

How and why Natural Intelligence can expedite the discovery of new antimicrobials

Rob Young,
H3D Foundation Webinar
28th August 2025



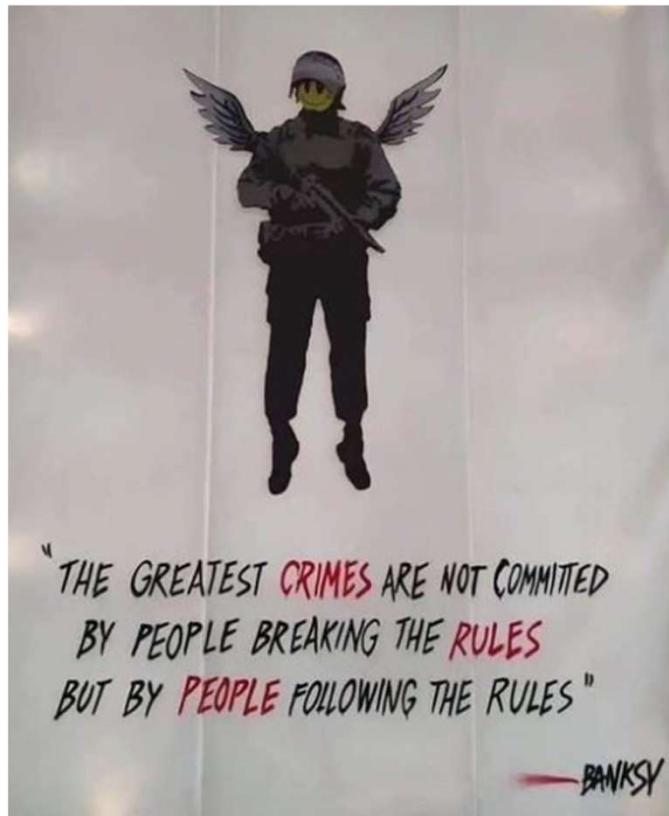
How and why Natural Intelligence can expedite the discovery of new antimicrobials

- Some philosophy
- The butterfly effect – where is led me
 - The Time and Place for Nature
- Antimicrobial discovery
 - Timelines & the “Discovery Void”
- Reflecting on practices and the transition from target data to bug killing
- Models, data and changing practices
 - Considering physical properties and their impact
- Why permeation often necessitates compromise – and how nature can help
- Natural Intelligence – what and why can we learn from the Natural World

A little bit of Philosophy

Reflections on rules and practices in drug discovery

“Rules are for the obedience of fools & guidance of the wise”



Robert Hannigan

- Formerly head of UK GCHQ
- Legacy of Alan Turing, Bletchley Park & WW2 ENIGMA code breakers

- Codebreaking = easier than Drug Discovery?
 - First computer helped 80+ years ago
- Importance of diversity of thought
 - “Groupthink” hinders progress!



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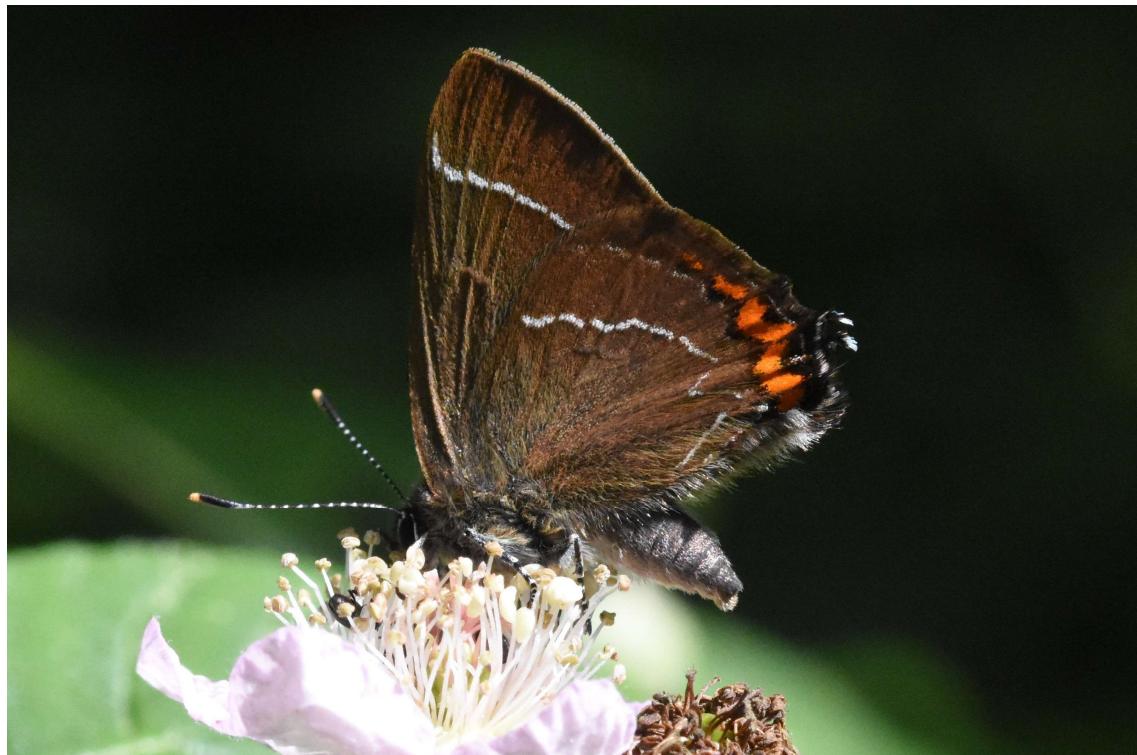


The “butterfly effect” – kicked off in June 2019

...before I left GSK on 05/07/19

- I'd just taken this picture of a beautiful White Letter Hairstreak
 - Found in a local “Place for nature”
- Realised that I would soon have more **Time** in such places

[https://www.blue-
burgundy.co.uk/?page_id=107](https://www.blue-burgundy.co.uk/?page_id=107)



The Time and Place for Nature in Drug Discovery

Made by a protein, better recognised by other proteins (biological targets & carriers)

JACS Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
JACS Au 2022, 2, 11, 2400–2416
pubs.acs.org/jacsau

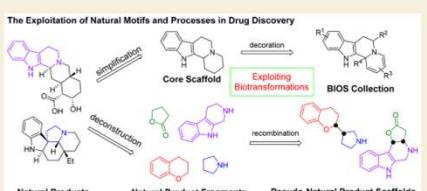
The Time and Place for Nature in Drug Discovery
Robert J. Young,* Sabine L. Flitsch, Michael Grigalunas, Paul D. Leeson, Ronald J. Quinn, Nicholas J. Turner, and Herbert Waldmann

Cite This: <https://doi.org/10.1021/jacsau.2c00415> | Read Online

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ABSTRACT: The case for a renewed focus on Nature in drug discovery is reviewed; not in terms of natural product screening, but how and why biomimetic molecules, especially those produced by natural processes, should deliver in the age of artificial intelligence and screening of vast collections both *in vitro* and *in silico*. The declining natural product-likeness of licensed drugs and the consequent physicochemical implications of this trend in the context of current practices are noted. To arrest these trends, the logic of seeking new bioactive agents with enhanced natural mimicry is considered; notably that molecules constructed by

The Exploitation of Natural Motifs and Processes in Drug Discovery



- “*Made by a protein*
- *Transported by a protein*
- *Inhibits a protein*”

<https://pubs.acs.org/doi/full/10.1021/jacsau.2c00415>

- Logical case for natural motifs?
 - Maybe 10^{70} is not appropriate?
 - Concepts validated by natural products

– *Natural Intelligence* – *Not Artificial Intelligence!*

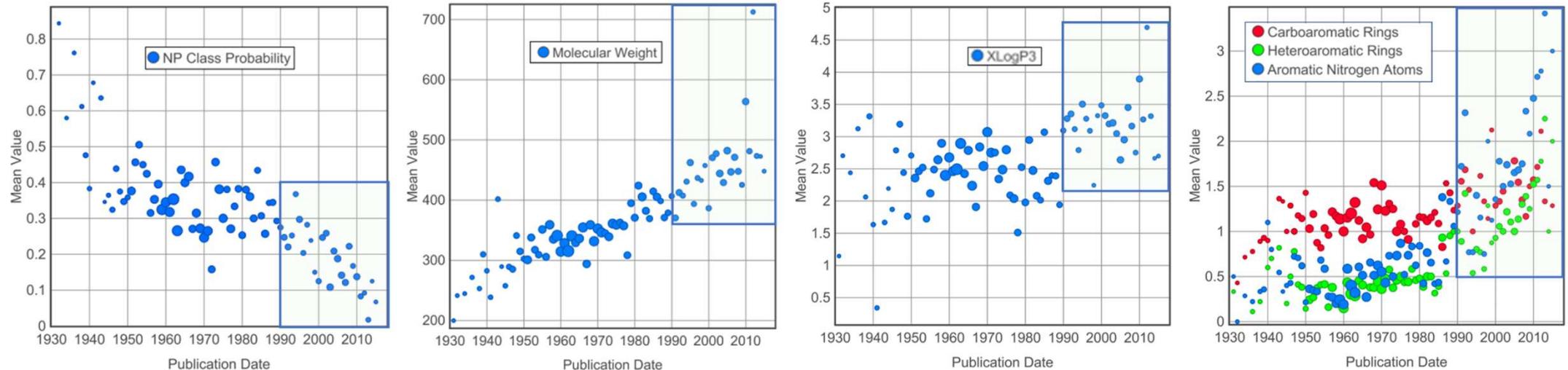
- Truly Organic molecules
 - Not “petrochemicals”

- Pay now or pay later?



The diminishing role of Nature in Drug Discovery?

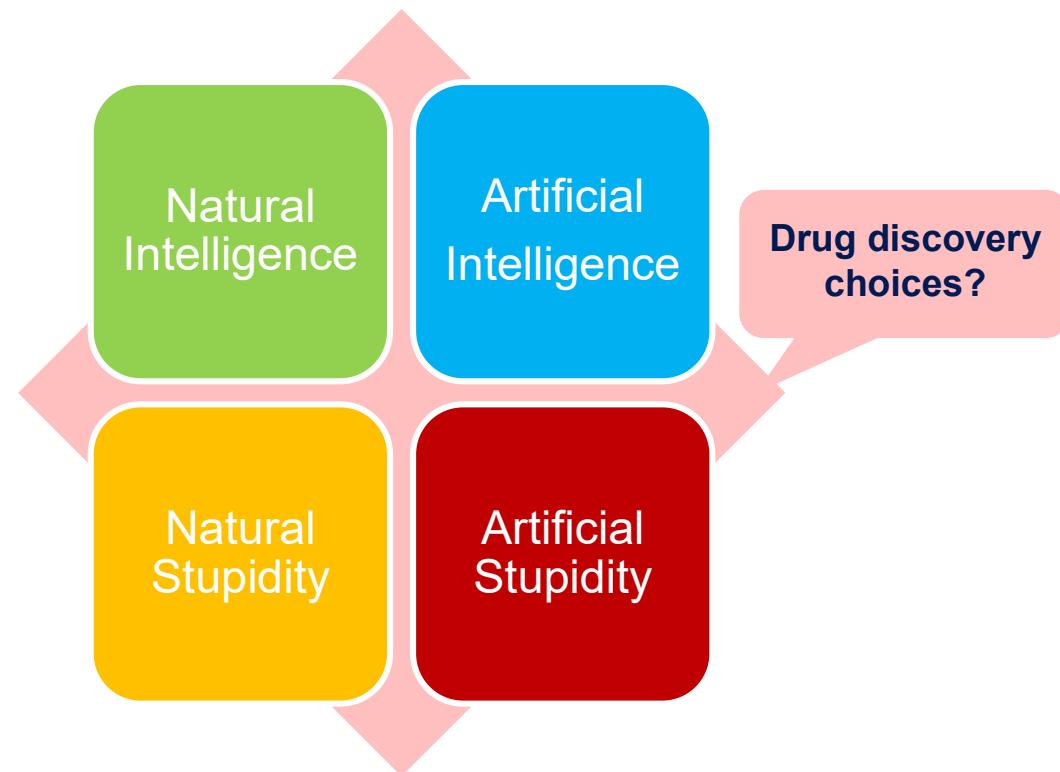
Paul Leeson's data as part of the TaPFN consortium



NP Scout algorithm: scale 0-1 Chen et al, *Biomolecules*, 2019, 9, 43 <https://nerdd.univie.ac.at/npscout/>
See: Young et al, *JACS au*, 2022, 2, 2400

Thinking differently in drug discovery?

HR analyses are so fond of 4-box models...



Building the Future of Innovation
on millions of years of Natural Intelligence

Leen Gorissen

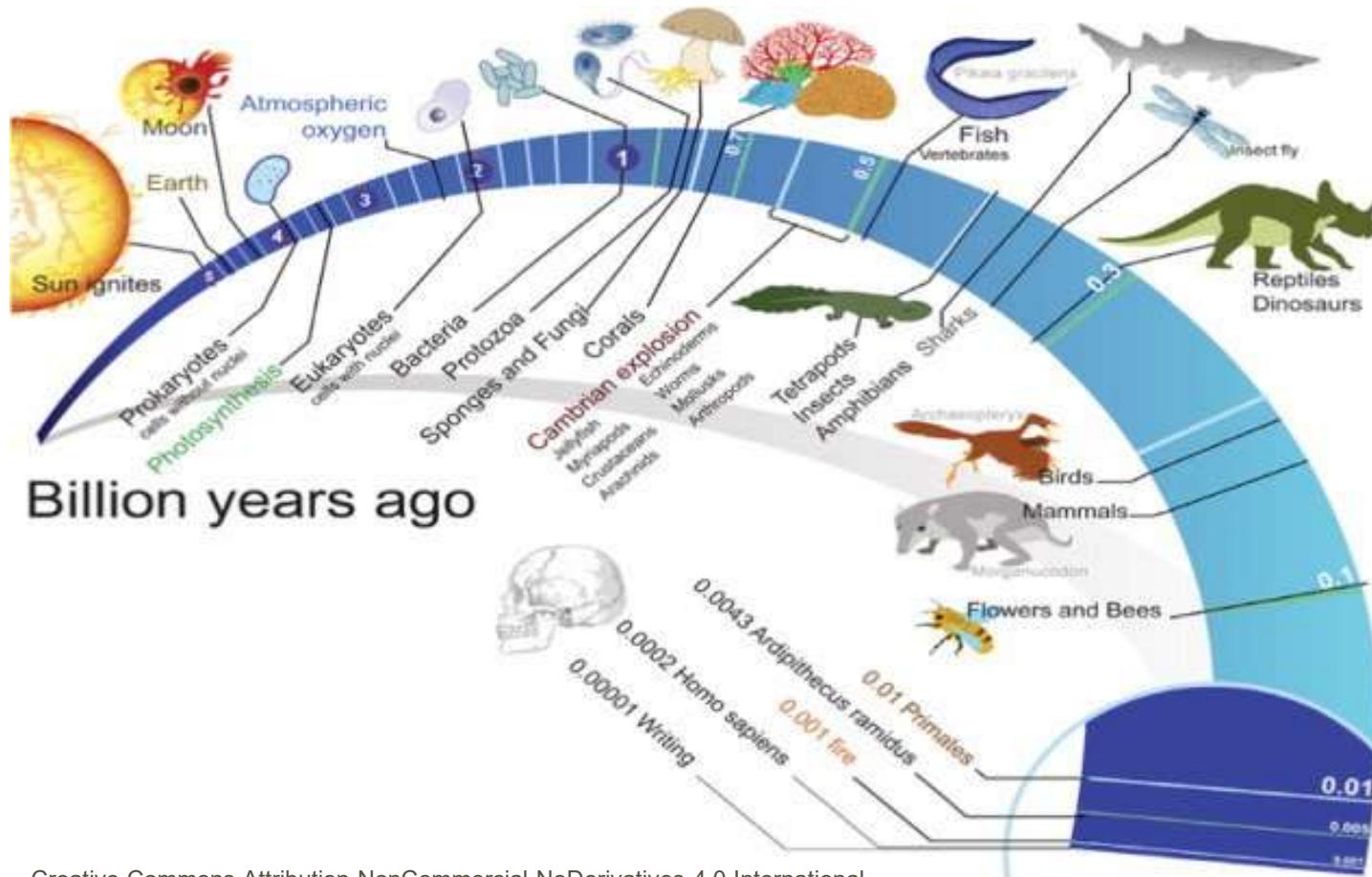
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- Thanks to Julio Martin for introducing me to the book and concept!

