

Design of Fragment Libraries

– Status and Challenges

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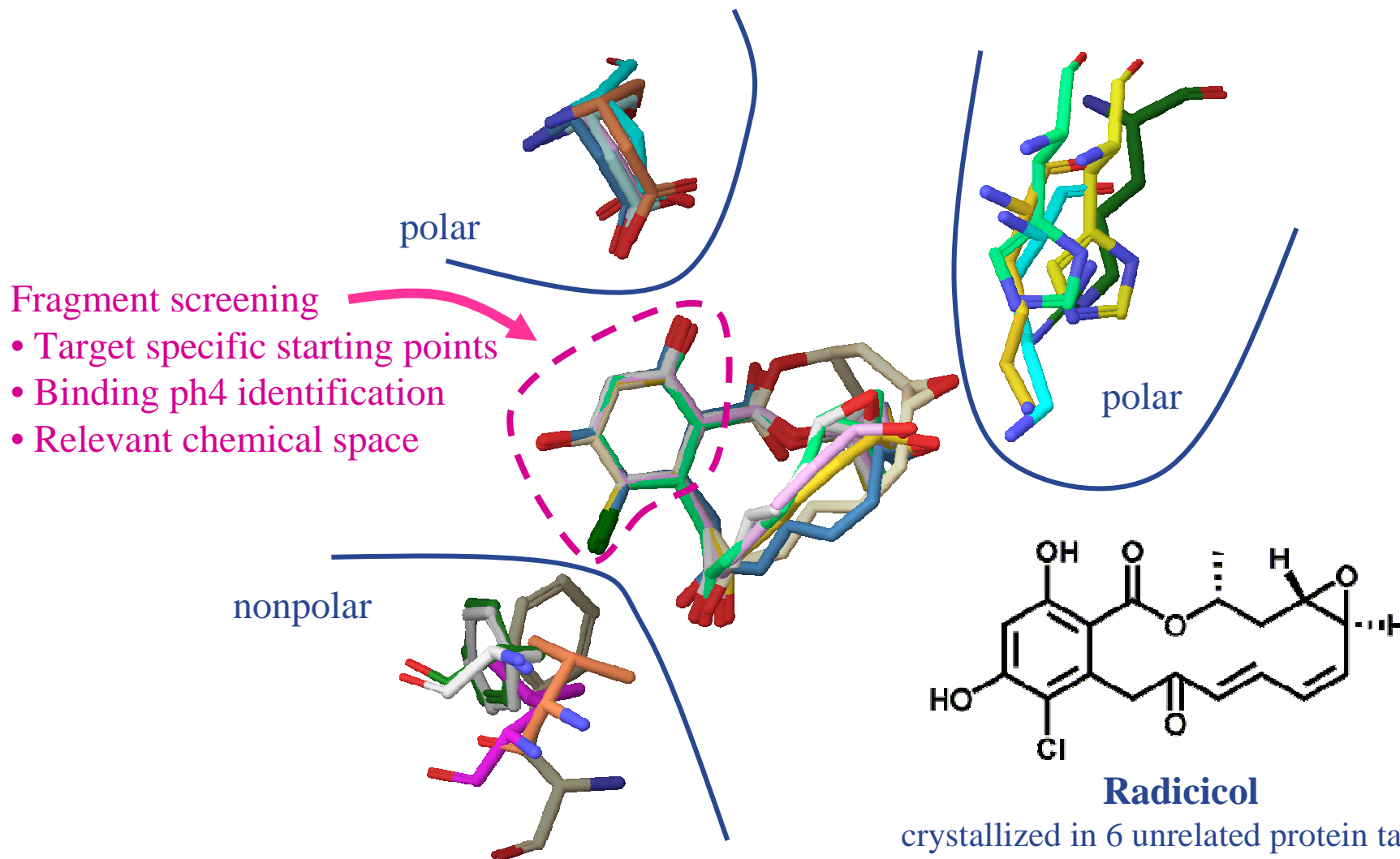


Agenda



- What is a fragment and why?
- Screening fragment libraries for ligands
- Fragment library design
- Patterns & observations
 - SeeDs hit rate as a hint of target druggability?
 - Are binders different from the overall library?
 - Fragments capturing key interaction pattern
 - Fragment binding modes
- Integrating SeeDs into drug discovery
- Conclusions

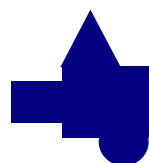
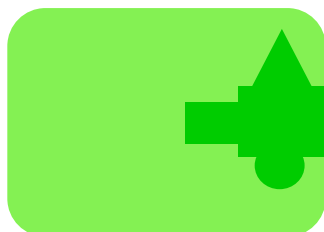
Fragments to Mimic Key Molecular Recognition



crystallized in 6 unrelated protein targets
(1BQ1, 1U0Z, 2HKJ, 2Q8I, 2ZBK, 3CGY)

Why Fragments in hit discovery ?

