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Fragment screening: a comparison with other hit ID methods and challenges

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Comparing leads derived from different hit ID methods – GSK experiences!

- Fragments screening
- HTS – ca. 2m compounds against diverse set of targets – biochemical and cellular.
- DNA encoded libraries technology – billions of compounds each tagged with a unique DNA sequence. Affinity selection so majority of targets screened as immobilized protein.
- Knowledge based. Computational selection of compounds from HTS or external suppliers based on structural or pharmacophore knowledge.

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	Potential Strengths	Potential Weaknesses
Fragment screening	Utilises the reduced complexity approach to increasing hit rate	Very sensitive biophysical methods (SPR, NMR, X-ray etc) needed to detect weak binding.
	Focus is on ligand efficient starting points	Cost of chemistry follow up required to establish a lead quality molecule.
	Efficient sampling of chemical diversity.	Primarily limited to structure enabled targets
	Fragments play to the strengths of structure based design and biophysics which are enabled at the outset	Reductionist approach may over simplify complexity of interactions – i.e cooperativity is lost
	Aims to build only the interactions required	Without continued attention to optimisation indices like LE and LLE it is very easy to waste a good starting point.

*Molecular complexity and fragment-based drug discovery: ten years on. Curr Opin Chem Biol. 2011 , 489-96. Leach AR, Hann MM
Introduction to fragment-based drug discovery. Erlanson, D.A. Top. Curr. Chem., 2012, 317, 1-32

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	Potential Strengths	Potential Weaknesses
Focussed screening	In silico selections possible from the widest diversity of tangible compounds using 2D or 3D selection methods	Prior knowledge of target may be wrong or limiting!
	Acoustic dispensing makes cherry picking from in house collections viable	Even state of the art virtual screening methods suffer from false positives and negatives. Docking and scoring algorithms still poor
	Good availability of diverse compounds from suppliers	

	Potential Strengths	Potential Weaknesses
DNA Encoded Libraries Technology	Huge numbers of compounds can be screened > 10^9	Chemistry must tolerate water and oxygen. Reactions can be done with 70-80% organic co-solvents (e.g., CH_3CN, DMF, DMA, etc.)
	Affinity selection and thus tends to identify highly selective, very potent compounds. Frequently with unique mechanisms of action	Complexity, size and lipophilicity of molecules tends to be high. This is Inherent in split-and-pool strategies, increasing the number of quality molecules in the library also comes with the downside of incorporating others with high MW, lipohilicity.
	Efficient screening process with minimal infrastructure compared to HTS	Encoded libraries cover pockets of chemical space in significant depth, but have not yet reached the diversity of chemical space covered by HTS collections
	Linker attachment point is an advantage for use of the molecule as probe or in bi-functional molecules	Cost of chemistry to confirm hits off DNA

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

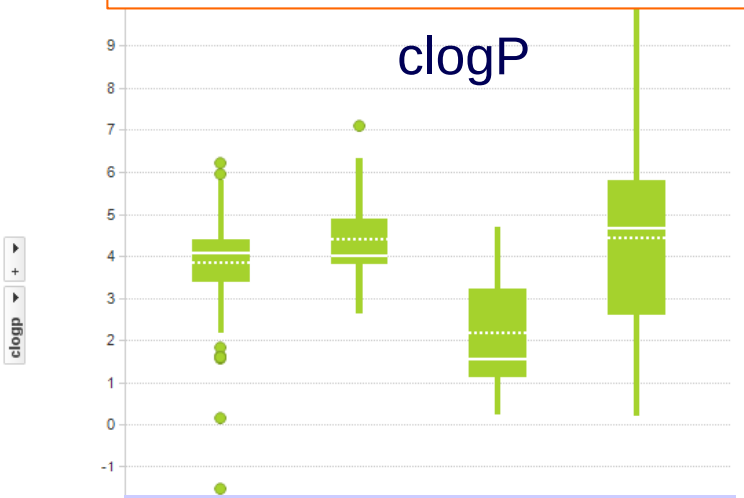
	Potential Strengths	Potential Weaknesses
High Throughput Screening	Diversity and breadth of chemotypes considered is very high with proven track record of delivering most diverse leads	Compound collection costs are high due to replacing compounds and adding new diversity. Cost of capital equipment for collection storage and screening
	Complex molecules display intramolecular cooperativity which may be absent in fragments.	The need to miniaturise assay can cost time and impact quality leading to high false positive rate. Combined with scale, creates need for orthogonal assay development and triage for follow up.
	Robustness based on automation and miniaturisation	Perception of dated approach although success rate suggests this is erroneous in terms of impact
	Broadly applicable to both biochemical and cellular assays	Seen as expensive and slow but not so once infrastructure is in place.

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.

Physical properties of leads derived from different hit ID methods.