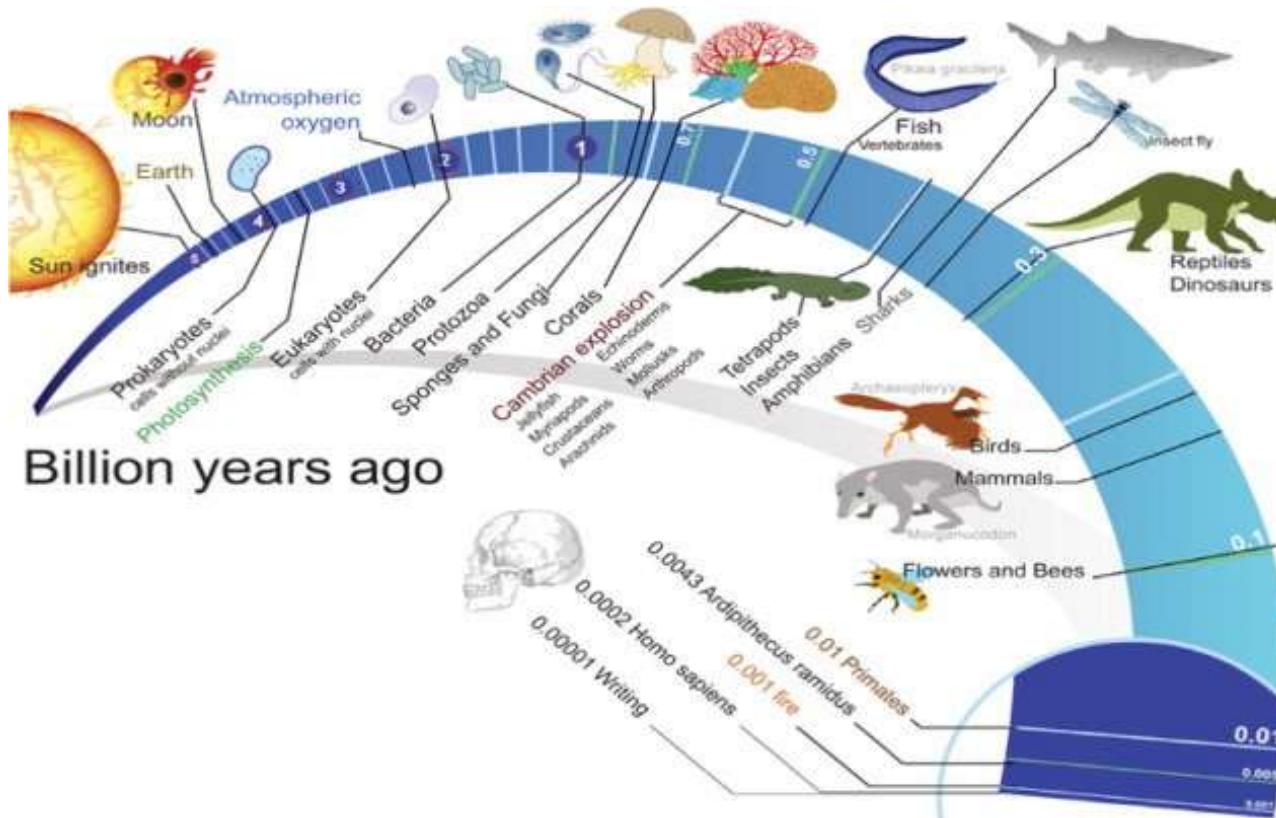
Considering 4 billion years of evolution

Life is a biochemical arms race – compounds are necessary to exist, thrive, defend...



Consider where human thought / practices fit within this

Use of potions/natural remedies towards introduction of synthetic drugs & antibiotics

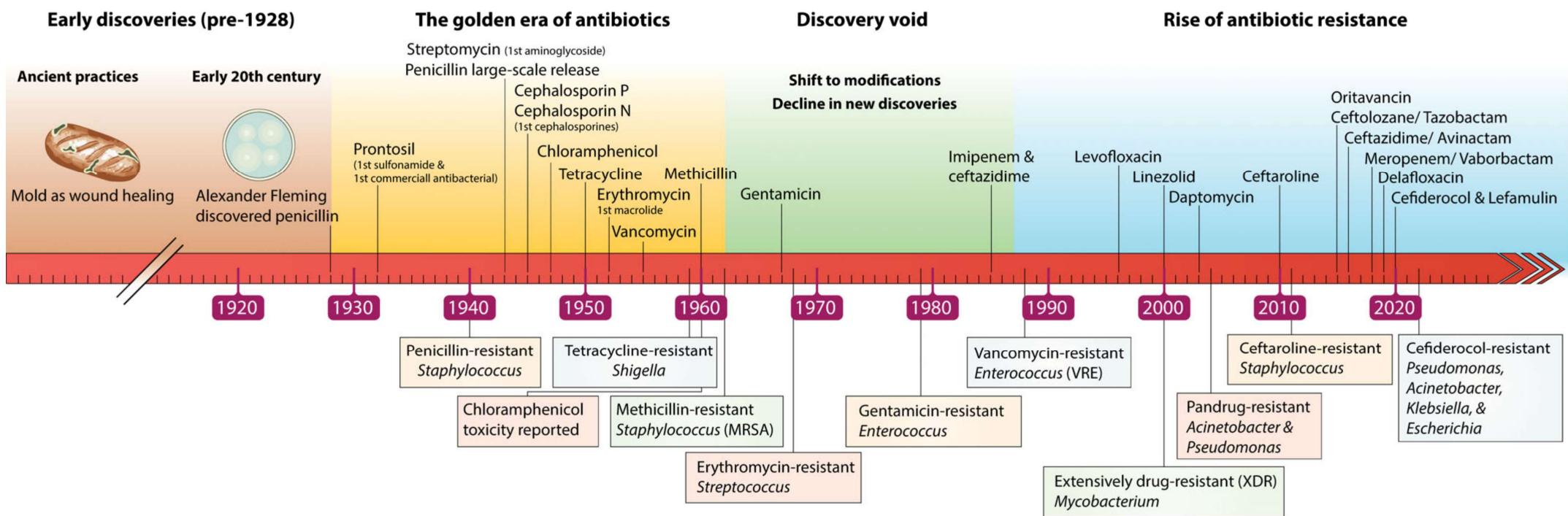


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Discovery and timelines of antibiotics and AMR

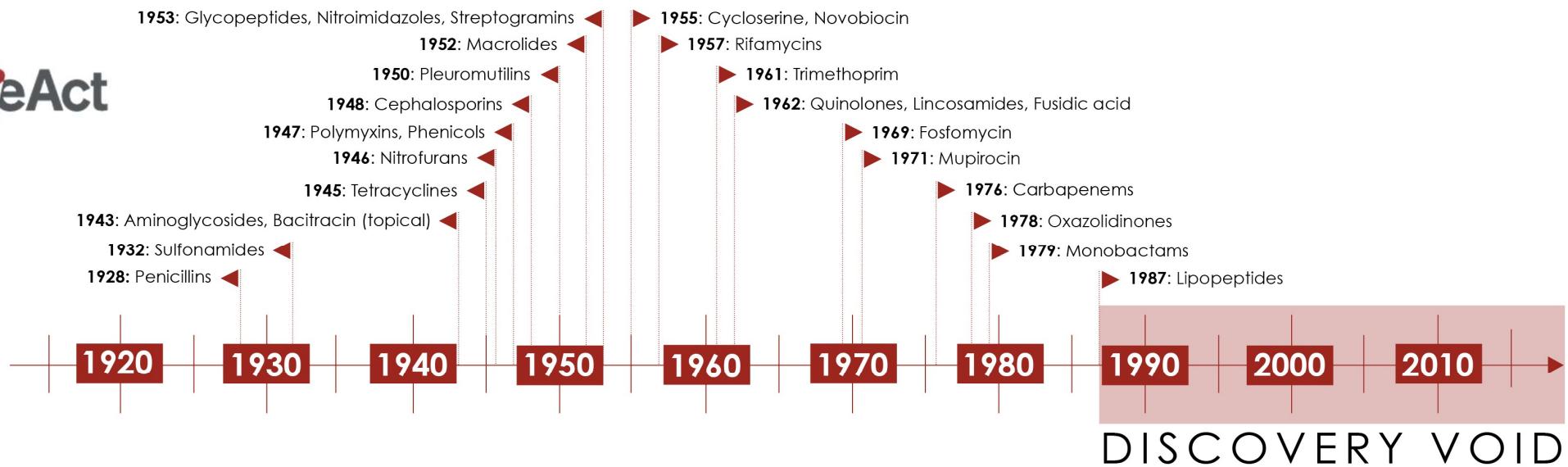
Minuscule on the evolutionary timescale – majority are Natural Products & derivatives



Tahmasebi, H.; et al From Cure to Crisis: Understanding the Evolution of Antibiotic-Resistant Bacteria in Human Microbiota. *Biomolecules* 2025, 15, 93. <https://doi.org/10.3390/biom15010093>
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The introduction of new classes of antibiotics

A little dated – but illustrates the *Discovery Void* 1990 to 2015

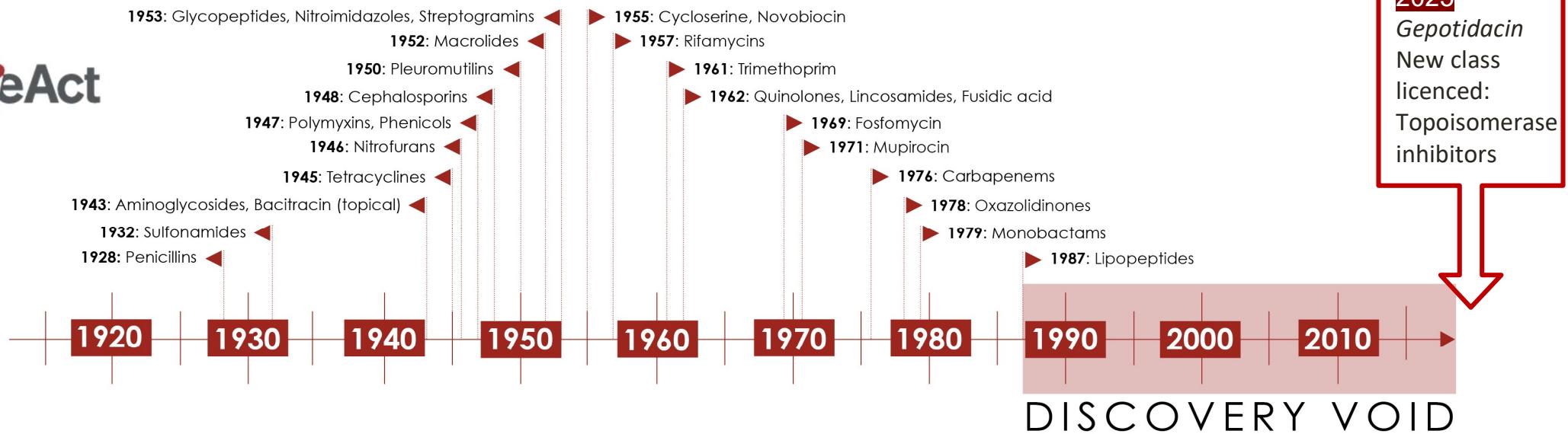


© ReAct Group 2015

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The introduction of new classes of antibiotics

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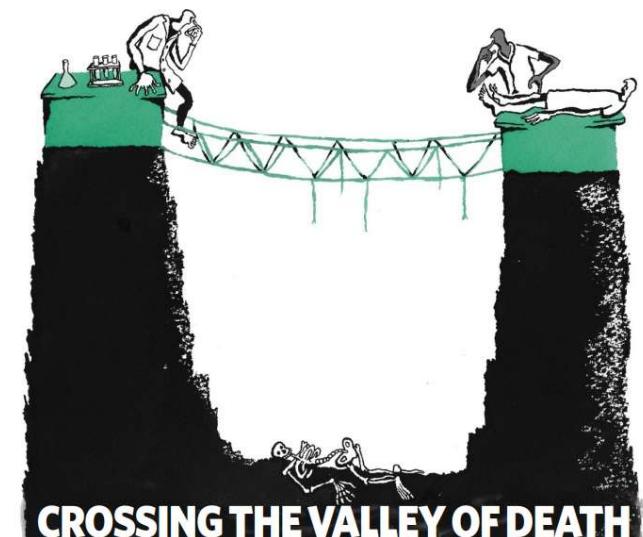
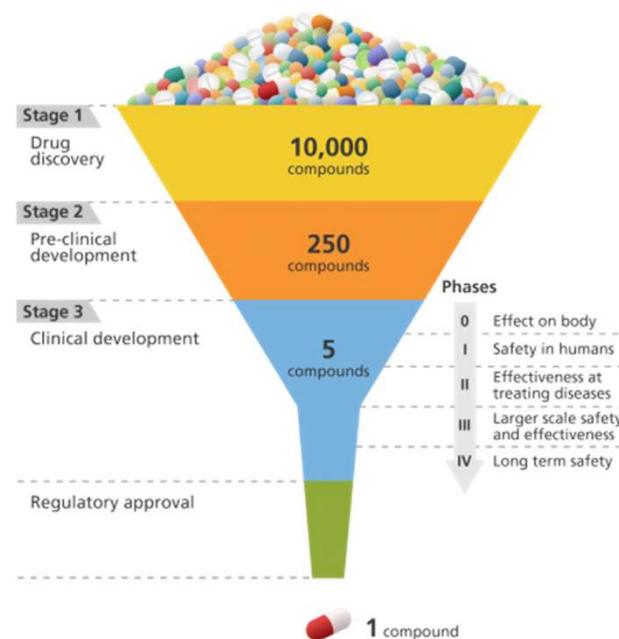
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The typical HTS-fuelled discovery funnel ~1995 onwards

This (and variations) became the workhorse & Drug Discovery Groupthink paradigm

- Drug Discovery leaders were fixated by numbers
 - How many compounds made?
 - Addicted to Potency
 - **Some still are...**
- Pour 2 million compounds in
 - Qualify hits, H₂Lead, Lead Op
 - *Industrialised paradigm*



Translational research: Crossing the valley of death
Declan Butler, Nature 453, 840–842 (2008)
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Hann, M; Molecular obesity, potency and other addictions in drug discovery
Med. Chem. Commun., 2011, 2, 349-355

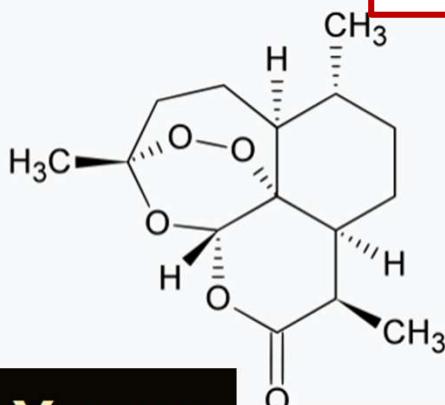
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But vast collections and HTS not always necessary

In vitro, in silico, ad infinitum have not always delivered – *in cerebro* still can!

Artemisinin



Consider impact of natural products!

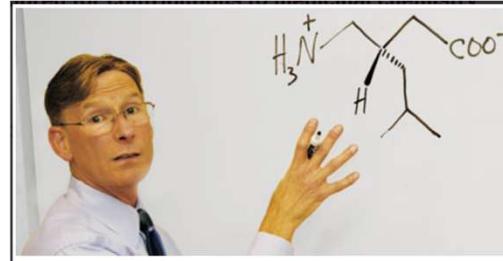
“

Every scientist
dreams of doing
something that can
help the world.

Tu Youyou



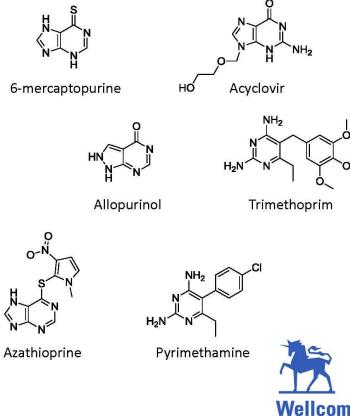
Rick Silverman, Lyrica®



Silverman describes the structure of pregabalin.

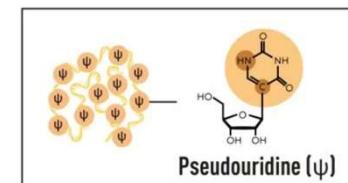
1988 Nobel Prize in Physiology or Medicine

George Hitchings & Gertrude Elion

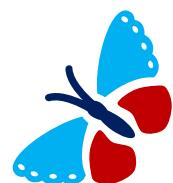


Nobel Prize winner Katalin Karikó

Base-modified mRNA

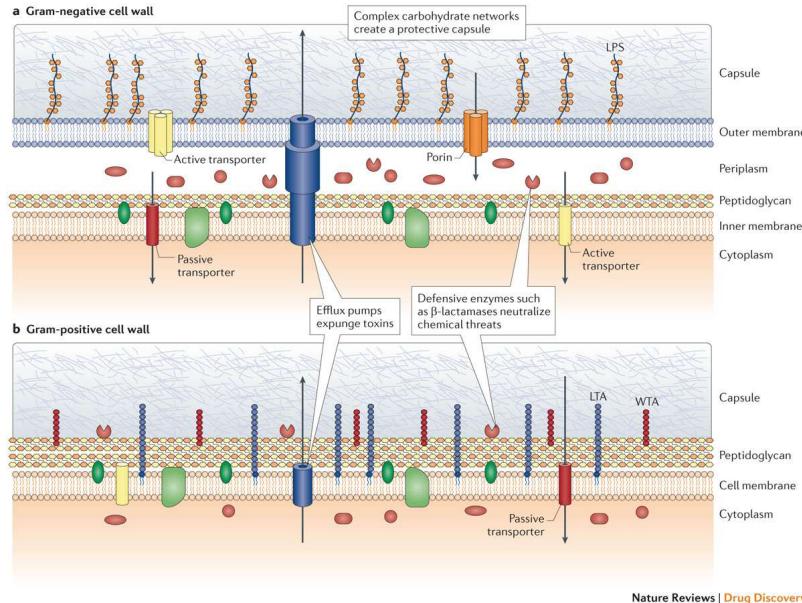


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A retrospective on antimicrobial screening at AZ

Lessons to be learned



...Although some promising agents are in the pipeline, there is an urgent need for new antibiotic scaffolds. However, antibacterial researchers have struggled to identify new small molecules with meaningful cellular activity, especially those effective against multidrug-resistant Gram-negative pathogens. This difficulty ultimately stems from an incomplete understanding of efflux systems and compound permeation through bacterial membranes.

Tommasi, R.; Brown, D. G.; Walkup, G. K.; Manchester, J. I.; Miller, A. A., ESKAPEing the labyrinth of antibacterial discovery. *Nature Reviews Drug Discovery* 2015, 14 (8), 529-542.
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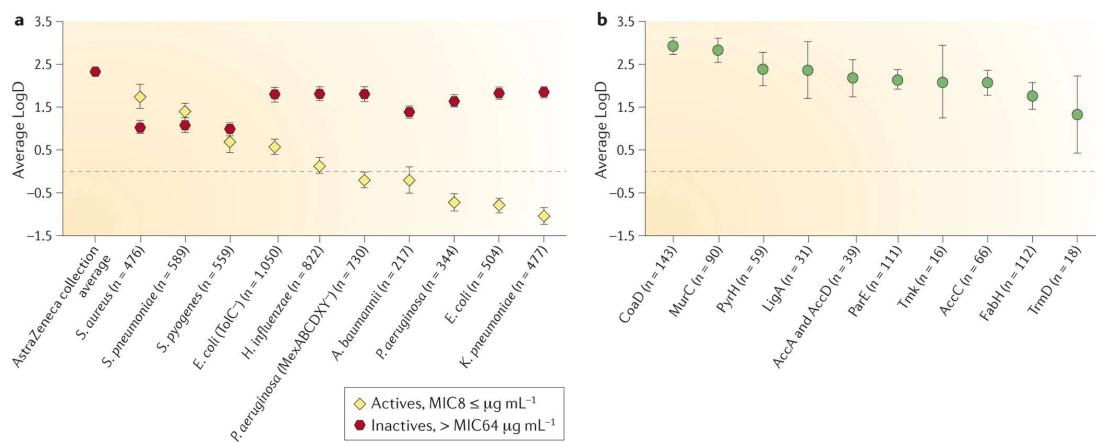
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Chasing potency, molecular obesity...?

