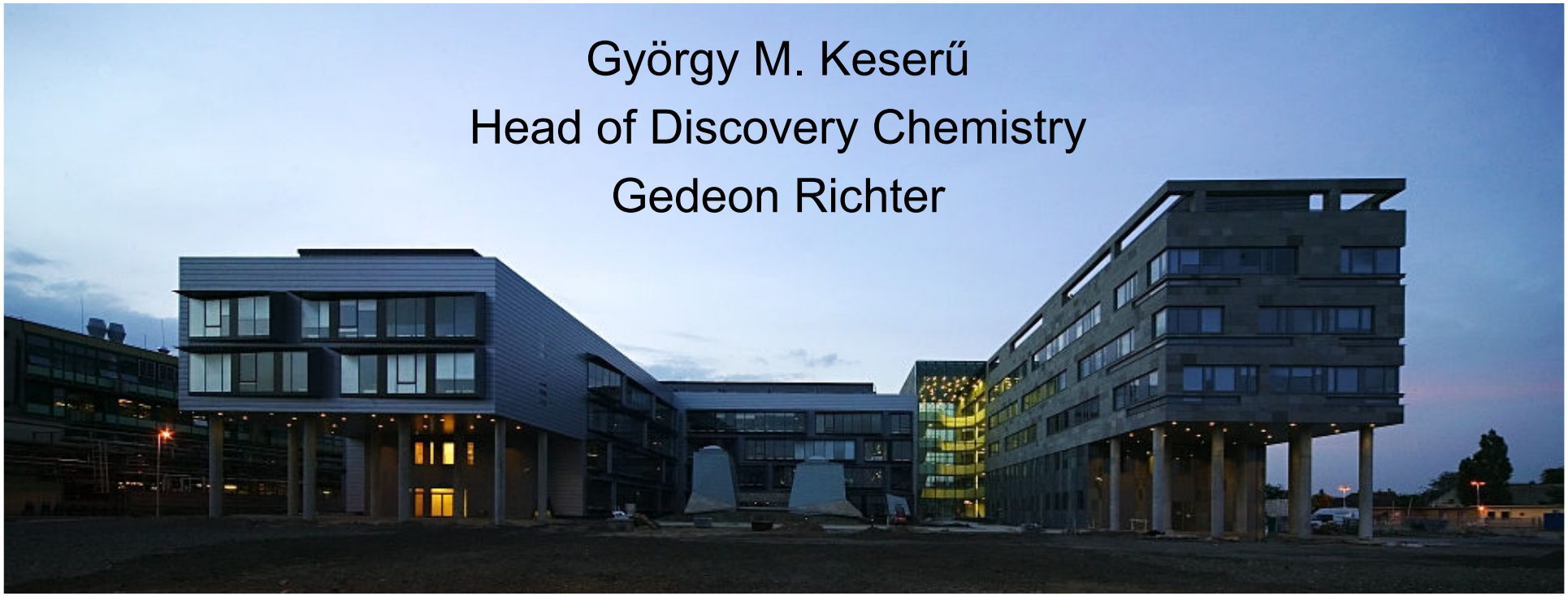
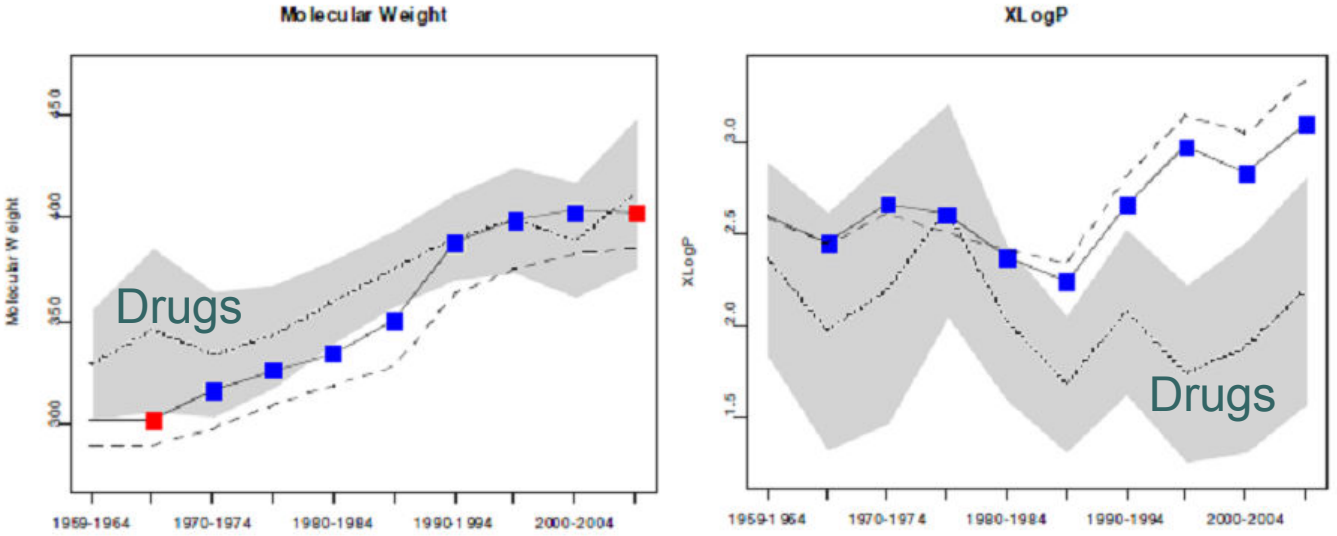
Thermodynamics guided lead discovery and optimization

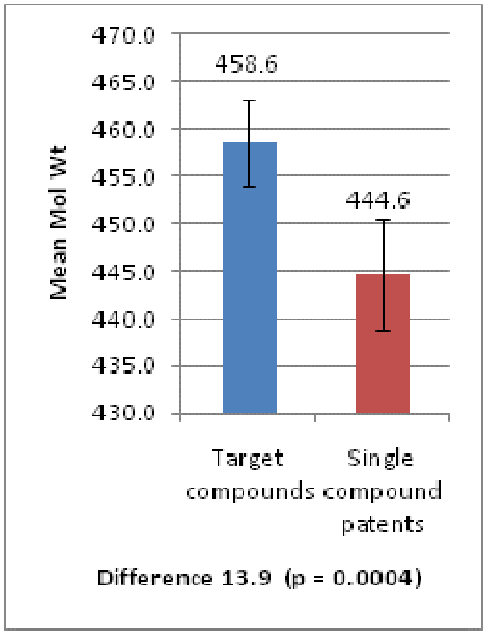


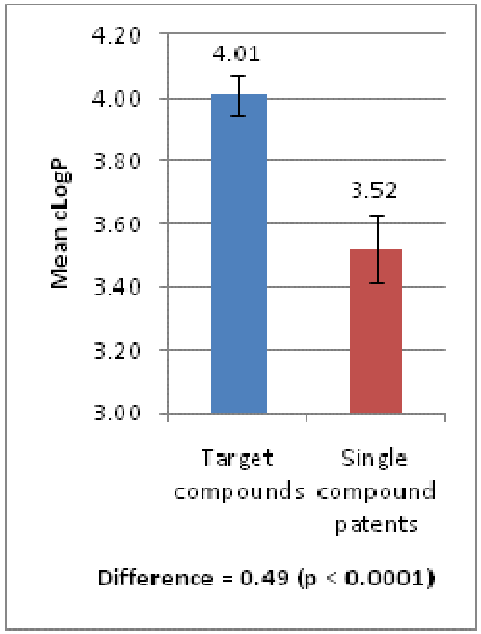
Property inflation in medicinal chemistry



J. Med. Chem. compounds (1959-2009)

Walters et al. JMC 2011





Patent compounds
18 companies (2000-2010)

