FRAGMENTS 2013
RSC BMCS workshop
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Fragment screening: a comparison with other hit ID methods and challenges

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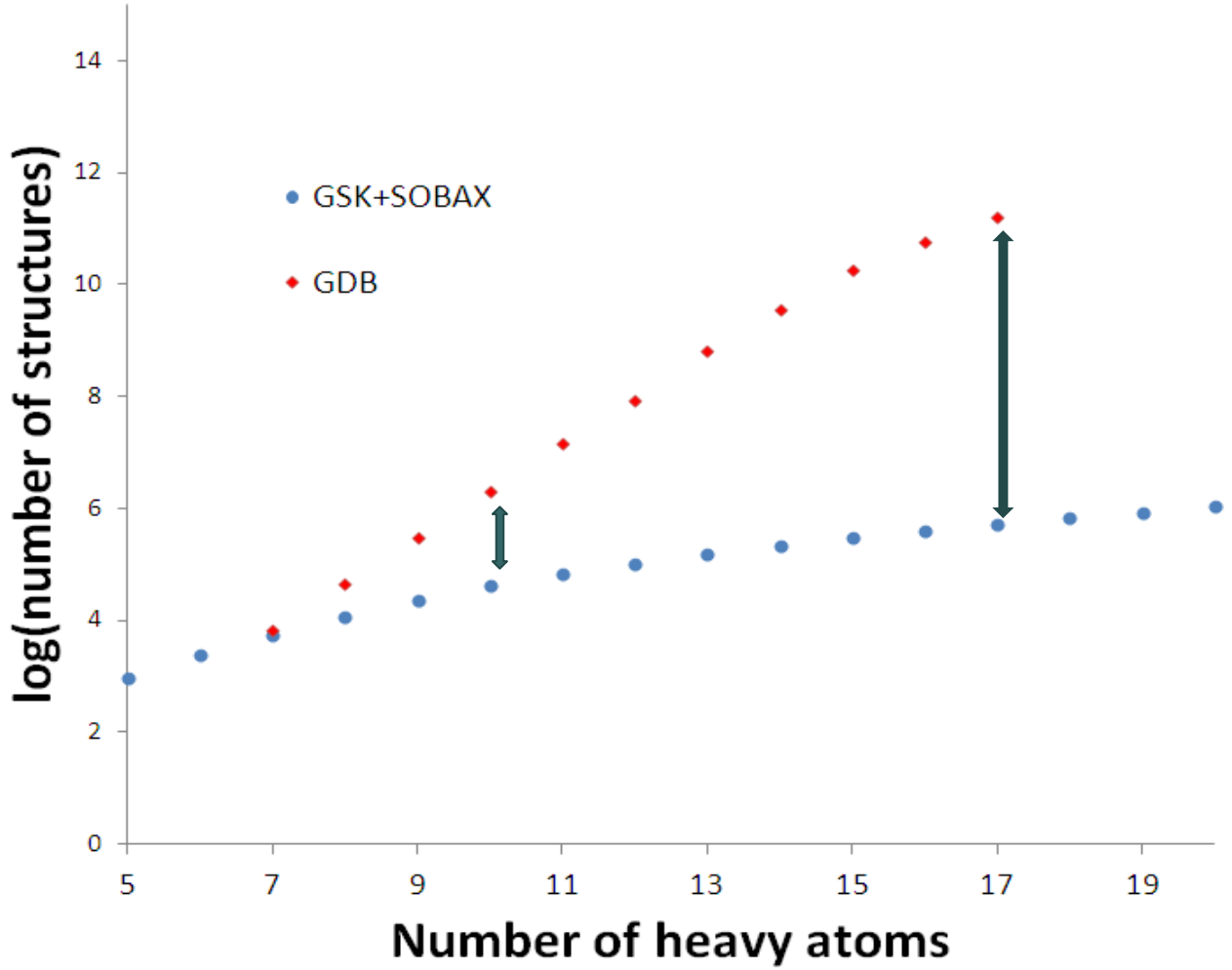
Five fortes of fragments

