBL-EBI)

Experimental validation

Nicolas Bosc (EMBL-EBI)
Eloy Felix (EMBL-EBI)
Mark Gardner (AMG)
James Mills (Sandexis)
Martijn Timmerman (PPSC)
Dennis Asveld (PPSC)
Kim Rensen (PPSC)
Partha Mukherjee (TCGLS)
Rishi Das (TCGLS)
Elodie Chenu (MMV)
Dominique Besson (MMV)
Jeremy Burrows (MMV)
James Duffy (MMV)
Benoît Laleu (MMV)
Eric Guantai (Uni. Narobi)
Andrew Leach (EMBL-EBI)

EMBL

BILL & MELINDA GATES foundation

AstraZeneca

gsk

NOVARTIS

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

MERCK

pivotpark screeningcentre

TCG Lifesciences | CHEMBIOTEK

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Built on partnerships | Stronger together

MMV
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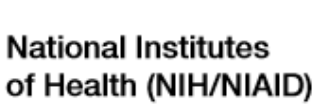
Committed Funders

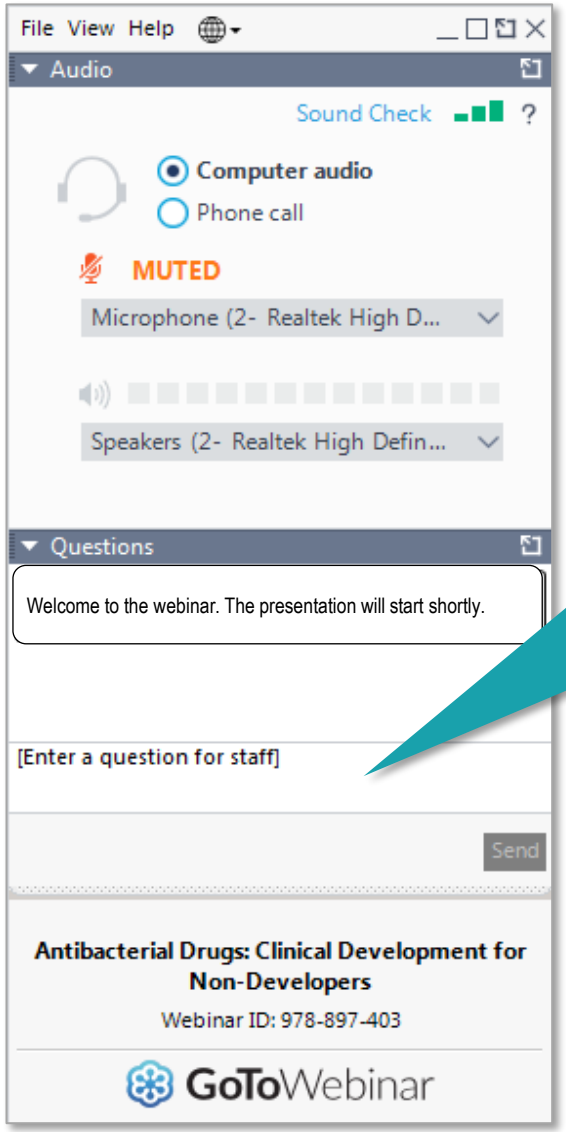


Thank You!

MMV Medicines for Malaria Venture @20

How to submit your questions

If your question is addressed to a specific speaker, please include their name when submitting the question.



The presentation will be followed by an interactive Q&A session.

Please submit your questions via the ‘questions’ window. We will review all questions and respond to as many as possible after the presentation.

Today’s speakers

Antimicrobial drug discovery: SAR optimization and QSAR

Alastair Parkes
Vice-President, Medicinal Chemistry
Evotec (United Kingdom)

James Duffy
Senior Director, Drug Discovery
Medicines for Malaria Venture – MMV (Switzerland)

Moderator:
Charles Mowbray
Discovery Director
Drugs for Neglected Diseases initiative (DNDi) (Switzerland)

Upcoming webinars

Register now!

In collaboration with: CCARB

Starting an antibacterial drug discovery screening programme

With Bruce Blough & Gerry Wright

5 September 2023, 17:00-18:30 CEST

Register now!

In collaboration with: ecraid

Clinical trials platforms for new and neglected antimicrobials

With Jesús Rodríguez-Baño & Julia Bielicki

20 September 2023, 11:00-12:30 CEST

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ANTIMICROBIAL CHEMOTHERAPY CONFERENCE (ACC) 2024

February **6-7** 2024

GARDP and BSAC are delighted to announce that the free virtual Antimicrobial Chemotherapy Conference will take place again next year in collaboration with the European Clinical Research Alliance on Infectious Diseases and the Netherlands Antibiotic Development Platform.

The scientific programme as well as the call for abstracts for posters and short oral presentations will be announced later in the year.

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BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY

ecraid

nadp netherlands antibiotic development platform

Thank you for joining us