Leeson, St-Gallay
NRDD 2011

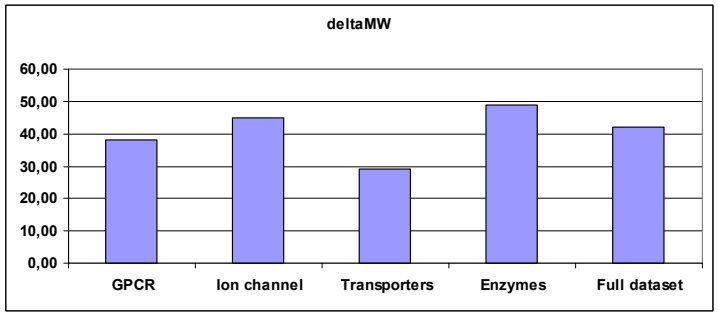
Diagnosis: molecular obesity

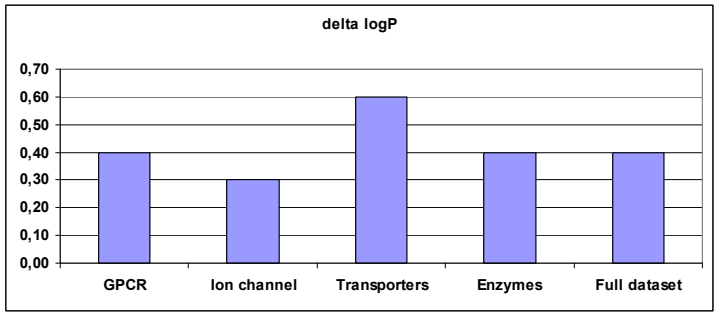
- A condition characterized by a suboptimal combination of physicochemical features that may affect lead discovery, optimization and further development adversely
- Diagnostic criteria:
  - High MW
  - High logP
  - Low LE, low LLE and high LELP (LELP=logP/LE)
- Main development risks:
  - Pharmakokinetics
  - Promiscuity, non-specific interactions, side effects
  - Toxicology

Keserű: Lead obesity DoF 2009
Hann: Molecular obesity MCC 2011

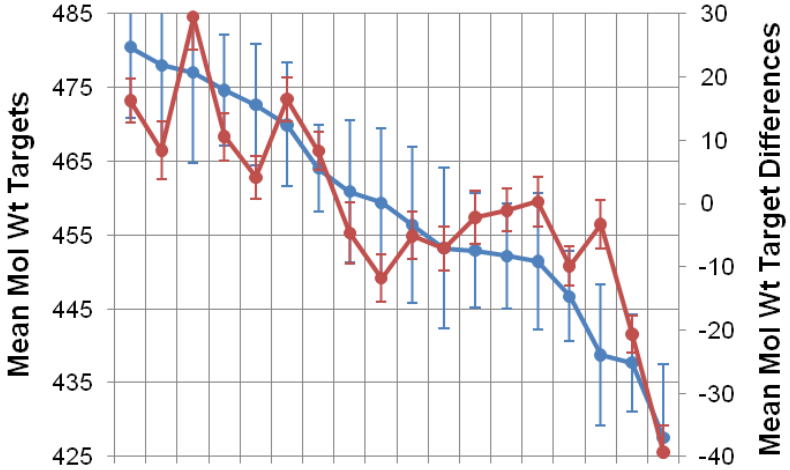
It is less dependent on the target

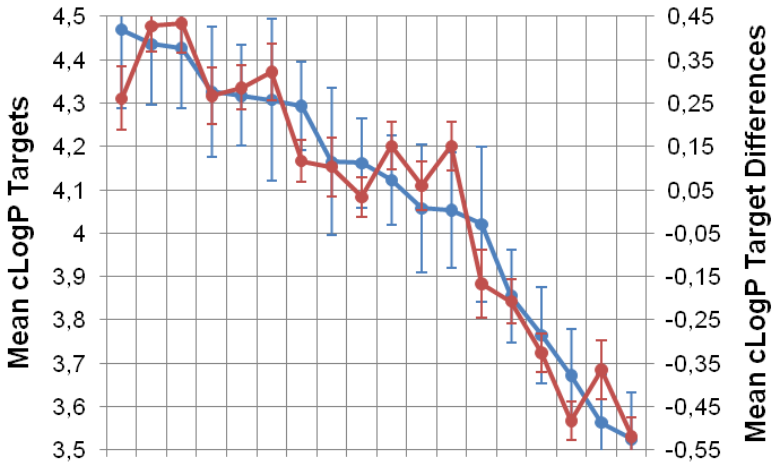
o Property changes in 1680 medicinal chemistry optimizations





Morphy JMC 2006



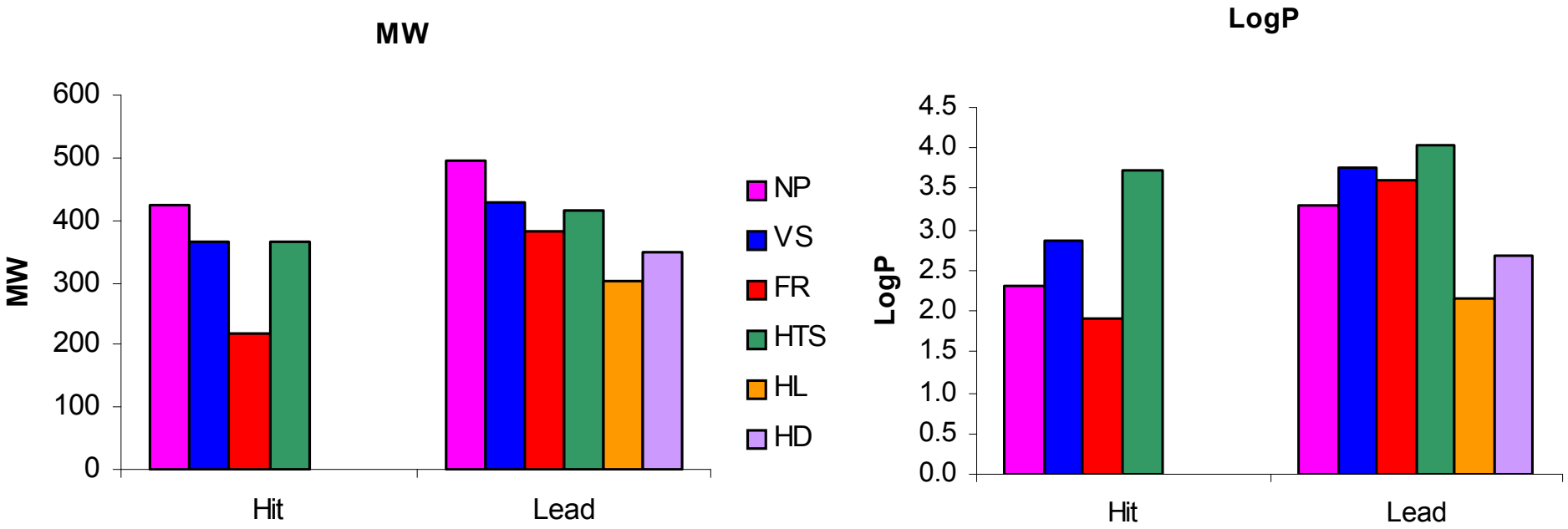


o 14435 patents, 791,722 compounds by 18 companies 2000-2010

o Molecular obesity might have cultural and strategic background

Leeson, St-Gallay NRDD 2011

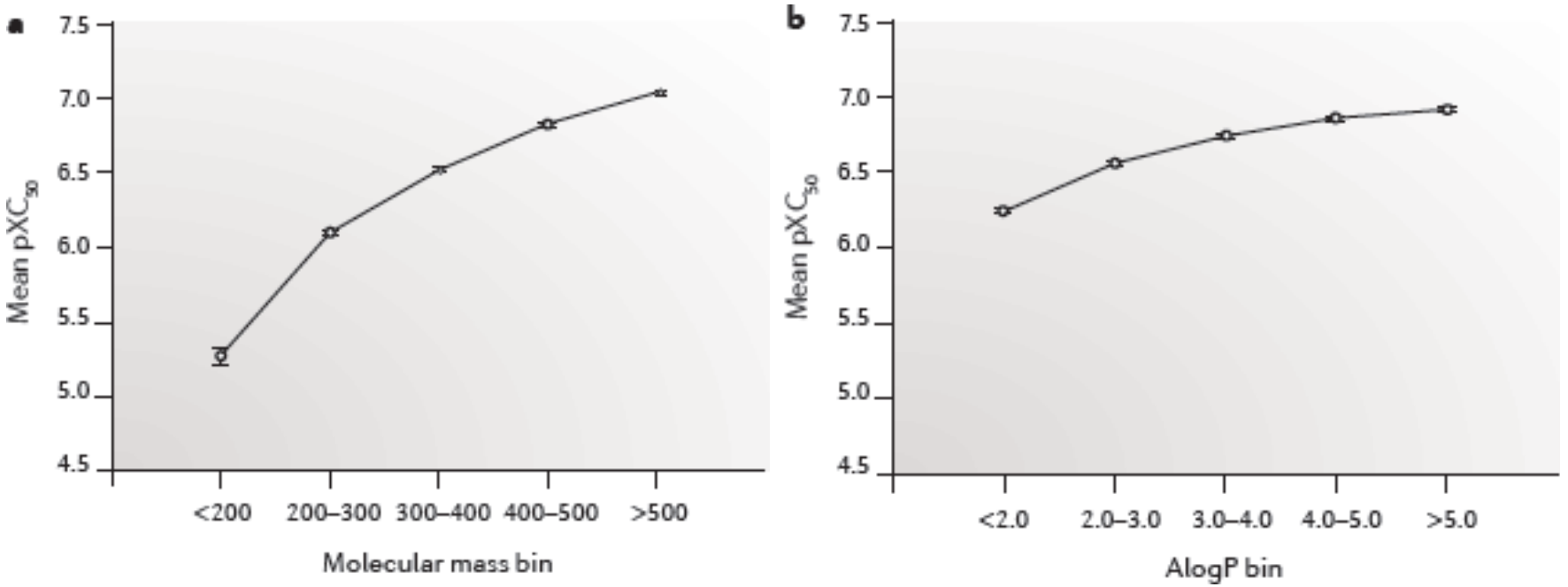
… and the lead generation strategy



- 335 HTS and 84 alternative hit-lead pairs from 2000-2008
- Present leads are more lipophilic and more complex than historic leads
- Molecular obesity seems independent on the lead generation strategy
- The influence of the optimization strategy and practice (cultural aspects)