Sub-plot: how well populated are screening decks for antimicrobials?

Figure 1: Mean LogD values for internal AstraZeneca antibacterial project compounds and for exemplar hits from other disease areas.

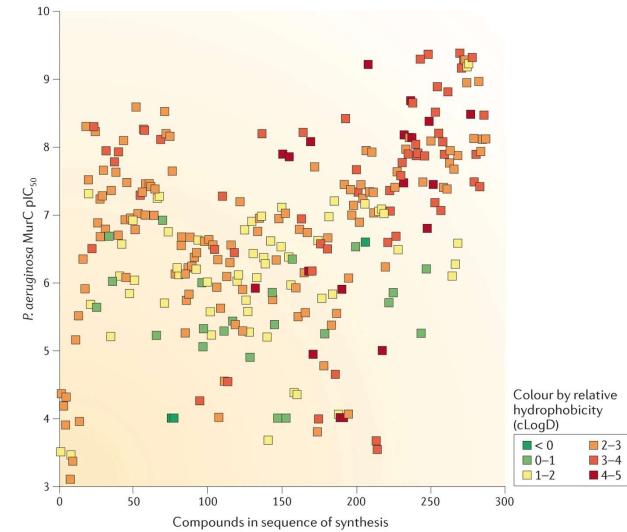


a | Mean LogD values for active compounds

b | The mean LogD values for hits from 10 HTS screens

Nature Reviews | Drug Discovery

Figure 2: The relationship over time between the biochemical potency against *Pseudomonas aeruginosa* MurC and the cLogD of newly synthesized programme compounds.



Nature Reviews | Drug Discovery

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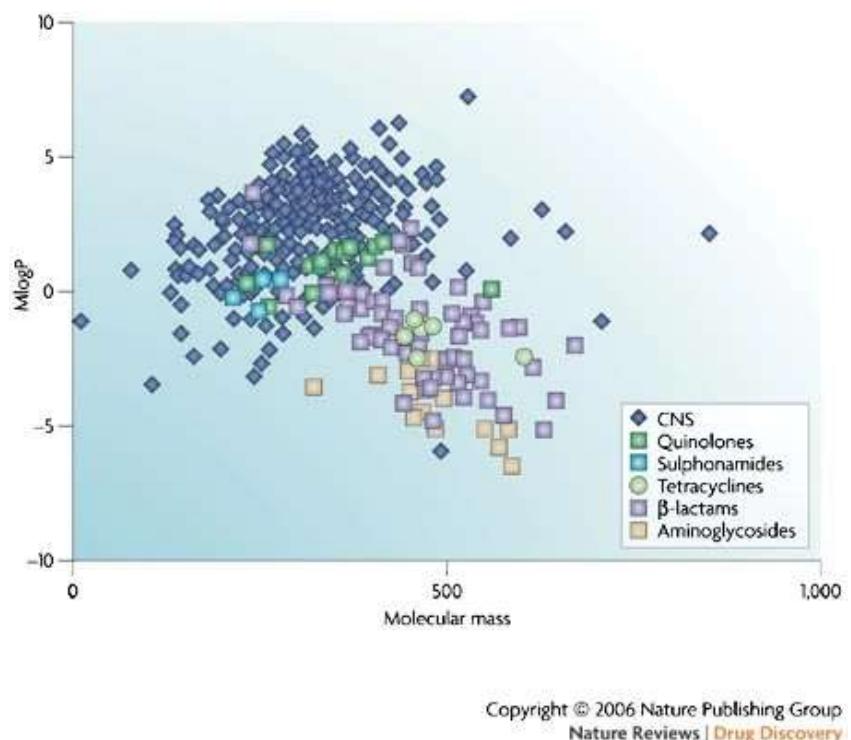
Tommasi, R.; Brown, D. G.; Walkup, G. K.; Manchester, J. I.; Miller, A. A., ESKAPEing the labyrinth of antibacterial discovery. *Nature Reviews Drug Discovery* 2015, 14 (8), 529-542.

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And from GSK...

Drugs for bad bugs: confronting the challenges of antibacterial discovery



- GSK ran more than 70 high-throughput screening (HTS) campaigns between 1995–2001.
- Blind spots in target validation and an inability to find lead compounds from HTS together...left an empty industrial antibacterial portfolio.
- GSK has found that optimizing novel chemical structures that inhibit highly validated targets for drug-like properties is a more promising, if less trendy, route. Since 2002, our strategy has been to invest heavily in a select number of programmes, with large teams of chemists synthesizing drug-like compounds and with biologists focused on accelerating the critical path pharmacology and microbiological efficacy studies for each new compound synthesized.
- This approach has produced more novel mechanism antibacterial development candidates at GSK in the past 4 years than in the previous 20. However, high attrition rates in clinical development demand a broader industrial involvement and more aggressive research efforts to assure novel mechanism agents for the future.

Payne, D. J.; et al Drugs for bad bugs: confronting the challenges of antibacterial discovery.

Nature Reviews Drug Discovery 2007, 6 (1), 29-40.

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“All models are wrong, but some are useful”

George Box *J. American Statistical Assoc*, 1976, 71, (356) pp. 791-799

- Parsimony
 - “Since all models are wrong the scientist cannot obtain a "correct" one by excessive elaboration. On the contrary following William of Occam *they* should seek an economical description of natural phenomena. Just as the ability to devise simple but evocative models is the signature of the great scientist so over-elaboration and over-parameterization is often the mark of mediocrity.
- Worrying Selectively
 - Since all models are wrong the scientist must be alert to what is importantly wrong. **It is inappropriate to be concerned about mice when there are tigers abroad.**

My contemporary view on the Ro5

“Weight doesn’t matter, lipophilicity has moved on, HBA[↑] as size[↑], donors matter...”

EXPERT OPINION ON DRUG DISCOVERY
2023, VOL. 18, NO. 9, 965–972
<https://doi.org/10.1080/17460441.2023.2228199>

PERSPECTIVE

Today's drug discovery and the shadow of the rule of 5

Robert J. Young 

Blue Burgundy (Drug Discovery Consultancy) Ltd, Bedford, UK

ABSTRACT

Introduction: The rule of 5 developed by Lipinski et al., a landmark and prescient piece of scholarship, focused the minds of drug hunters by systematically characterizing the physical make-up of drug molecules for the first time, noting many sub-optimal compounds identified by high-throughput screening practices. Its profound influence on thinking and practices, whilst providing benefit, perhaps etched the guidelines too strongly in the minds of some drug hunters who applied the bounds too literally without understanding the implications of the underlying statistics.

Areas covered: This opinion is based on recent key developments that take thinking, measurements, and standards beyond those first set out, particularly the influences of molecular weight and the understanding, measurement, and calculation of lipophilicity.

Expert opinion: Techniques and technologies for physicochemical estimations set new standards. It is timely to celebrate the significance and influence of the rule of 5, whilst taking thinking to new levels with better characterizations. The shadow of the rule of 5 may be long, but it is not dark, as new measurements, predictions and principles emerge as guiding lights in the design and prioritization of higher-quality molecules redefining the meaning of beyond the rule of 5.



 Check for updates

ARTICLE HISTORY

Received 12 April 2023
Accepted 19 June 2023

KEYWORDS

Drug discovery;
physicochemical properties;
rule of 5; lipophilicity;
solubility; permeability; drug
transporters

“In times of profound change, the learners inherit the earth, while the learned find themselves beautifully equipped to deal with a world that no longer exists”

Eric Hoffer

A lot more has changed in drug discovery since 1997!

- In late 1990s Lipinski, Lombardo et al were learners!
- Ro5 stands the test of time, *with provisos!*
- *Exceptions noted for transported molecules*

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Contemporary view on the Ro5

"Weight doesn't matter, lipophilicity has moved on, HBA[↑] as size[↑], donors matter..."

EXPERT OPINION ON DRUG DISCOVERY
2023, VOL. 18, NO. 9, 965–972
<https://doi.org/10.1080/17460441.2023.2228199>

PERSPECTIVE

Today's drug discovery and the

Robert J. Young 

Blue Burgundy (Drug Discovery Consultancy) Ltd, Bedfo



- Mol Wt = Mouse? – Lipophilicity = Tiger?
 - Chrom logD_{7.4} is a very good tiger detector!
- Key: understand probability and 90th centiles
 - The fives are not thresholds!
 - ACS Med Chem Lett 2015 6 (7), 722-725

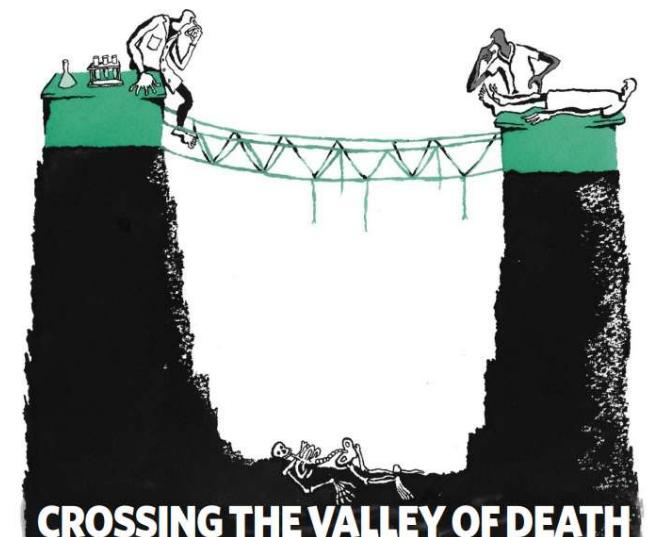
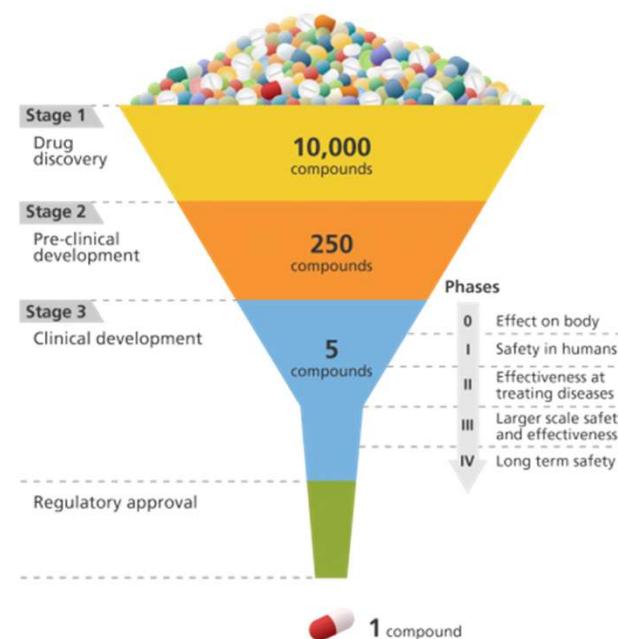
*A lot more has changed in
drug discovery since 1997!*



The typical HTS-fuelled discovery funnel ~1995 onwards

This (and variations) became the workhorse & Drug Discovery Groupthink paradigm

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 - How many compounds made?
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Translational research: Crossing the valley of death
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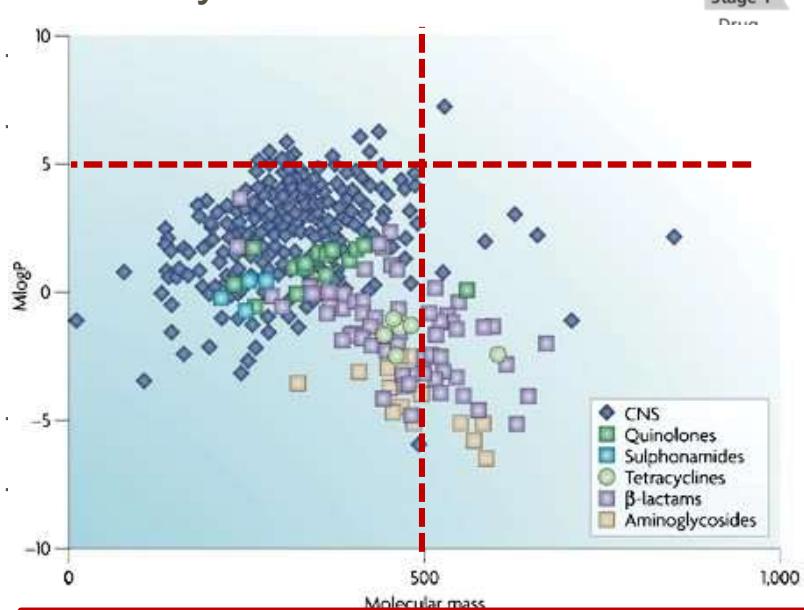
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The typical HTS-fuelled discovery funnel ~1995 onwards

This (and variations) became the workhorse & Drug Discovery Groupthink paradigm

- Drug Discovery leaders were fixated by numbers



--- = Ro5 90th Centile boundaries

Nature Reviews | Drug Discovery

"We cannot solve our problems with the same thinking we used when we created them."
• Albert Einstein

Albert Einstein

► 1987: Lipopeptides

1990

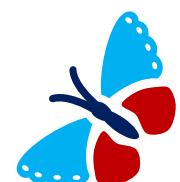
2000

2010

DISCOVERY VOID

alley of death
(008)
mmercial-

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What does a good drug look like?

The multibillion-dollar question? Or our contributions to enhancing and/or saving lives?

“Without convincing evidence to the contrary, drugs should be made as hydrophilic as possible without loss of efficacy”

Hansch C., Bjorkroth J., Leo A., *J. Pharm. Sci.*, **76**, 663 (**1987**)

What does a good drug look like?

But can we be prescriptive in definitions?

“Without convincing evidence to the contrary, drugs should be made as hydrophilic as possible without loss of efficacy”

Hansch C., Bjorkroth J., Leo A., *J. Pharm. Sci.*, **76**, 663 (**1987**)

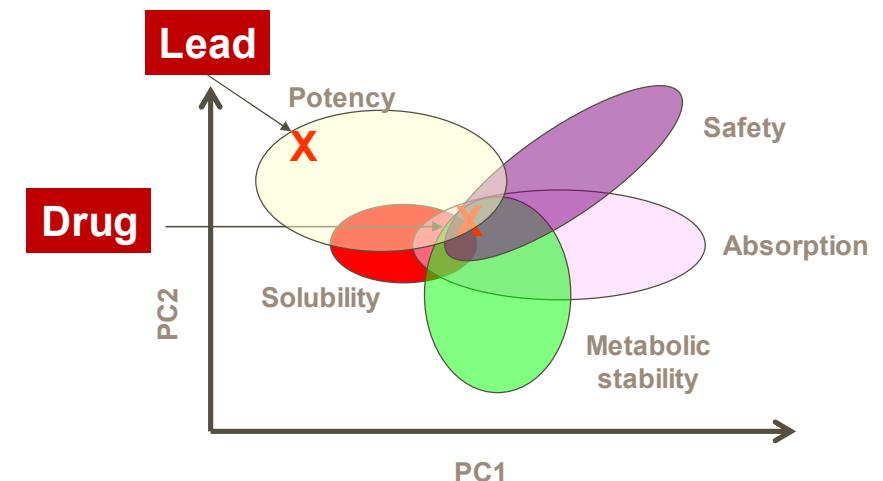
The essence of the widely-accepted Ligand Lipophilicity Efficiency (LLE = $pXC_{50} - \log P$)

- In reality: no simple or prescriptive answers...
- Different drugs have different roles, different methods for administration
 - *Following slides illustrate some solid principles to follow*
 - *Drug discovery is a process of compromises in optimisation*
- *HOWEVER: Physicochemical properties underline all behaviour and disposition*



Keeping the plates spinning in your series

It is all a matter of balance to secure *efficacy* with the compounds



– Thanks to Darren Green

ADMET Guidebook from RSC

Chapter 1: Patrick Schnider's summary of lipophilicity impact

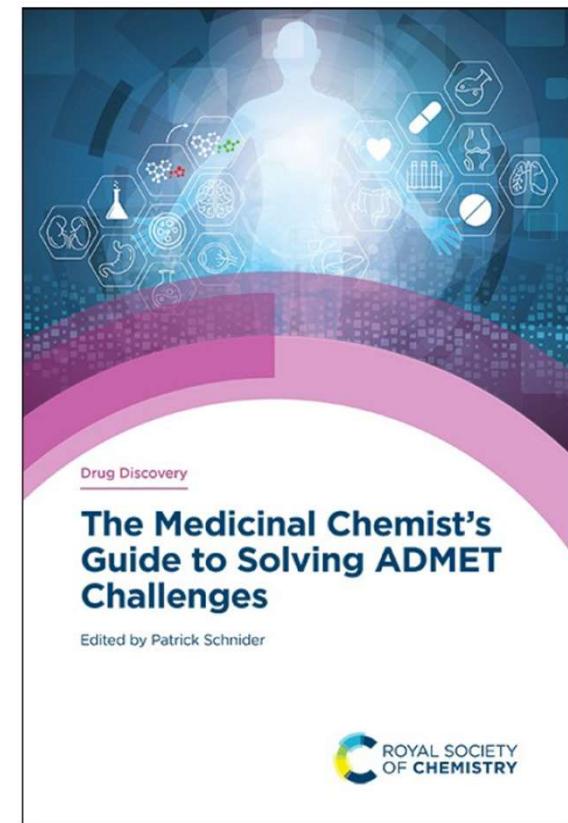
Numerous examples in each well-referenced chapter

- at a glance guide to general trends in Chapter 1

1.3 Strategies by Molecular Properties

Table 1.1 High-level overview of the effects of key molecular properties on ADMET properties.

