# FRAGMENTS 2015
# RSC BMCS Workshop
# March 3rd

## INTRODUCTION TO
## FBLG/FBDD – BACKGROUND

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# What is FBDD all About?


# Where Does “FBDD” Come From?

- By early 1980s
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Courtesy of Rod Hubbard

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    - Goodford, *J. Med. Chem.* (1985), **28**, 849
    - Example of OH probe on surface of lysozyme

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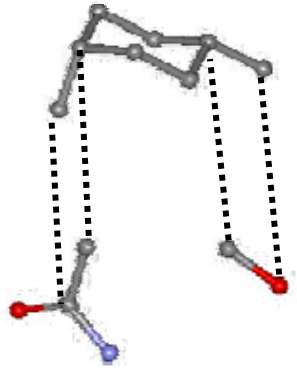
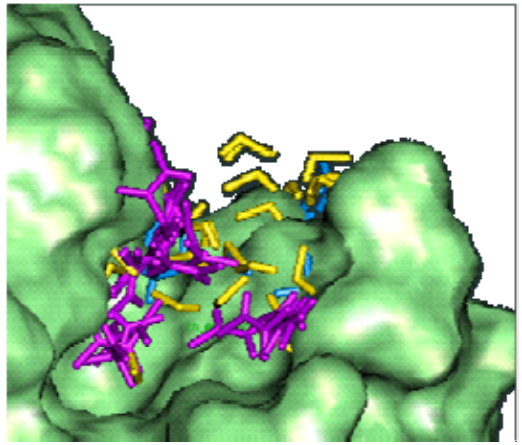
  - ✓ Karplus, Miranker, Eisen, Hubbard – MCSS / Hook
    - Karplus and Miranker, *Proteins* (1991), **11**, 29.
    - Eisen et al. *Proteins* (1994), **19**, 119.
    - English, Groom & Hubbard, *Prot Eng,* (2001), **14**, 47.





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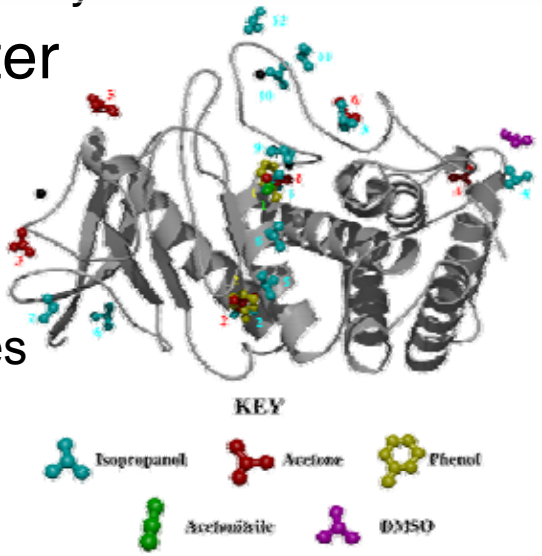
- 1990s
  - ✓ Ringe – Xray mapping of solvent binding to active sites
    - English, Groom & Hubbard, *Prot. Eng.*, (2001), **14**, 47-59

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- 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.)
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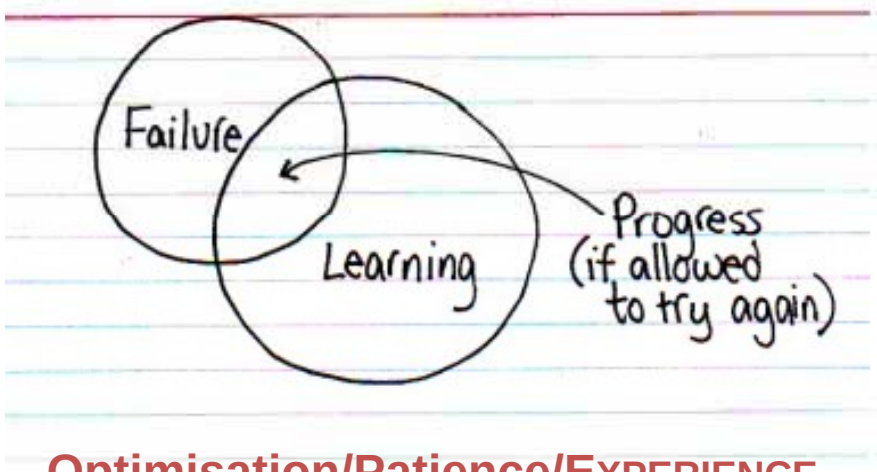
# What Do You Need?