HTS Approach



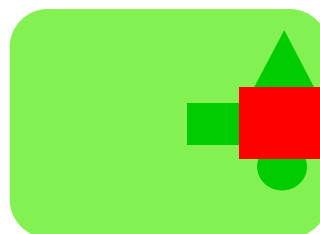
HTS requires the “right” compound

- ~ μM binding

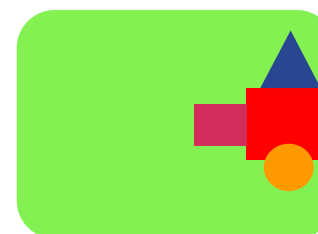
Fragment Approach



- X-ray
- NMR
- SPR



- Structures
- Modelling
- Chemistry

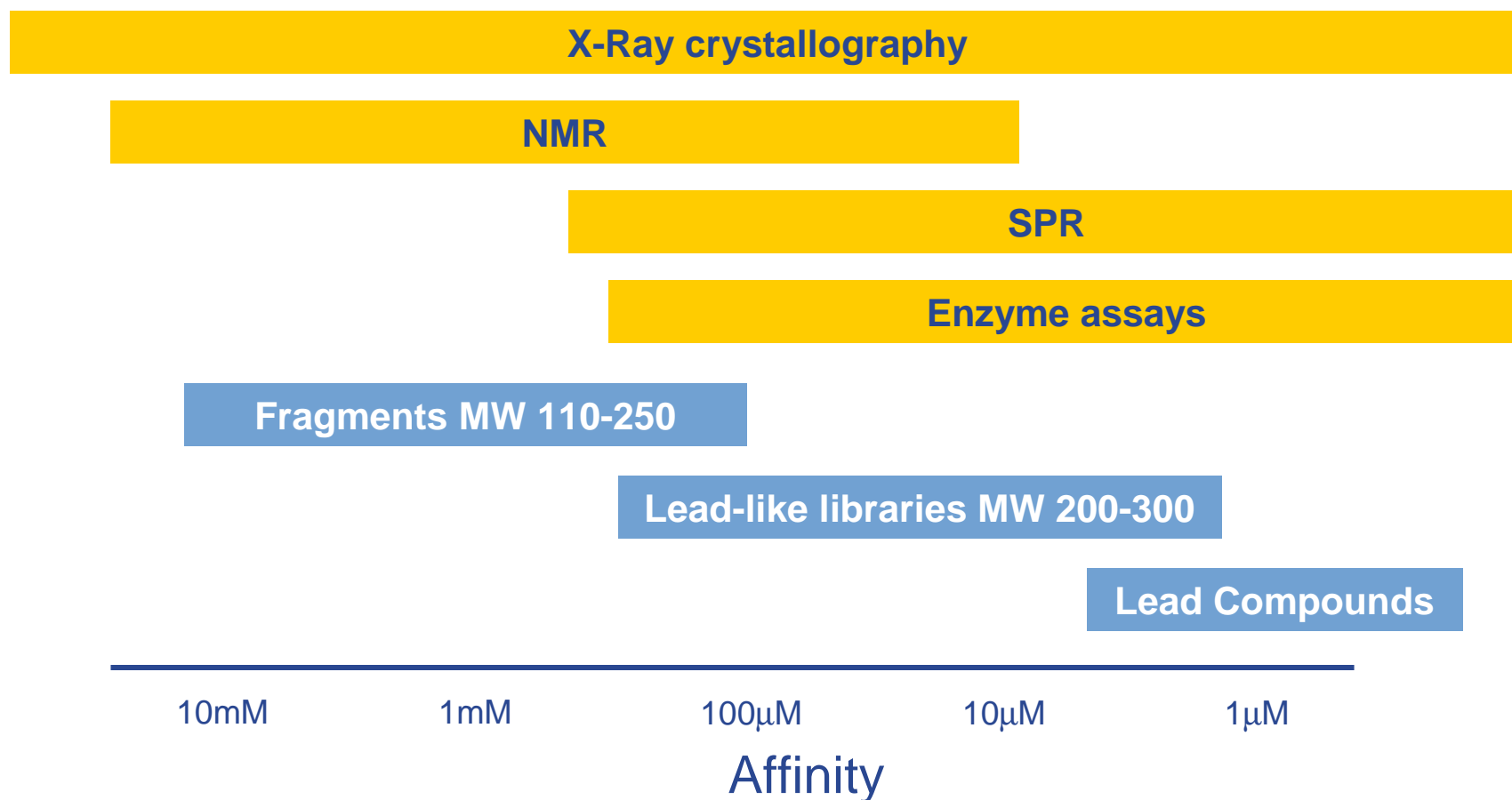


- ~ mM binding

Detection of *direct binding*

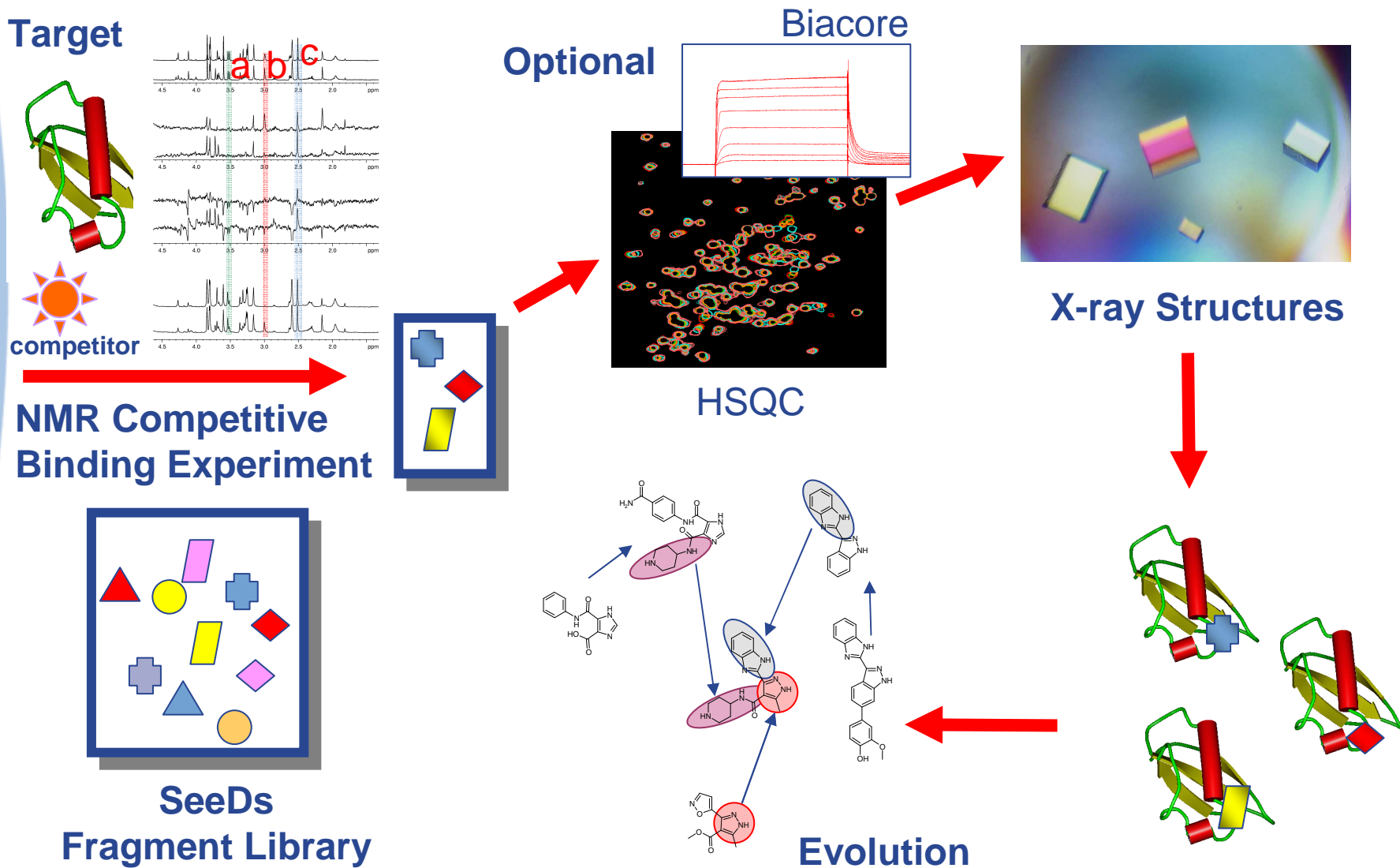
Screening fragment libraries

- Different experimental approaches have different strengths and limitations



The SeeDs process*

“Structural Exploitation of Experimental Drug Startpoints”



*Hubbard *et al* Curr Topics Med Chem 2007

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Fragment library design reviews



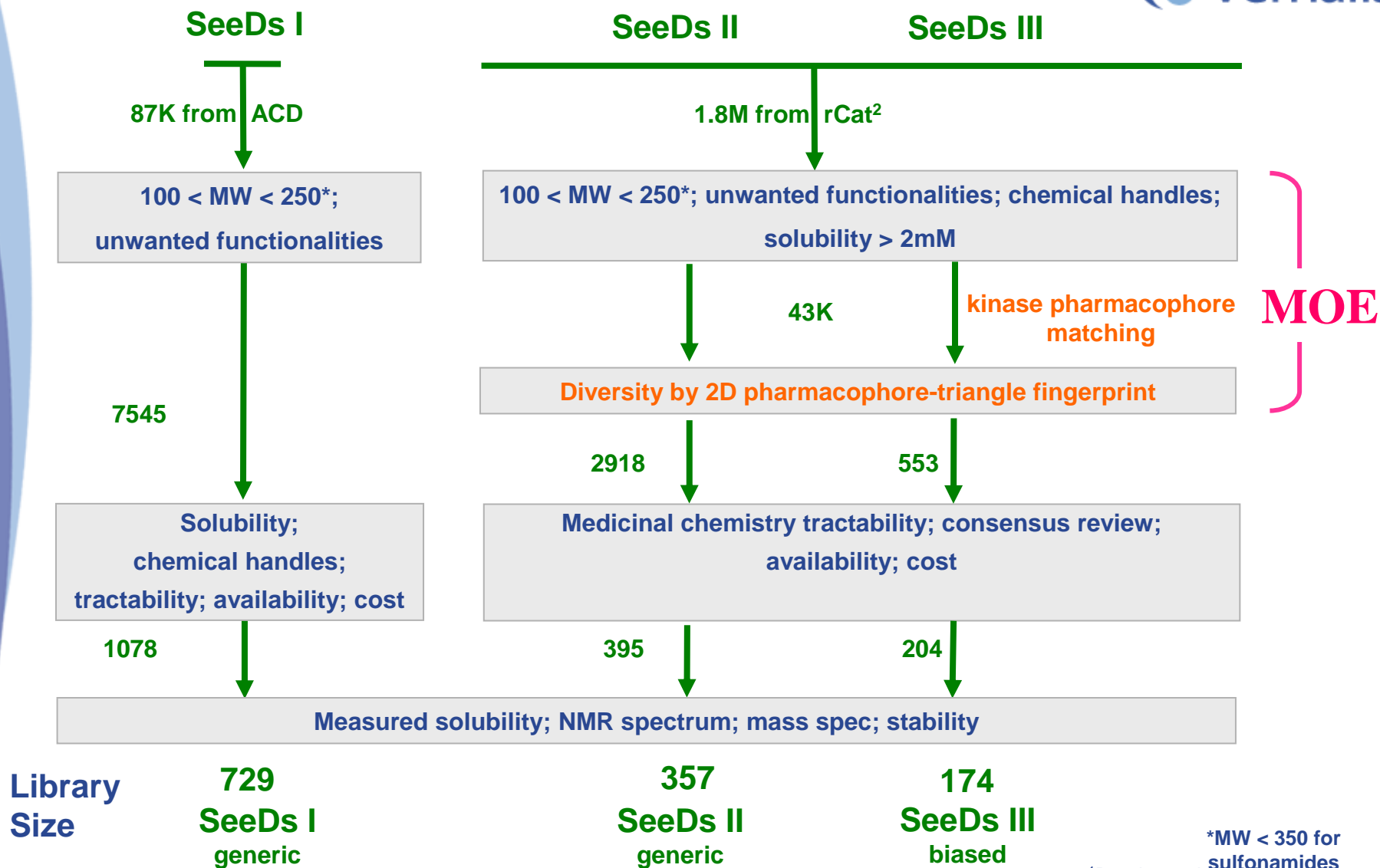
Screening Technique	Company	Author	Publication
NMR	Abbott	Shuker et al.	Science, 1996. 274:1531-1534
	Novartis	Schuffenhauer et al.	Curr Top Med Chem. 2005,5, 751-762.
	Vernalis	Baurin et al.	J. Chem. Inf. Comput. Sci., 2004. 44:2157-2166
	Vertex	Moore et al.	J. Synchrotron Rad., 2004. 11:97-100
	Zobio/Pyxis	a. Siegal et al. b. Verheij	a. Drug Discov Today, 2007. 12:1032-1039 b. Molecular Diversity, 2006. 10:377-388
X-ray	Astex	Rees et al.	Nat Rev Drug Discovery, 2004. 3:660-672
	SGX	Blaney et al.	Fragment-Based Approaches in Drug Discovery, 2006, 215-248
Mass Spec	Sunesis	Erlanson et al.	Annu Rev Biophys Biomol Struct., 2004. 33:199-223
High Concentration Screening	AZ	Albert et al.,	Curr Top Med Chem., 2007. 7:1600-1629
	Evotec	Hesterkamp et al	Curr Top Med Chem., 2007. 7:1582-1591
	Plexxicon	Card et al.	Nat Biotechnol, 2005. 23:201-207

Fragment library design



- Fit for purpose
 - Constrained by screening and evolution strategies
- Physical properties
 - Low MW (110-250)
 - Soluble (2mM in water)
- Sensibly lead-like
 - Unwanted functionalities (toxicology / reactivity)
- Chemically tractable
- Chemical diversity
- Size of library
 - Constraints of techniques
 - Screening time and data analysis
 - Maintenance
- Compound constraints
 - Pure, stable, available
- Generic or target biased
 - Balance novelty with improving hit rate