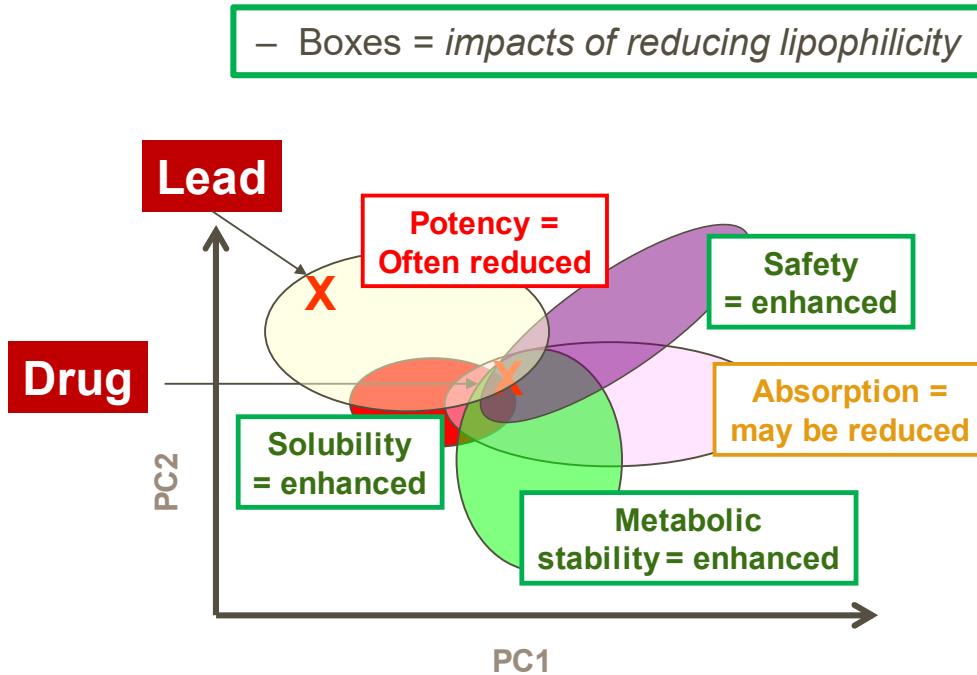
ADMET property	Lipophilicity	Charge	Molecular weight	Aromatic/planar rings	HBD	HBA
Solubility	↑	↓	↑	↓ planarity/ring count	↑/↓	↑/↓
Plasma protein binding	↓	↓ (positive, neutral)	↓ negative	↓	↓	
Volume of distribution	↓	↓ (positive, neutral)	↓ positive (↑ negative)	(↓)		
Passive permeability	↑	↑	↓ negative	↓	↓	(↓)
P-glycoprotein (and BCRP)	↓ Efflux	(↑)	↓	↓	↓	(↓)
OCTs	↓ Transport	↑	↓ positive	↑		
	↓ Inhibition	↓	↓ positive	↓		
OATs	↓ Transport	↑	↓ negative	↑		
	↓ Inhibition	↓	↓ negative	↓		
OATPs	↓ Transport	↑	↓ negative	↓		
	↓ Inhibition	↓	↓ negative	↓		
BSEP	↓ Inhibition	↓	(↓ negative, ↑ positive)	↑	↓	
CYP450 metabolism	↓ Metabolism	↓				
CYP450 induction	↓ 3A4 induction	(↓)				
CYP450 inhibition	↓ 1A2 inhibition					
	↓ 2C9 inhibition	↓				
	↓ 2C19 inhibition	↓				
	↓ 2D6 inhibition	↓	↓ positive			
	↓ 3A4 inhibition	↓	↑ (negative)	↓		



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Impact of properties on measured developability data

Table is based on PFI and iPFI so #Ar impact too; => in vitro ADMET assays



Physical properties in drug design, in *Tactics in Contemporary Drug Design*, Springer Berlin Heidelberg, 2014, pp. 1-68.

Also: *Drug discovery today* 2011 16, 822-830

27

– Remember = **Efficacy** **NOT** **potency** is what matters!

Assay / target value	PFI = mChrom log D _{pH7.4} + #Ar								
	<3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	>10
Solubility >200 µM	89	83	72	58	33	13	5	3	2
%HSA <95%	88	80	74	64	50	30	17	8	4
2C9 pIC ₅₀ ^a <5	97	90	83	68	48	32	23	22	38
2C19 pIC ₅₀ <5	97	95	91	82	67	52	42	42	56
3A4 pIC ₅₀ <5	92	83	80	75	67	60	58	61	66
Cl _{int} <3 ml/min/kg	79	76	68	61	54	42	41	39	52
Papp >200 nm/s	20	30	46	65	74	77	65	50	33
iPFI = mChrom log P + #Ar									
hERG pIC ₅₀ <5 (+1 charge)	86	93	88	70	54	36	29	21	11
^b Promiscuity <5 hits with pIC ₅₀ >5	85	78	74	65	49	30	20	13	7
% Oral Drugs with F>30%	35	17	13	10	13	6			5

Colours:

% of compounds in that bin meeting Set criteria

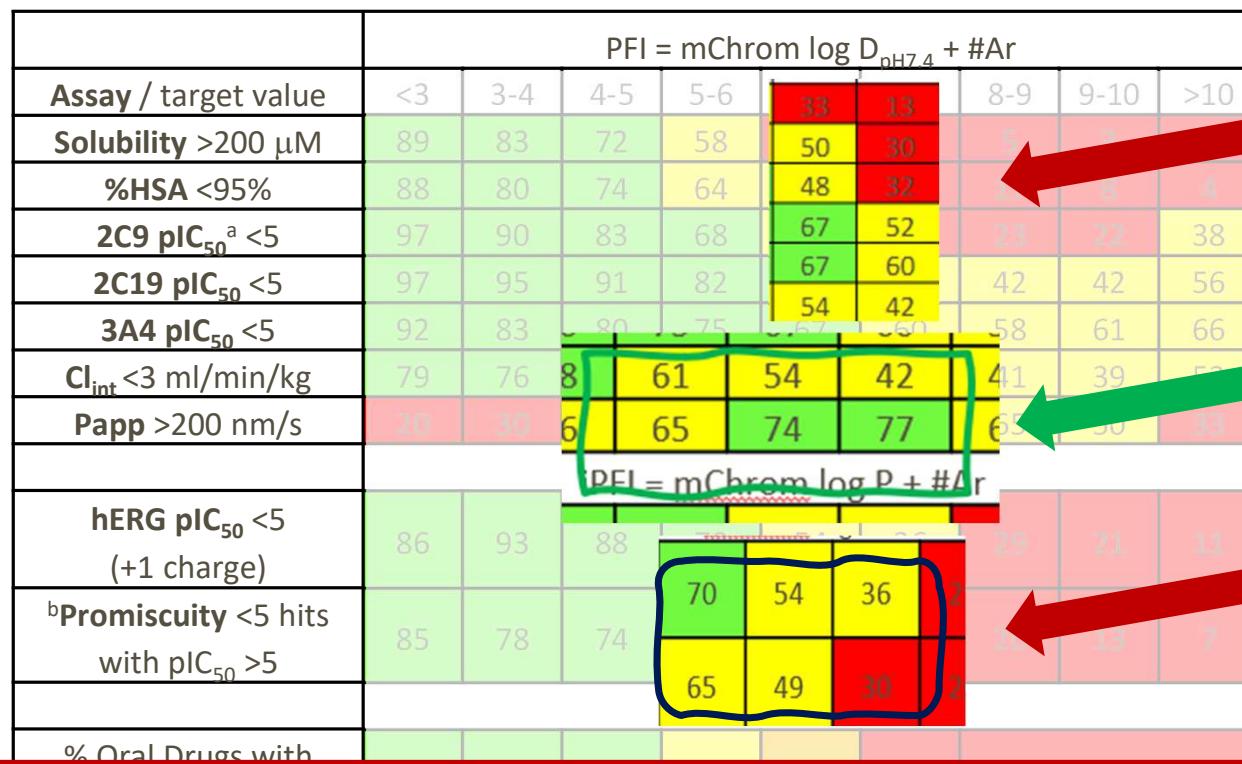


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Why Lipophilicity Needs to be Optimised for Oral Drugs

Need sufficient exposure/distribution to achieve efficacy



ADME constraints

Benefit
improved permeation

Off Target (Tox) Risks

"Without convincing evidence to the contrary, drugs should be made as hydrophilic as possible without loss of efficacy"

28

Hansch C., Bjorkroth J., Leo A., *J. Pharm. Sci.*, **76**, 663 (1987)

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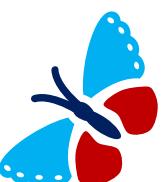
Poor properties = increased risks and issues in development

Not a no-go zone – but the risks are MUCH higher & chances of success with lower PFI

	PFI = mChrom log D _{pH7/4} + #Ar								
Assay / target value	<3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	>10
Solubility >200 μM	89	83	72	58	33	13	5	3	2
%HSA <95%	88	80	74	64	50	30	17	8	4
2C9 pIC ₅₀ ^a <5	97	90	83	68	48	32	23	22	38
2C19 pIC ₅₀ <5	97	95	91	82	67	52	42	42	56
3A4 pIC ₅₀ <5	92	83	80	75	67	60	58	61	66
Cl _{int} <3 ml/min/kg	79	76	68	61	54	42	41	39	52
Papp >200 nm/s	20	30	46	65	74	77	65	50	33
	iPFI = mChrom log P + #Ar								
hERG pIC ₅₀ <5 (+1 charge)	86	93	88	70	54	36	29	21	11
^b Promiscuity <5 hits with pIC ₅₀ >5	85	78	74	65	49	30	20	13	7
% Oral Drugs with F>30%	35	17	13	10	13	6	5		

Very low precedent for success!
And % of failures much higher!

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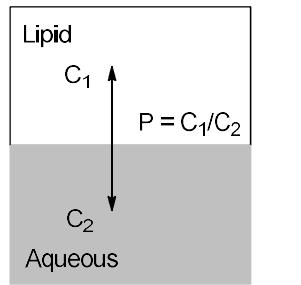
Understanding / rationalising permeation

Two camps in a long-running debate in literature

Pharmaceutical drug transport: The issues and the implications that it is essentially carrier-mediated only

Douglas B. Kell^{1,2}, Paul D. Dobson^{1,2,3} and Stephen G. Oliver^{4,5}

Drug Disc Today, 2011, 16, 704



OPINION

Coexistence of passive and carrier-mediated processes in drug transport

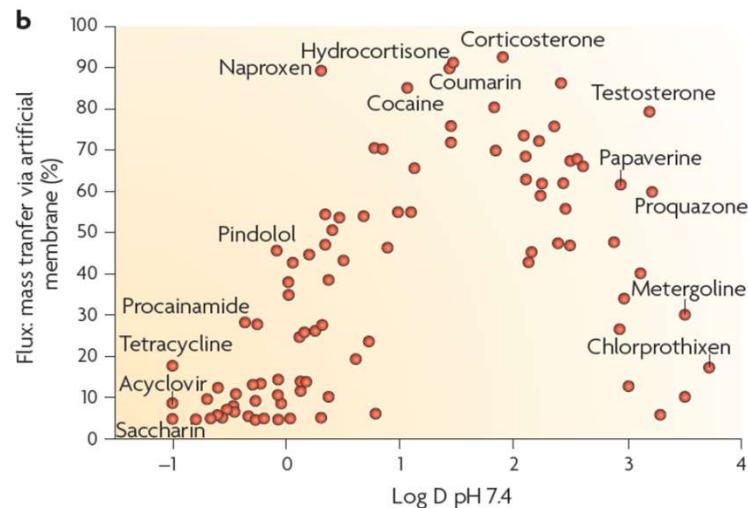
Kiyohiko Sugano, Manfred Kansy, Per Artursson, Alex Avdeef, Stefanie Bendels, Li Di, Gerhard F. Ecker, Bernard Faller, Holger Fischer, Grégoire Gerebtzoff, Hans Lennernaes and Frank Senner

Nature Rev Drug Disc 2010, 9, 597

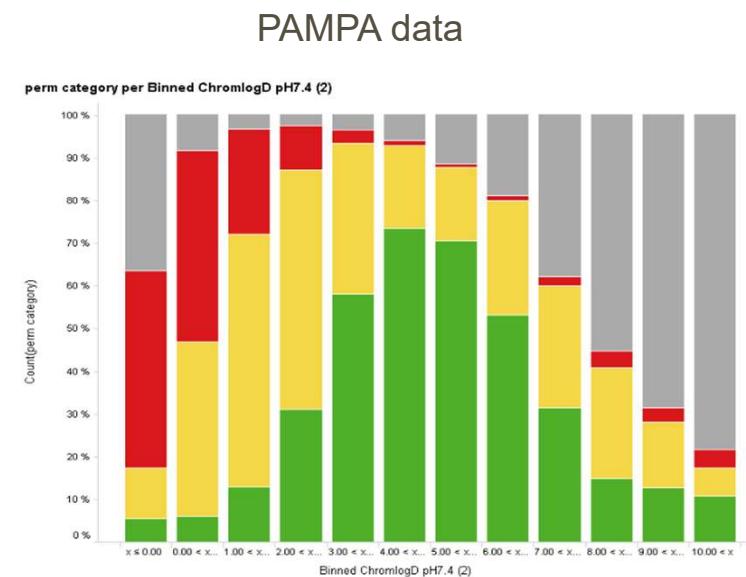
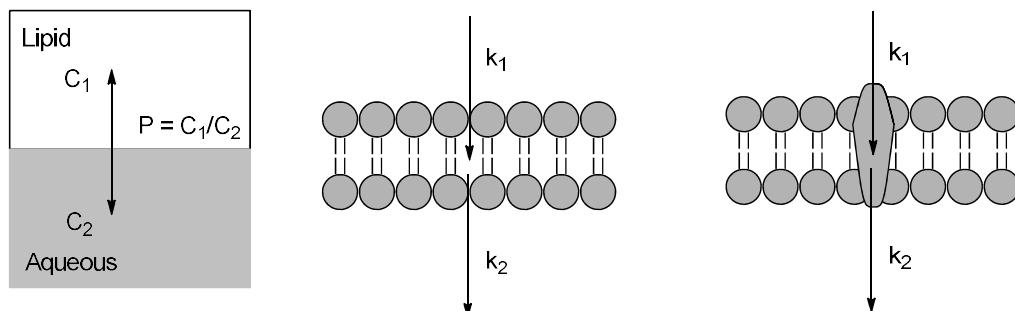


Understanding / rationalising permeation

The bilinear relationship of permeation vs lipophilicity often forgotten!



Nature Rev Drug Disc 2010, 9, 597



Drug Discovery Today
2011, 16, 822-830

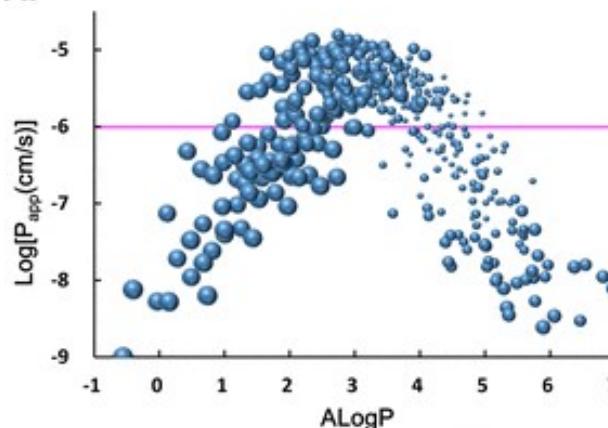
Blue Burgundy



Understanding / rationalising permeation

The bilinear relationship of permeation vs lipophilicity often forgotten!

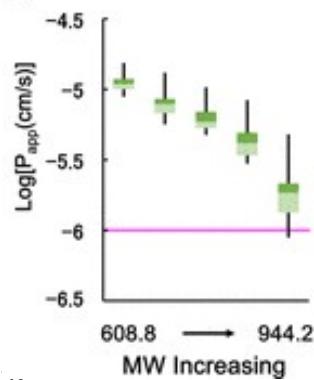
A.



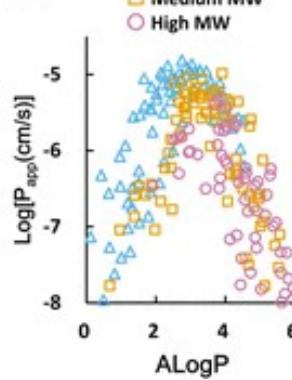
Furukawa, A.; Townsend, C. E.; Schwochert, J.; Pye, C. R.; Bednarek, M. A.; Lokey, R. S., Passive Membrane Permeability in Cyclic Peptomer Scaffolds Is Robust to Extensive Variation in Side Chain Functionality and Backbone Geometry. *J. Med. Chem.* 2016, 59 (20), 9503-9512.

- Sized by recovery from donor/acceptor wells

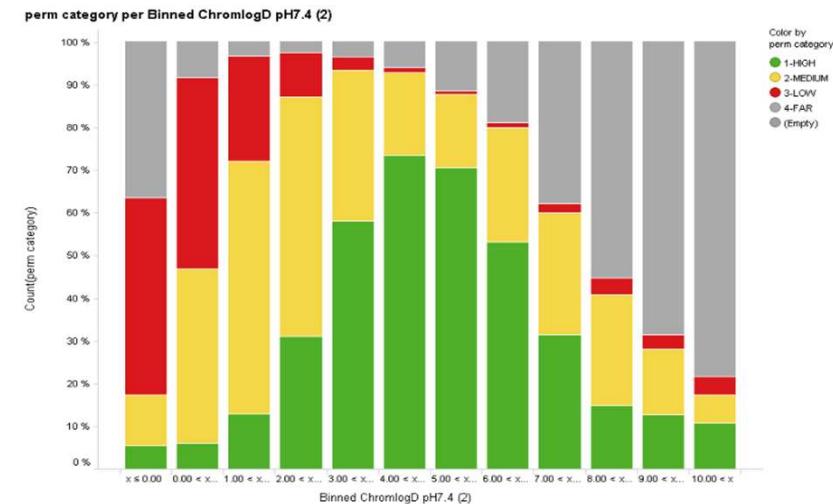
C.



