INTRODUCTION TO "FBDD"

BACKGROUND

Thorsten Nowak

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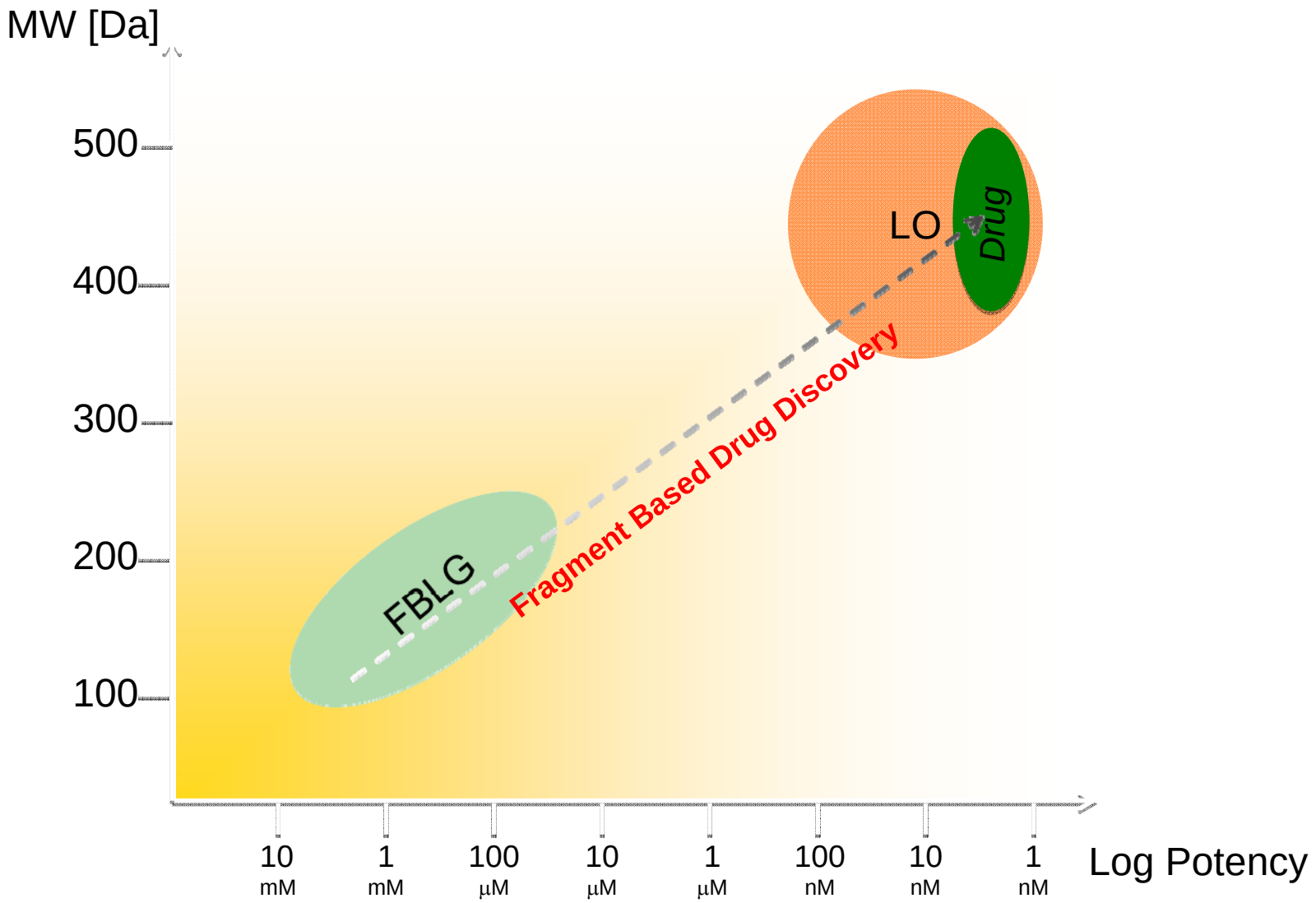
What is FBDD all About?

What is “FBDD”?