Vernalis SeeDs¹ library

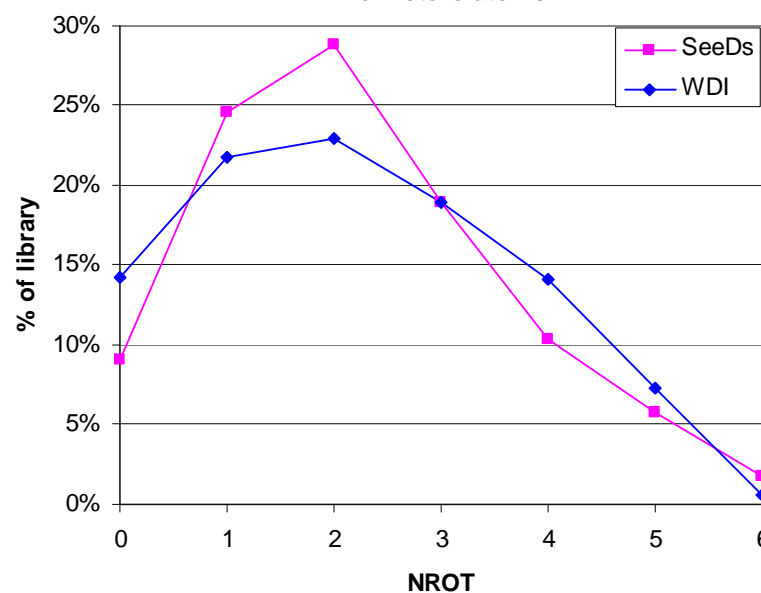
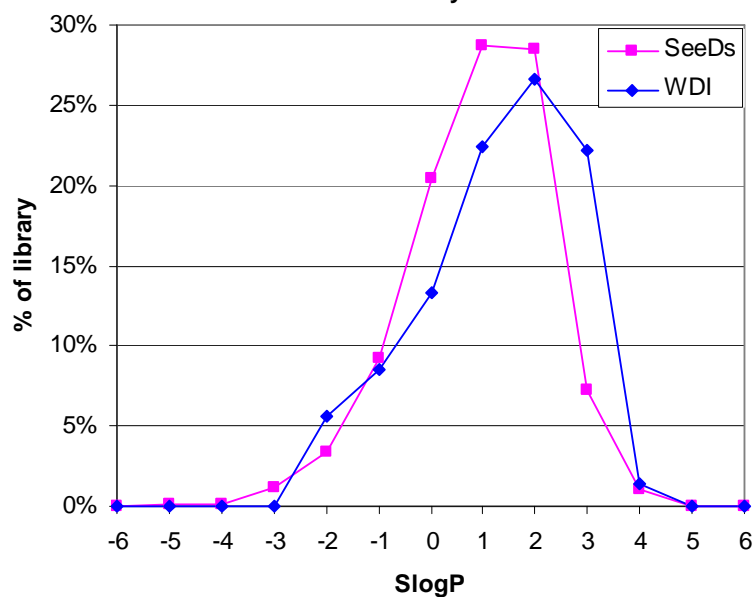
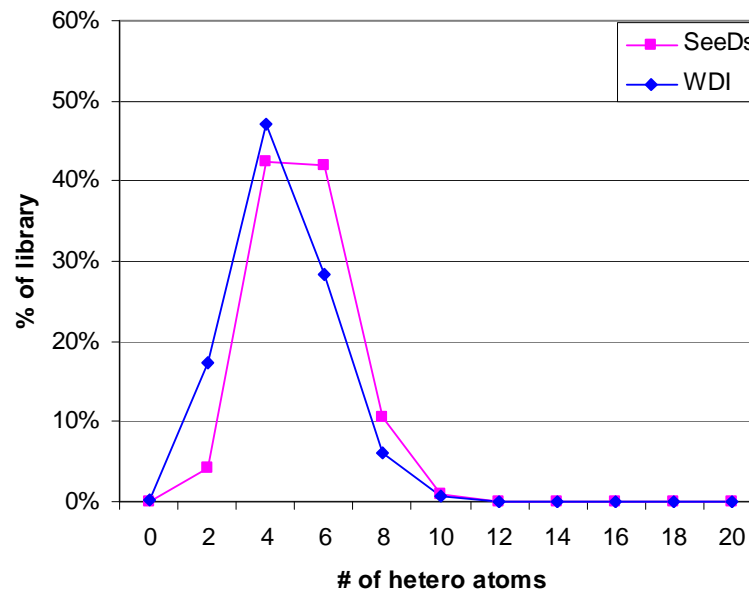
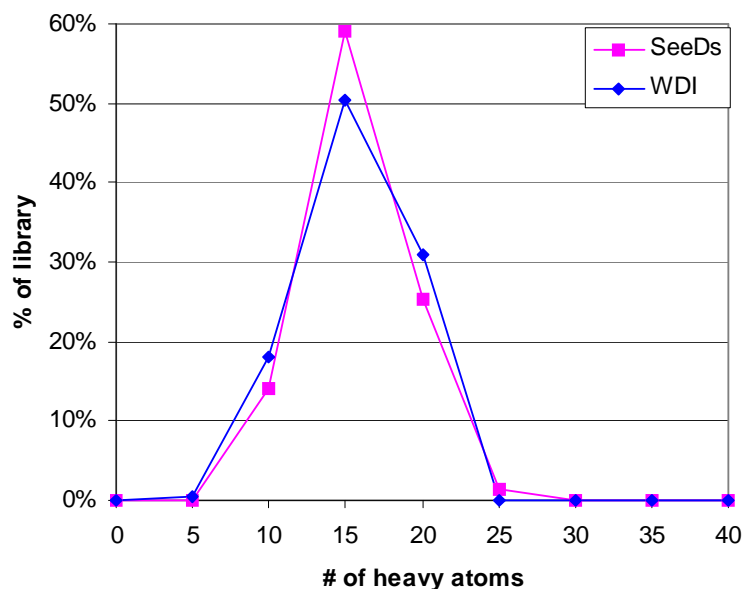


*MW < 350 for sulfonamides

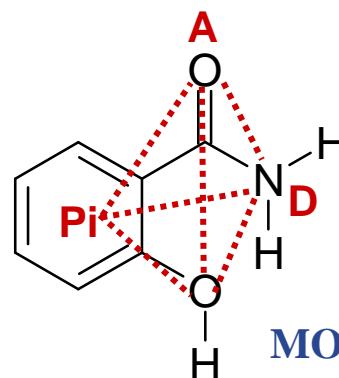
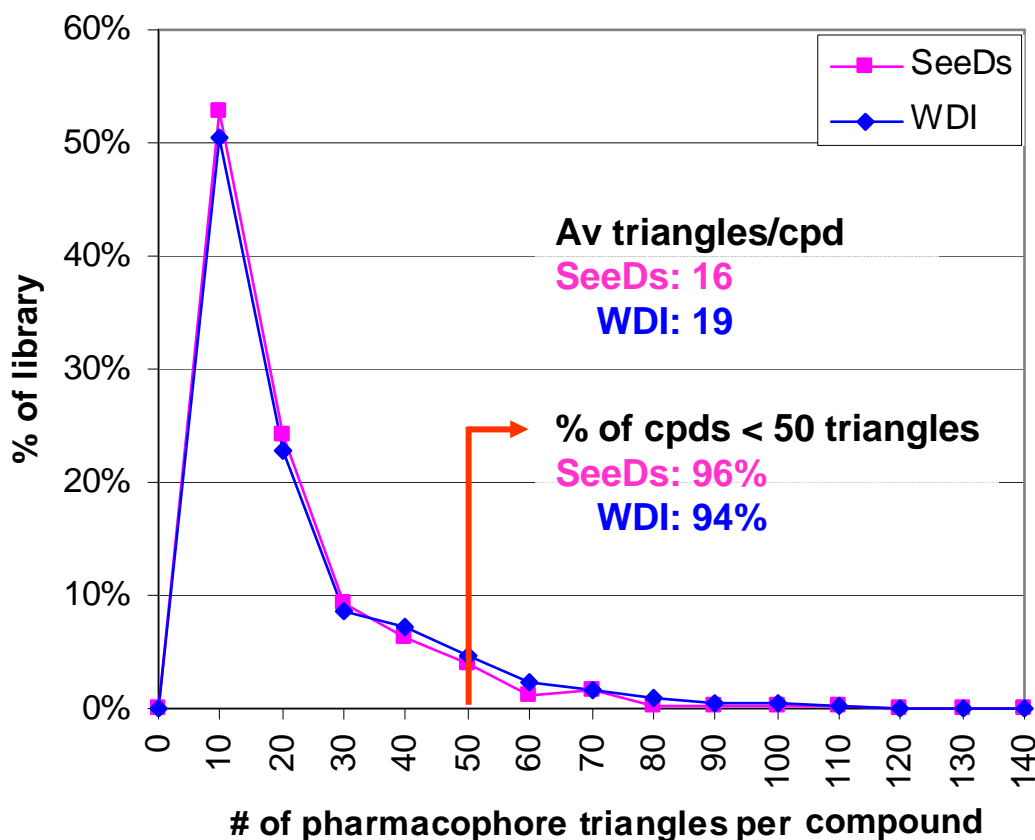
¹Baurin *et al* JCICS, 44, 2157, 2004