D.



PAMPA data



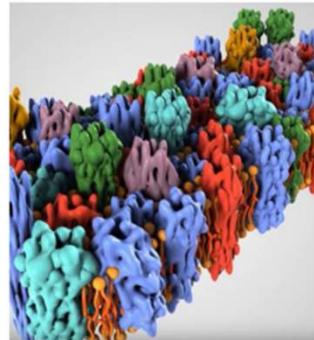
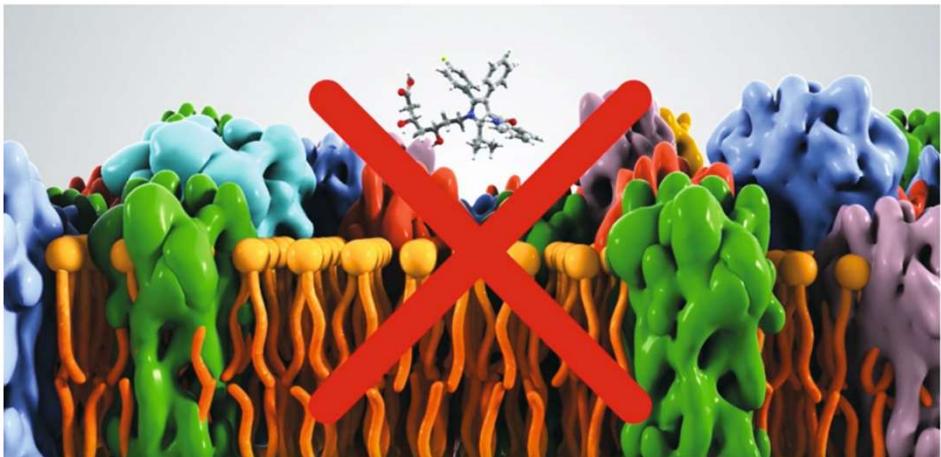
Drug Discovery Today
2011, 16, 822-830

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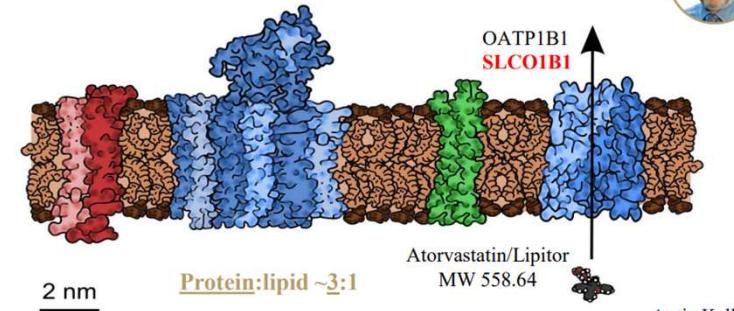


But how do compounds enter cells?

Kell, D. B. Hitchhiking into the Cell. *Nat. Chem. Biol.* 2020, 16, 367-368.



A typical biomembrane drawn to scale

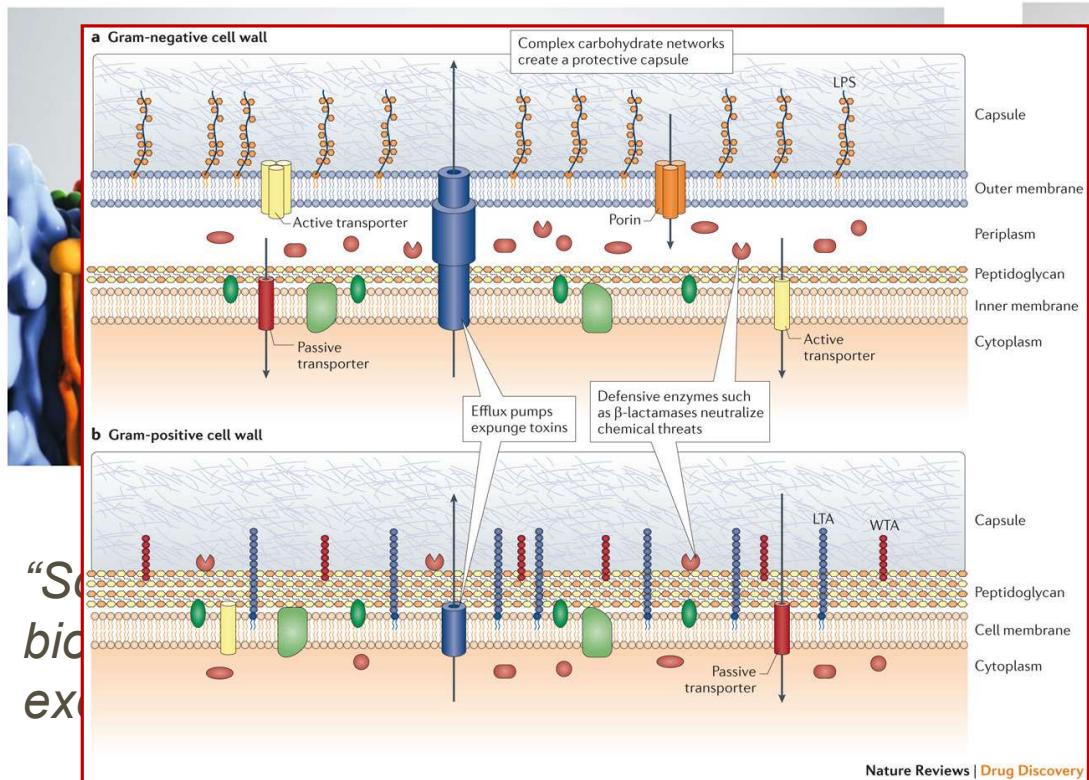


“Solute carriers are required for drug transport across cellular membranes. Real biomembranes in cells have protein:phospholipid ratios (by mass) that are well in excess of one, and this minimizes any bilayer transport of small molecules.”



So how about crossing bacterial membrane?

Compounds must surely go through on transporters?



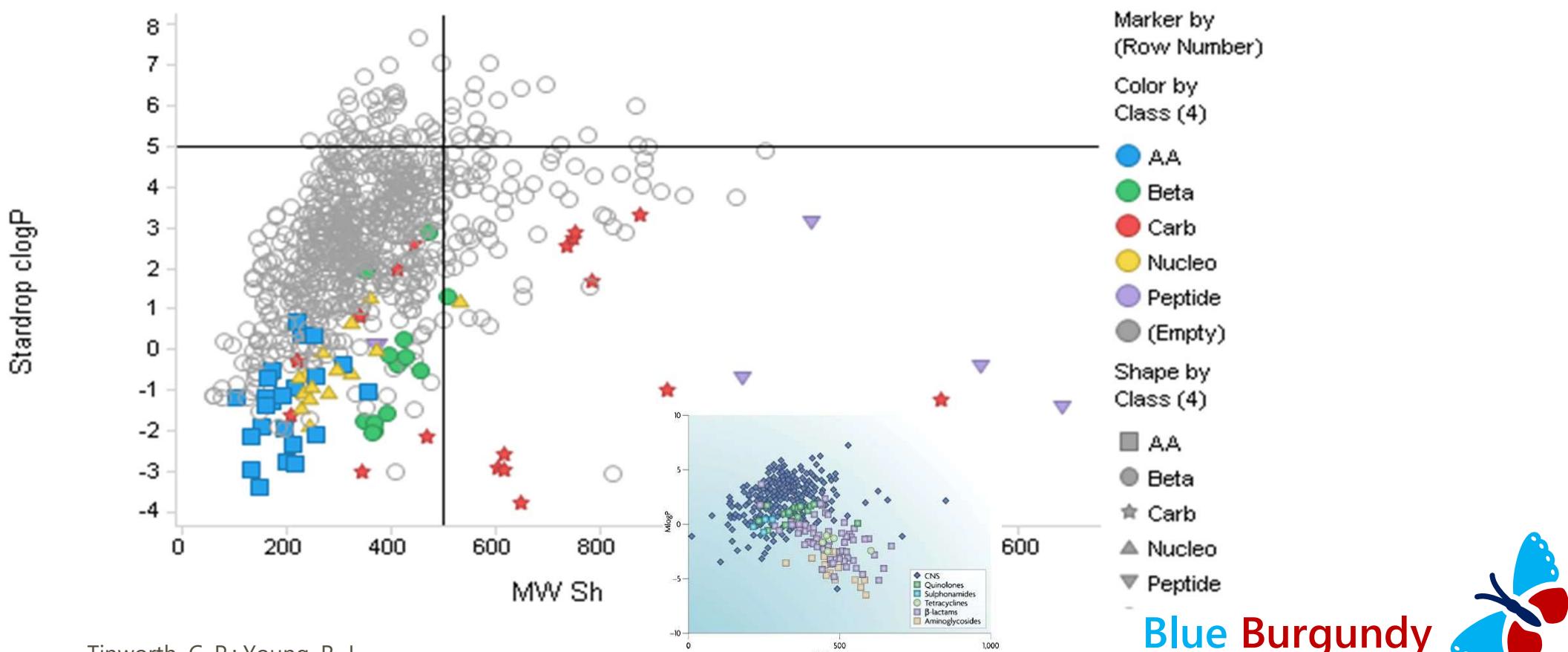
"So how about crossing bacterial membranes?"
"So how about crossing bacterial membranes?"
"So how about crossing bacterial membranes?"

- Microbial membranes
- Must mimic something the bug requires to be recognised to cross
 - The “diet” may change within a life cycle
 - Must also “escape” efflux mechanisms and other potential metabolism
 - 4 Billion years of evolution to design compounds to navigate this labyrinth!

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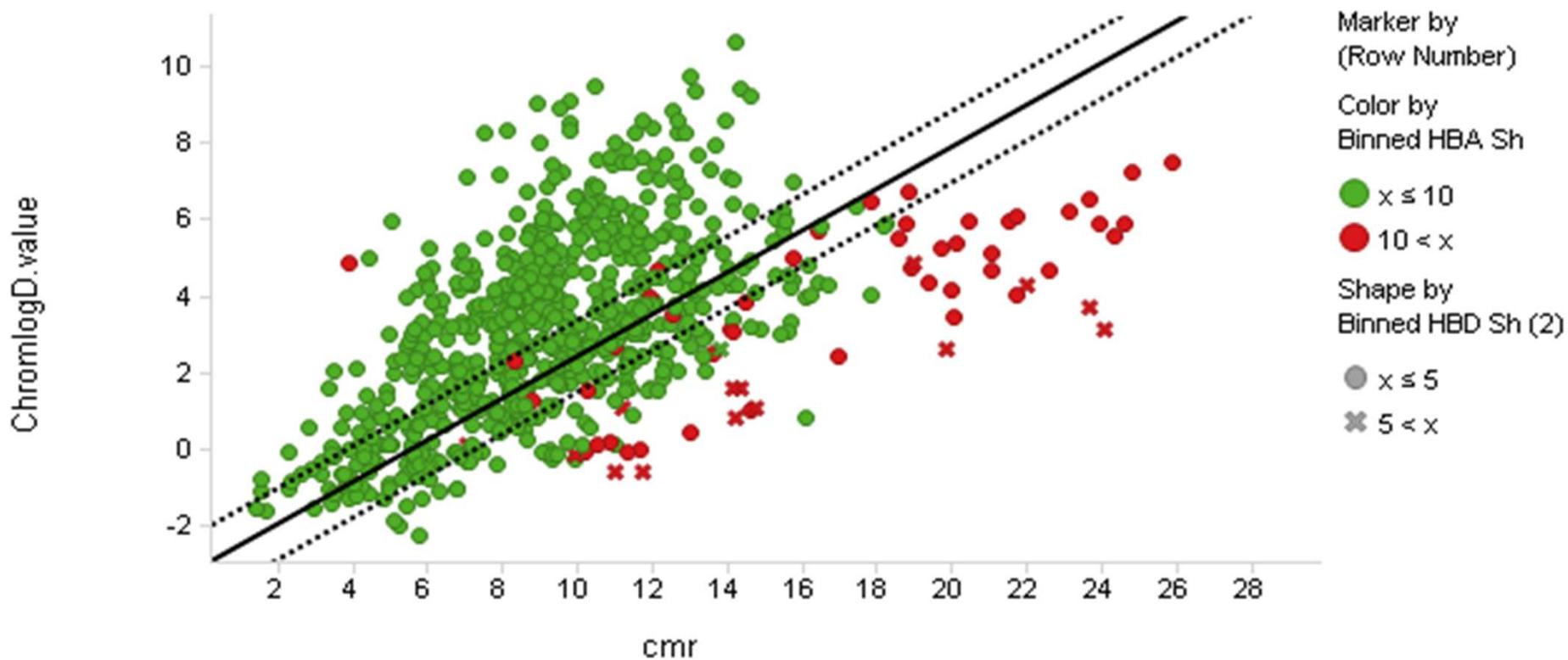
A variation on previous Ro5 analysis

Remember Ro5 provisos made for transported compounds...



Same data set – different view

GSK permeability predictor: calc Chrom logD_{pH7.4} vs cmr – best predictor out there!



36

Tinworth, C. P.; Young, R. J. *J. Med. Chem.* **2020**, 63, 10091-10108.

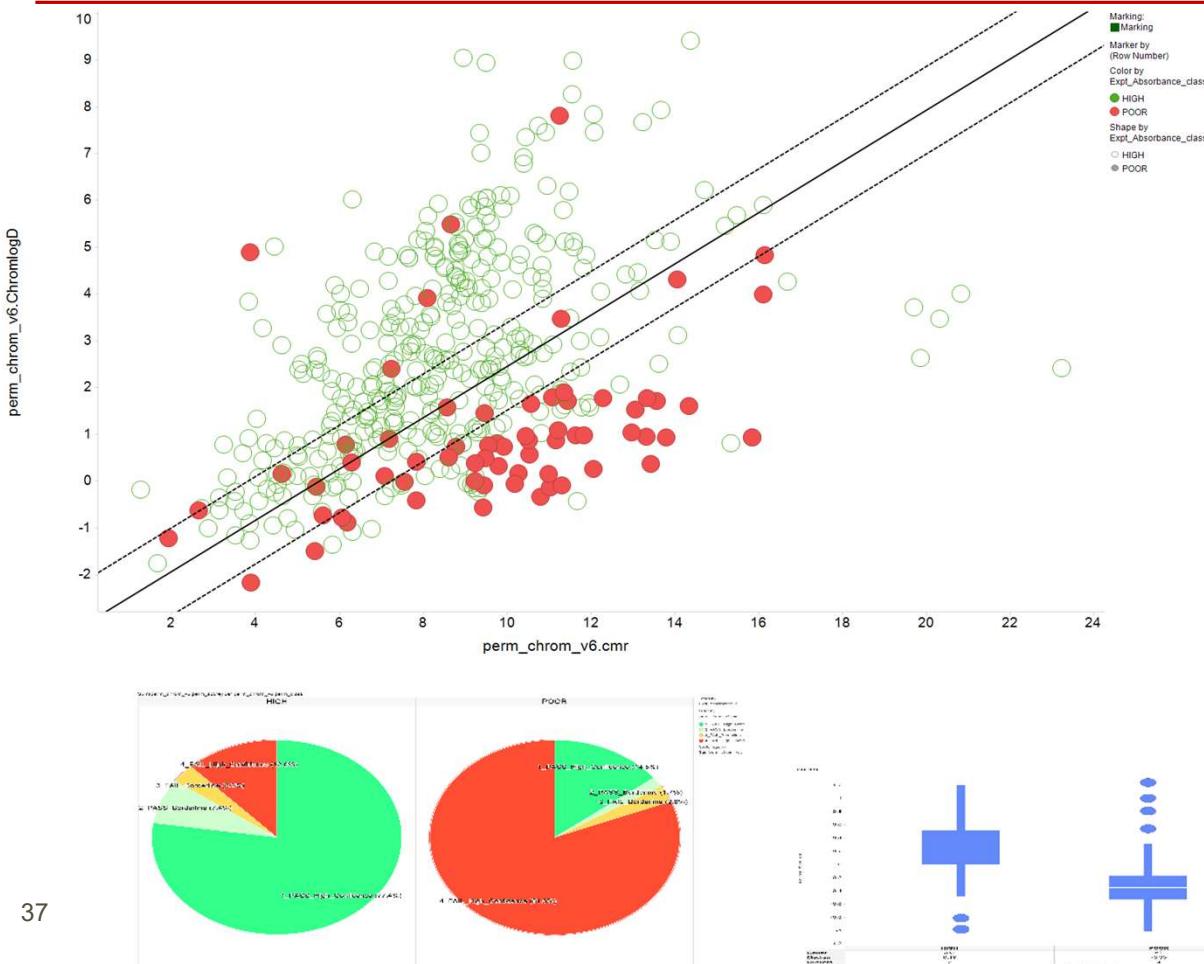
Young, R. J. Today's drug discovery and the shadow of the rule of 5. *Expert Opin Drug Discov* **2023**, 18 (9), 965-972.

Blue Burgundy



How to understand permeability?

In my experience this model better than PAMPA, Caco-2, MDCK...