Keserű, Makara NRDD 2009

but seems to depend on potency



More than 200,000 compounds from ChEMBL database

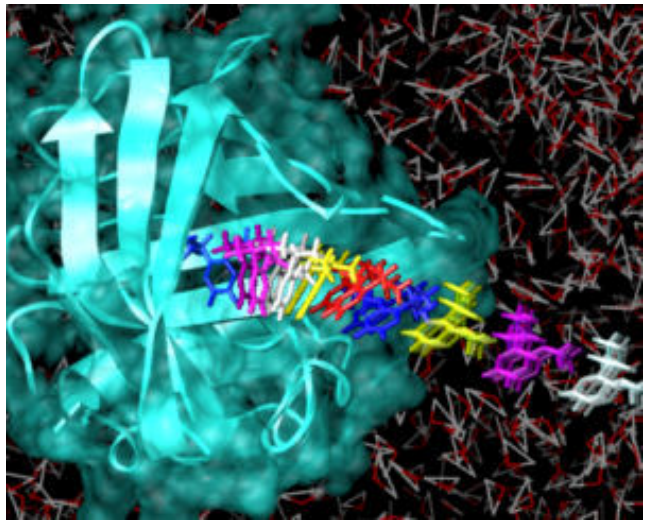
Gleeson et al. NRDD 2011

Potency optimization as a primary drive of molecular obesity

Process	pPot change	MW change	logP change	Reference
Early opt.	1.39	51.5	0.27	Keserű et al. Nature Rev Drug Disc 2009
Lead opt. (average)		42.0	0.5	Hann et al. J. Chem Inf Sci 2001
Lead opt. (successful)	2.08	89.9	0.05	Perola J Med Chem 2010

Potency addiction from a thermodynamic perspective

- Ligand
  - conformational rearrangement
  - desolvation



- Receptor
  - conformational rearrangement
  - desolvation by the ligand

- Receptor- ligand complex
  - Receptor mediated resolvation of the ligand

Ferenczy, Keserű DDT 2010

Optimization strategies

- The primary objective of optimization is increasing affinity

$$RT\ \ln K_d = \Delta G_{binding} = \Delta H - T\Delta S$$

- The optimization challenge is overriding enthalpy-entropy compensation
- Optimization strategies
  - Enthalpic optimization: decreasing ΔH
  - Entropic optimization: increasing ΔS
  - Combined optimization

Ferenczy, Keserű DDT 2010

Enthalpic optimization

- Decrease in ΔH needs new interactions between the ligand and the receptor
  - H-bonds, salt bridges
  - van der Waals contacts
- Enthalpic optimization is difficult:
  - New interactions require new donors/acceptors
  - Only H-bonds with good geometry provide ΔH reward
  - These new heteroatoms disfavor desolution resulting ΔS penalty
  - New interactions reduce flexibility resulting ΔS penalty
- Gain in ΔH could easily be compensated by ΔS penalty from multiple sources

Ferenczy, Keserű DDT 2010

Entropic optimization

- Increase in ΔS from ligand side could be achieved by
  - Increasing the lipophilicity
  - Decreasing flexibility
- Entropic optimization is less difficult
  - More lipophylic compounds desolvate easily resulting significant reward in ΔS
  - Lipophilic compounds replace water at lipophilic binding sites resulting further reward in ΔS
  - Chain-ring strategies decrease ΔS_{conf} penalty
- Gain in ΔS could hardly be compensated by ΔH penalty

Ferenczy, Keserű DDT 2010

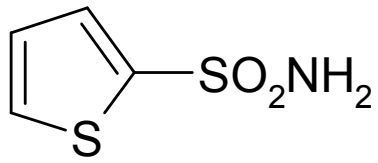
Physchem profile of high affinity and high enthalpy compounds

Physicochemical property	High affinity (pK_d>8, n = 172)	High entropy (pK_S>8, n = 123)	High enthalpy (pK_H>8, n = 188)
pK_d	9.19	8.07	6.66
Molecular mass	557.30	596.60	384.99
LogP	3.36	3.29	1.56
Number of non-hydrogen atoms	39.56	42.47	26.72
Number of rotatable bonds	11.26	12.59	7.44
Number of charged atoms	0.08	0.10	0.30
Number of hydrogen-bond acceptors	6.44	6.84	6.59
Number of hydrogen-bond donors	3.95	4.56	3.34
Apolar surface area	404.55	444.58	240.86

Hann, Keserű NRDD2012

Enthalpic optimization is not always straightforward

- Enthalpic optimization via hydrophobic interactions – the role of binding site waters (carbonic anhydrase)



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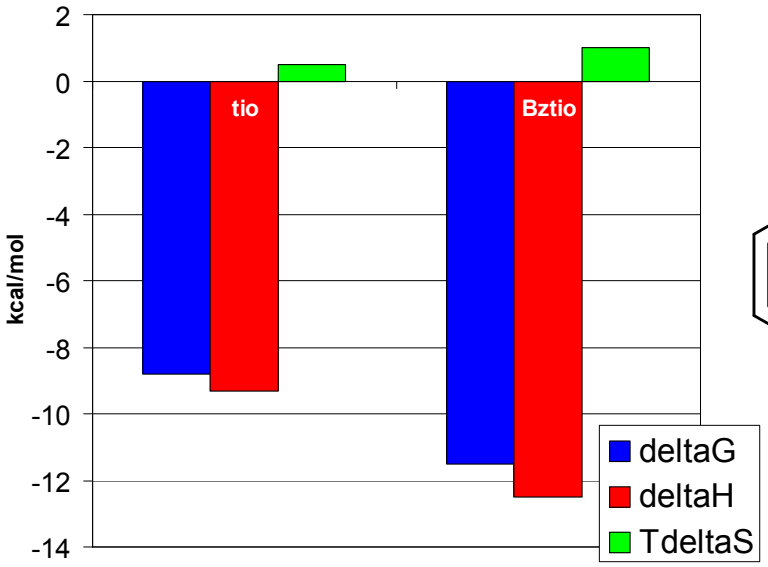
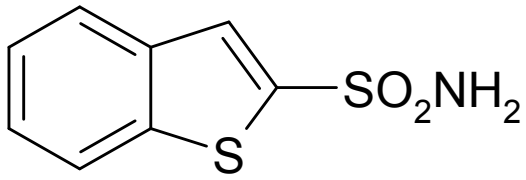




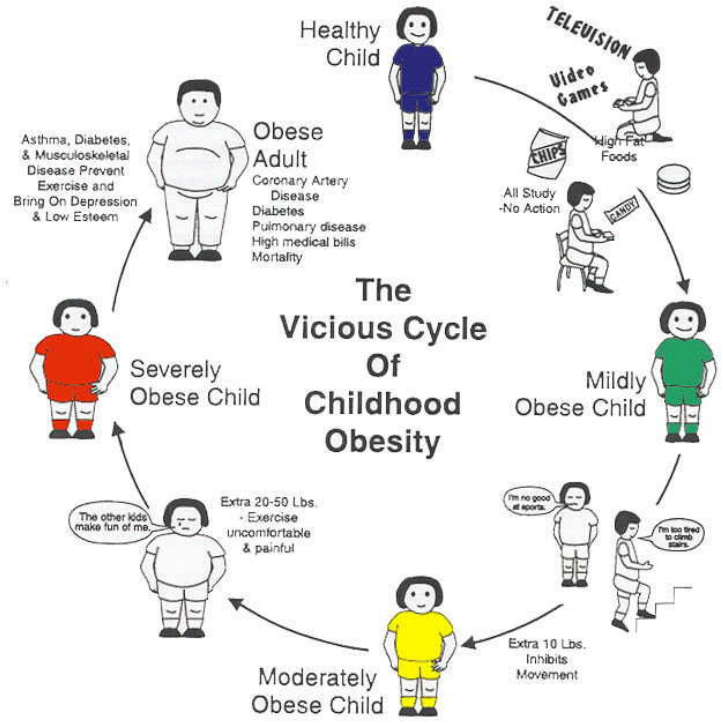
Bztio

- Cooperativity in H-bonding and hydrophobic interactions (thrombin)