MW [Da]
500
400
300
200
100
LO
Drug
Fragment Based Drug Discovery
FBLG
10 mM
1 mM
100 µM
10 µM
1 µM
100 nM
10 nM
1 nM
Log Potency

Where Does "FBDD" Come From?

- By early 1980s
  - ✓ Jencks "On the Attribution and Additivity of Binding Energies"
    - *Proc. Nat. Acad. Sci. USA* (1981), **78** (**7**). 4046-4050.
    - ΔG= - RTlnK => twice the energy – square the affinity

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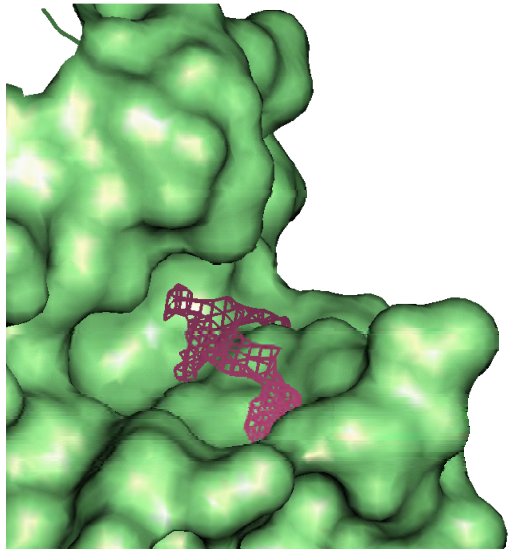
  - ✓ Peter Goodford and GRID – computation to map where functional groups could bind to active sites
    - Goodford, *J. Med. Chem.* (1985), **28**, 849
    - Example of OH probe on surface of lysozyme



Courtesy of Rod Hubbard

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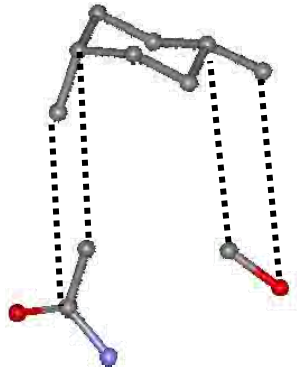
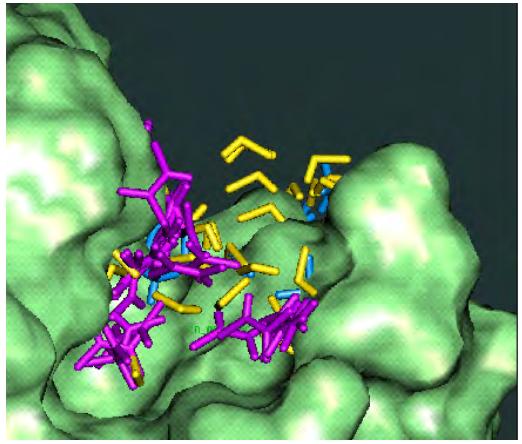
- Early 1990s – linking fragments by computer
  - ✓ Bartlett - the Caveat program
  - ✓ Karplus, Miranker, Eisen, Hubbard – MCSS / Hook
    - Karplus and Miranker, *Proteins* (1991), **11**, 29.
    - Eisen et al. *Proteins* (1994), **19**, 119.
    - English, Groom & Hubbard, *Prot Eng,* (2001), **14**, 47.





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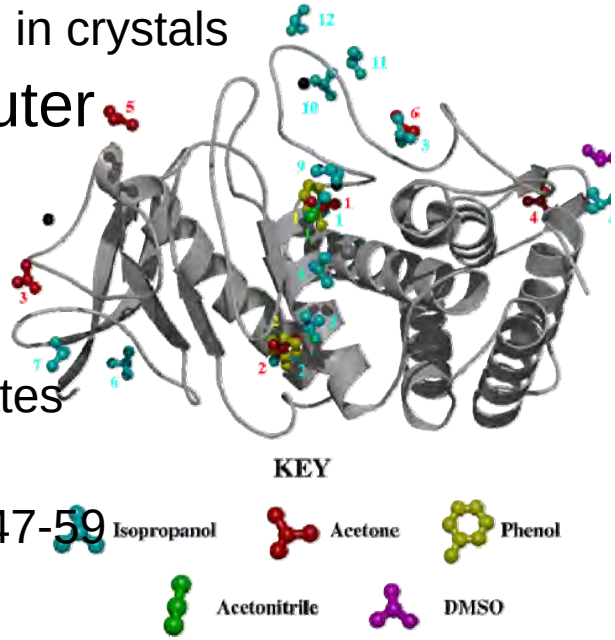
- 1990s
  - ✓ Ringe – Xray mapping of solvent binding to active sites
  - ✓ Extended to other systems and titrated (affinity?)
  - ✓ English, Groom & Hubbard, *Prot. Eng.*, (2001), **14**, 47-59