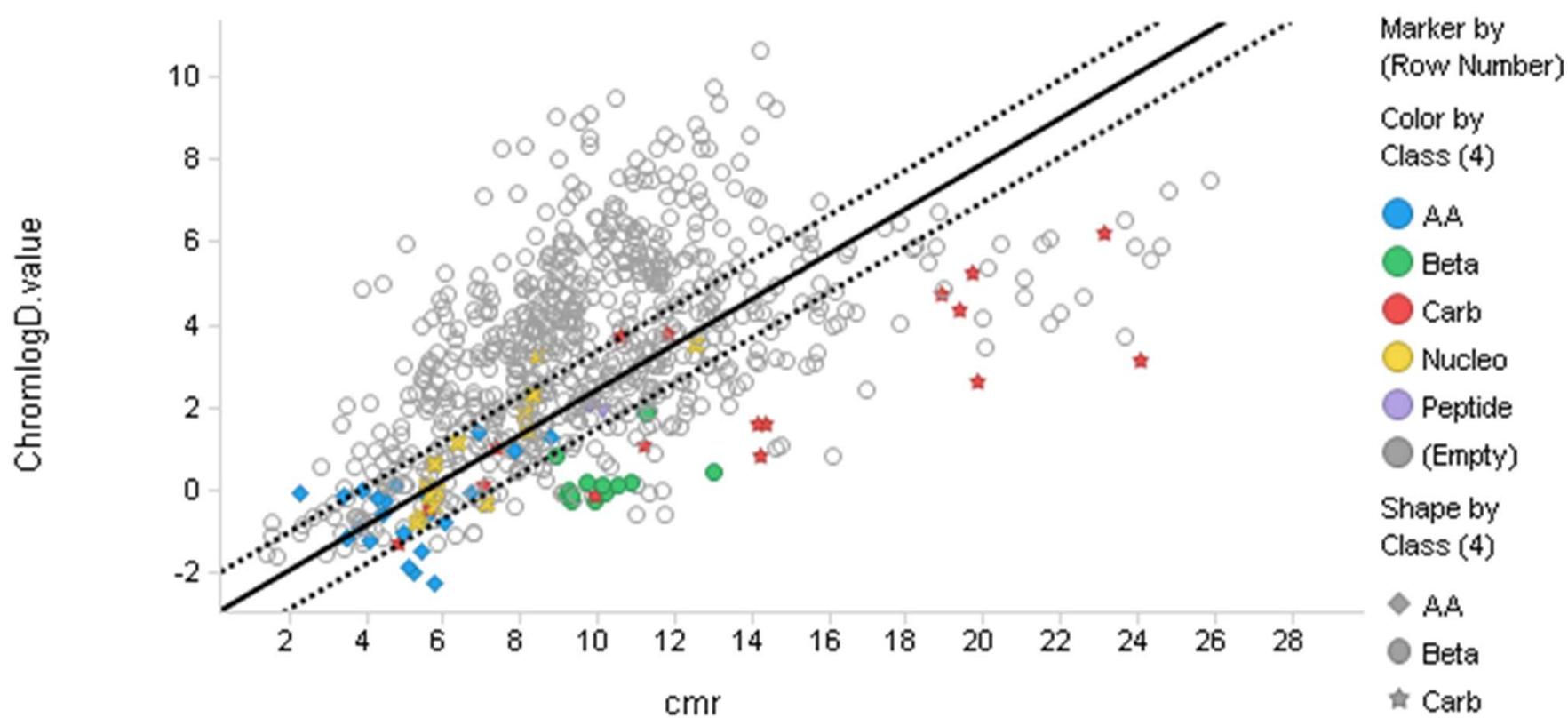
- GSK log D_{7.4} vs cmr model
 - very powerful predictor of permeability / oral exposure
 - *J. Med. Chem.* **2020, 63**, 10091-10108.
- Observations fit optimum logD_{7.4}
 - Compare AbbVie MPS
- Statistically very sound, even with clear exceptions
 - These are where Nat Pros abound
 - Particularly antimicrobials

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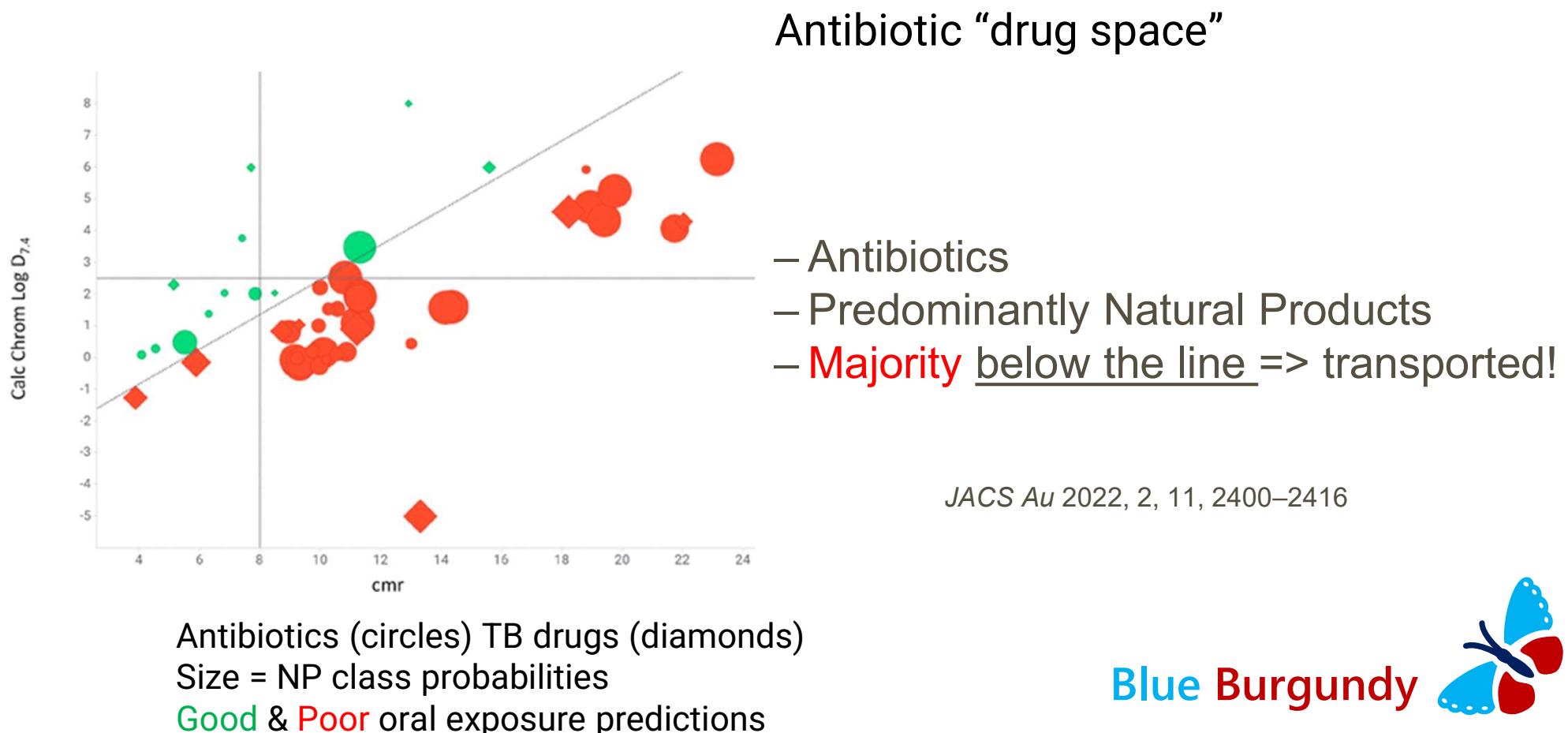
Chrom logD_{pH7.4} vs cmr with classifications

Classifying as before: where do transporters begin and end?!



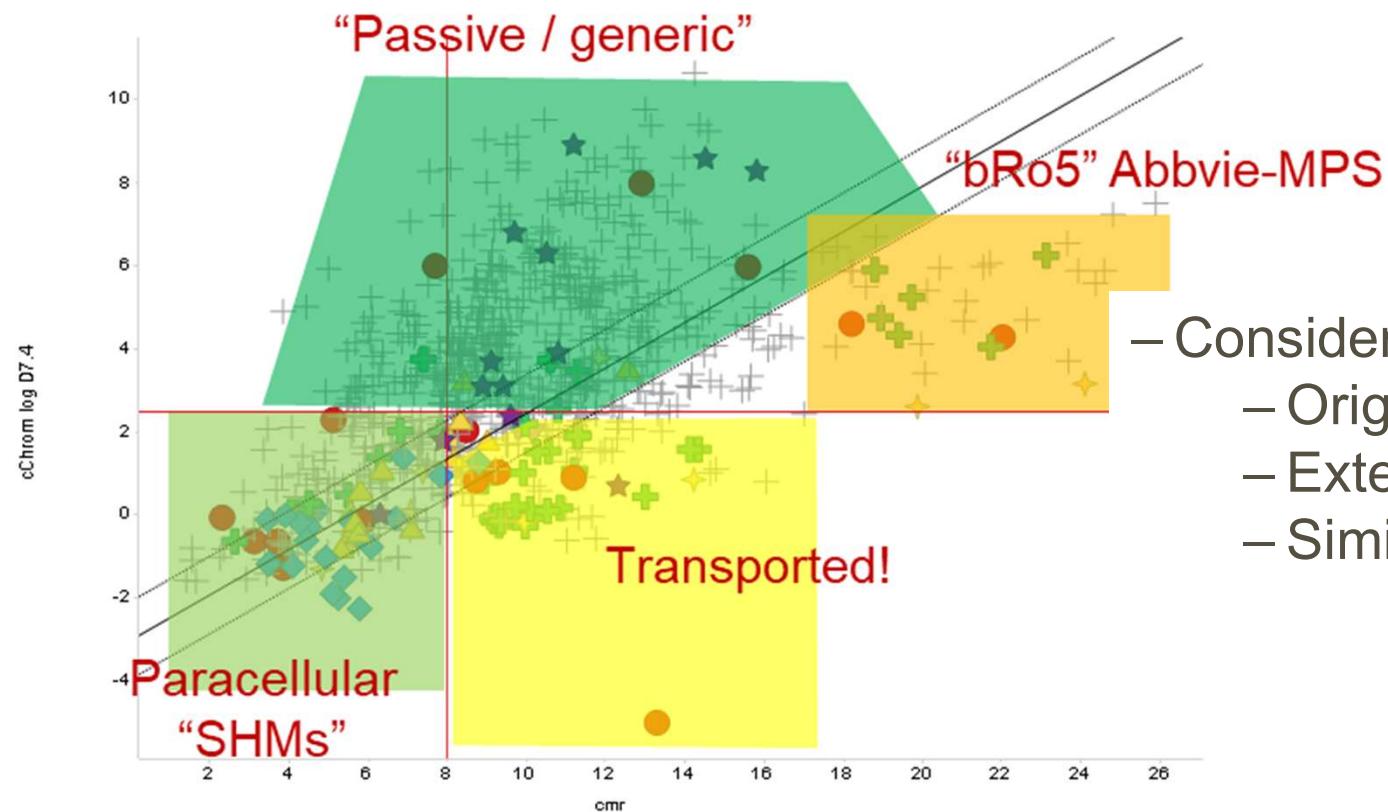
Have we looked in the right place for new antimicrobials?

Maybe not surprising few new antibiotics? Natural Intelligence not very evident...



A new way to consider permeation going forward?

No simple catch all rule? – may be applicable beyond *Mycobacterium tuberculosis*

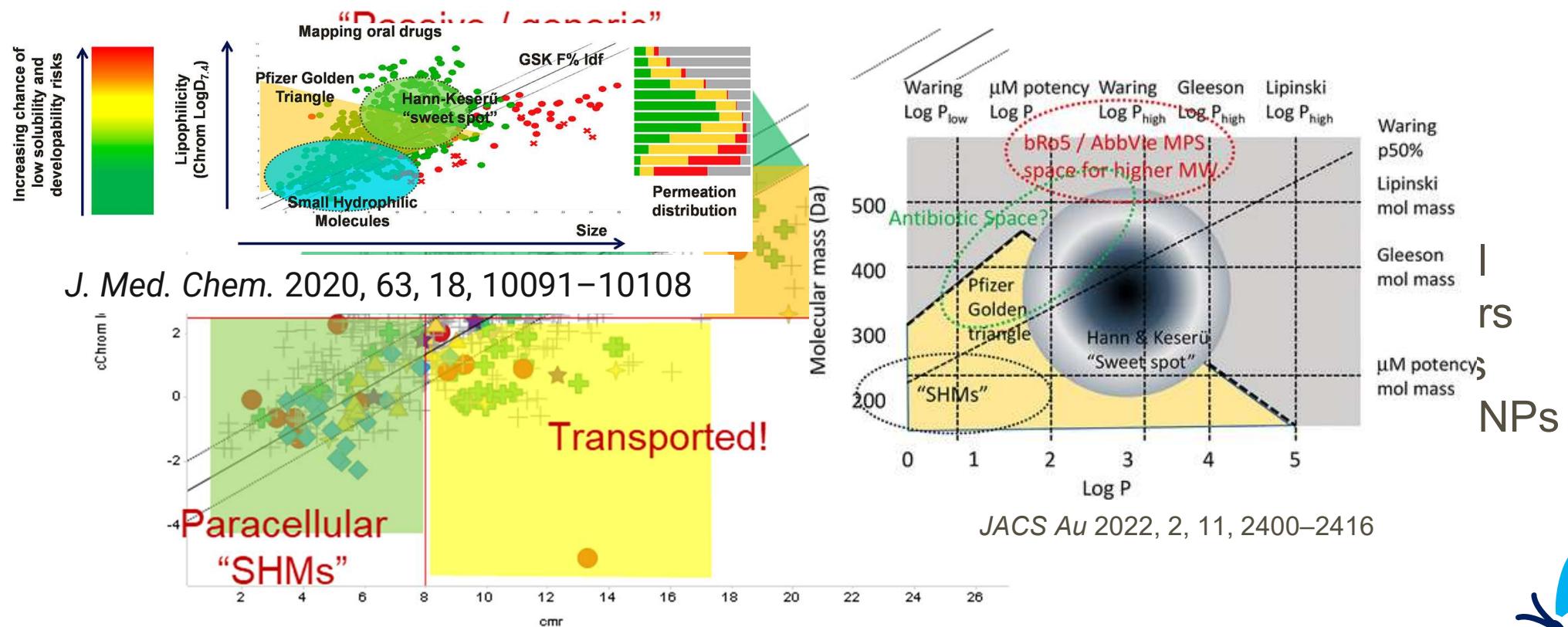


- Consider work of Doug Kell
 - Origins of transporters
 - Extent of transporters
 - Similarity of drugs to NPs



A new way to consider permeation going forward?

Bigger picture considerations



Thinking with natural intelligence?

How natural are our experimental molecules?



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Thinking with natural intelligence

How many perfect molecules evolved?

- Were many perfect proteins made?
 - Smaller peptides?

Thinking with natural intelligence

Why are so many natural molecules glycosylated?

- Were many perfect proteins made?
 - Smaller peptides?
 - Or are they all covered in carbohydrates?
 - Other post-translational modifications?
- A fully glycosylated protein
 - *How many ££\$\$€€ has Drug Discovery invested on single phosphorylation events?*

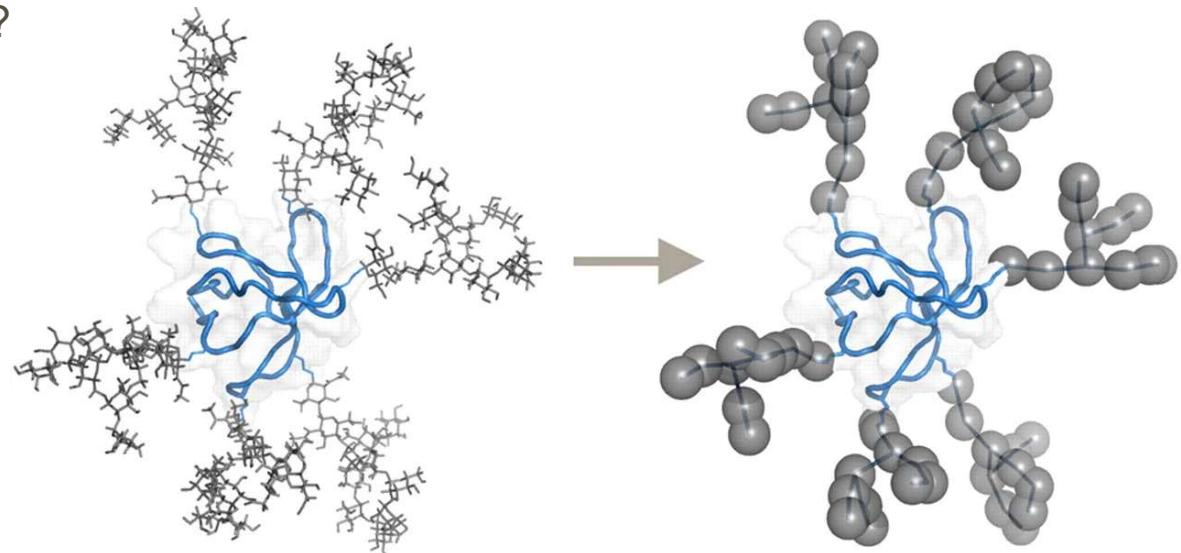
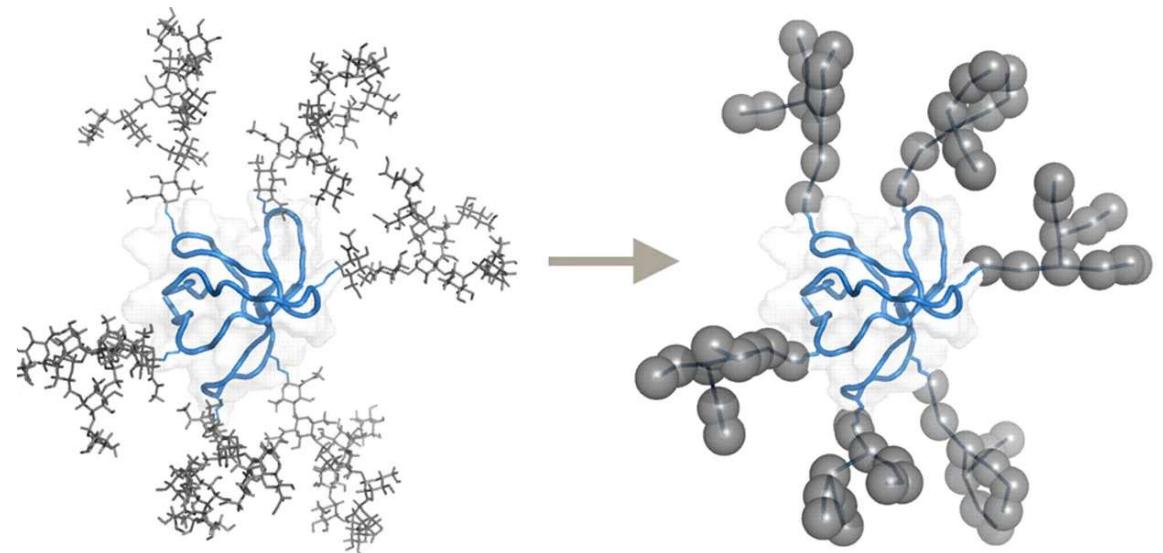
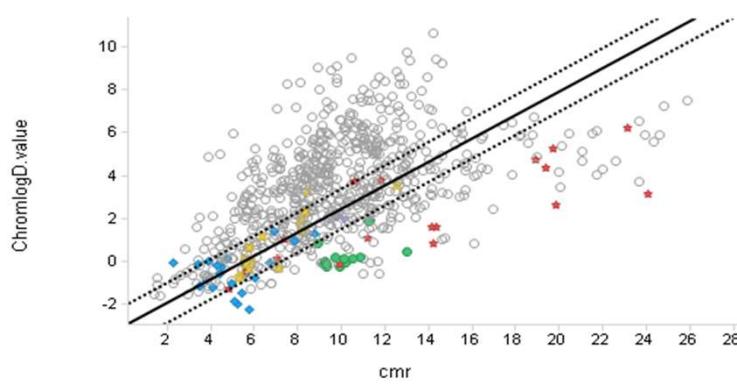