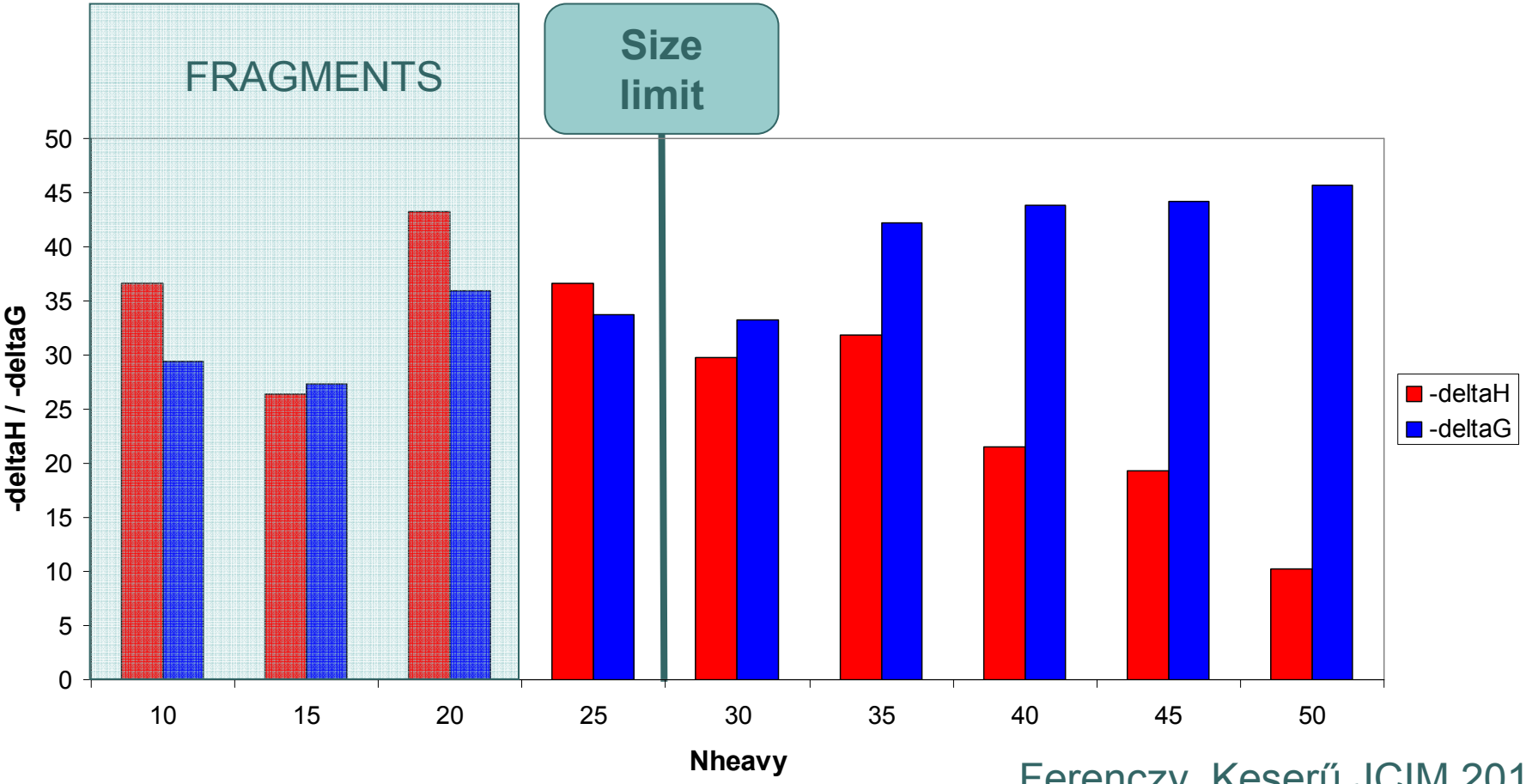
Sherman and Whitesides PNAS 2011; Klebe JMC 2010

How could medicinal chemistry contribute to high quality DCs?

- Being enthalpic in Nature and Nurture
  - Select enthalpic starting points (enthalpic nature)
  - Optimize these enthalpically (enthalpic nurture)