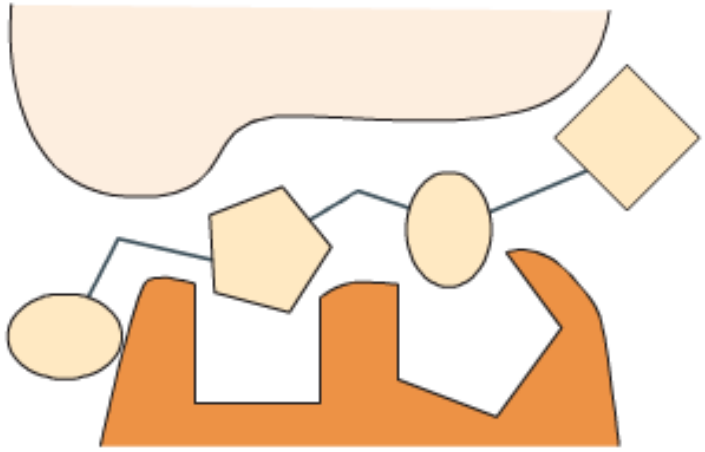
Where Does "FBDD" Come From?

- 1996 - SAR by NMR from Abbott group (Fesik and Hajduk)
- 1999 - SAR by Xray from Abbott group (Nienaber)
- Late 1990s / early 2000s
  - ✓ Big pharma for targets that failed HTS
    - ➢ Roche, Novartis, AZ
  - ➢ Small technology oriented companies started developing the methods (Astex, Vertex, RiboTargets (Vernalis), SGX, Plexxikon, …….)
- Additional conceptual framework developed
  - ✓ Hann et al analysis of compound size, complexity and finding hits (*J. Chem. Inf. Comp. Sci.* **2001**, *41*, 856-864.)
  - ✓ Ligand efficiency
  - ✓ Kuntz and maximal affinity – (*PNAS*, **1999**, *96*, 9997-10002.)
  - ✓ Ligand Efficiency – DG / HAC – (*Drug Disc Today*, **2004,** *9*, 430-431.)
- Mid-2000s
  - ✓ A number of fragment-derived compounds selected for clinical trials
  - ✓ Unlike many other technologies – methods developed and relevance understood (with minimal hype) before large-scale take-up

Why Do “FBDD”?

Potency
μM -> nM

Properties
ADMET What is a real hit



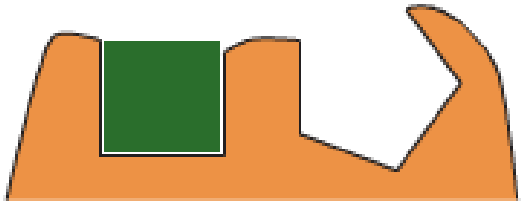
Poor Fit to Target
Need to “deconstruct”

Relevance of Chemical Space
Need for millions..

Low absolute Potency
High Lig. Eff.
mM -> μM

Poor Fit to ***any*** Target
Need to “construct”