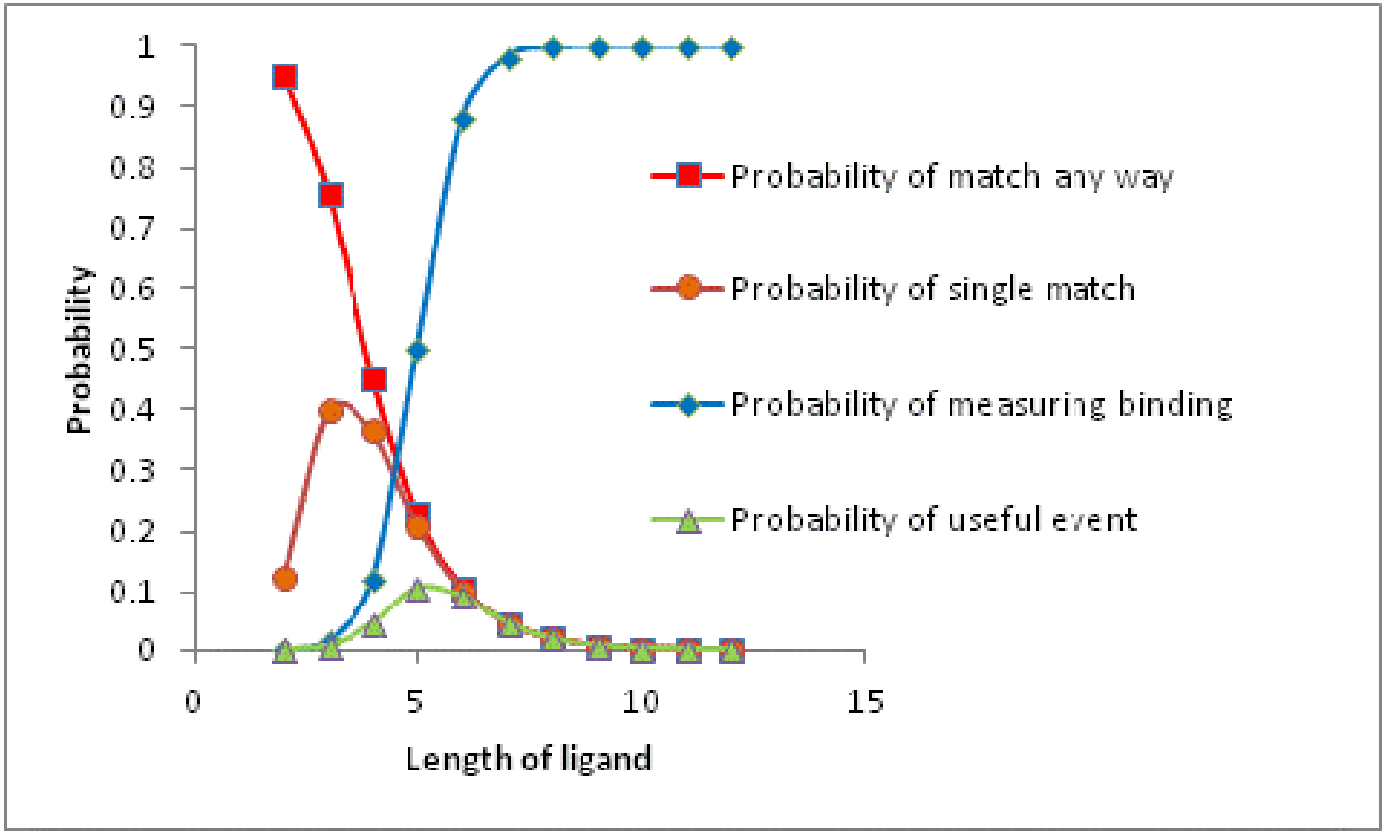
- The combinatorial explosion of chemistry space means that fragments can sample more of the available chemistry space at that level of complexity than is possible with more complex molecules.
- At lower complexity there is a higher probability of compounds matching the receptor even though they may be harder to detect. More complex molecules are more likely to have more “clashes” and thus do not fit.
- Medicinal chemists like to build molecules and so fragments are a great boot strap for structure based design. This plays to the strength of computational chemistry design
- By starting small and selecting the most Ligand Efficient compounds (eg DGbinding/number of heavy atoms), more Lead-like starting points are found which enhance the chances of successful Lead Optimisation campaigns.
- By reducing the number of pharmacophores in initial lead, only necessary interactions are built in to the compound as it is optimised. This should help ensure good developability properties of the resulting candidates

The divergence of sampling rates of real compounds compared to the size of virtual chemistry space from the GDB* database at increasing levels of ligand complexity (as measured by the number of heavy atoms) – note the log scale.



*Ruddigkeit, L., van Deursen, R., Blum, L.C., and Reymond, J-L., "Enumeration of 166 Billion Organic Small Molecules in the Chemical Universe Database GDB-17," JACS , 52(11), 2864-2875, 2012.

The probabilities that ligands of different complexity (ie length) can match, be detected and the resultant “useful event”.



Fragment Screening

Strengths	Weaknesses
•Utilises the reduced complexity approach to increasing hit rate •Focus on ligand efficiency •Efficient sampling of chemical diversity. •Enables structure based design and biophysics at outset •Builds what you need	•Specialised methods needed to detect week binding. •Chemistry follow up needed to establish a lead quality molecule. •Primarily limited to structure enabled targets •Reductionist approach may over simplify complexity of interactions – i.e cooperativity lost •Easy to squander a good hit •Cost
Opportunities	**Threats**
•Target tractability assessment •Integration with other methods •Increasing sensitivity of biophysics	•More potent initial compounds from other methods.

Molecular complexity and fragment-based drug discovery: ten years on. Curr Opin Chem Biol. 2011 , 489-96. Leach AR, Hann MM.

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High Throughput Screening HTS

Strengths	Weaknesses
•Diversity •Proven track record •Robustness •Automation and miniaturisation •Broadly applicable to biochem and cellular assays	•Compound collection maintenance •False positives •Cost – particularly infrastructure
Opportunities	**Threats**
•Synergy with other hit ID methods •Spare capacity •Label free detection methods (eg MS) •Phenotypic screens	•Seen as expensive/slow but not so once infrastructure is in place. •Perception as old technology!

Impact of high-throughput screening in biomedical research.,Nature Rev Drug Discov. 2011 Mar;10(3):188-95..
Macarron R, Banks MN, Bojanic D, Burns DJ, Cirovic DA, Garyantes T, Green DV, Hertzberg RP, Janzen WP, Paslay JW, Schopfer U, Sittampalam GS.

Encoded Libraries Technology – ELT*

Strengths	Weaknesses
•Huge numbers of compounds can be screened > 10^9 •Affinity selection and thus can give very potent compounds •Minimal infrastructure cf HTS •Initial screening very quick	•Affinity only hence non-functional in absence of other assays •Aqueous chemistry only •Complexity and size of molecules tends to be high •Diversity is focussed around certain chemistries. •Cost – chemistry making libraries and follow up off DNA to confirm hits.
Opportunities	**Threats**
•Target tractability assessment	

*Design, synthesis and selection of DNA-encoded small-molecule libraries
Nature Chemical Biology 5, 647 - 654 (2009), Matt Clark, Barry Morgan et al

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Knowledge based screening

Strengths	Weaknesses
•In silico selects from widest diversity of tangible compounds in 2D or 3D •Acoustic dispensing makes cherry picking easy from in house collections •Good availability of compounds from suppliers	•Knowledge may be wrong or limiting! •Docking and scoring poor •Still need good assays! •Cost of compounds if many purchased
Opportunities	**Threats**
•Improvements in force fields and methods	