Enthalpy driven binding is limited to small compounds

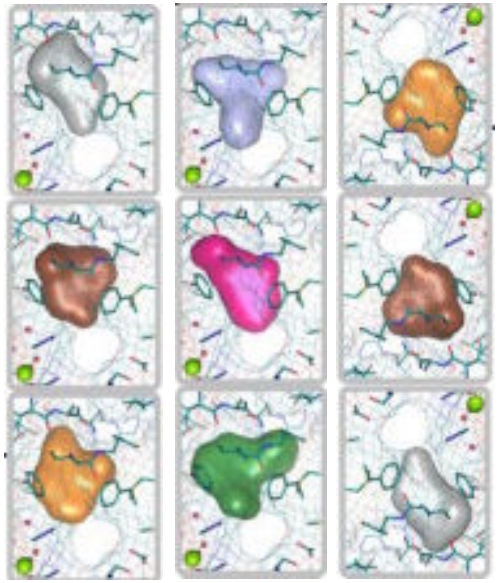


ITC data for 757 protein-ligand complexes

Ferenczy, Keserű JCIM 2010
Hann, Keserű NRDD 2012

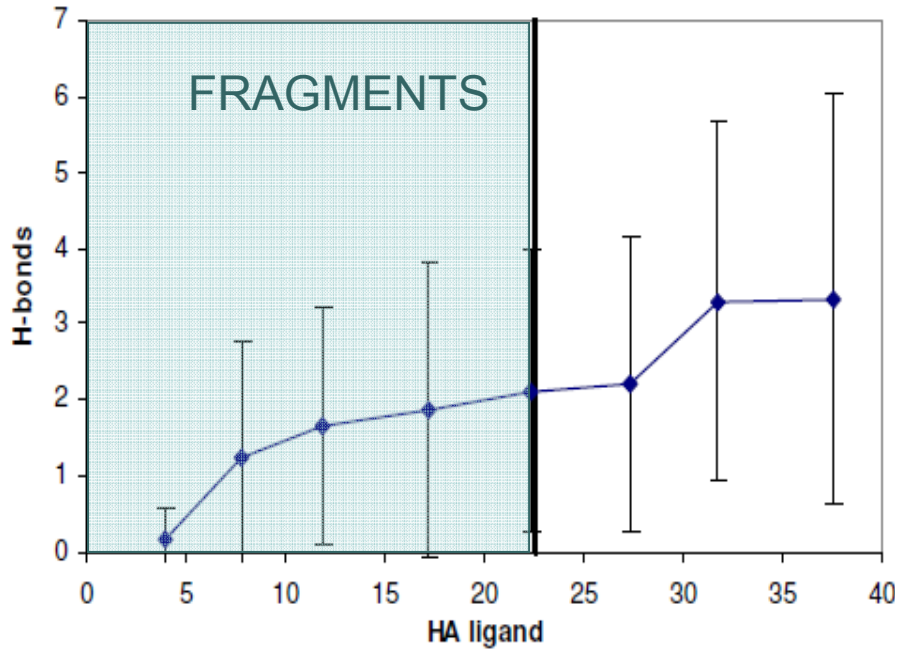
Fragment based approaches

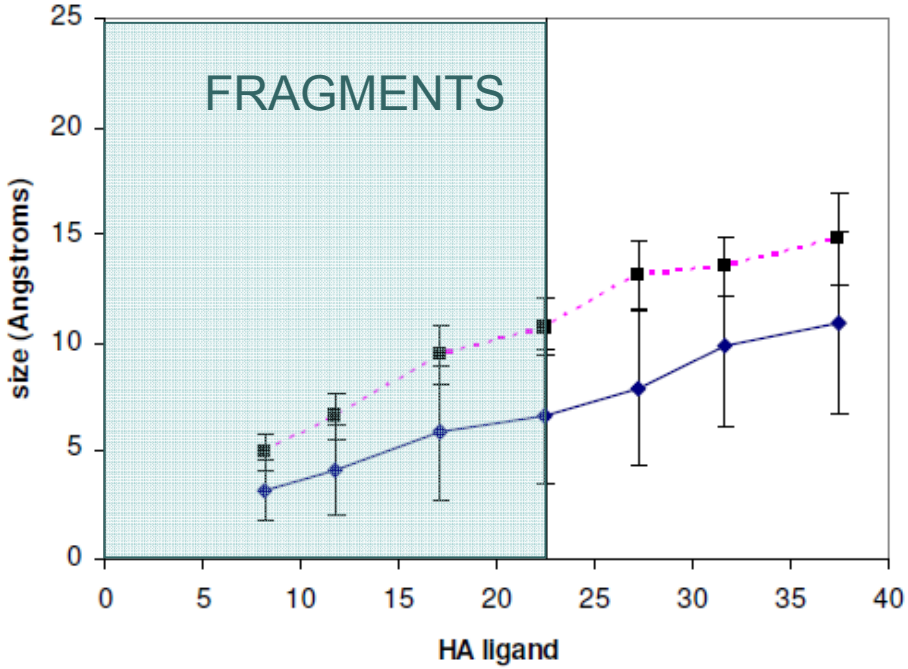
- Low molecular weight, low complexity, polar and soluble compounds
- Properties fit well to that of enthalpic compounds
  - MW $\leq$ 300 ($N_{heavy} \leq 22$)
  - Log P $\leq$ 3
  - H-donors $\leq$ 3
  - H-acceptors $\leq$ 3
  - Number of rotational bonds $\leq$ 6
  - Polar surface $\leq$ 130 Å^2
  - Number of rings 1-3
  - Sufficient water solubility



Fragments bind to hot spots

- Fragments form limited number of polar interactions within a small region of protein binding sites



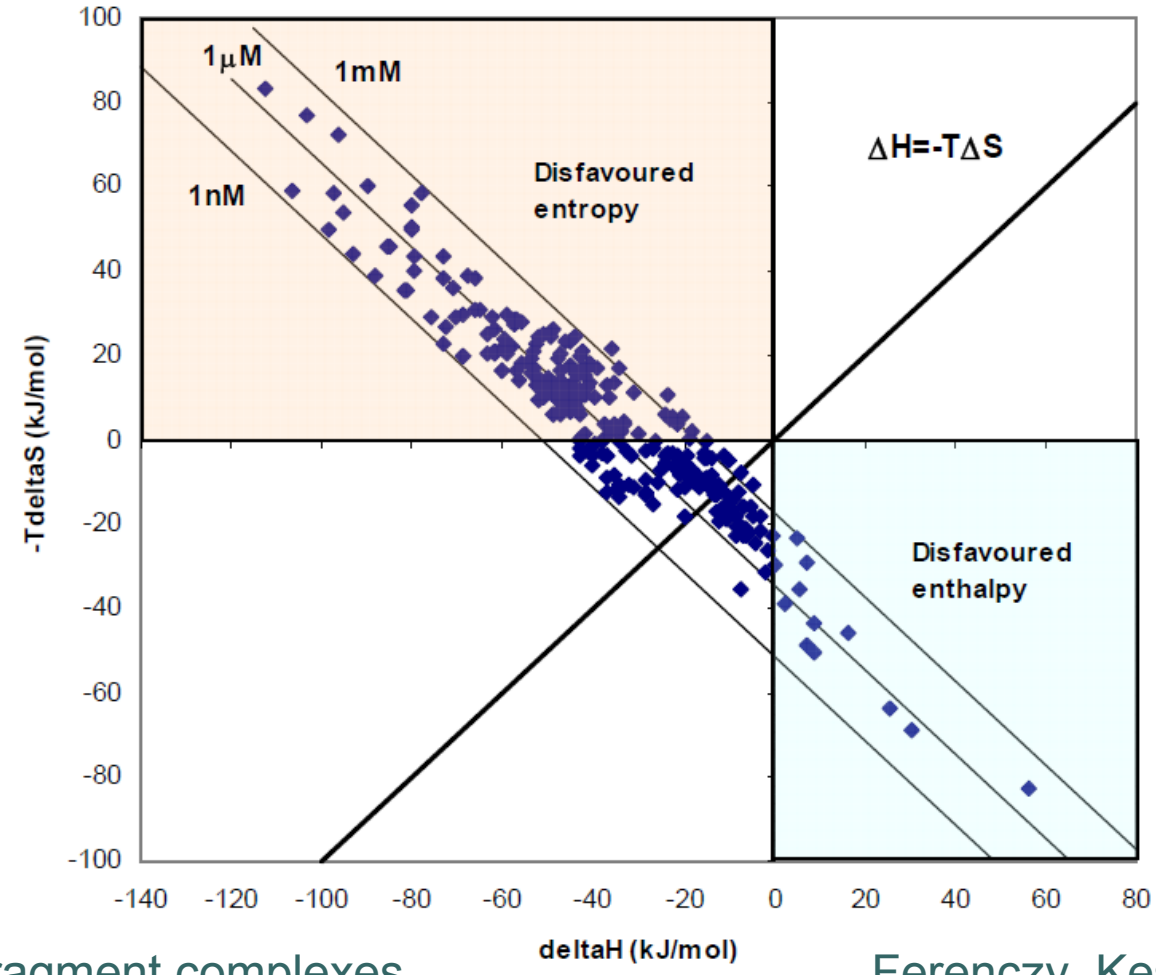


Data from 1297 high resolution PDB complexes with optimal H-bonding geometries

Ferenczy, Keserű JCIM 2012

Fragments bind enthalpically

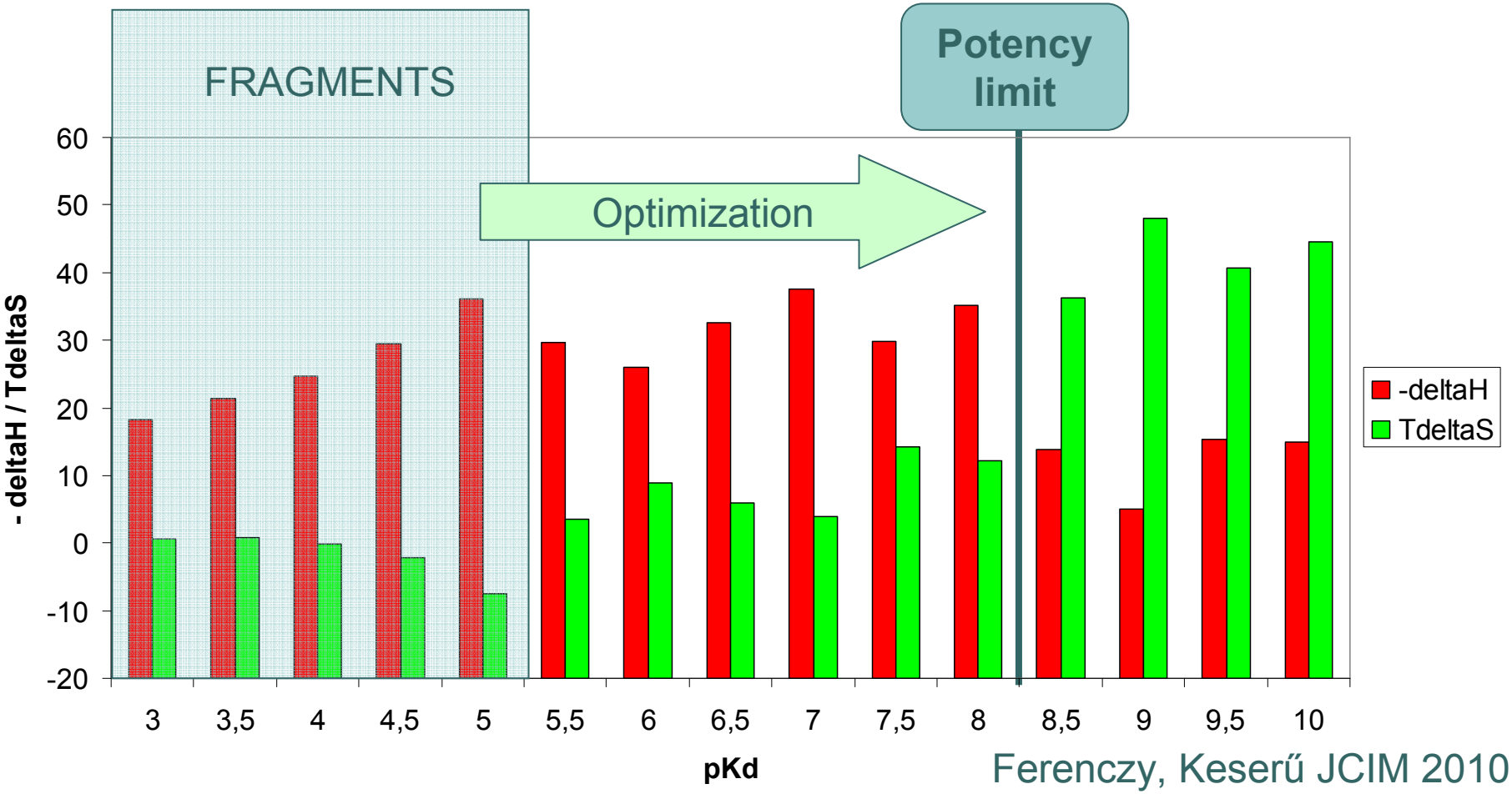
- Fragments are suitable enthalpic starting points