**Target**


**Library**

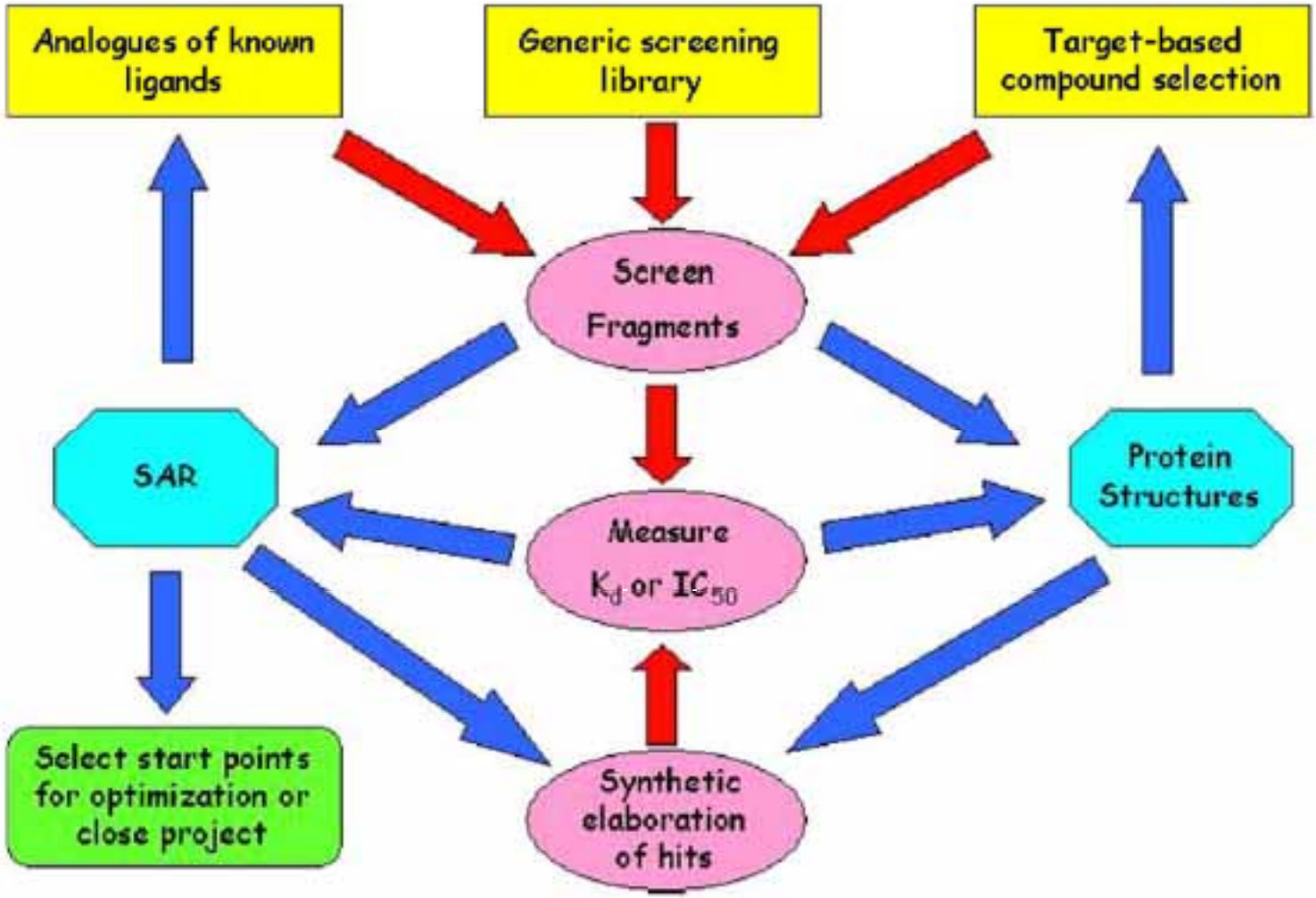
*conducting an experiment to test the discoveries were hit on by accident"*