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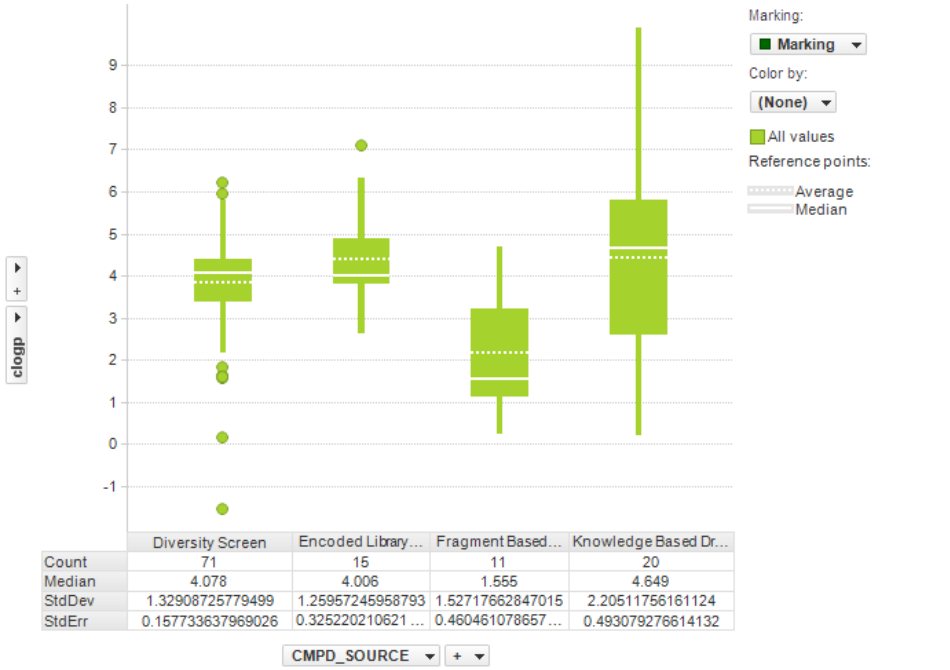
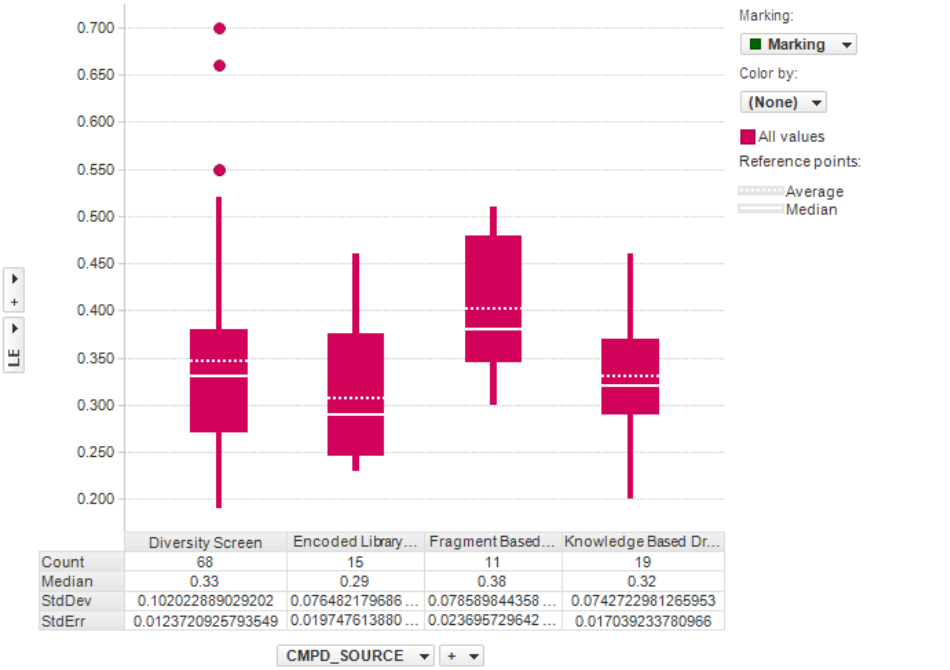
Box Plot



	Diversity Screen	Encoded Library...	Fragment Based...	Knowledge Based Dr...
Count	71	15	11	20
Median	4.078	4.006	1.555	4.649
StdDev	1.32908725779499	1.25957245958793	1.52717662847015	2.20511756161124
StdErr	0.157733637969026	0.325220210621 ...	0.460461078657...	0.493079276614132

CMPD_SOURCE +

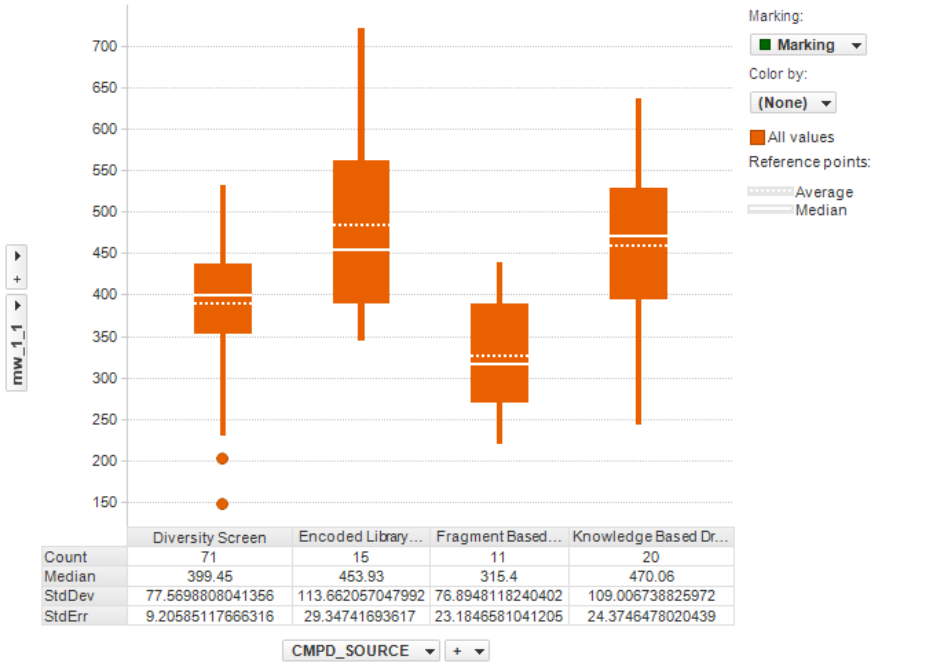
Box Plot



	Diversity Screen	Encoded Library...	Fragment Based...	Knowledge Based Dr...
Count	68	15	11	19
Median	0.33	0.29	0.38	0.32
StdDev	0.102022889029202	0.076482179686 ...	0.078589844358 ...	0.0742722981265953
StdErr	0.0123720925793549	0.019747613880 ...	0.023695729642 ...	0.017039233780966