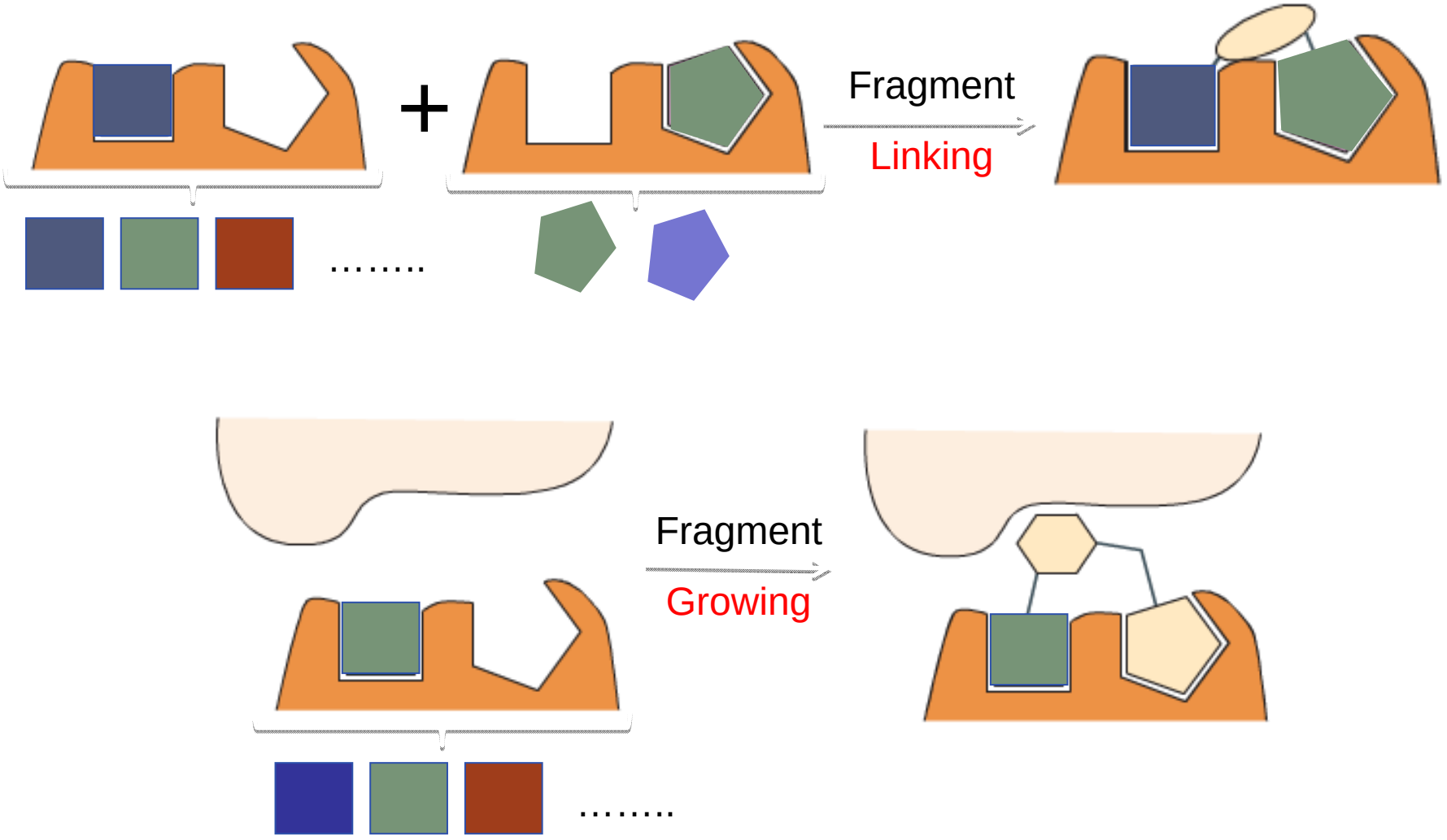
Excellent Properties
ADMET What is a real hit



Ultimate Relevance of Chemical Space
Hundreds -> Thousands

Rees, D.; Congreve, M.; Murray, C.; Carr, R. Fragment-based lead discovery. Nature reviews. Drug discovery (2004), **3**, 660–72.

Strategy of Fragment Exploitation



Rees, D.; Congreve, M.; Murray, C.; Carr, R. Fragment-based lead discovery. Nature reviews. Drug discovery (2004), **3**, 660–72.

What Are The Advantages & Principles Of FBDD?

- Complexity of large molecules
- Coverage of chemical space with conventional lead like libraries
- Ligand Efficiency and other considerations
- Fragment expansion strategies

Molecular Complexity: Hann, M.; Leach, A.; Harper, G. Journal of chemical information and computer sciences (2001**)**, **41**, 856–64.