**Screening**



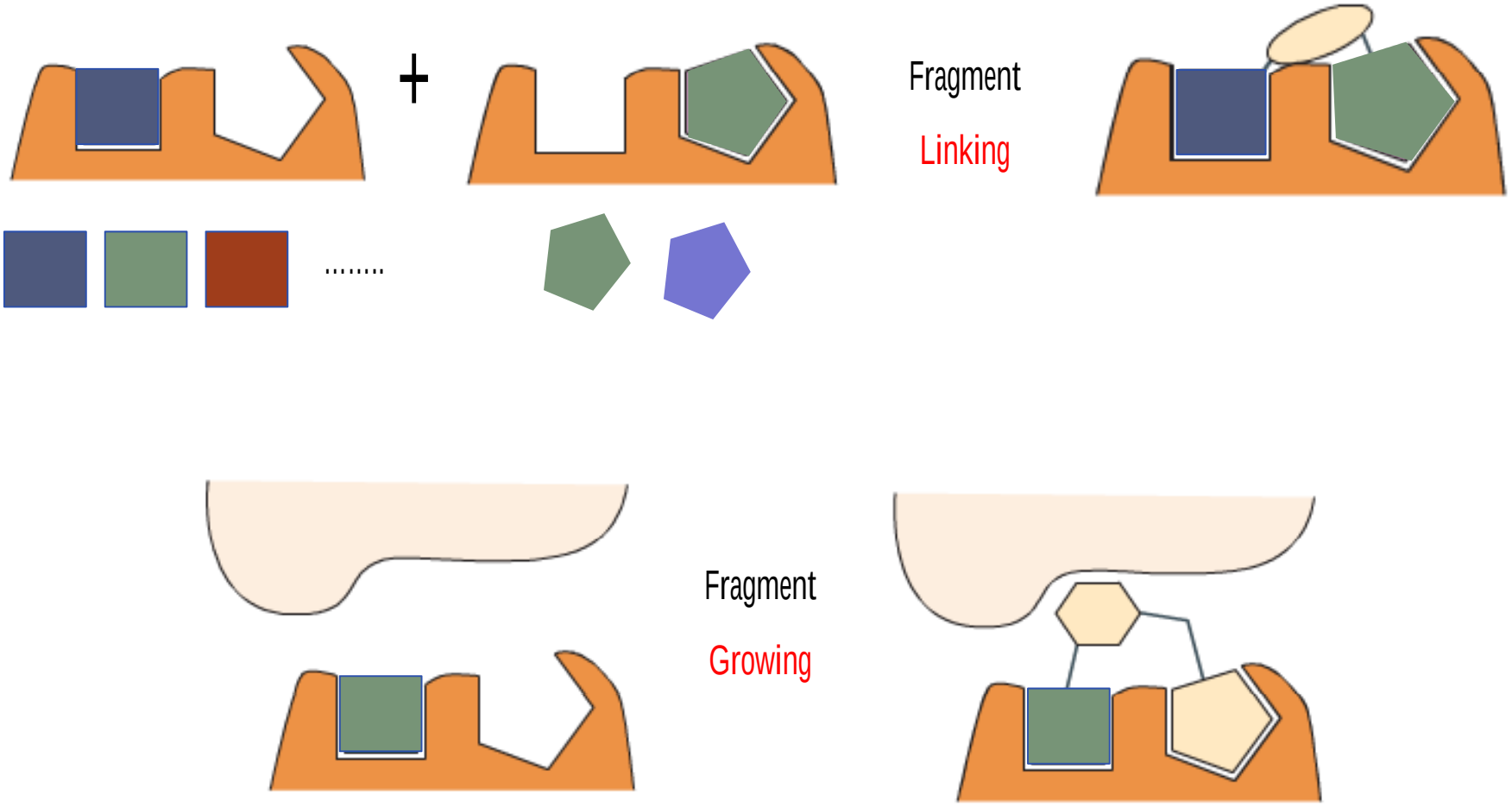

**Optimisation/Patience/EXPERIENCE**

# How Is It Done? – Principal Workflow



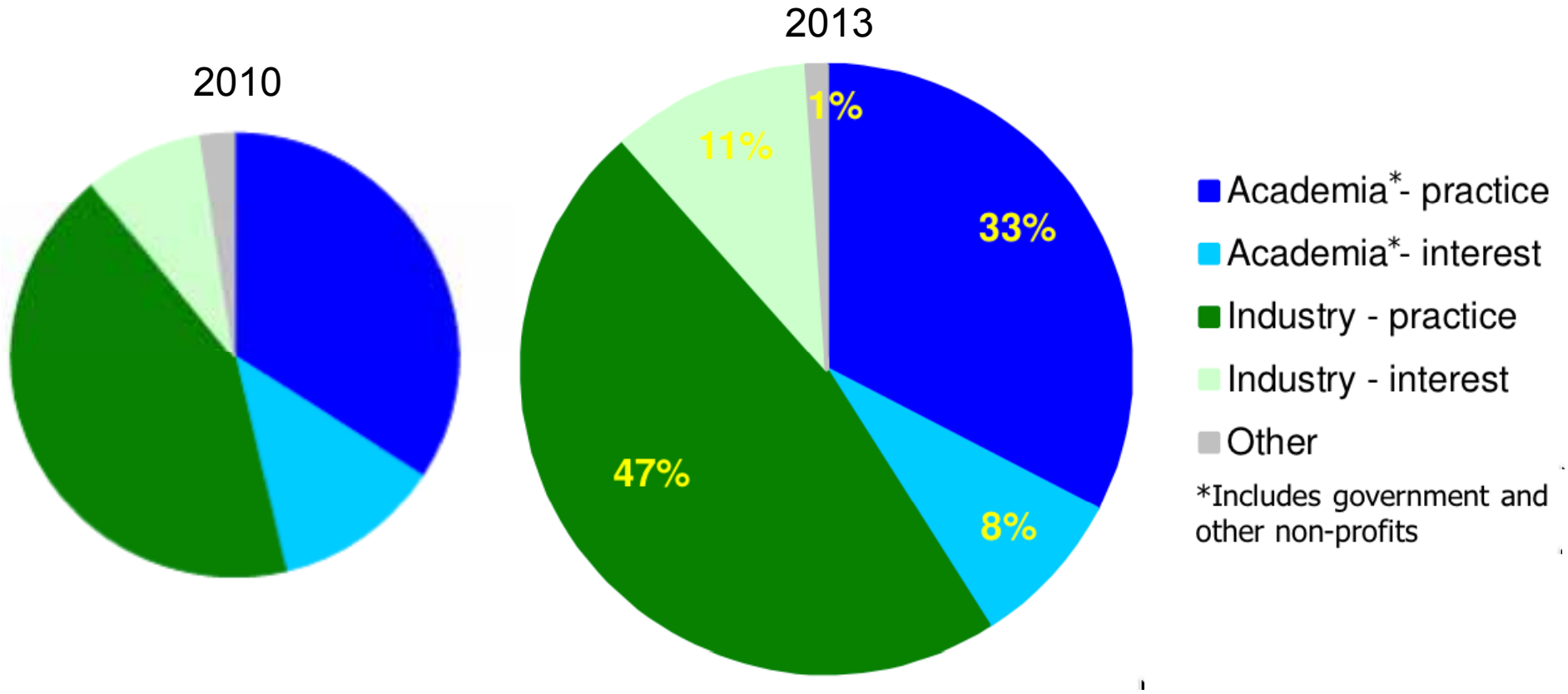

Blomberg, N.; Cosgrove, D.; Kenny, P.; Kolmodin, K. Journal of computer-aided molecular design (2009), **23**, 513–25.

# Strategies of Fragment Exploitation




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

# Where is FBDD Applied?




Taken from a poll carried out on Practical Fragments (2013) and is based on 95 responses
http://practicalfragments.blogspot.co.uk/2014/01/poll-results-affiliation-fragment.html

# FBDD Impact – Business

| Drug | Company | Target |
|---|---|---|
| **Approved!** | | |
| Vemurafenib | Plexxikon | B-Raf(V600E) inhibitor |
| **Phase 3** | | |
| ABT-199 | Abbott | Selective Bcl-2 inhibitor |
| LEE011 | Novartis/Astex | CDK4 inhibitor |
| MK-8931 | Merck | BACE1 inhibitor |
| **Phase 2** | | |
| AT13387 | Astex | HSP90 inhibitor |
| AT7519 | Astex | CDK1,2,4,5 inhibitor |
| AT9283 | Astex | Aurora, Janus kinase 2 inhibitor |
| AUY922 | Vernalis/Novartis | HSP90 inhibitor |
| AZD3293 | AstraZeneca/Astex/Lilly | BACE1 inhibitor |
| AZD5363 | AstraZeneca/Astex/CR-UK | AKT inhibitor |
| Indeglitazar | Plexxikon | pan-PPAR agonist |
| Linifanib (ABT-869) | Abbott | VEGF & PDGFR inhibitor |
| LY2886721 | Lilly | BACE1 inhibitor |
| LY517717 | Lilly/Protherics | FXa inhibitor |
| Navitoclax (ABT-263) | Abbott | Bcl-2/Bcl-xL inhibitor |
| PLX3397 | Plexxikon | FMS, KIT, and FLT-3-ITD inhibitor |

http://practicalfragments.blogspot.co.uk/2015/01/fragments-in-clinic-2015-edition.html