CMPD_SOURCE +

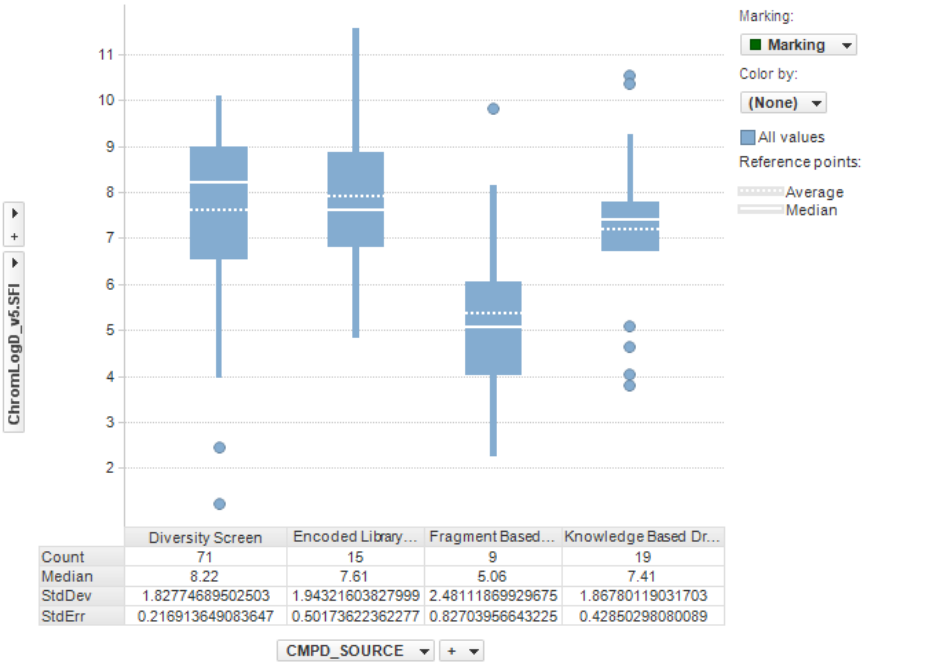
Box Plot



	Diversity Screen	Encoded Library...	Fragment Based...	Knowledge Based Dr...
Count	71	15	11	20
Median	399.45	453.93	315.4	470.06
StdDev	77.5698808041356	113.662057047992	76.8948118240402	109.006738825972
StdErr	9.20585117666316	29.3474169361 7	23.1846581041205	24.3746478020439

CMPD_SOURCE +

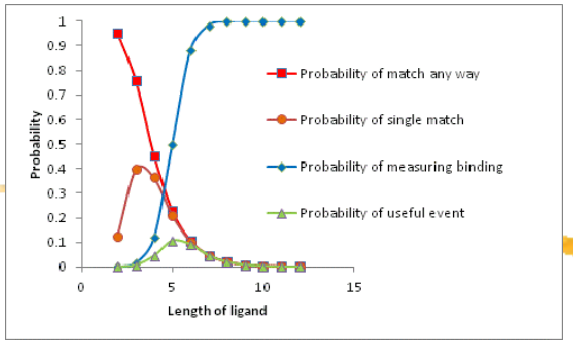
Box Plot



	Diversity Screen	Encoded Library...	Fragment Based...	Knowledge Based Dr...
Count	71	15	9	19
Median	8.22	7.61	5.06	7.41
StdDev	1.82774689502503	1.94321603827999	2.48111869929675	1.86780119031703
StdErr	0.216913649083647	0.50173622362277	0.82703956643225	0.42850298080089

CMPD_SOURCE +

Challenges for Fragments



- **With ever more sensitive detection methods how small should we go with the fragments we screen?**
  - Re-exploring chemistry space is daunting if you get too elemental!
  - Non- additivity requires serendipidity to overcome so don't go too small!
- **The challenge of fragment evolution without structures to guide?**
- **Enabling selective Polypharmacology**
- **Thinking its easy and thus not applying sufficient rigour and discipline to evolving towards a candidate.**
- **Integration not isolation and competition – the real opportunity for all these methods.**

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Medicinal chemistry guidelines

- **Consider the chemical tractability (ligandability) of the target, and if it is poor then investigate different mechanisms of action or different pathways**
- **Select multiple, low-complexity polar starting points with high binding enthalpy, and optimize enthalpically towards the lead compound**
- **Select appropriate metrics for multidimensional optimization; use ligand efficiency and lipophilic efficiency metrics in hit-to-lead optimization and change to more complex metrics emphasizing dosage to support lead optimization**
- **Evaluate available chemistries when entering extensive optimization; prepare what you designed and really want rather than what you can readily synthesize; design, synthesize and use proprietary building blocks rather than depend on chemistry catalogues**
- **Do not be afraid to retrench to a series of lower potency if it has better physicochemical properties, particularly solubility; leave suboptimal scaffolds early; extensive optimization of a scaffold that is not amenable to achieving a desirable balance of potency and ADME (absorption, distribution, metabolism and excretion) properties is likely to be a waste of time and resources**
- **Stay focused on the 'sweet spot' and committed to deliver high-quality compounds, but remain open-minded to the many ways this can be achieved**
- **Resist timelines that compromise compound quality**

The challenge of medicinal chemistry – the role for nature and nurture in lead discovery and optimization
M Hann and G Keseru. Nature Reviews in Drug Discovery. 2012 Apr 30;11(5):355-65