Image: D. Shental-Bechor, & Y. Levy, Effect of glycosylation on protein folding: A close look at thermodynamic stabilization, Proc. Natl. Acad. Sci. U.S.A. 2008, 105 (24) 8256-8261
Used under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International

Thinking with natural intelligence

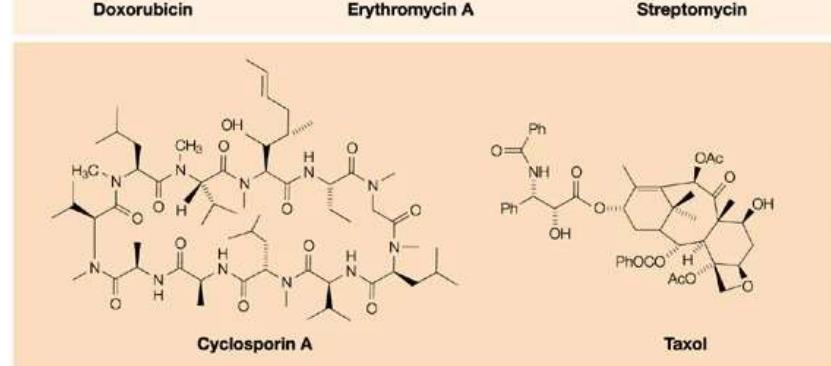
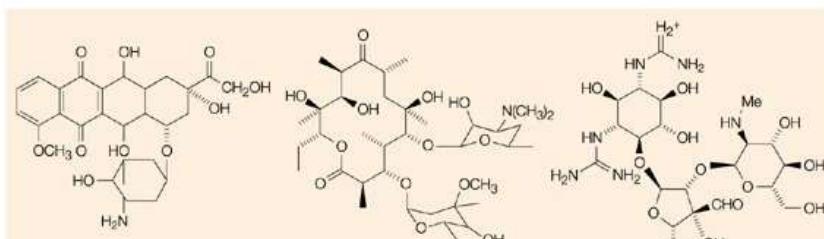
Why are so many natural molecules glycosylated?

- Were many perfect proteins made?
 - Smaller peptides?
 - Or are they all covered in carbohydrates?
 - Other post-translational modifications?
- What about smaller molecules?



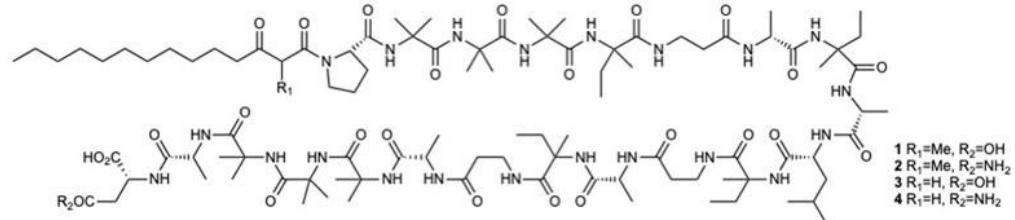
Where next for antibiotic molecules?

What “natural” modifications might be made to enhance permeability?

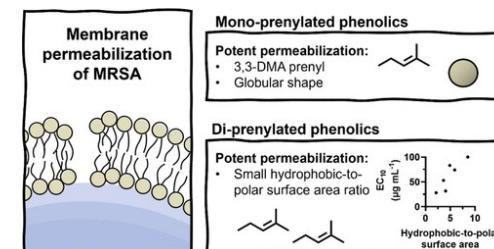


Nature Reviews | Drug Discovery

Khosla, C.; Keasling, J. D. Metabolic engineering for drug discovery and development. *Nature Reviews Drug Discovery* 2003, 2 (12), 1019-1025.



X Chen et al, *Nat. Commun.*, 2025, 16, 7337
(DOI: [10.1038/s41467-025-62630-z](https://doi.org/10.1038/s41467-025-62630-z))



Ritsema, J. et al. *J. Nat. Prod.* 2025, in press
<https://doi.org/10.1021/acs.jnatprod.5c00540>

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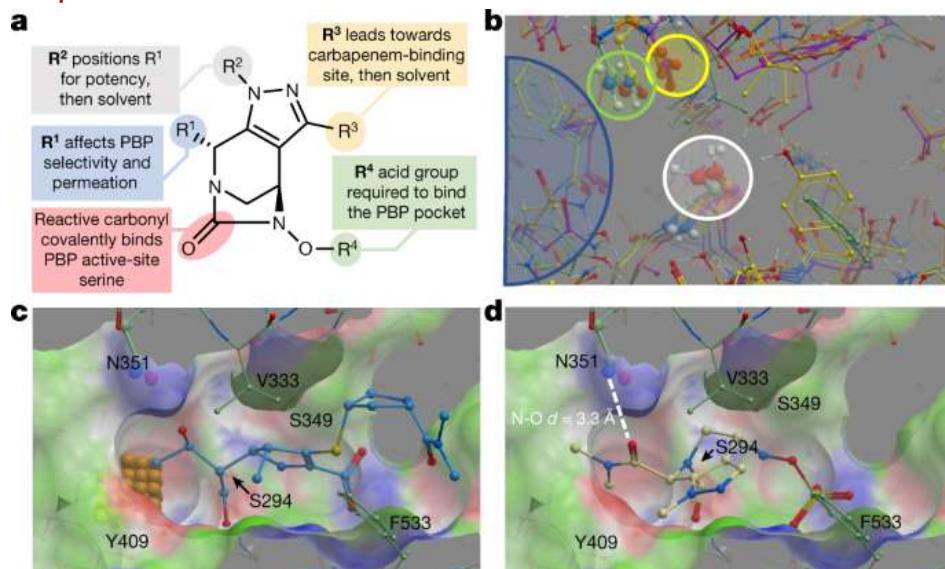


A Natural intelligence approach?

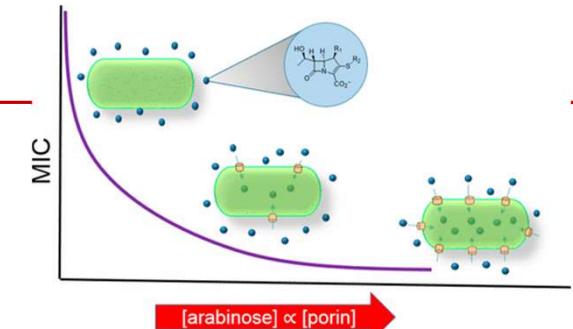
New structural class of antibiotics for gram negative infections

Durand-Reville, T. F.; et al. Rational design of a new antibiotic class for drug-resistant infections. *Nature* **2021**.

<https://www.nature.com/articles/s41586-021-03899-0>



"An improved optimization strategy leveraged porin permeation properties concomitant with biochemical potency in the lead-optimization stage."



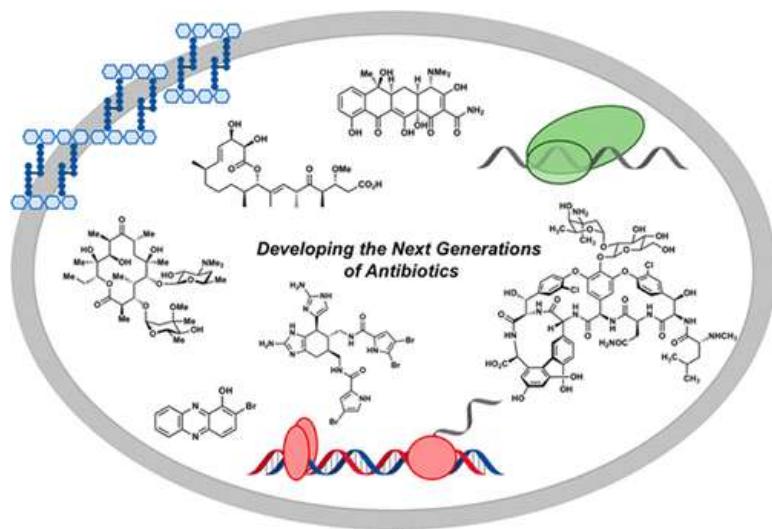
Iyer, R.; et al. Whole-Cell-Based Assay To Evaluate Structure Permeation Relationships for Carbapenem Passage through the *Pseudomonas aeruginosa* Porin OprD. *ACS Infectious Diseases* **2017**, 3 (4), 310-319.

*"Although it is well-known that outer membrane porins represent the main route of entry for small, hydrophilic molecules across the Gram-negative cell envelope, the structure–permeation relationship for porin passage has yet to be defined. To address this knowledge gap, we developed a sensitive and specific whole-cell approach in *Escherichia coli* called titrable outer membrane permeability assay system (TOMAS)."*

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Natural Products as Platforms To Overcome Antibiotic Resistance

Natural product-like or pseudo natural products are althernative description of this...



Natural products have served as powerful therapeutics against pathogenic bacteria since the golden age of antibiotics of the mid-20th century. However, the increasing frequency of antibiotic-resistant infections clearly demonstrates that new antibiotics are critical for modern medicine. Because combinatorial approaches have not yielded effective drugs, we propose that the development of new antibiotics around proven natural scaffolds is the best short-term solution to the rising crisis of antibiotic resistance. We analyze herein synthetic approaches aiming to reengineer natural products into potent antibiotics. Furthermore, we discuss approaches in modulating quorum sensing and biofilm formation as a nonlethal method, as well as narrow-spectrum pathogen-specific antibiotics, which are of interest given new insights into the implications of disrupting the microbiome.

Rossiter, S. E.; Fletcher, M. H.; Wuest, W. M., Natural Products as Platforms To Overcome Antibiotic Resistance. *Chem. Rev.* **2017**, 117 (19), 12415-12474.

Are there actually less potential drug motifs out there?

The Time and Place for Nature?

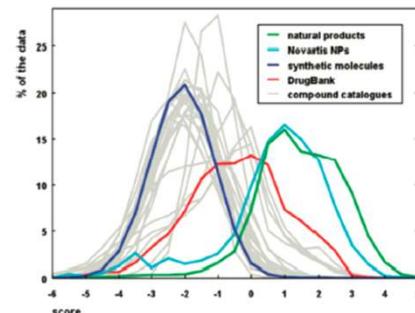
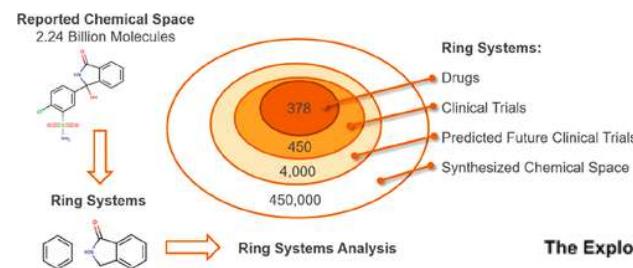


Figure 3. Natural products differ from most synthetic molecules but overlap with drugs which have been optimized for biocompatibility. NPs are pre-optimized. Reproduced with permission from ref 13. Copyright 2008 American Chemical Society.

Ertl, P.; Roggo, S.; Schuffenhauer, A., Natural Product-likeness Score and Its Application for Prioritization of Compound Libraries. *J. Chem. Inf. Model.* **2008**, 48 (1), 68-74.

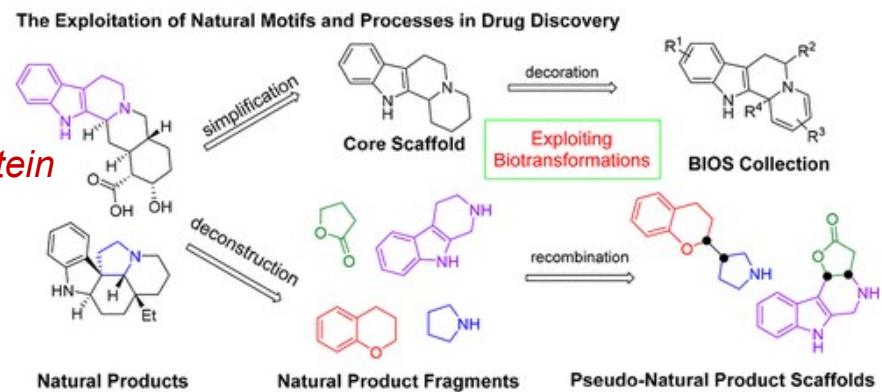
Chen, Y.; Stork, C.; Hirte, S.; Kirchmair, J. NP-Scout: Machine Learning Approach for the Quantification and Visualization of the Natural Product-Likeness of Small Molecules. *Biomolecules* **2019**, 9 (2), 43

Shearer, J.; Castro, J. L.; Lawson, A. D. G.; MacCoss, M.; Taylor, R. D., Rings in Clinical Trials and Drugs: Present and Future. *J. Med. Chem.* **2022**, 65 (13), 8699-8712.



- “Made by a protein”
- “Transported by a protein”
- “Inhibits a protein”

“We show 67% of small molecules in clinical trials comprise only ring systems found in marketed drugs, which mirrors previously published findings for newly approved drugs.”



Pseudonatural Products for Chemical Biology and Drug Discovery
Griener, L. et al *J. Med. Chem.* 2025, 68, 14, 14137–14170

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Evidence for “Natural Selection”

Adding some data to hypotheses in “Time and Place for Nature”

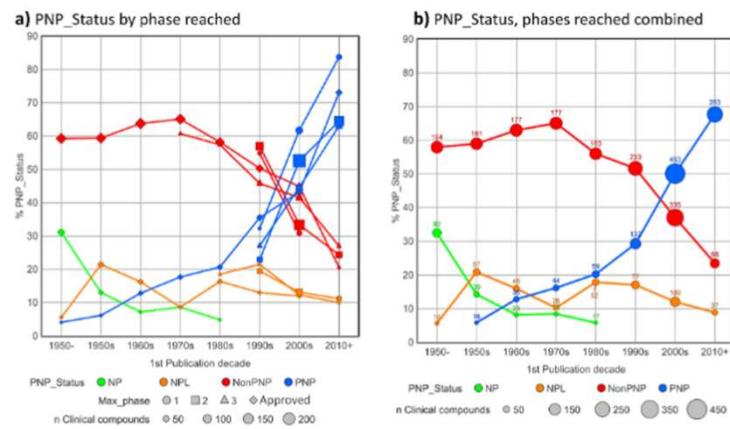
Occurrence of “Natural Selection” in Successful Small Molecule Drug Discovery

Published as part of *Journal of Medicinal Chemistry* virtual special issue “Natural Products Driven Medicinal Chemistry”.

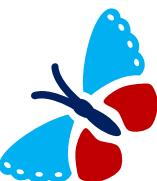
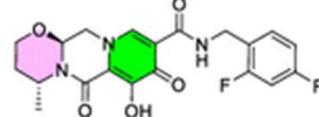
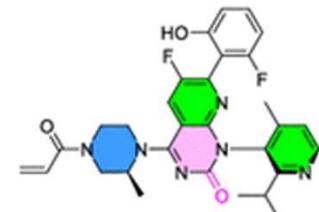
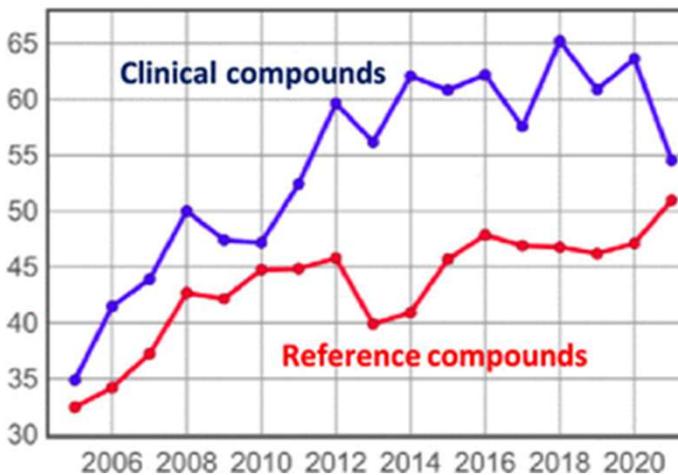
A. Lina Heinzke, Axel Pahl, Barbara Zdrazil, Andrew R. Leach, Herbert Waldmann, Robert J. Young, and Paul D. Leeson*

Cite This: *J. Med. Chem.* 2024, 67, 11226–11241

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% Compounds that are *pseudo-natural products*



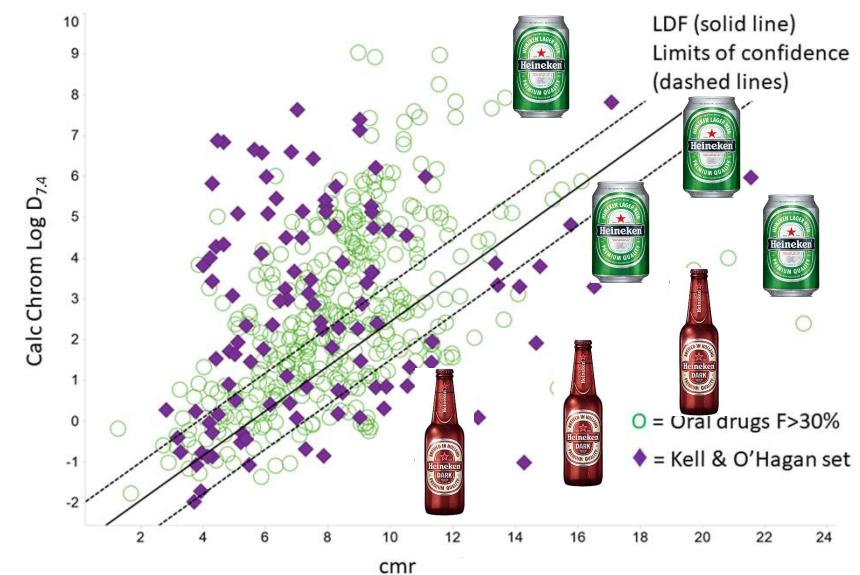
Can we truly “expand chemical space”

Are **Natural Products** and **Natural Motifs** the **Heineken beers** of Drug Discovery?