# FBDD Impact – Business

| Drug | Company | Target |
|---|---|---|
| **Phase 1** | | |
| ABT-518 | Abbott | MMP-2 & 9 inhibitor |
| ABT-737 | Abbott | Bcl-2/Bcl-xL inhibitor |
| AT13148 | Astex | AKT p70S6K inhibitor |
| AZD3839 | AstraZeneca | BACE1 inhibitor |
| AZD5099 | AstraZeneca | Bacterial topoisomerase II inhibitor |
| DG-051 | deCODE | LTA4H inhibitor |
| IC-776 | Lilly/ICOS | LFA-1 inhibitor |
| JNJ-42756493 | J&J/Astex | FGFr inhibitor |
| LP-261 | Locus | Tubulin binder |
| LY2811376 | Lilly | BACE1 inhibitor |
| PLX5568 | Plexxikon | kinase inhibitor |
| (RG-7129) | Roche | BACE1 inhibitor |
| SGX-393 | SGX | Bcr-Abl inhibitor |
| SGX-523 | SGX | Met inhibitor |
| SNS-314 | Sunesis | Aurora inhibitor |
| Undisclosed | Vernalis/Servier | Bcl-2 inhibitor |

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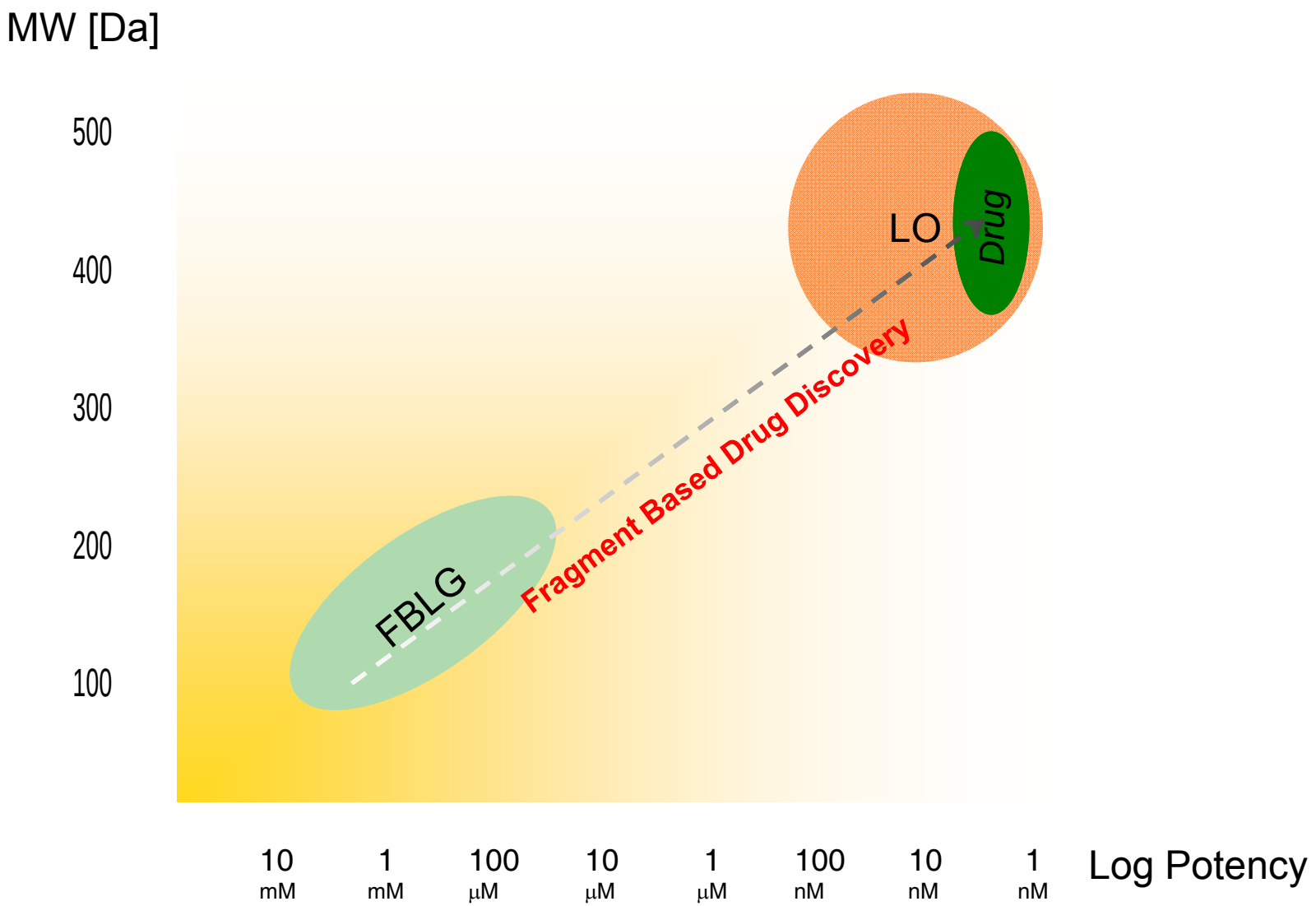
# FBDD Impact – Science