Acknowledgements

- **Many at GSK present and past:**
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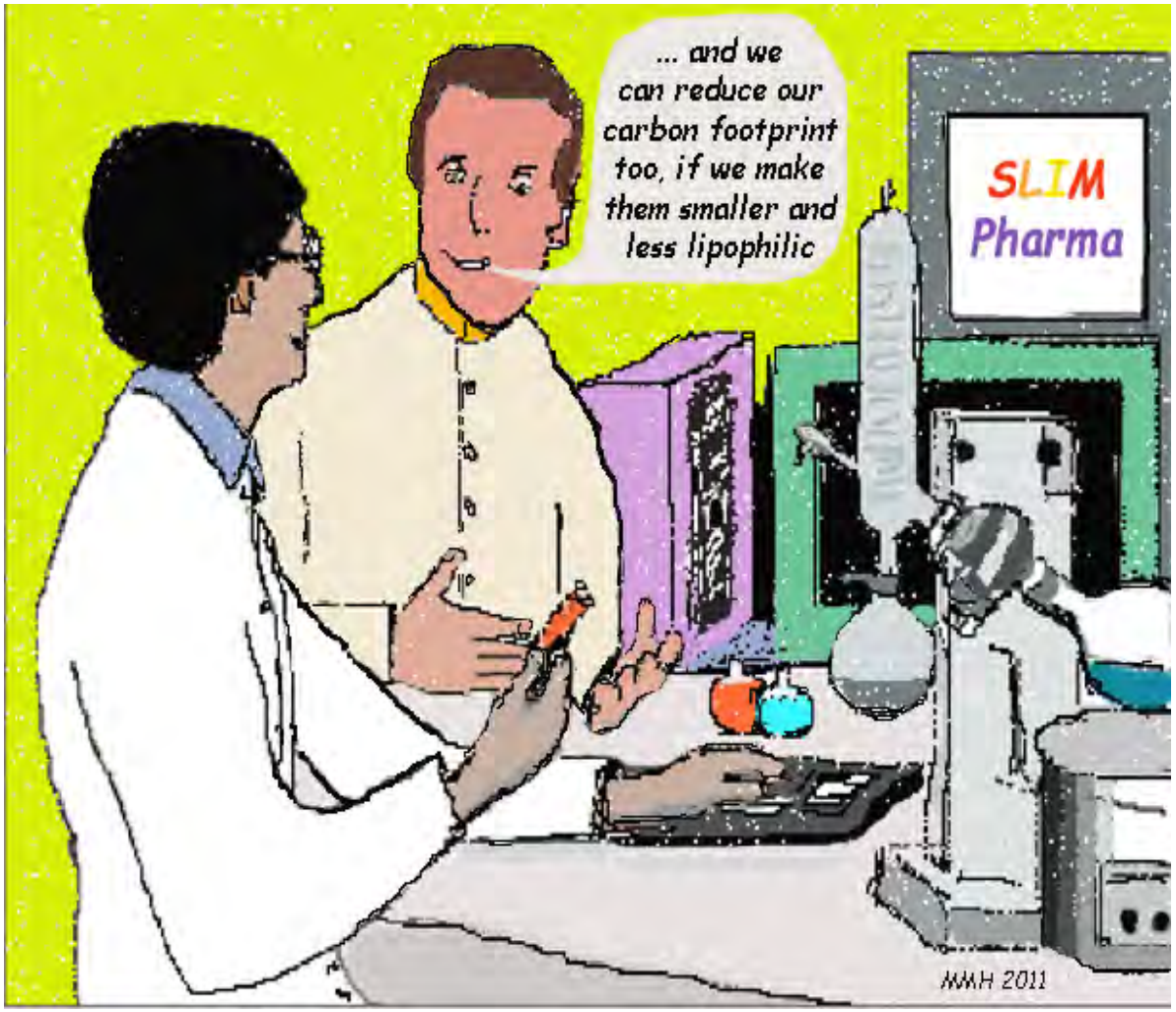
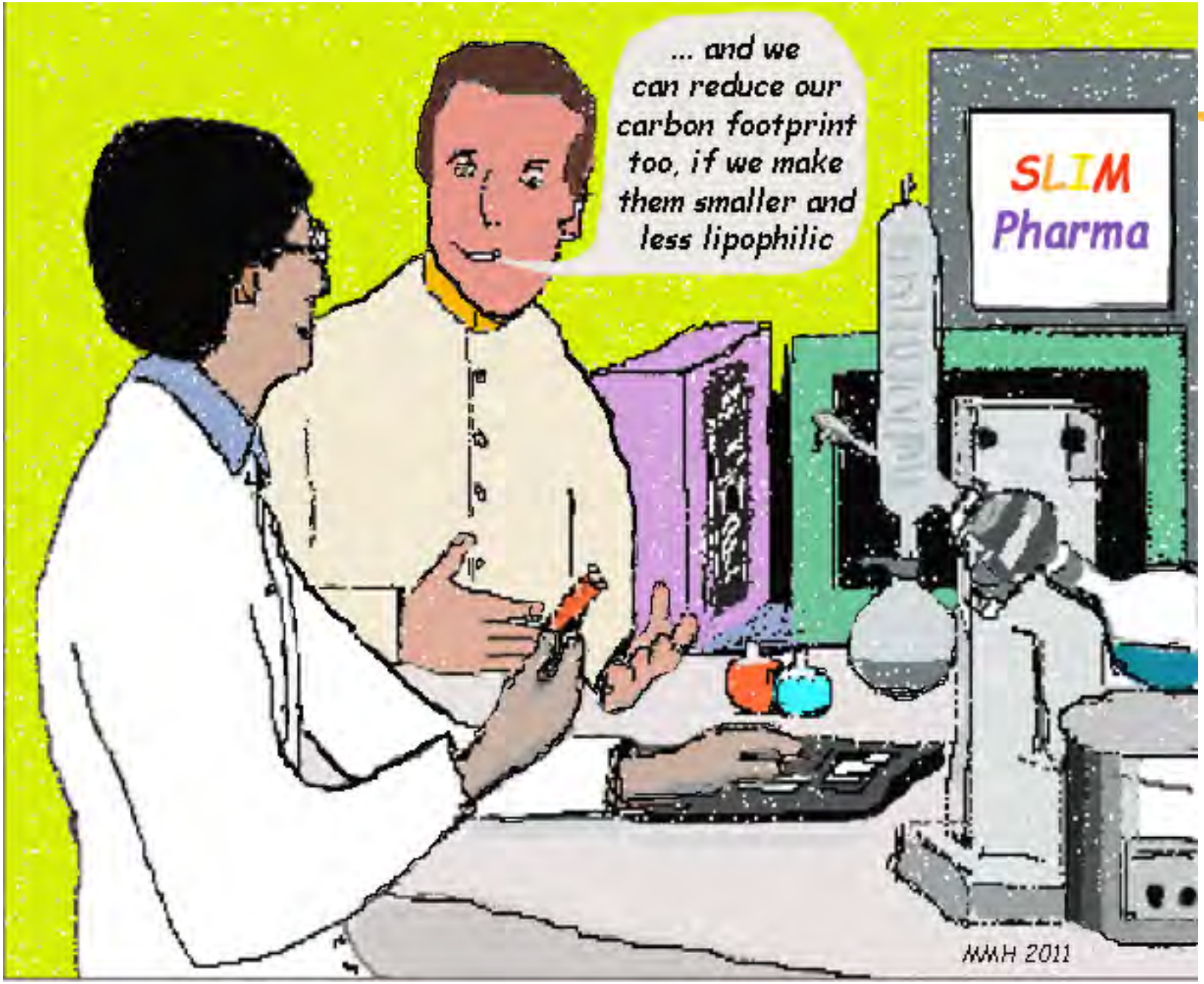
  James Butler, Rob Young,
  Alan Hill, Stephen Pickett, et al
- Anne Hersey, John Bradshaw,
  Gavin Harper, Paul Gleeson,
  Malcolm Weir, Harren Jhoti,
  Barry Morgan