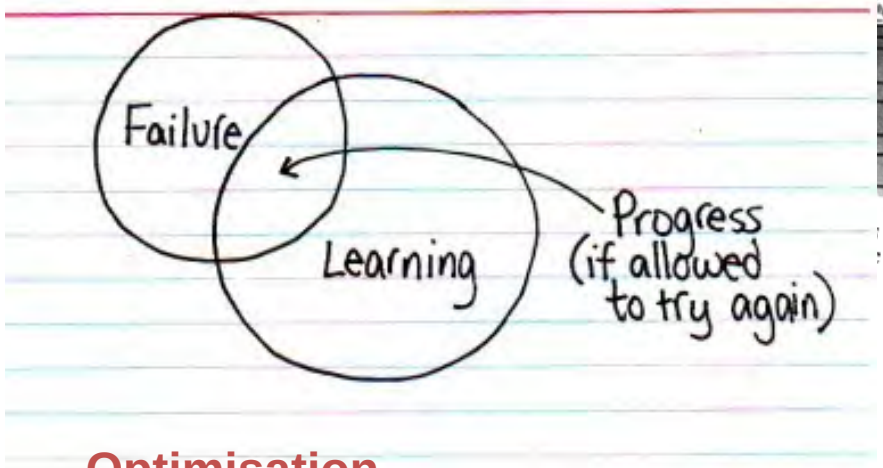
What Do You Need?

Target

Library

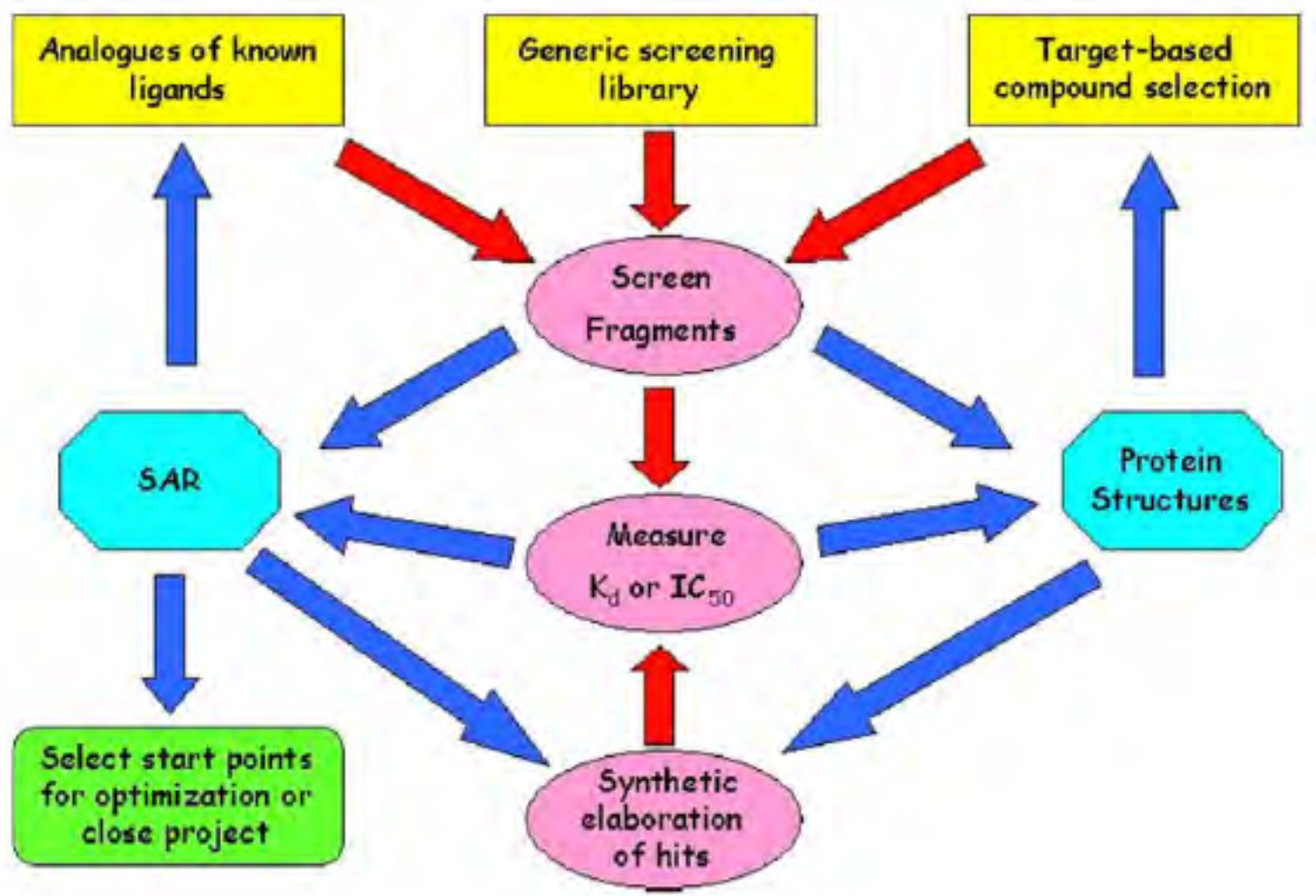
conducting an experiment to test the
discoveries were hit on by accident"