²Baurin *et al* JCICS, 44, 643, 2004

Comparison of SeeDs Library and World Drug Index (WDI)



Diversity analysis



MOE FP:GpiDAPH3

Common Ph4 triangles	SeeDs
WDI	65%

~35% unique ph4 triangles

- Importantly ...
 - Fragments are **small** but **complex** (enough)
 - Information content per molecule is high
 - Pertinent to the drug chemical space

Fragment Library follow-up and maintenance



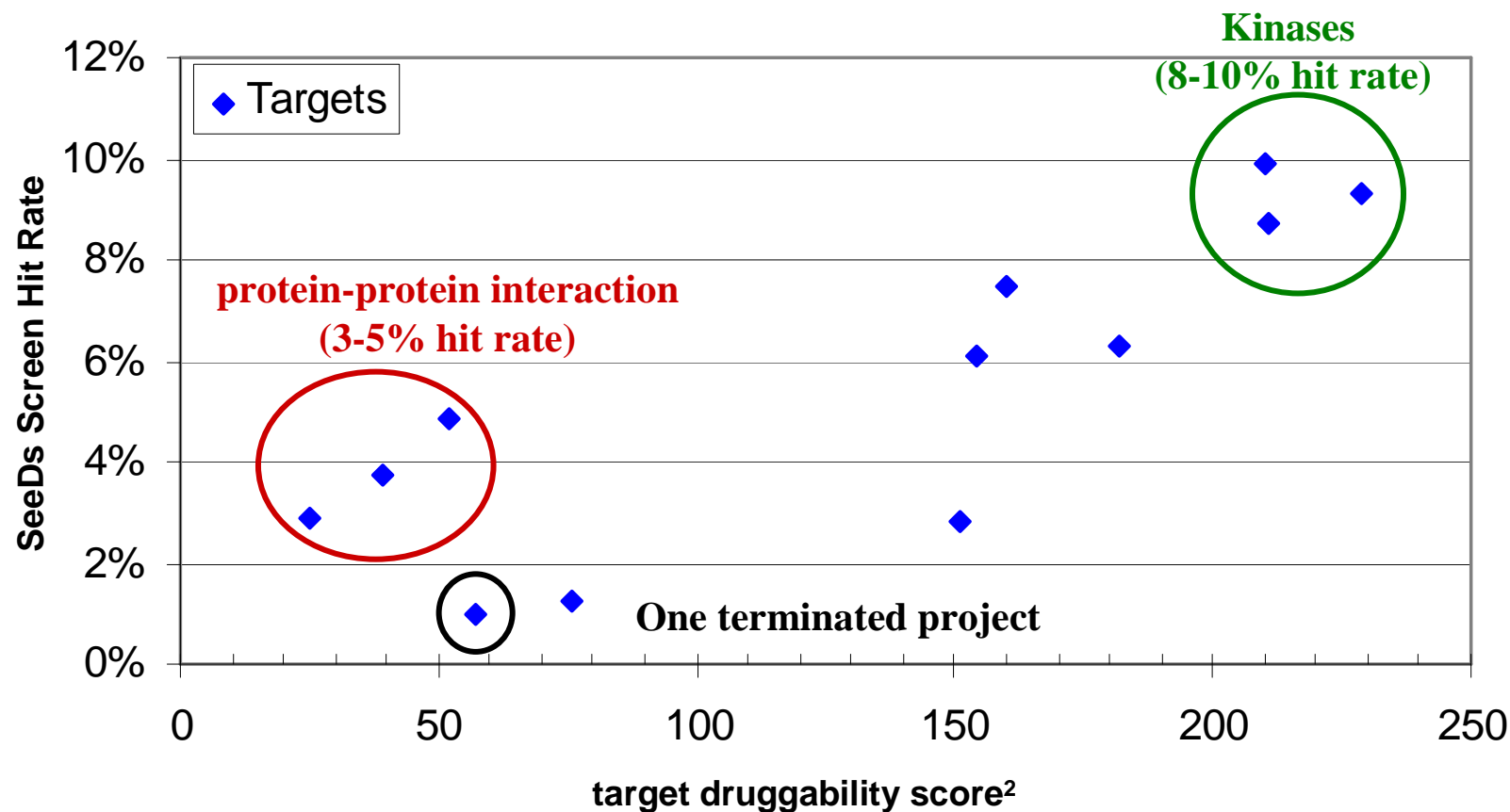
- QC biannually and maintenance of existing library
- Re-apply incrementally diverse selection when necessary
- In-house chemistry => novel fragments
- Ongoing med chem feedback
- Current library about 1200 compounds

Agenda



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SeeDs hit rate vs Druggability¹?

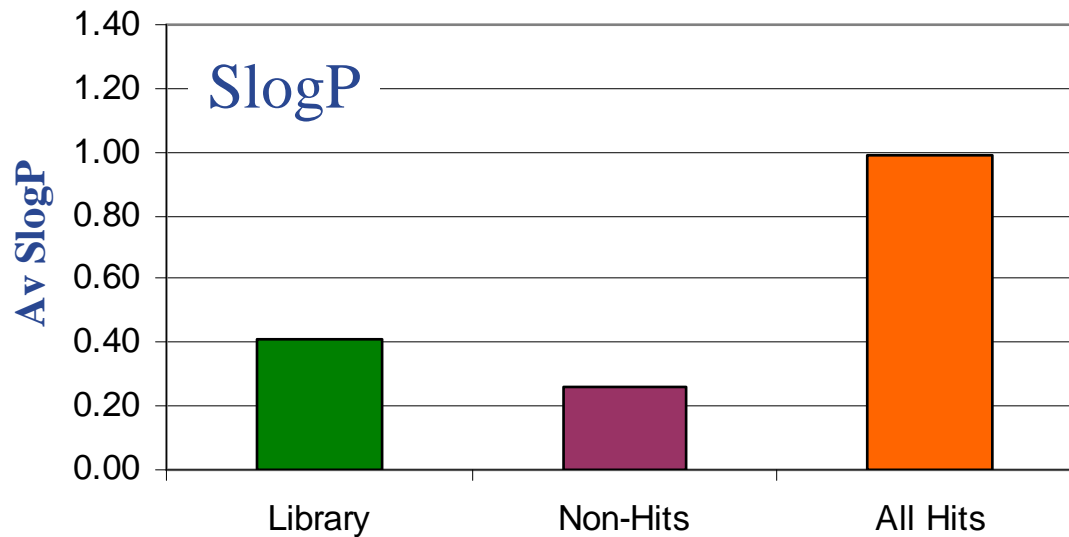


Hit rate dependent on protein families

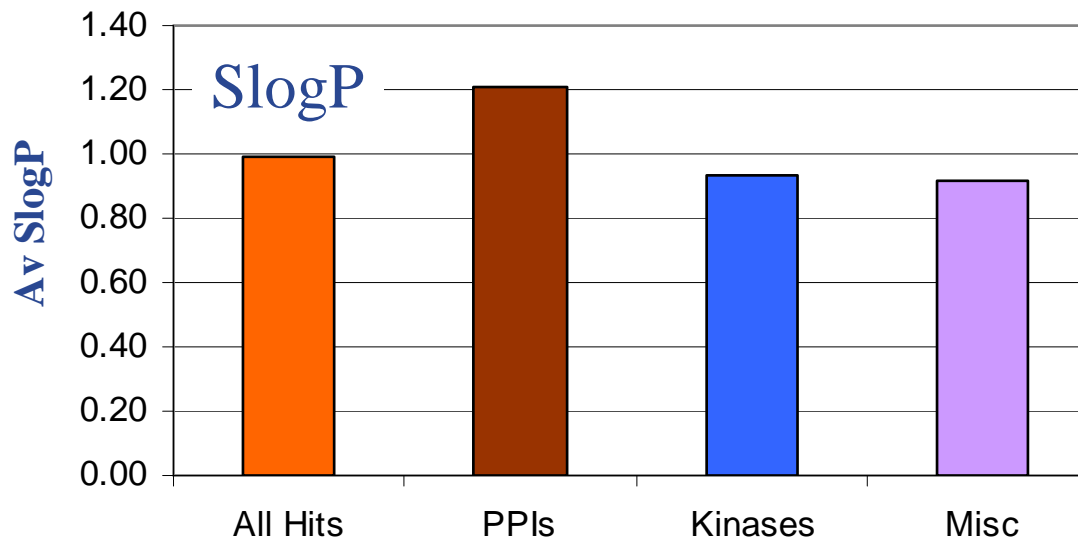
¹the ability to develop potent small molecular binders in a *timely* fashion

²estimated using SiteMap algorithm (Chem Biol Drug Des 2007; 69: 146–148)