Back ups

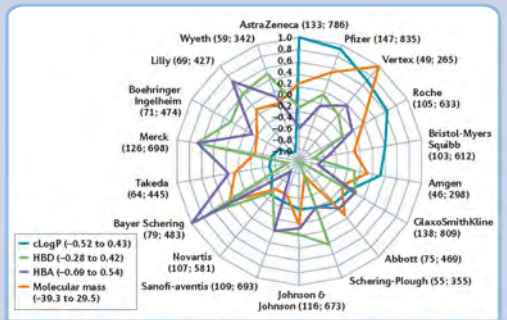
A final thought on Fragment Based Drug Discovery



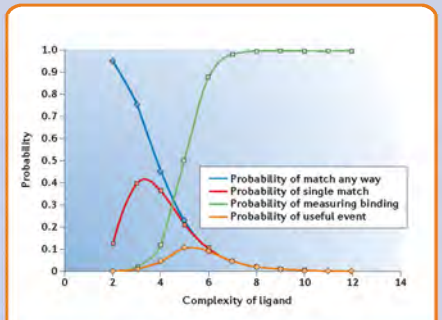
Finding the sweet spot in medicinal chemistry

Michael M. Hann and György M. Keserü

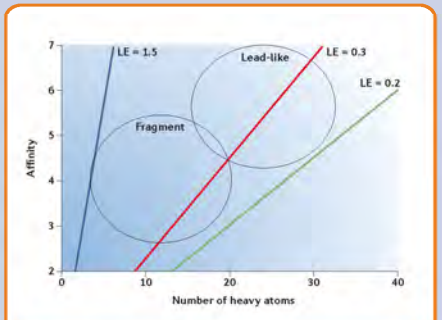
Given its position at the heart of small-molecule drug discovery, medicinal chemistry can have a key role in tackling the well-known productivity challenges in pharmaceutical research and development. In recent years, extensive analyses of successful and failed drug compounds have improved our understanding of the role of physicochemical properties in drug attrition, and clarified the difficulties in finding the 'sweet spot' in lead discovery and optimization. This figure summarizes suggested guidelines for improving compound quality.



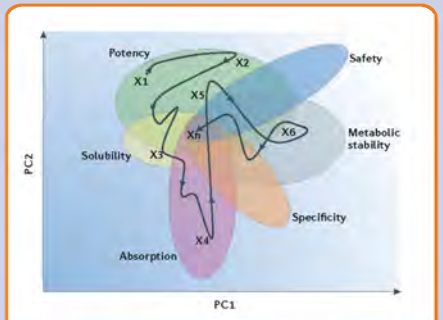
Cultural changes are difficult and need supporting throughout an organization and at all phases. Exchange of views and access to data-driven knowledge are important and will help reduce behavioural 'addictions'. In-depth analysis of drug discovery case studies and success stories contributes substantially to these efforts, and towards the understanding of true compound quality



Select multiple, low-complexity polar starting points with high binding enthalpy, and optimize enthalpically towards the lead compound



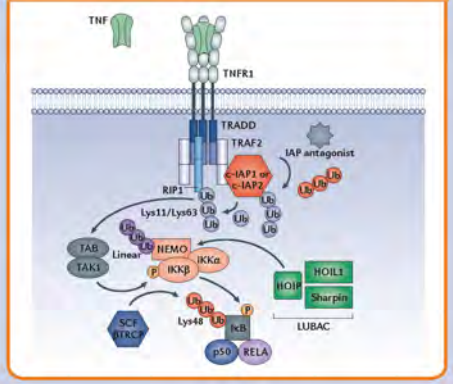
Select appropriate metrics for multidimensional optimization; use ligand efficiency and lipophilic efficiency metrics in hit-to-lead optimization and change to more complex metrics emphasizing dosage to support lead optimization



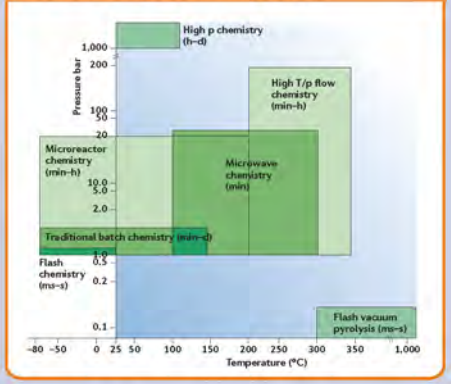
Do not be afraid to revert to a series of lower potency if it has better physicochemical properties. Extensive optimization of a scaffold that is not amenable to achieving a desirable balance of potency and ADME properties is likely to be a waste of time and resources