Screening



Optimisation

How Is It Done? – Principal Workflow



Blomberg, N.; Cosgrove, D.; Kenny, P.; Kolmodin, K. Journal of computer-aided molecular design (2009), **23**, 513–25.

What Are The Main Pitfalls?

- Reliable assessment of technical feasibility of a new target
- Time from Gen-to-Structure
- Need for reliable affinity and high concentration biochemical assay
- SBDD – expertise

Glossary

- **LE** = Ligand Efficiency
- **LLE** = Lipophilicity Ligand Efficiency
- **SBDD** = Structure Based Drug Design
- **FBDD** = Fragment Based Drug Discovery
- **FBLG** = Fragment Based Lead Generation

Definitions

Ligand Efficiency

- ✓ Scaling factor to correct affinity/potency for size

Fragment Growing

- ✓ Building new interactions into fragment start points; expanding into neighbouring pockets

Fragment Linking

- ✓ Tether fragment screening hits together that bind in adjacent pockets, thus adding the affinities of the individual fragments -> Potency jumps

Affinity Screening

- ✓ Screening of molecule applying a biophysical approach which will determine the dissociation constant (k_D) as a measure of affinity i.e. how tightly a molecule binds to a target.

“Efficiency” Indices

Type	Metrics	Definition	Use	Reference
Ligand efficiency	LE	-RTln(K_d or pK_i)/HA	Prioritization of starting points, early optimization	Hopkins AL, Groom CR, Alex A. Drug Discov Today 2004;9(10):430-1
	BEI	(pK_i or pK_d)/MW		Abad-Zapatero C, Metz JT. Drug Discov Today 2005;10(7):464-9
Size independent ligand efficiency	FQ	LE/(0.0715 + 7.5328/HA+25.7079/$(HA)^2$+ –361.4722/$(HA)^3$	Size unbiased comparison of compounds in early optimization	Reynolds CH, Tounge BA, Bembenek SD. J Med Chem 2008;51(8):2432-8
	%LE	LE/($1.614^{log2(10/HA)}$)*100		Orita M, Ohno K, Niimi T. Drug Discov Today 2009;14(5-6):321-8
	SILE	-RTln(pK_i)/$(HA)^{03}$		Nissink JWM. J Chem Inf Model 2009;49(6):1617-22
Lipophilic ligand efficiency	LLE	pK_i - cLogP (or LogD)	Control of lipophilicity in lead optimization	Leeson PD, Springthorpe B. Nat Rev Drug Discov 2007;6(11):881-90
	LLE_{Astex}	0.11*ln(10)*RT(logP-log(K_d or pK_i or IC_{50})/HA	Lipophilic efficiency assessment for fragments	Paul N. Mortenson • Christopher W. Murray J Comput Aided Mol Des DOI 10.1007/s10822-011-9435-z
	LELP	logP/LE	Control lipophilicity in optimization, assessment of druglikeness	Keseru GM, Makara GM. Nat Rev Drug Discov 2009;8(3):203-12
Enthalpic efficiency	EE	ΔH/HA	Enthalpy driven potency optimization	J. E. Ladbury, G. Klebe, E. Freire *Nature Rev. Drug Disc*. **2010**, *9*, 23-27
	SIHE	(-$\Delta H/40$*2.303*RT)* $HA^{0.3}$	Size independent assessment of binding enthalpy contributions	G. G. Ferenczy, G. M. Keserű, *J. Chem. Inf. Comput. Sci.* **2010**, *50*, 1536-1541
Complex metrics	MPO	clogP, clogD pH=7.4, MW, TPSA, HBD, pK_a	Supporting the optimization of CNS compounds	Travis T. Wager, Xinjun Hou, Patrick R. Verhoest, and Anabella Villalobos ACS Chem. Neurosci. (2010), 1, 435–449
	CSE	in vitro promiscuity and toxicity data, cLogP, TPSA and pK_a	Control toxicity related attrition	Kevin Dack, Designing Safer Medicines in Discovery symposium, SCI, , 17th March 2011
	DRUGeff	Biophase Concentration * 100/Dose	Estimation of in vivo efficacy in combination with *in vitro* potency	Expert Opinion on Drug Discovery 2010, 5(7), 609-618; S Braggio, D Montanari, T Rossi & E. Ratti