Characteristics of fragment hits: lipophilicity

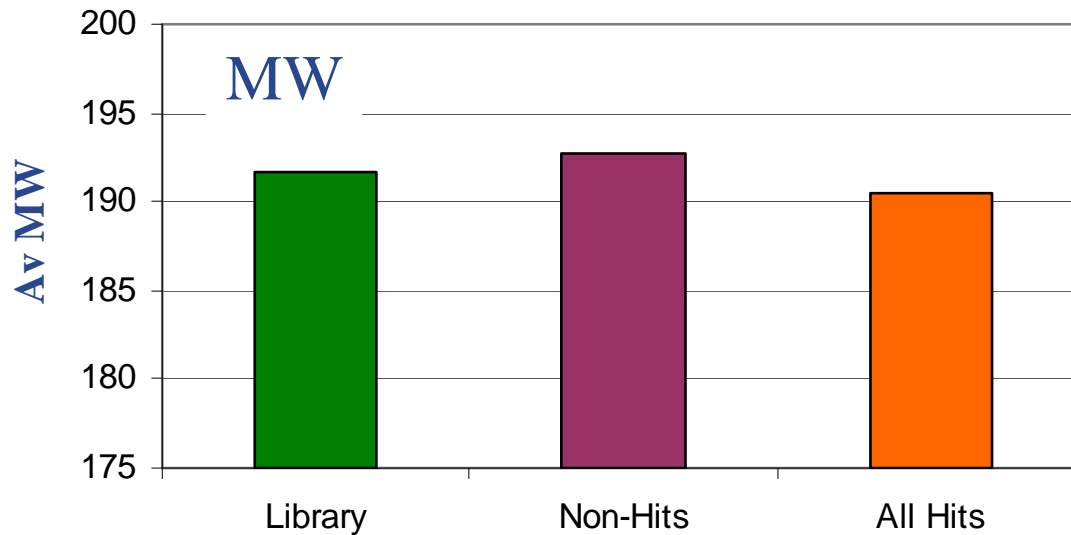


Clear separation
between hits and
non-hits by SlogP

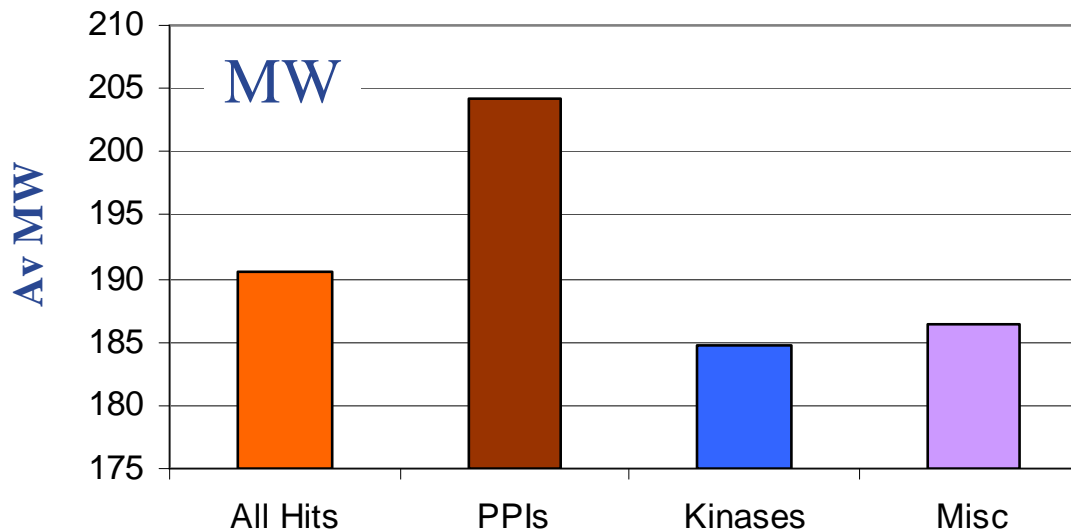


Variation in av SlogP
reflects on different
protein classes

Characteristics of fragment hits: MW

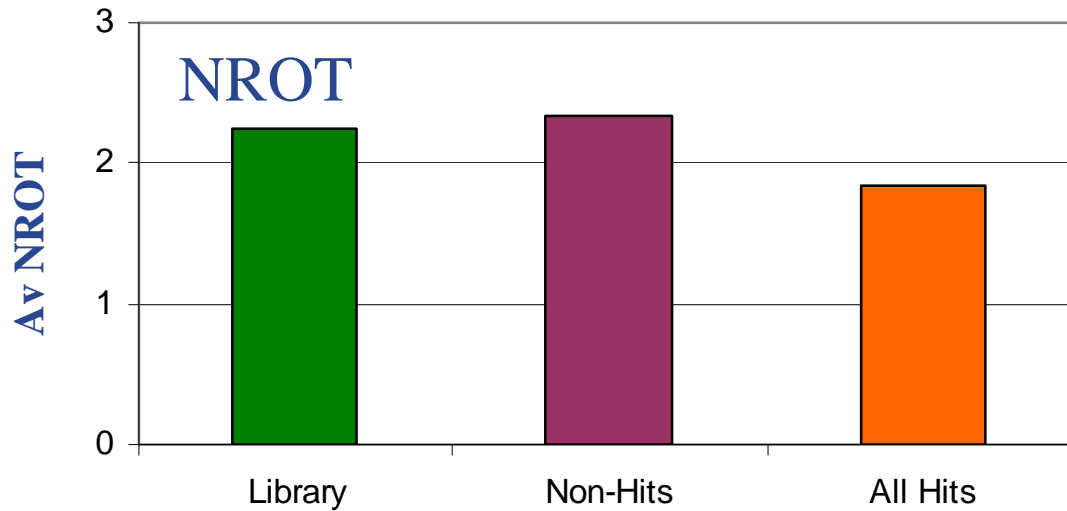


Similar av MW for all three classes

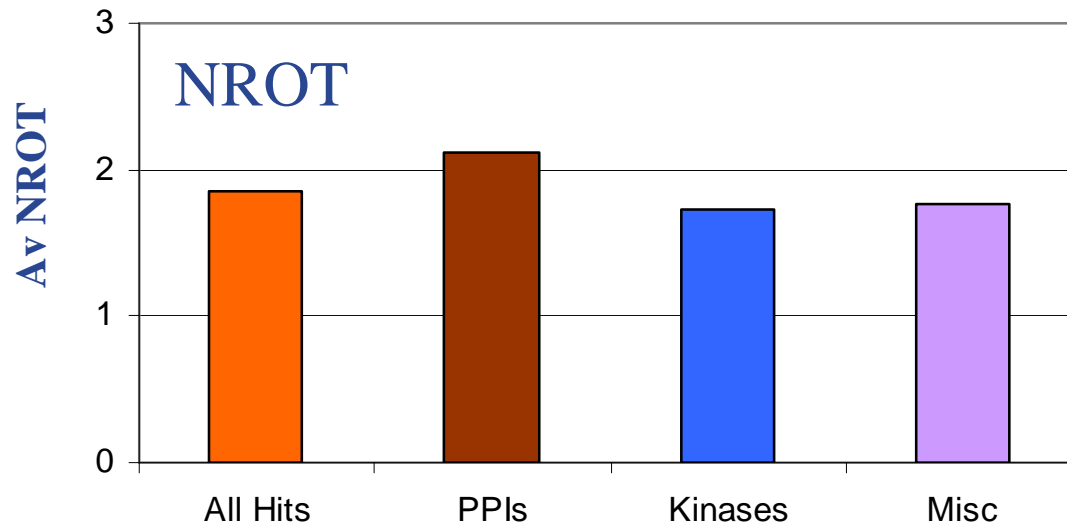


Variation in av MW reflects on different protein classes

Characteristics of fragment hits: Rotatable Bonds

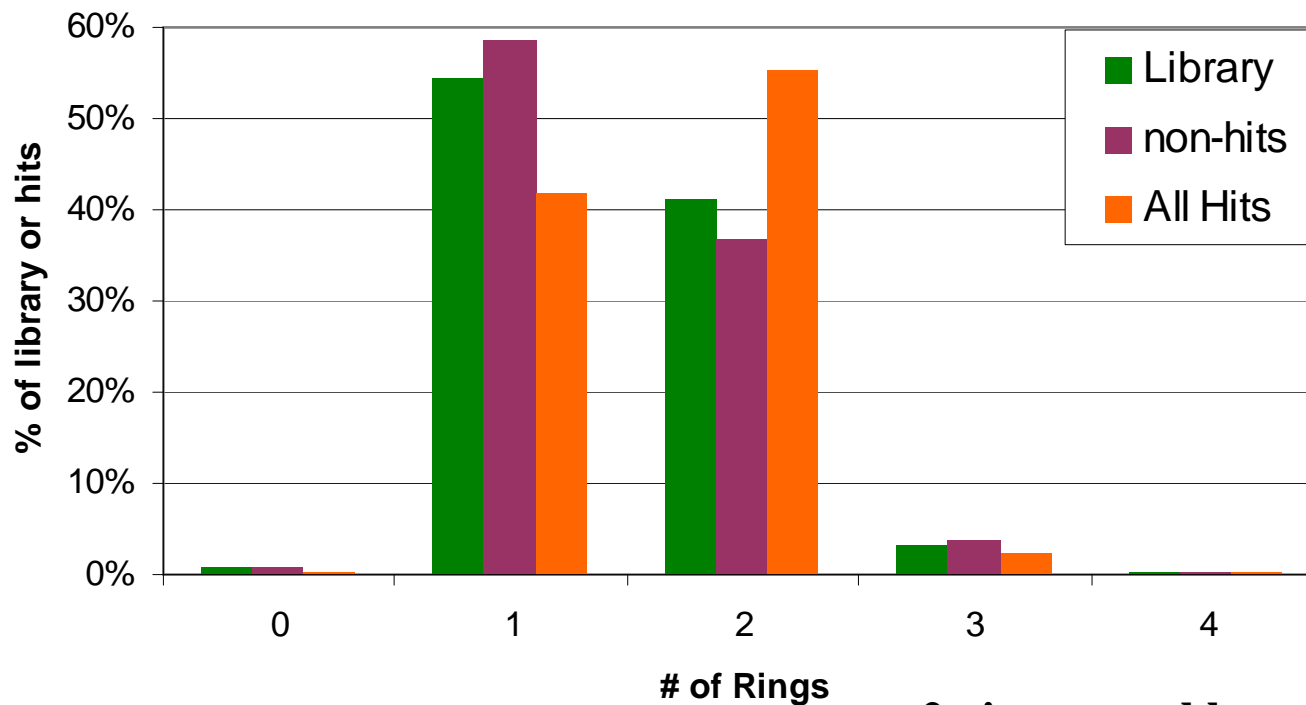


Hits more rigid than non-hits



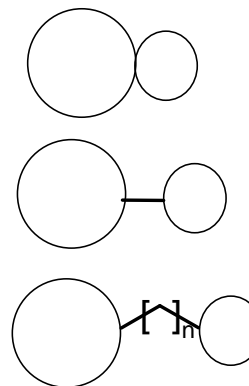
Variation in av NROT reflects on different protein classes