ITC data for 284 fragment complexes

Ferenczy, Keserű JCIM 2012

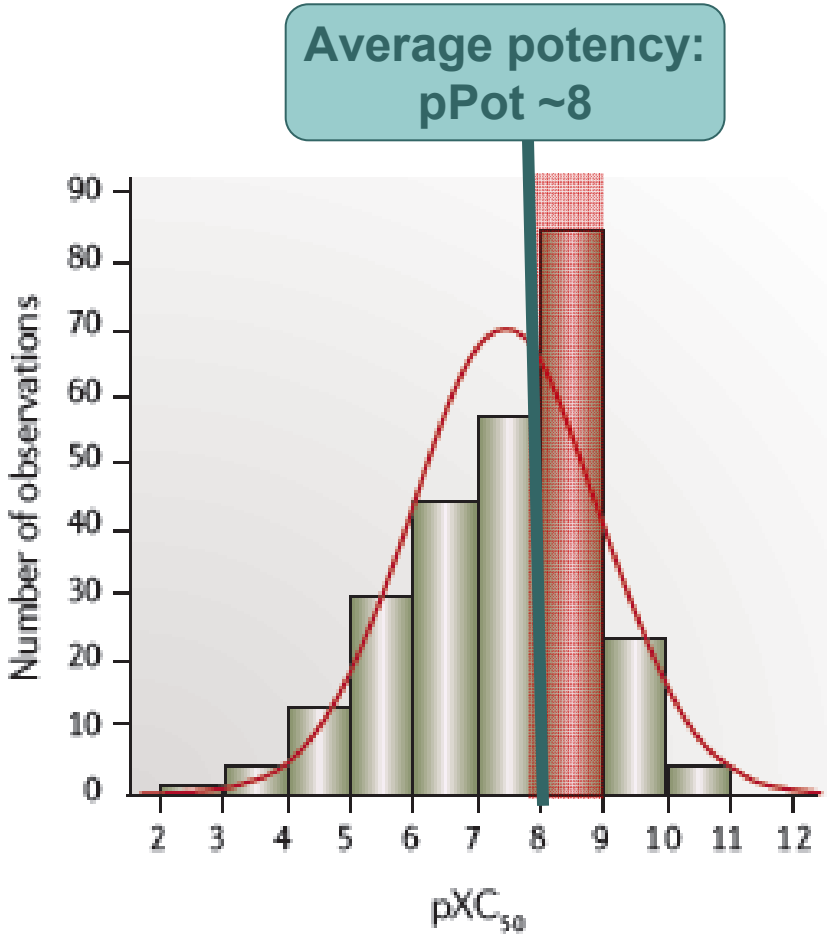
High potency is typically achieved by entropy

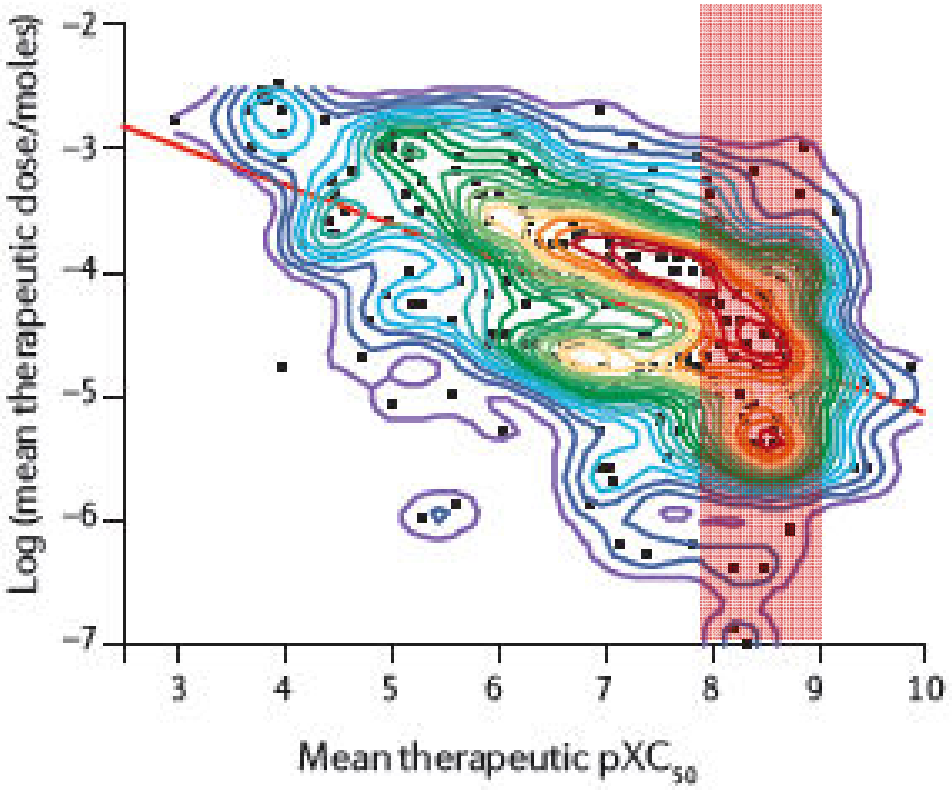


ITC data for 757 protein-ligand complexes

Ferenczy, Keserű JCIM 2010
Hann, Keserű NRDD 2012

How much potency is needed?