Target identification → Hit discovery → Lead discovery → Lead optimization → Candidate selection

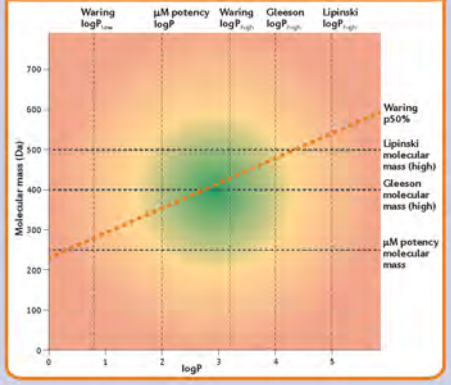
Consider the chemical tractability (ligandability) of the target, and if it is poor then investigate different mechanisms of action or different pathways



Evaluate available chemistries when entering extensive optimization; prepare what you designed and really want rather than what you can readily synthesize; design, synthesize and use proprietary building blocks rather than depend on chemistry catalogues



Stay focused on the 'sweet spot' and committed to deliver high-quality compounds, but remain open-minded to the many ways this can be achieved



Figures depicted in the boxes (numbered from top left to bottom right) are adapted from the following sources: Box 1: Leeson, P. D. & St-Gallay, S. A. The influence of the 'organizational factor' on compound quality in drug discovery. *Nature Rev. Drug Discov.* **10**, 749–765 (2011). The property differences are scaled to either +1, where the company with a positive ('best') property value had the highest magnitude, or −1, where the company with the lowest ('worst') value had the highest magnitude.; Box 2: Leach, A.R. & Hann, M. M. Molecular complexity and fragment-based drug discovery: ten years on. *Curr. Opin. Chem. Biol.* **15**, 489–496 (2011); Box 3: Siegall, G, Ab, E. & Schultz, J. Integration of fragment screening and library design. *Drug Discov. Today* **12**, 1032–1039 (2007); Box 4: Hann, M. M. Molecular obesity, potency and other addictions in drug discovery. *Med. Chem. Commun.* 2, 349–355 (2011); Box 5: Fulda, S. & Vucic. D. Targeting IAP proteins for therapeutic intervention in cancer *Nature Rev. Drug Discov.* **11**, 109–124 (2012); Box 6: Keserű, G. M.; Soós, T. & Kappe, O. C. Anthropomorphic factors in organic chemistry — the missing link between chemical intuition and the available chemistry space. *Nature Chem.* (submitted); Box 7: Hann, M. M. & Keserű, G. M. Finding the sweet spot: the role of nature and nurture in medicinal chemistry. *Nature Rev. Drug Discov.* **11**, 355–365 (2012). The authors are grateful to Pauline Ashley and Mark Whiting (GSK) and Veronika Györfi (Gedeon Richter) for their contribution to the poster design. Abbreviations: ADME, absorption, distribution, metabolism and excretion; clogP; the computed octanol–water partition coefficient; HBD, number of hydrogen bond donors; HBA, number of hydrogen bond acceptors; LE, ligand efficiency defined as the binding free energy per non-hydrogen atom; PC1 and PC2, principal components representing the chemistry space explored in multidimensional optimization programs; X1…Xn, compounds prepared in multidimensional optimization programs.

It’s the dose, stupid!!

- **Concepts such as Drug Efficiency tells us how much of the dose actually is available in the biophase of interest.**
- ***DRUGeff = Biophase Concentration * 100/Dose***

Drug efficiency: a new concept to guide lead optimization programs towards the selection of better clinical candidates. Expert Opinion on Drug Discovery 2010, 5(7), 609-618; S Braggio, D Montanari, T Rossi & E. Rattl

- **And more recently the use of Drug Efficiency Index as a strategy towards low therapeutic dose**
- **DEI = Log[DRUGeff(%)] + pKd**

DEI is a correction of the *in vitro* affinity by the *in vivo* pharmacokinetic potential.

It is a simple descriptor directly connected to efficacy and therapeutic dose with the potential to probe the balance between *in vitro* affinity and ADME properties.

Application of drug efficiency index in drug discovery: a strategy towards low therapeutic dose. Montanari, Dino; Chiarparin, Elisabetta; Gleeson, Matthew Paul; Braggio, Simone; Longhi, Raffaele; Valko, Klara; Rossi, Tino. Expert Opinion on Drug Discovery, Volume 6, Number 9, September 2011 , pp. 913-920(8)

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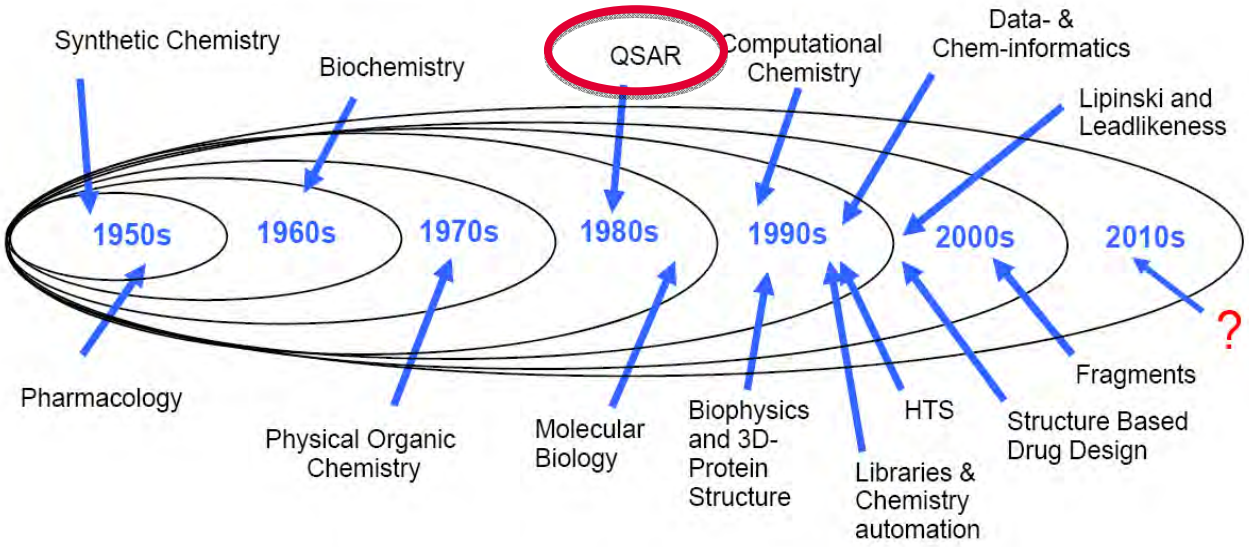
What we have come to know (or rediscover!)