Chemical space

Might application of **Natural Intelligence** properly enable access to regions of “Chemical Space” that **synthetic molecules** cannot reach?

- accessible via transporters and natural recognition



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In summary

Lessons learned & how to shape consider antibiotic discovery in future

- Sometimes need to be brave and go against the prevailing wind / practices or *think differently*
 - E.g. Lipinski, Lombardo et al and patterns observed in post-HTS hits
 - Focus on data – patterns and objectivity, **efficacy** not **potency!**
 - Be **decisive if translation to bug killing is poor**
- Drug discovery is a very difficult pursuit & relies on many compromises in optimisation
 - Don't try and work against nature!
- To update an old quote (Sir James Black) “the best place to find a new drug is to start with an old one...” - or a *natural product or a deliberate mimic of one displaying precedented motifs recognised by nature*



Acknowledgments

Apologies to anyone forgotten – or not cited/referenced on slides

TaPFN consortium

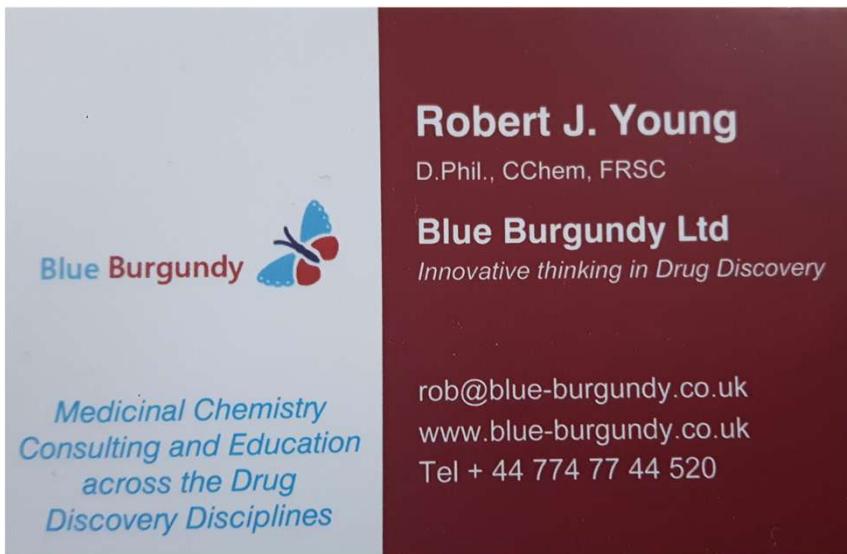
- Paul Leeson (& in many ways!)
- **Herbert Waldmann & team**
- **Michael Grigalunas**
- **(Axel Pahl, Luca Griener)**
- **Sabine Flitsch**
- **Nick Turner**
- **Ron Quinn**
- Andrew Leach & Barbara Zdrazil,
Lina Heinzke & ChEMBL team

- Alan Hill
- Darren Green
- Mike Hann
- Chris Luscombe, Tim Ritchie
 - Many more at GSK over the years!
- Liz Fullam
- Nicola, Susan & H3D team for kind invitation

Rob Young

Blue Burgundy (Drug Discovery Consulting) Ltd

- Wellcome, GlaxoWellcome & GSK Valentine's Day 1990 to 5th July 2019
 - “Retired” to form Blue Burgundy Sept 2019
 - See [LinkedIn](#) – or [Blue Burgundy website](#)



Large **Blue** and Duke of **Burgundy** Butterflies
my own photos taken in 2019
Companies house refused Duke of Burgundy name!

Blue Burgundy



Exogenous natural products

Most important substrates for transporters – Doug Kell's work

ADMET & DMPK 5(2) (2017) 85-125; doi: 10.5599/admet.5.2.376



Open Access : ISSN : 1848-7718

<http://www.pub.iapchem.org/ojs/index.php/admet/index>

Original scientific paper

Consensus rank orderings of molecular fingerprints illustrate the 'most genuine' similarities between marketed drugs and small endogenous human metabolites, but highlight exogenous natural products as the most important 'natural' drug transporter substrates

Steve O'Hagan^{1,2}, Douglas B. Kell^{1,2,3,*}

ADMET and DMPK 2017, 5, 85-125.

Drug-metabolite likenesses



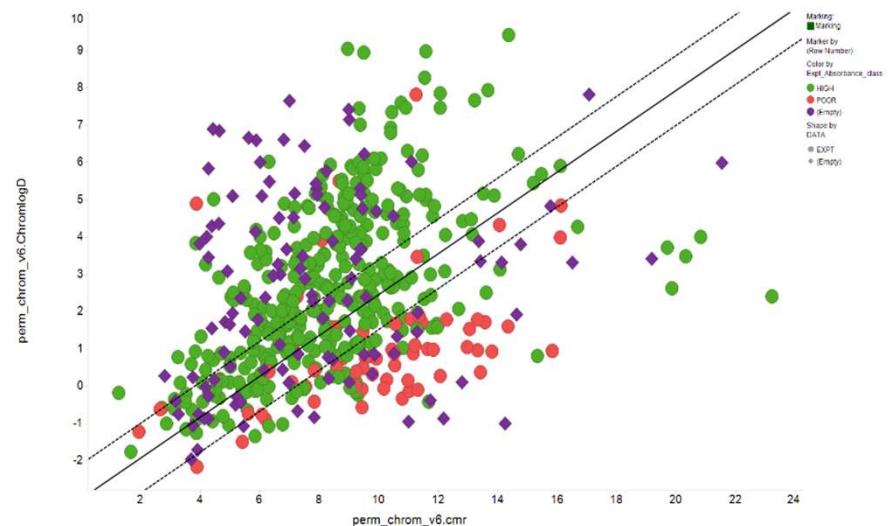
Metabolomics
DOI 10.1007/s11306-014-0733-z

11, 323-339 (2015)

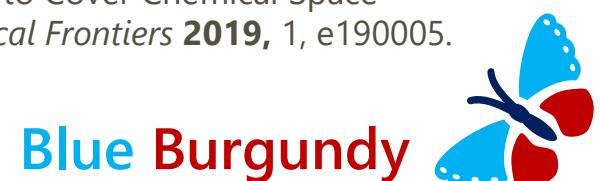
ORIGINAL ARTICLE

A 'rule of 0.5' for the metabolite-likeness of approved pharmaceutical drugs

Steve O'Hagan · Neil Swainston · Julia Handl ·
Douglas B. Kell

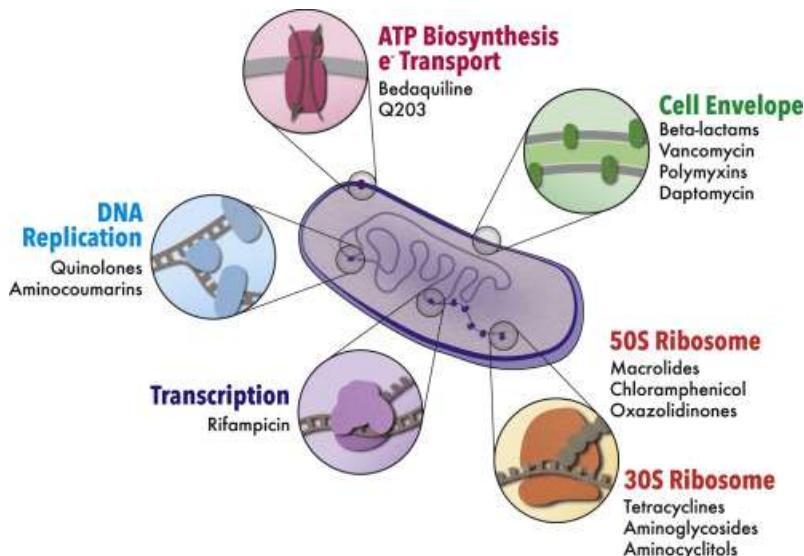


O'Hagan, S.; Kell, D. B. Generation of a Small Library of Natural Products Designed to Cover Chemical Space Inexpensively. *Pharmaceutical Frontiers* 2019, 1, e190005.



Bacterial Metabolism and Antibiotic Efficacy

Understand what your enemy is up to when trying to engage – what transporters active?



Antibiotics target energy-consuming processes. As such, perturbations to bacterial metabolic homeostasis are significant consequences of treatment. Here, we describe three postulates that collectively define antibiotic efficacy in the context of bacterial metabolism: (1) antibiotics alter the metabolic state of bacteria, which contributes to the resulting death or stasis; (2) the metabolic state of bacteria influences their susceptibility to antibiotics; and (3) antibiotic efficacy can be enhanced by altering the metabolic state of bacteria. Altogether, we aim to emphasize the close relationship between bacterial metabolism and antibiotic efficacy as well as propose areas of exploration to develop novel antibiotics that optimally exploit bacterial metabolic networks.

Stokes, J. M.; Lopatkin, A. J.; Lobritz, M. A.; Collins, J. J., Bacterial Metabolism and Antibiotic Efficacy. *Cell Metab.* **2019**, 30 (2), 251-259.

Paul Hergenrother: eNTRY & PA_SsagE Rules

Useful principles and possible “rescue” mechanisms? What do they mimic?

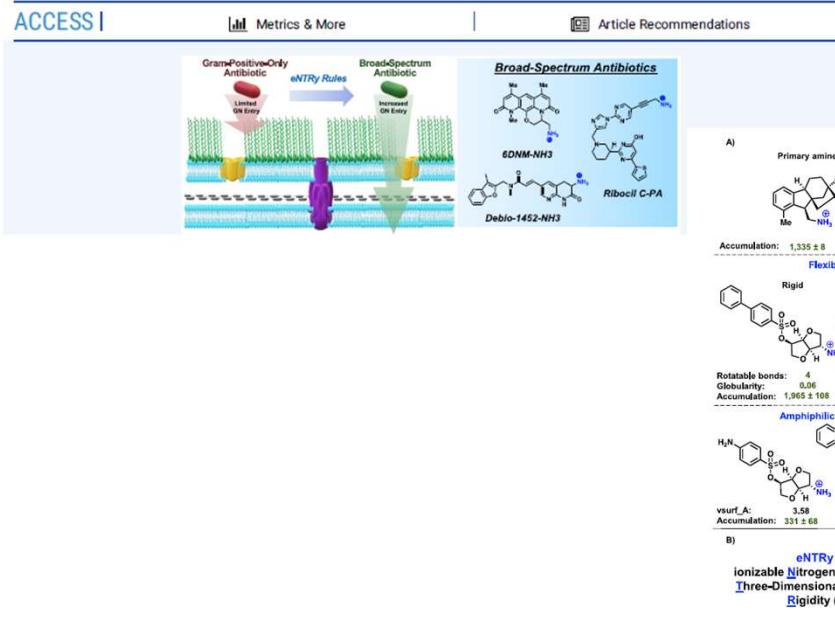
Facilitating Compound Entry as a Means to Discover Antibiotics for Gram-Negative Bacteria

Published as part of the Accounts of Chemical Research special issue “Bacterial Multi-Drug Resistance”.

Kristen A. Muñoz and Paul J. Hergenrother*

Cite This: Acc. Chem. Res. 2021, 54, 1322–1333

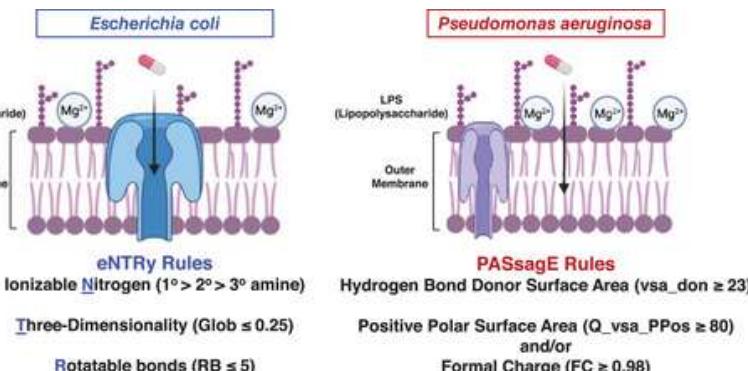
Read Online



Using permeation guidelines to design new antibiotics—A PA_SsagE into *Pseudomonas aeruginosa*

Brett N. Cain, Paul J. Hergenrother ✉

First published: 01 March 2024 | <https://doi.org/10.1002/ctm2.1600> | Citations: 1



The Value of the Soundbite – “Escape from Flatland”

Citations as of Feb 2025

ARTICLE | October 14, 2009

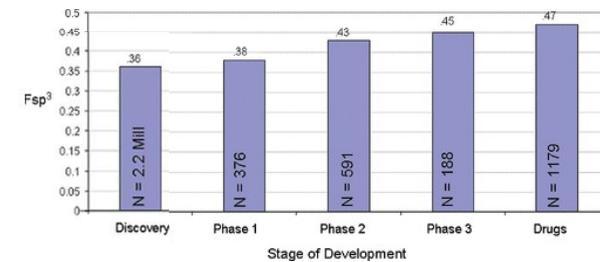
Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success

Frank Lovering^{*†}, Jack Bikker[‡], and Christine Humblet[§]

3152

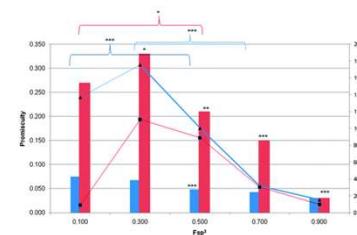
Escape from Flatland 2: complexity and promiscuity

Frank Lovering^{*a}



Average promiscuity for compounds binned by Fsp3.
Blue non-aminergic compounds red aminergic

1179



The impact of aromatic ring count on compound developability – are too many aromatic rings a liability in drug design?

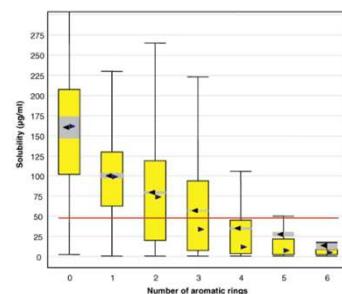
Timothy J. Ritchie and Simon J.F. Macdonald

Respiratory CEDD, GlaxoSmithKline Research Medicines Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK

The impact of aromatic ring count (the number of aromatic and heteroaromatic rings) in molecules has been analyzed against various



TIM RITCHIE
Tim Ritchie has over 20 years experience as a medicinal chemist in the pharmaceutical industry. After his PhD and post-doctoral studies, he worked for several years on neuroscience-related



The impact of aromatic ring count on compound developability: further insights by examining carbo- and hetero-aromatic and -aliphatic ring types

Timothy J. Ritchie¹, Simon J.F. Macdonald², Robert J. Young³ and Stephen D. Pickett⁴

432

Blue Burgundy



690

The Value of the Soundbite – “Escape from Flatland”

It is the **Principle** that matters!

ARTICLE | October 14, 2009

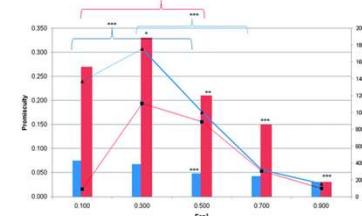
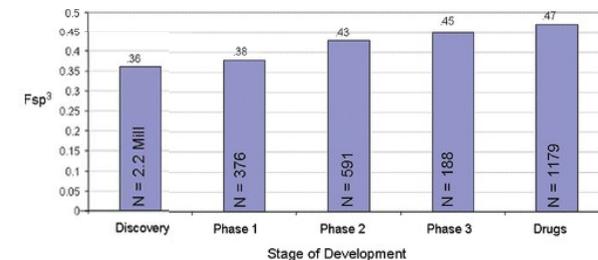
Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success

Frank Lovering^{*†}, Jack Bikker[‡], and Christine Humblet[§]

Escape from Flatland 2: complexity and promiscuity

Frank Lovering^{*a}

- In increasing fsp^3 , then #Ar will decrease
- Not new to point out flaws in fsp^3 ... Some have been doing so for years
 - Leeson, P. D.; Bento, A. P.; Gaulton, A.; Hersey, A.; Manners, E. J.; Radoux, C. J.; Leach, A. R. Target-Based Evaluation of “Drug-Like” Properties and Ligand Efficiencies. *J. Med. Chem.* **2021**, *64*, 7210-7230.
 - Bottom line: #Ar analysis holds (& heterocycles are key players).



Average promiscuity for compounds binned by Fsp^3 .
Blue non-aminergic compounds red aminergic



Best Practices in Medicinal Chemistry Working Group

Subject matter on Med Chem Processes



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