Hann, M.; Keserü, G. Finding the sweet spot: the role of nature and nurture in medicinal chemistry. *Nature reviews. Drug discovery* (2012), **11**, 355–65.

Some Literature

- **Web Resources:** Fragment Blog Practical Fragment by Dan Erlanson: http://practicalfragments.blogspot.co.uk
- **Web Resources:** Fragment-Based Drug Discovery & Molecular Design by Pete Kenny: http://fbdd-lit.blogspot.co.uk
- **General Review:** Rees, D.; Congreve, M.; Murray, C.; Carr, R. Fragment-based lead discovery. Nature reviews. Drug discovery (2004), **3**, 660–72.
- **General Review:** Albert, J.; Blomberg, N.; Breeze, A.; Brown, A.; Burrows, J.; Edwards, P.; Folmer, R.; Geschwindner, S.; Griffen, E.; Kenny, P.; Nowak, T.; Olsson, L.-L.; Sanganee, H.; Shapiro, A. An integrated approach to fragment-based lead generation: philosophy, strategy and case studies from AstraZeneca's drug discovery programmes. *Current topics in medicinal chemistry* (2007), **7**, 1600–29.
- **Molecular Complexity:** Hann, M.; Leach, A.; Harper, G. Molecular complexity and its impact on the probability of finding leads for drug discovery. Journal of chemical information and computer sciences (2001**)**, **41**, 856–64.
- **Fragment Library Design:** Blomberg, N.; Cosgrove, D.; Kenny, P.; Kolmodin, K. Design of compound libraries for fragment screening. *Journal of computer-aided molecular design* (2009), **23**, 513–25.
- **Fragment Library Design:** Brewer, M.; Ichihara, O.; Kirchhoff, C.; Schade, M.; Whittaker, M. Assembling a Fragment Library. *Fragment-Based Drug Discovery: A Practical Approach* (2008), 39–62.
- **Critical retrospective:** Hajduk, P.; Greer, J. A decade of fragment-based drug design: strategic advances and lessons learned. *Nature reviews. Drug discovery* (2007), **6**, 211–9.
- **Efficiency indices:** Hann, M.; Keserü, G. Finding the sweet spot: the role of nature and nurture in medicinal chemistry. *Nature reviews. Drug discovery* (2012), **11**, 355–65.
- **Efficiency indices:** Andrew L. Hopkins, Colin R. Groom, Alexander Alex, Ligand efficiency: a useful metric for lead selection, Drug Discovery Today, (2004) **9**, 430.
- **Structure Based Drug Design:** Böhm, H.-J.; Klebe, G.; What Can We Learn from Molecular Recognition in Protein–Ligand Complexes for the Design of New Drugs?. Angew. Chem. Int. Ed. Engl. (1996), **35**, 2588
- **Structure Based Drug Design:** Bissantz, C.; Kuhn, B.; Stahl, M. A medicinal chemist's guide to molecular interactions. *Journal of medicinal chemistry (*2010), **53**, 5061–84.