Characteristics of fragment hits: Rings

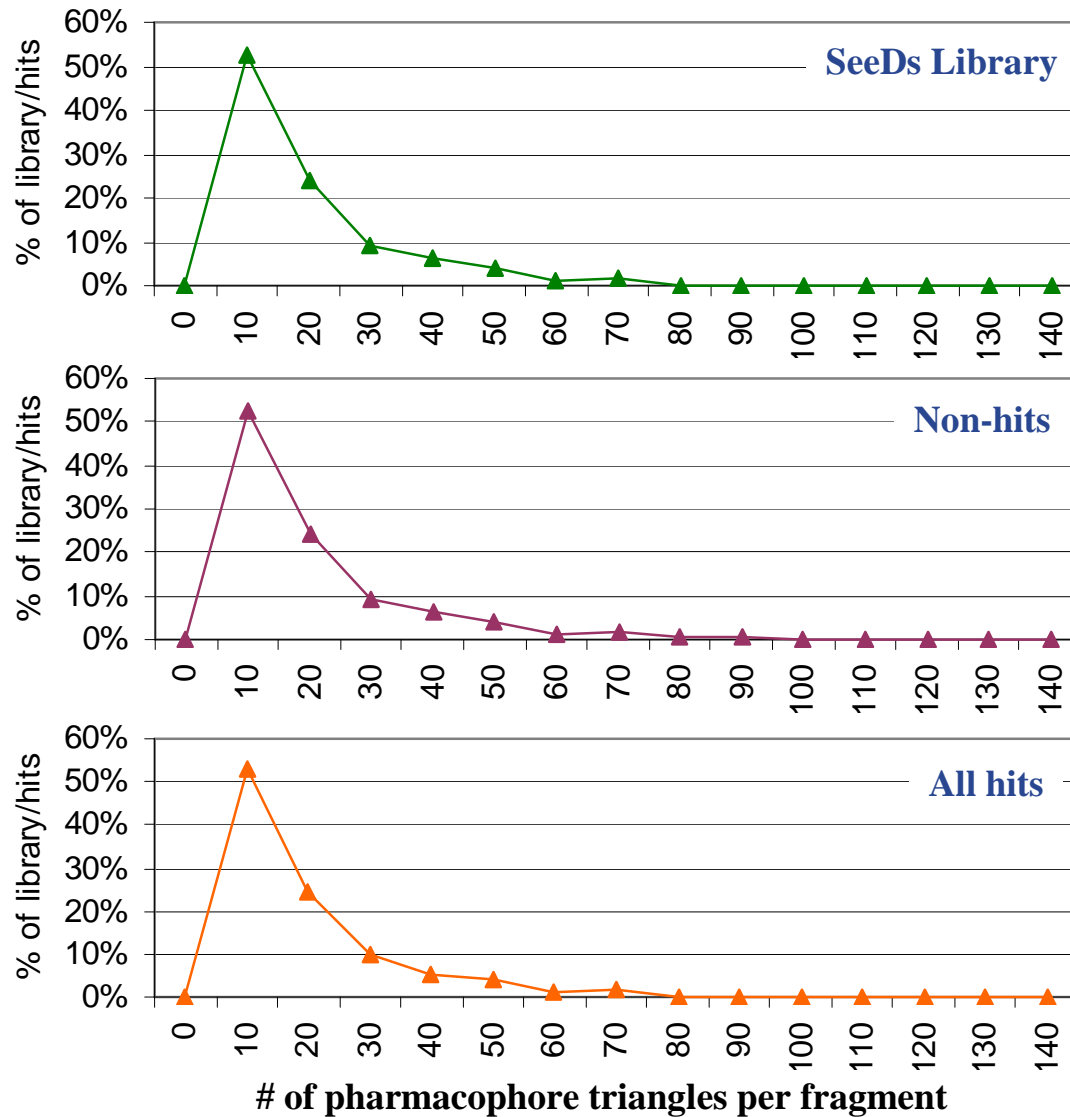


Two-ring assembly have the highest hit rate

2-ring assembly



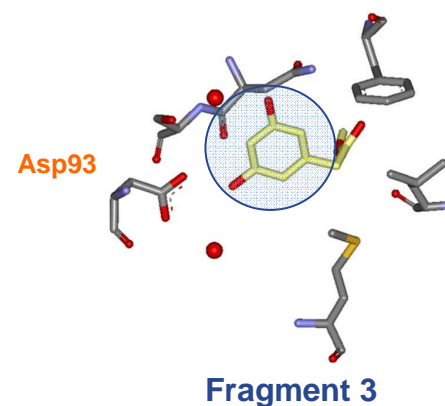
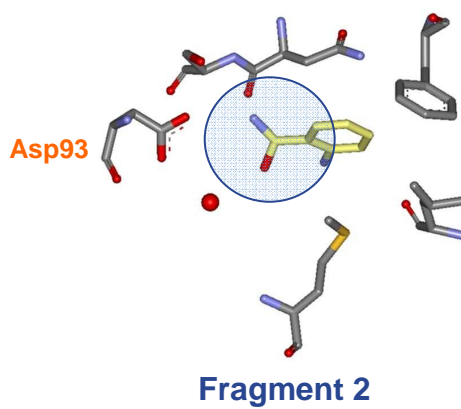
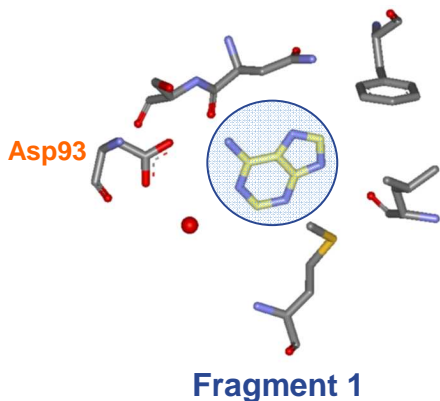
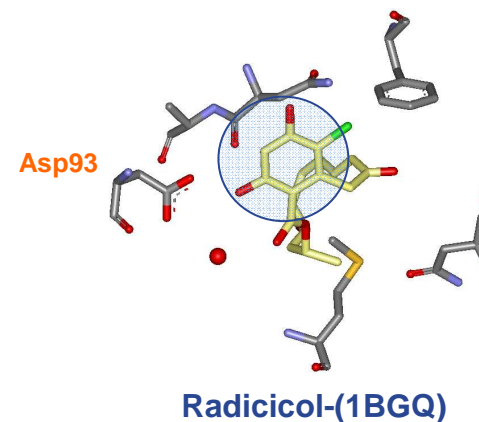
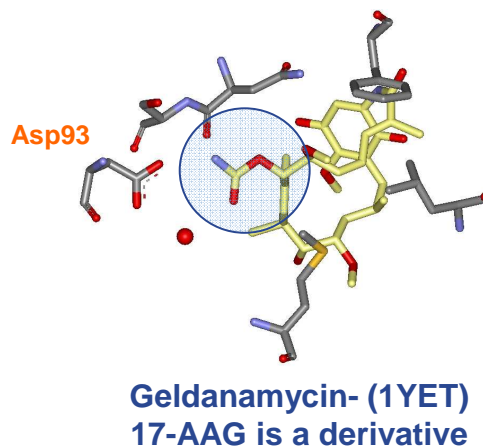
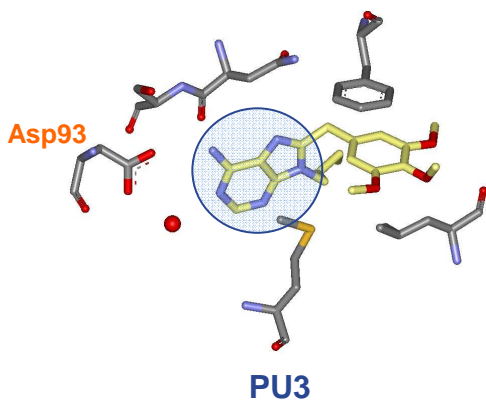
Number of pharmacophore triangles per fragment



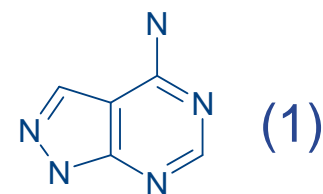
No difference between hits and non-hits w.r.t. GpiDAPH3 ph4 triangles (total or specific)

GpiDAPH3 too simplistic for the question we asked?