Box Plot

clogP

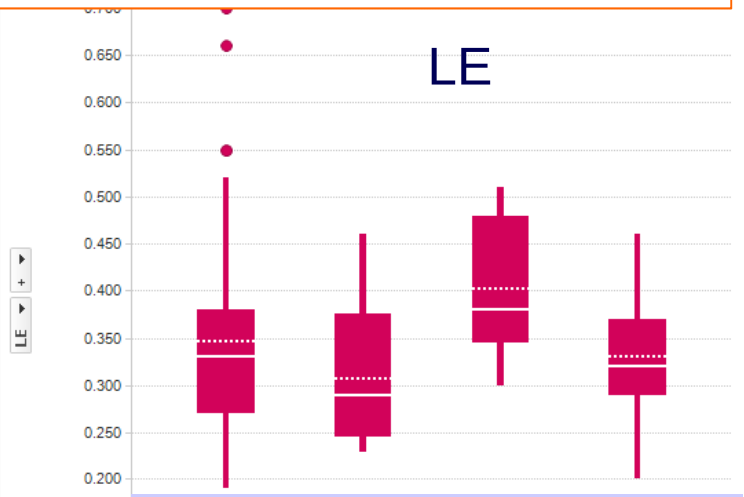


	HTS	Encoded libraries	Fragment	Focussed
Count	71	15	11	20
Median	4.078	4.006	1.555	4.649
StdDev	1.32908725779499	1.25957245958793	1.52717662847015	2.20511756161124
StdErr	0.157733637969026	0.325220210621 ...	0.460461078657 ...	0.493079276614132

CMPD_SOURCE

Box Plot

LE

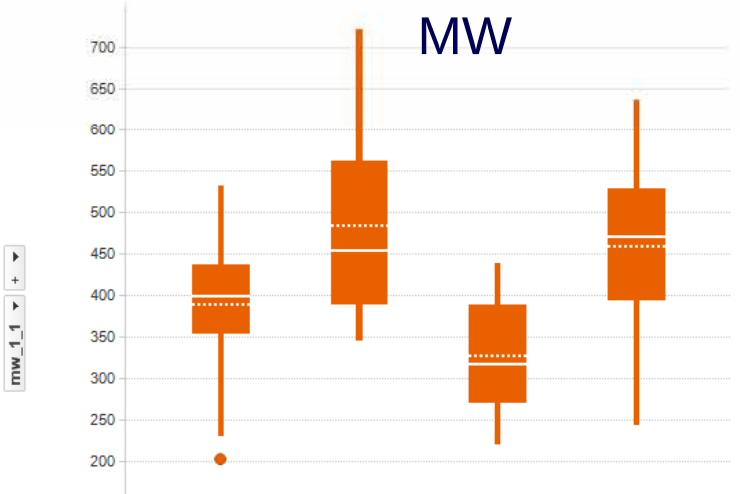


	HTS	Encoded libraries	Fragment	Focussed
Count	68	15	11	19
Median	0.33	0.29	0.38	0.32
StdDev	0.102022889029202	0.076482179686 ...	0.078589844358 ...	0.0742722981265953
StdErr	0.0123720925793549	0.019747613880 ...	0.023695729642 ...	0.017039233780966

CMPD_SOURCE

Box Plot

MW

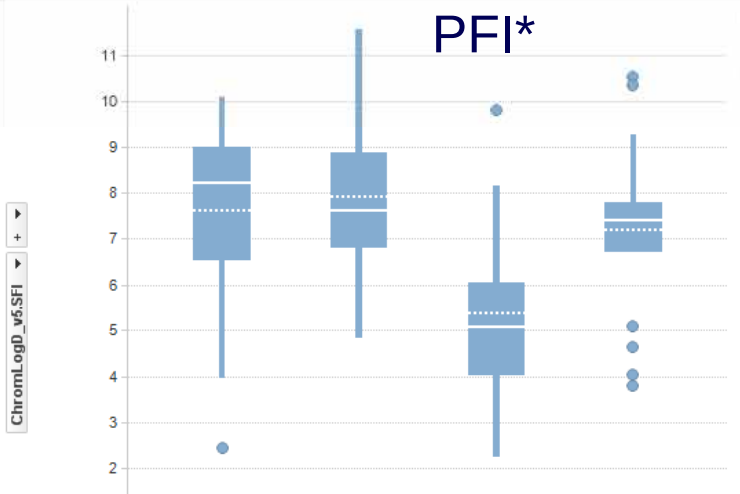


	HTS	Encoded libraries	Fragment	Focussed
Count	71	15	11	20
Median	399.45	453.93	315.4	470.06
StdDev	77.5698808041356	113.662057047992	76.8948118240402	109.006738825972
StdErr	9.20585117666316	29.3474169361 7	23.1846581041205	24.3746478020439

CMPD_SOURCE

Box Plot

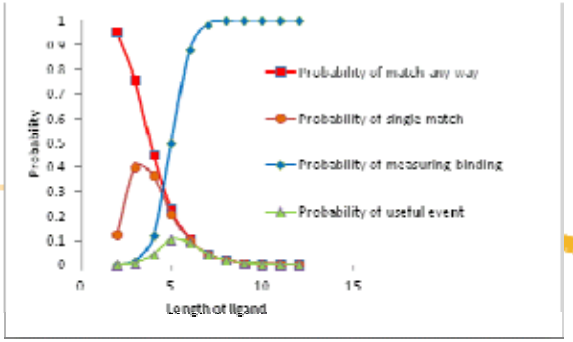
PFI*



	HTS	Encoded libraries	Fragment	Focussed
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

*PFI = Property Forecast Index = logD7.4 + # Aromatic rings . DDT 2011,16, 823-830. Young et al.

Challenges for Fragments



- **With ever more sensitive detection methods how small should we go with the fragments we screen?**
  - Re-expanding into 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 applying insufficient rigour and discipline to evolve towards a quality candidate.**
- **Integration not isolation and competition – the real opportunity for all these methods.**

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Medicinal chemistry guidelines and "fragment opportunities"

- **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' of optimal activity and physchem properties, 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 biggest challenge for fragments?**

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

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