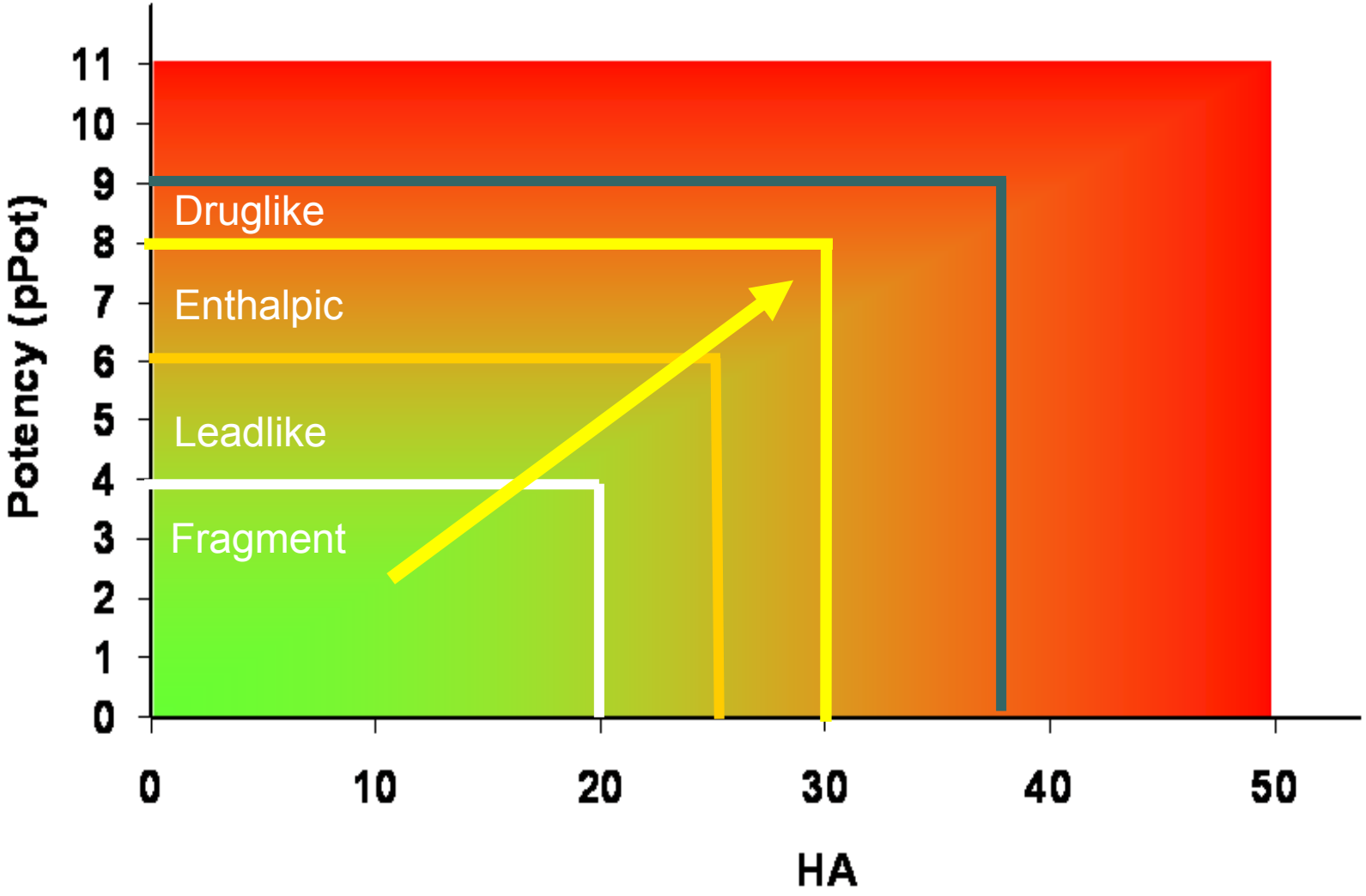




Data for 261 oral drugs

Gleeson et al. NRDD, 2011

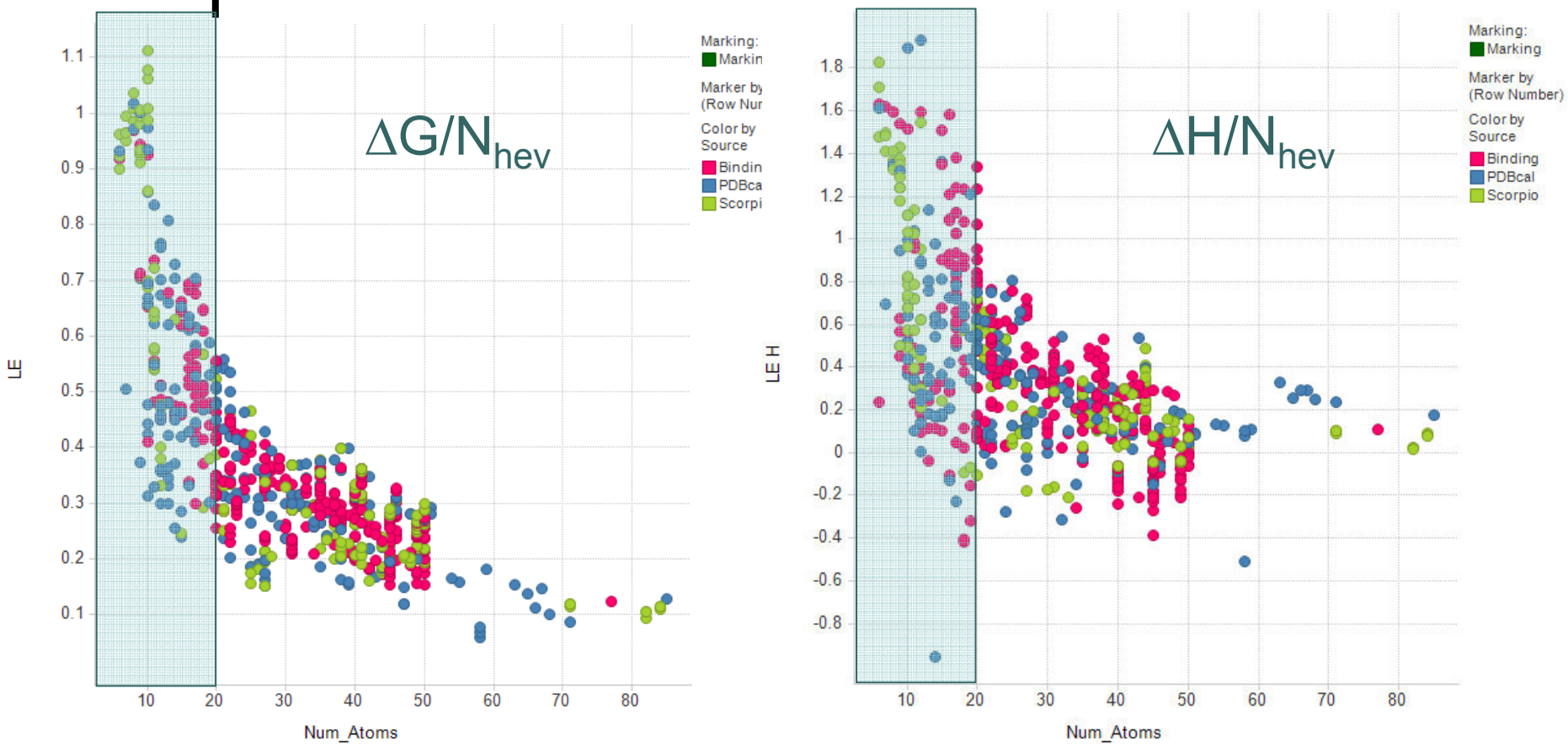
Potency optimization – enthalpic in nurture



Control in size and lipophilicity

- Improve the potency with minimal increase in size and lipophilicity
- Ligand efficiency concept
  - LE = $\Delta G/N_{hev}$ and derivatives
  - SILE= $\Delta G/(N_{hev})^{0.3}$
- Lipophilic efficiency metrics
  - LLE = pPot - logP
  - LELP = logP / LE (includes size)

LEI and thermodynamics

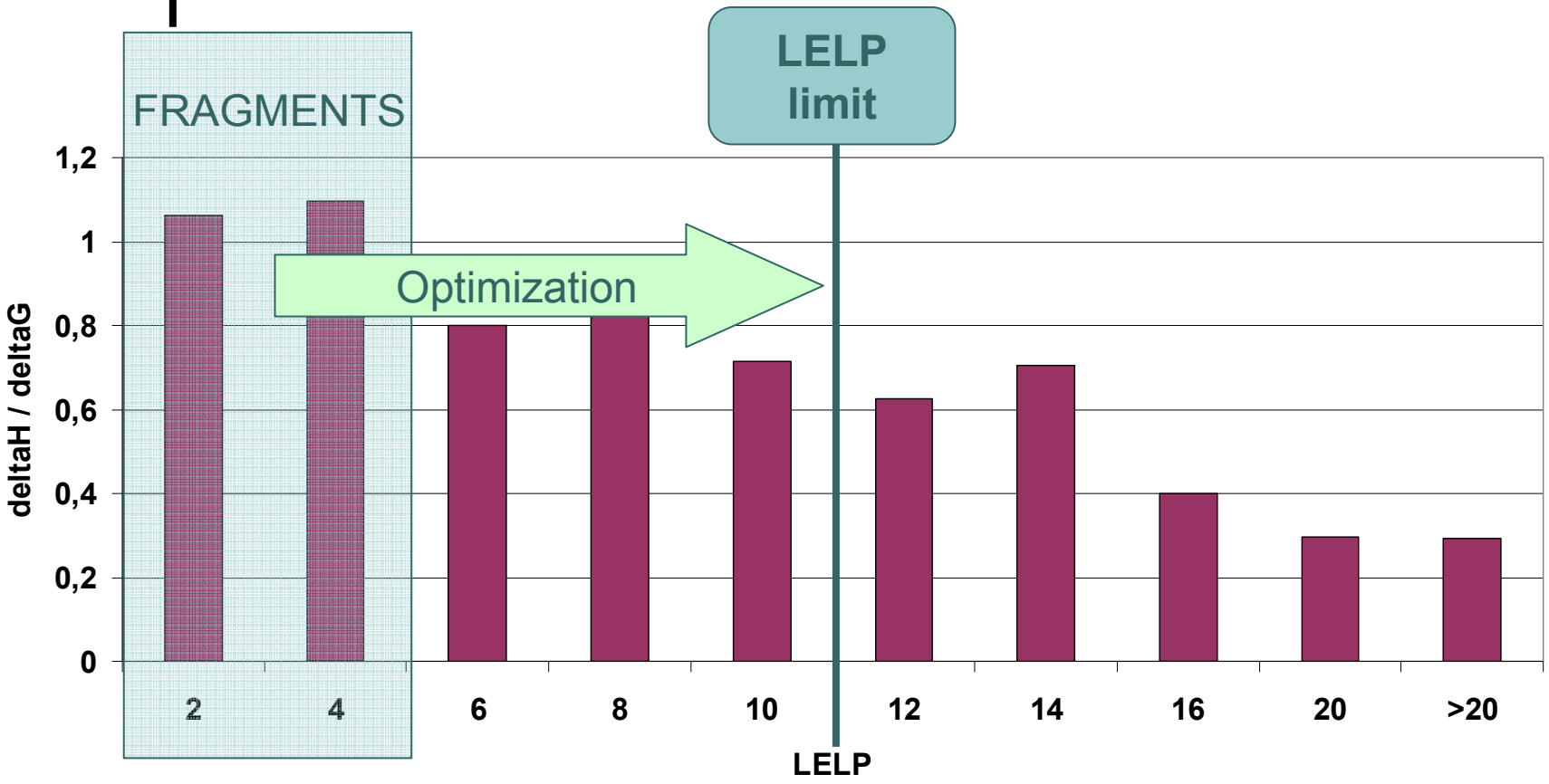


- Size dependence on ligand efficiency is mostly the consequence of enthalpy
- High enthalpy fragments are typically more potent
- Focusing on binding enthalpy would maximize the ligand efficiency of fragments

ITC data for 757 protein-ligand complexes

Reynolds, Leeson, Keserű 2012 in prep.