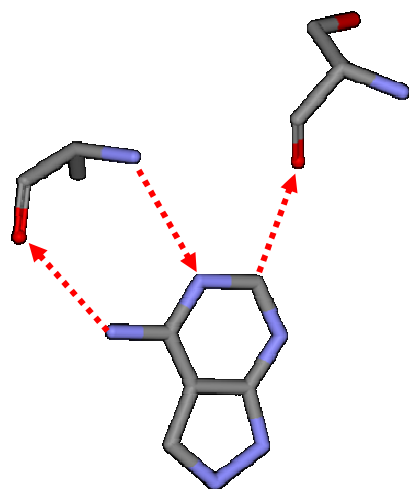
Hsp90: fragments recapitulate cores of known inhibitors



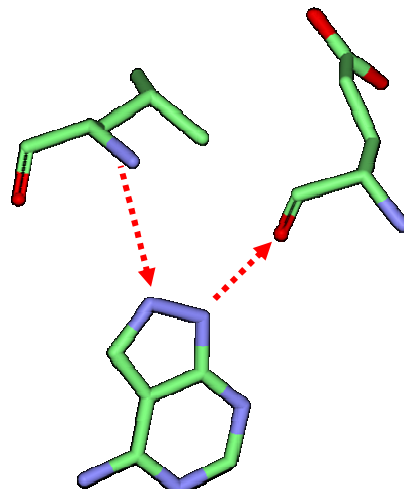
Fragment binding modes



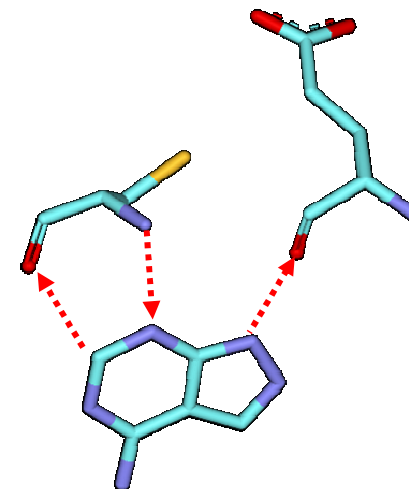
Same fragment (1) in three kinases – different binding modes



Kinase A
 $IC_{50} = 30\mu M$



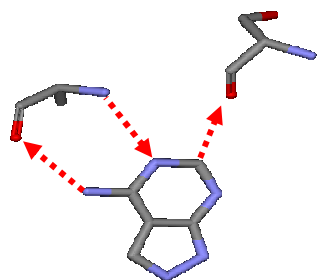
Kinase B
 $IC_{50} = 71\mu M$



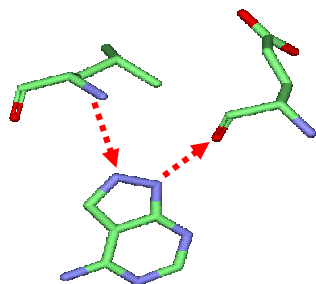
Kinase C
 $IC_{50} = 19\mu M$

All three are high resolution structures with clear density maps
Caution, as crystallisation conditions vary

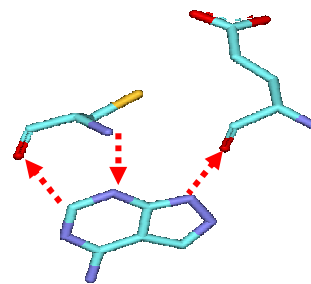
Evolved Fragment binding modes



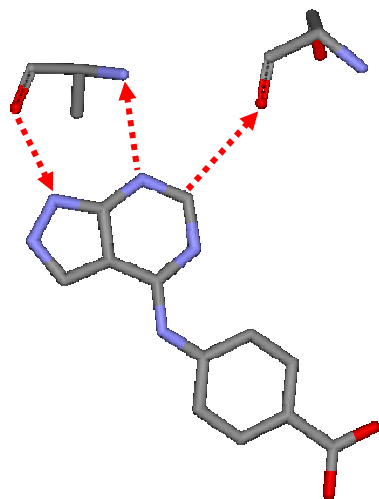
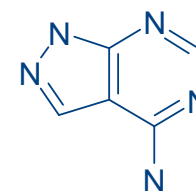
Kinase A
 $IC_{50} = 30\mu M$



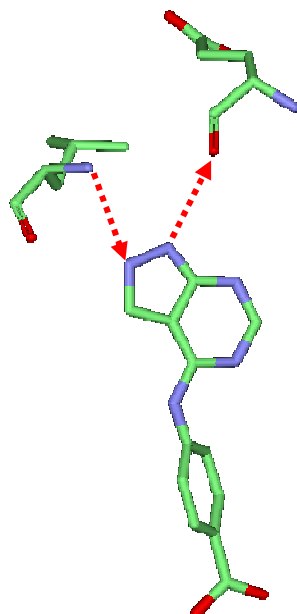
Kinase B
 $IC_{50} = 71\mu M$



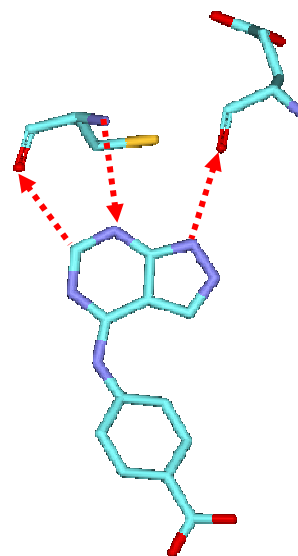
Kinase C
 $IC_{50} = 19\mu M$



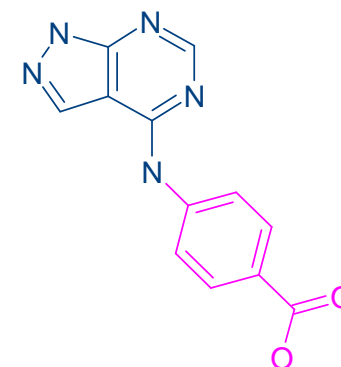
$IC_{50} = 21\mu M$



$IC_{50} = 16\mu M$



$IC_{50} = 7\mu M$



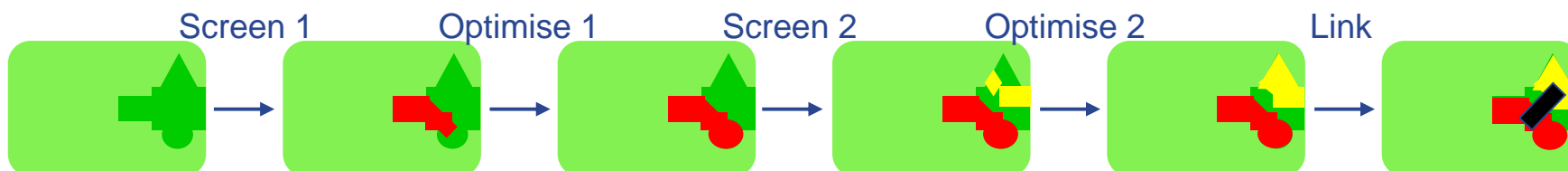
Agenda



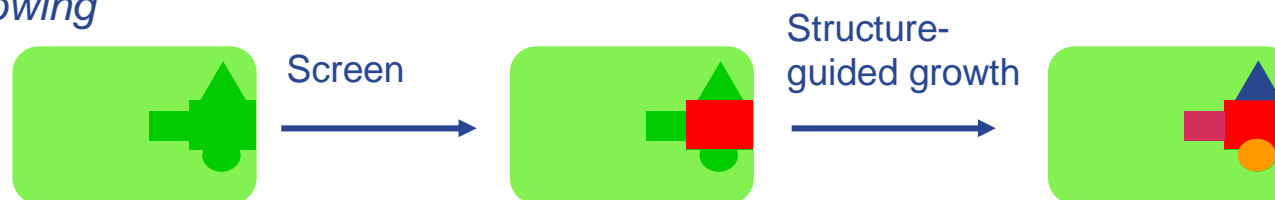
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Evolving Fragments into Leads