- Large and lipophilic molecules are increasingly seen once more as bad!
- Lipinski's 500/5 for oral bioavailability is increasingly seen as too lenient when it comes to the wider ADMET issues.
- We should be thinking 400/4 as a ceiling for better developability of drugs.



The expanding "sciences" of Medicinal Chemistry

- In hindsight, the rush to numbers as a solution to productivity obscured our collective memory and experience!

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Property Forecast Index

Drug Discovery Today • Volume 16, Numbers 17/18 • September 2011 REVIEWS

TABLE 2

Percentages of compounds achieving defined target values in the various developability assays categorised by PFI or iPFI bins[a]

	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} <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
Promiscuity <5 hits with pIC_{50} >5	85	78	74	65	49	30	20	13	7

POTENCY

Sweet spots for absorption and potency are in conflict with sweet spots for other desirable properties?

Getting physical in drug discovery II: the impact of chromatographic hydrophobicity measurements and aromaticity, RJ Young, DVS. Green, CN. Luscombe, AP Hill, Drug Discovery Today, 16 (17/18), 2011, 822-830

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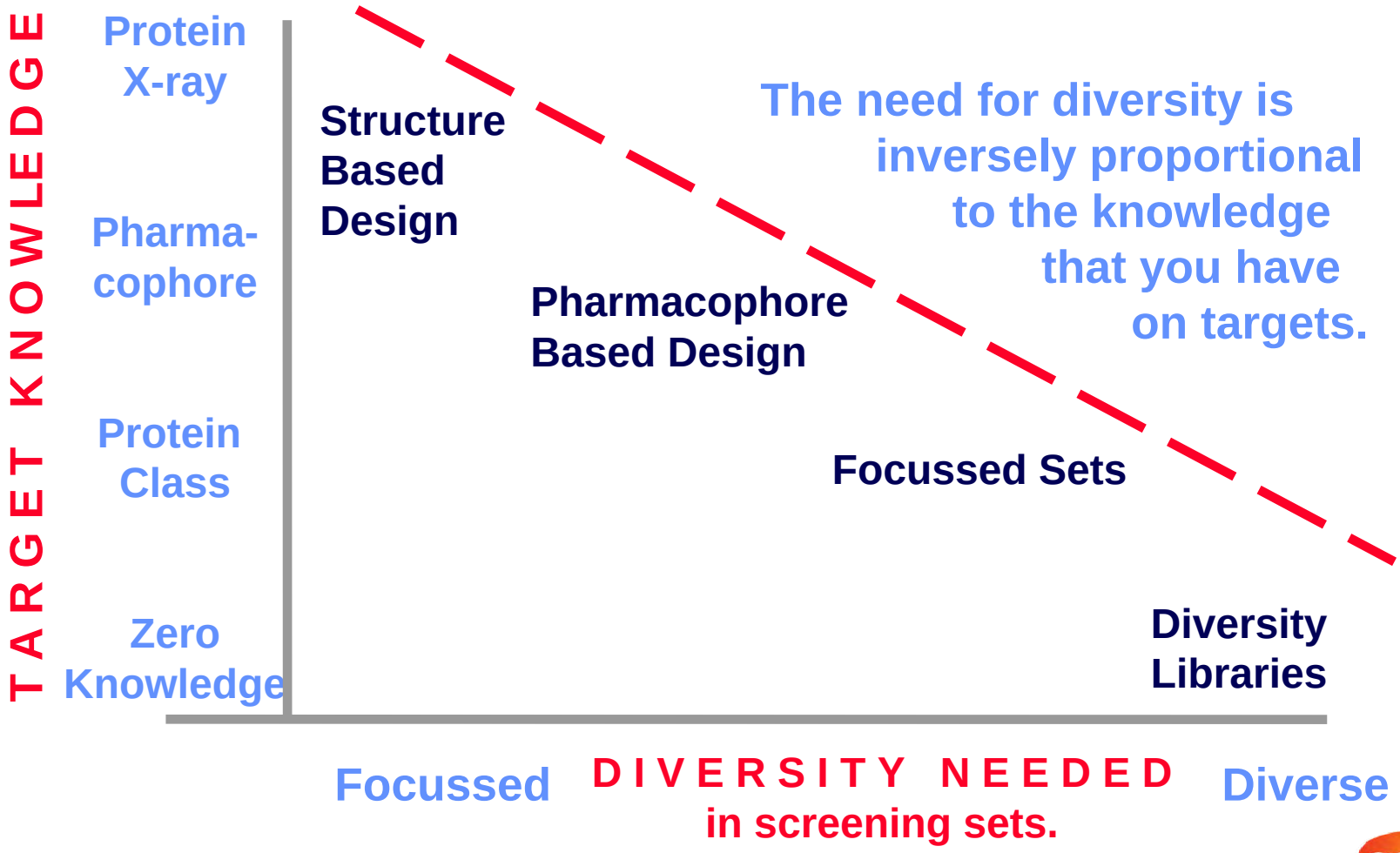
The Knowledge Plot and how it influences Screening Strategies



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The properties of drug molecules are ultimately a compromise between many different and often competing characteristics