- Tighter integration of biophysical methods in med. chem.
  - ✓ Kinetic and Thermodynamic profiling
  - ✓ Diversification of techniques and increases in throughput and efficiency
- Protein crystallography
  - ✓ High throughput approaches in data collection, analysis
- Mind-set changes
  - ✓ Composite optimisation parameters – Efficiency indices
  - ✓ Concepts of druggability/ligandability

# But WHY “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

# FRAGMENTS 2015
# RSC BMCS workshop
# March 23rd


Mike Hann

Director of Bio-Molecular Structure

Computational and Structural Chemistry

GSK Medicines Research Centre

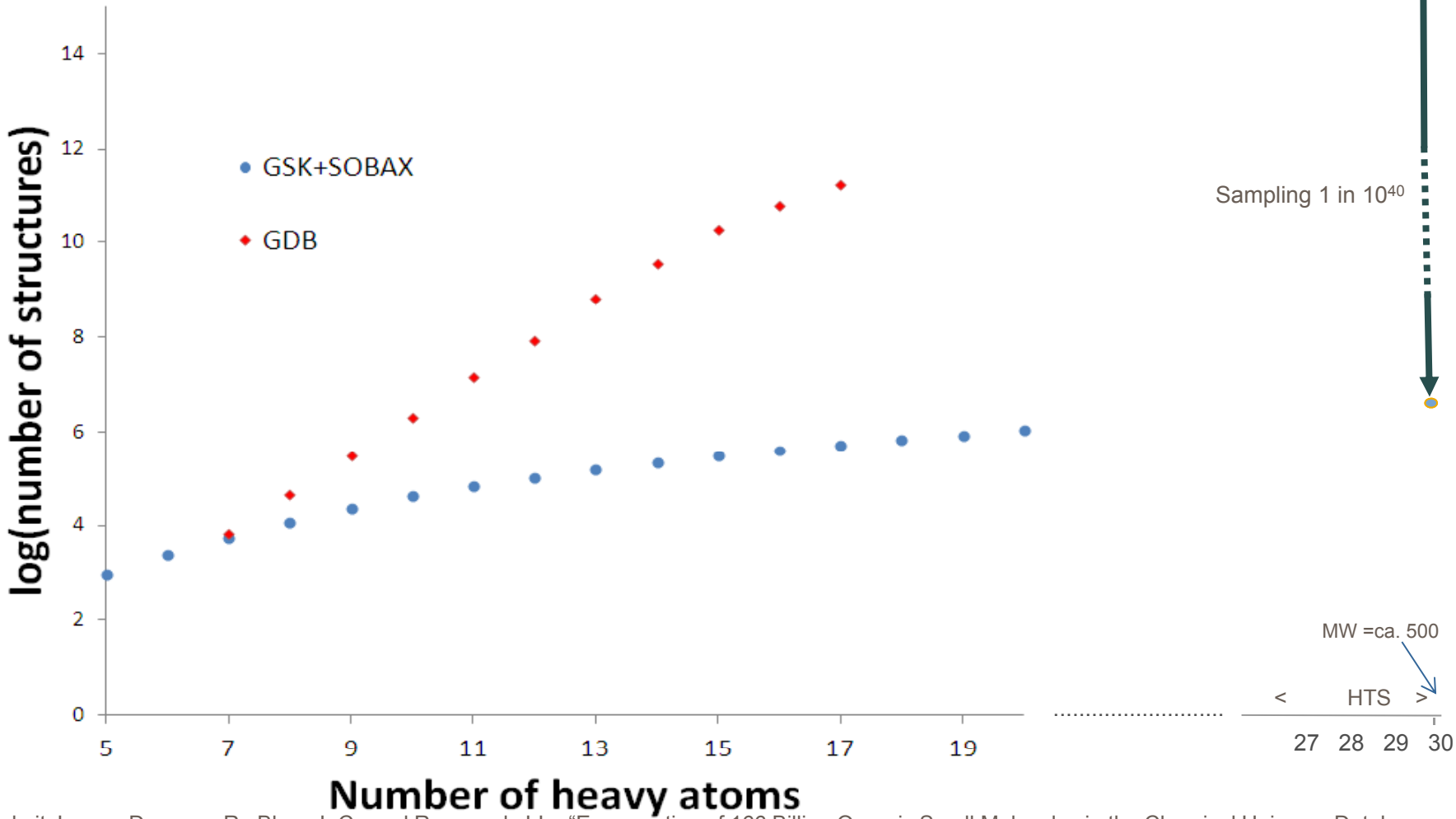
Stevenage, UK

Mike.M.Hann@gsk.com

# 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* , (2012), **52**(11), 2864-2875.

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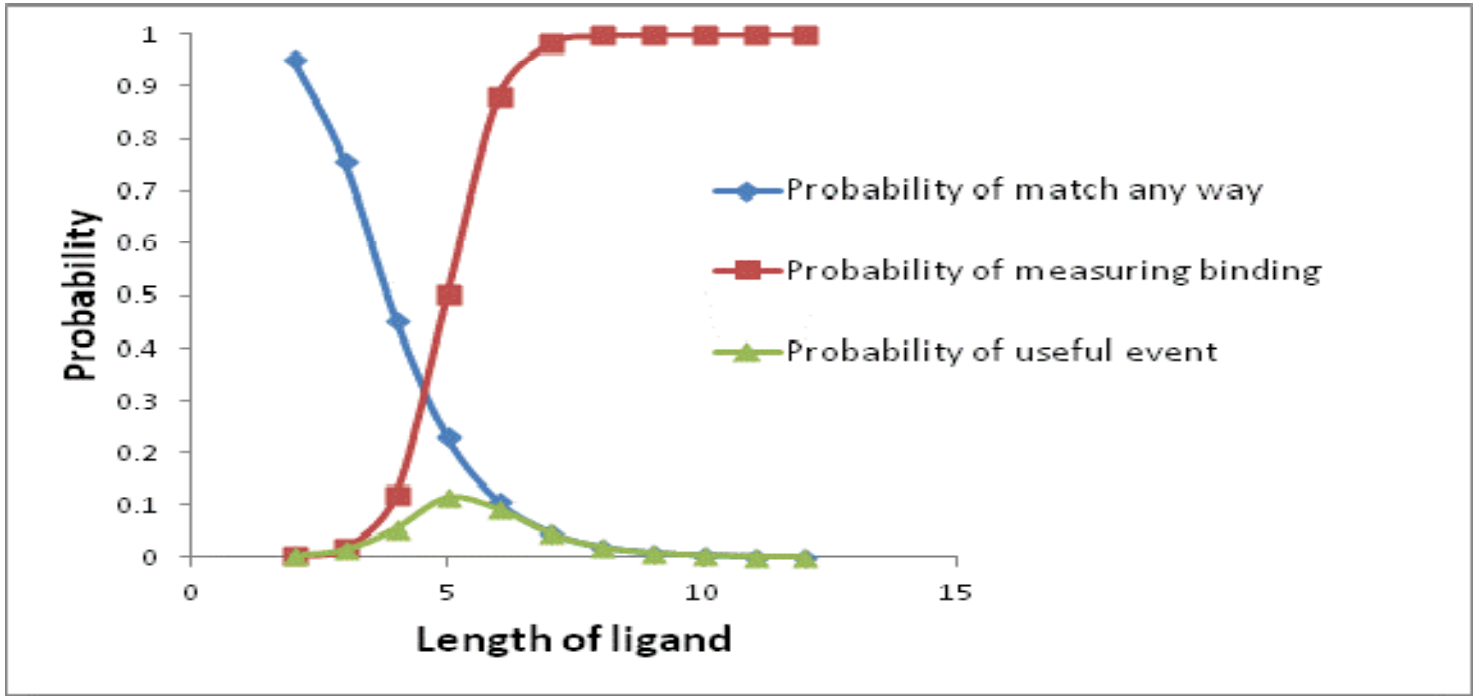
# The probabilities that ligands of different complexity (ie length) can match, be detected and the resultant “useful event”.

```
Receptor:          1 2 3 4 5 6 7 8 9
features:          - - + - + - - + -

Ligand A mode 1    + + -
Ligand A mode 2              + + -
Ligand B unique                    - + +   (note it wraps round!!)
```