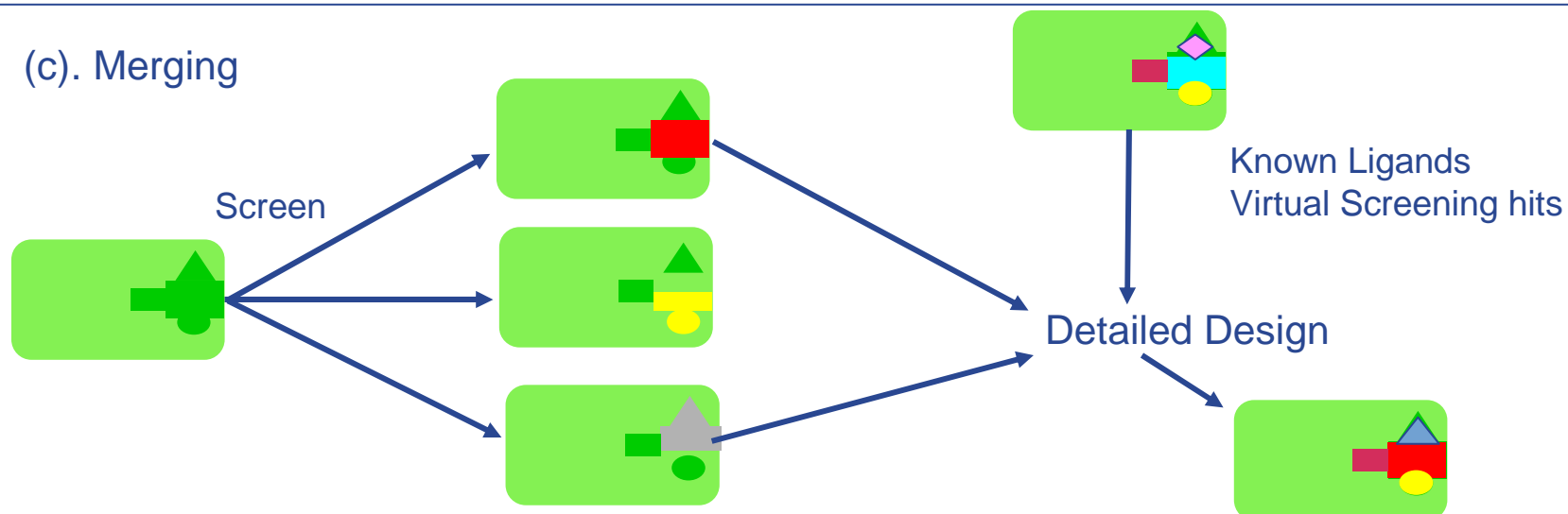
(a). Linking



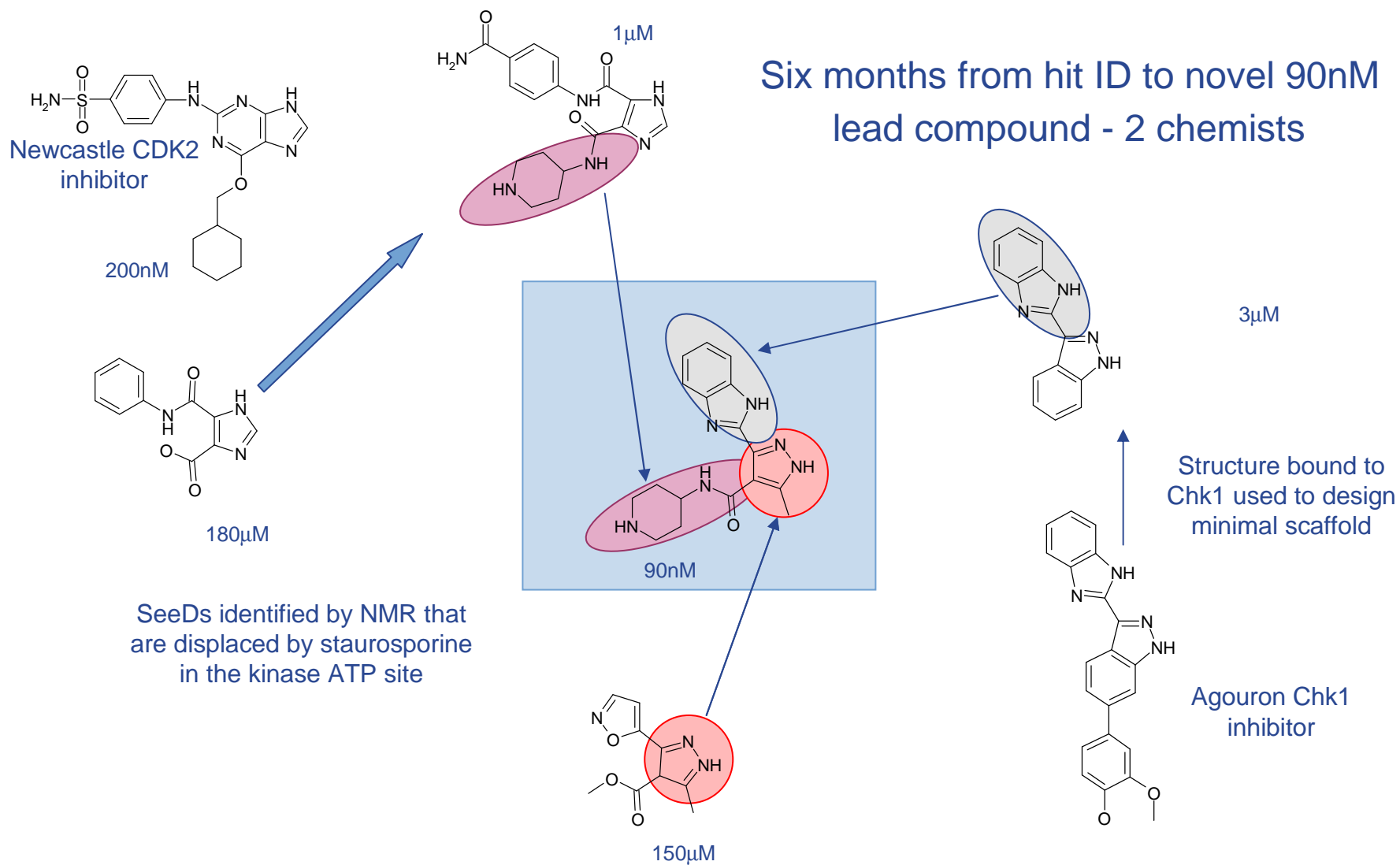
(b). Growing



(c). Merging



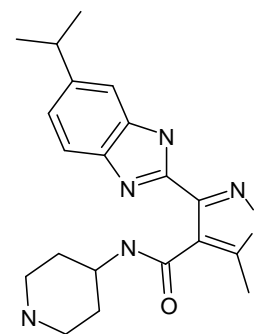
PDK1 – merging fragments



Series Has Good PK and PD



- Series optimised
 - PDK1 IC₅₀ = 15nM
 - Selective vs several kinases
 - Potent on cells; HCT116 GI₅₀ = 80nM
 - Also active on a wide cancer panel



10mg/kg MTD

Control (3day vehicle)

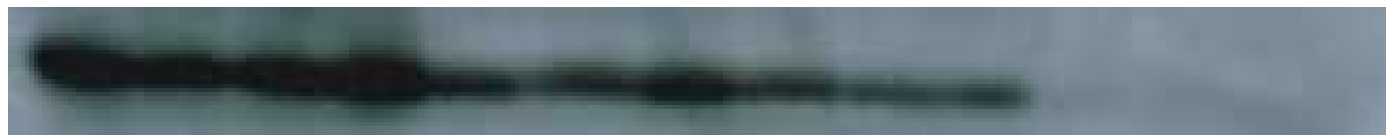
3days compound

4hrs post last dose

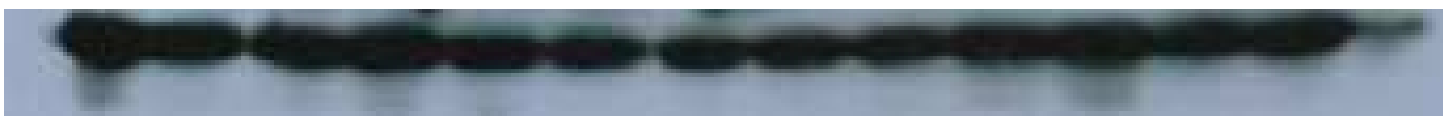
Samples from 2-3 week

treated animals,

24hrs post last dose



GSK3β-P



GAPDH

Fragments – reflections



- Fragments: small but versatile, weak but efficient
 - evolve novel hits and leads from fragments
- Design of library is crucial
 - Small number of fragments sample large chemical diversity
 - Tailored for your needs
 - Maintenance to maximize its usage
- Analysis of SeeDs hits
 - More grease please!
 - Properties of SeeDs hits reflect on different protein classes
 - SeeDs screen hit rate depends on protein families
- Critical is integration of structure (X-ray and NMR), modelling and chemistry
- Main benefit: choice in discovery
 - Number of fragments
 - Number of hit compounds
 - Number and quality of leads

Acknowledgements



- *SeeDs* –Nicolas Baurin (Aventis), Ben Davis, Rod Hubbard, Heather Simmonite, Christophe Fromont, & many medicinal chemists at Vernalis
- *Modelling* – Christine Richardson (Biofocus), Nicolas Foloppe, Alba Macias
- *Hsp90* – Martin Drysdale, Brian Dymock, many other team members
- *PDK1* – Lee Walmsley, Jon Moore, Chris Torrance, many other team members
- *Crystallography* – James Murray, Pawel Dokurno, Lisa Baker, Alan Surgenor

End



FBLD2009:
Fragment Based Discovery:
Modelling and Design
Challenges
(in association with MGMS)

York: Sept 2009

<http://www.fbld2009.com>

Hubbard, R.E., Chen, I., Davis, B. (2007), "Informatics and modelling challenges in fragment-based drug discovery", **Current Opinion in Drug Discovery and Development**, **10**, 289-297
Hubbard, R.E., Chen, L., Davis, B., Drysdale, M.J. (2007), "The SeeDs approach: Integrating Fragments into Drug Discovery", **Current Topics Medicinal Chemistry**, **7**, 1568-1581



Who are Vernalis?



- **Combination of a number of companies**
 - RiboTargets – early adapters / innovators in virtual screening and fragment-based methods.
 - 1997 - SBDD on RNA targets
 - 2001 – SBDD and FBLD on protein targets
 - 2003 - RiboTargets => British Biotech (FTSE)
 - 2003 + Vernalis + Pintex (2004) + Ionix + Cita (2005)
- **Programmes in clinical trials (Phase, II, I, pre-clinical)**
- **Portfolio of discovery projects**
 - Integrating structure, fragments, modelling with medicinal chemistry
- **~60 in research**
 - 25 in chemistry, 15 in structure
 - Based in Cambridge, UK (Granta Park)
- **Collaborations with large and small pharma**
 - Access to the proven SBDD capabilities of Vernalis
 - Risk sharing – FTE funding, milestones and royalties