Hann MM, Leach AR, Harper G., Molecular complexity and its impact on the probability of finding leads for drug discovery. *JCICS (*2001), **41**(3) 856-64
Leach AR, Hann MM. Molecular complexity and fragment-based drug discovery: ten years on. Curr Opin Chem Biol. 2011 Aug;15(4):489-96.

# There are More Reasons

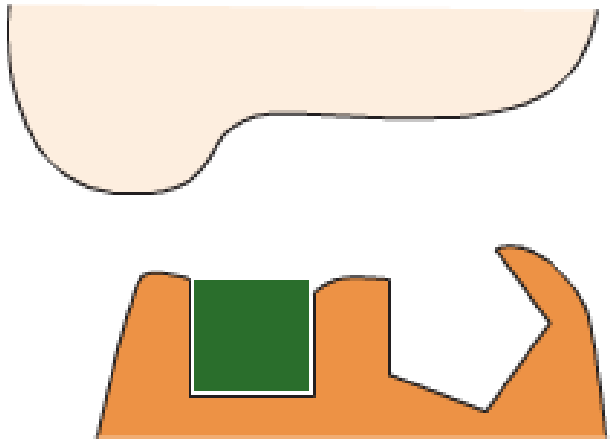
*Low* absolute Potency

*High Lig. Eff.*

*mM -> µM*

*Excellent* Properties

*ADMET* *What is a real hit*



Poor Fit to *any* Target

*Need to "construct"*

*Ultimate* Relevance of Chemical Space

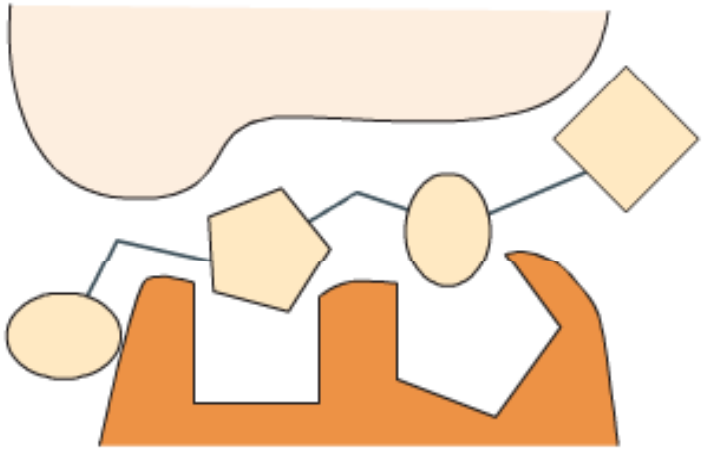
*Hundreds -> Thousands*

Potency

µM -> nM

Properties

ADMET What is a real hit



Poor Fit to Target

Need to "deconstruct"

Relevance of Chemical Space

Need for millions..

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

# What Are The Main Pitfalls?

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

Experience and Mindset
are a driver of success in FBDD

Glossary of terms

Definitions

General references for background information

# Glossary

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

# Definitions

**Efficiency Indices**

- ✓ Scaling factor to correct affinity/potency for size, lipophilicity etc.

**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 | Δ*H*/HA | Enthalpy driven potency optimization | J. E. Ladbury, G. Klebe, E. Freire *Nature Rev. Drug Disc*. **2010**, *9*, 23-27 |
| | SIHE | (-Δ*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.