LEI and thermodynamics



- Enthalpic contribution decreases with increasing LELP
- Monitoring LELP values might help enthalpic optimizations

ITC data for 543 protein-ligand complexes

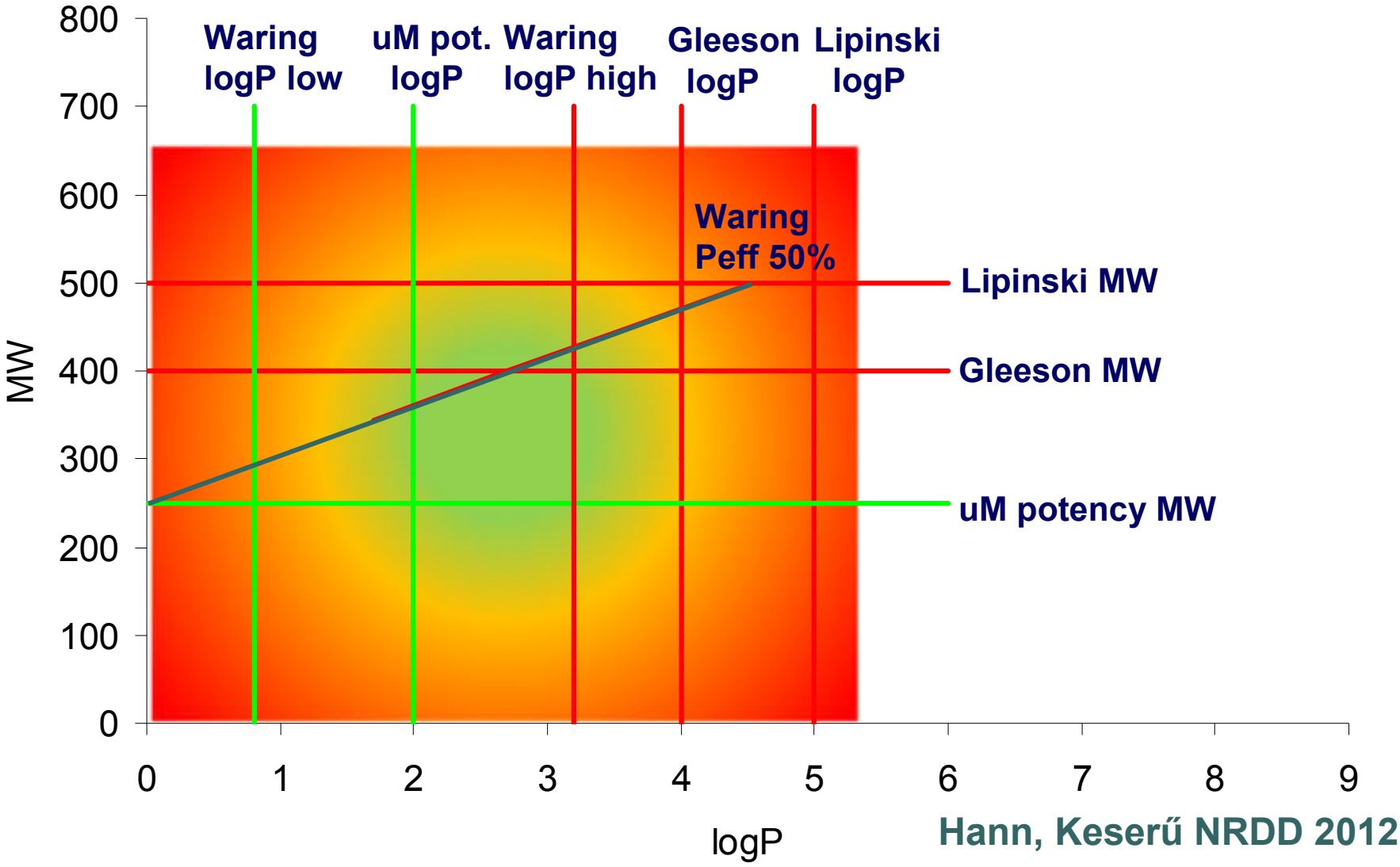
Keserű unpublished 2012

Trends in optimizations

Process	pPot change	MW change	logP change	LE change	SILE change	LLE change	LELP change
HTS based optim.	1.39	51.5	0.27	0.02	0.58	1.1	0.1
Fragment optim.	2.71	185.1	1.3	-0.04	0.72	1.4	4.8
Fragment – successful	3.05	168.1	0.7	-0.02	0.84	2.6	1.5
Lead opt. – successful	2.08	89.9	0.05	0.01	0.85	2.1	-1.1

Keserű, Makara NRDD 2009; Perola JMC 2010; Keserű, Ferenczy 2012 in prep.

The sweet spot



Hann, Keserű NRDD 2012

How to reach the sweet spot?

- Pick up enthalpic leads
- This provides a suitable strating point with balanced potency and physchem profile
- Optimize parallel against potency, selectivity and ADME
- Monitor ligand efficiency indices rather than potencies
- Stop optimization if further increase in potency could only achieved at the expense of the physchem parameters
- This point can be detected by monitoring binding thermodynamics

Nutrition Facts

Serving Size 1 compound
Servings Per Discovery Program 2

Amount Per Serving

Calories 260 Calories from Fat 120

		% Value*
Total entropy	kcal	**20%**
conformational		**25%**
solvation		16%
molecular mass		
logP		
Total enthalpy	kcal	**10%**
Specific interactions		25%
conformational		12%
solvation		16%

*Percent Values are based on asuccesful drugs.

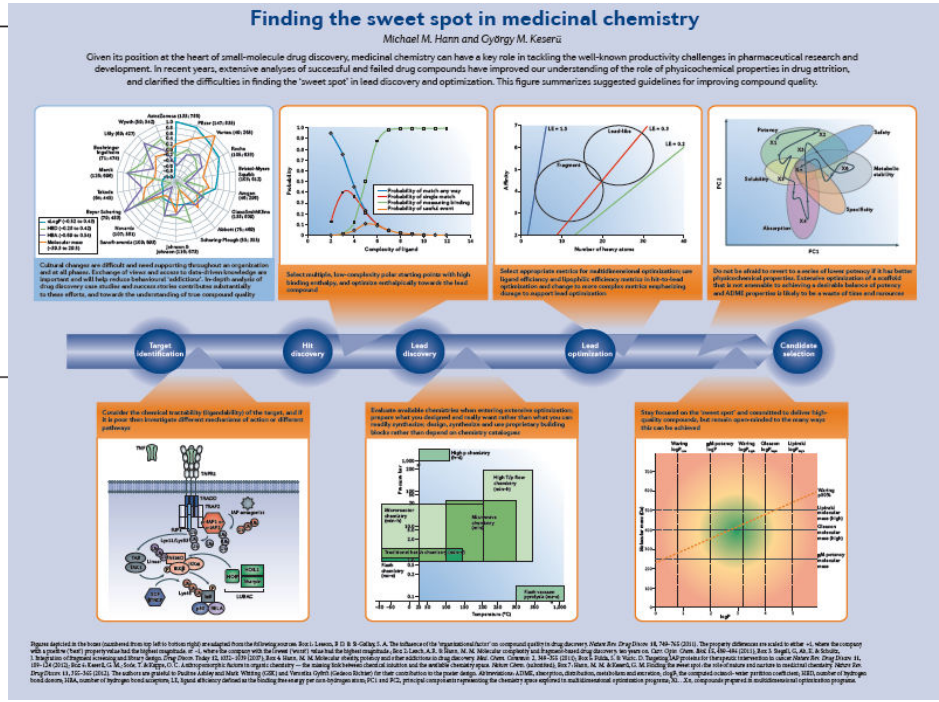
Finding the sweet spot
- with a free poster to download

A GUIDE TO DRUG DISCOVERY — OPINION

Finding the sweet spot: the role of nature and nurture in medicinal chemistry

Michael M. Hann and György M. Keserü

nature REVIEWS DRUG DISCOVERY



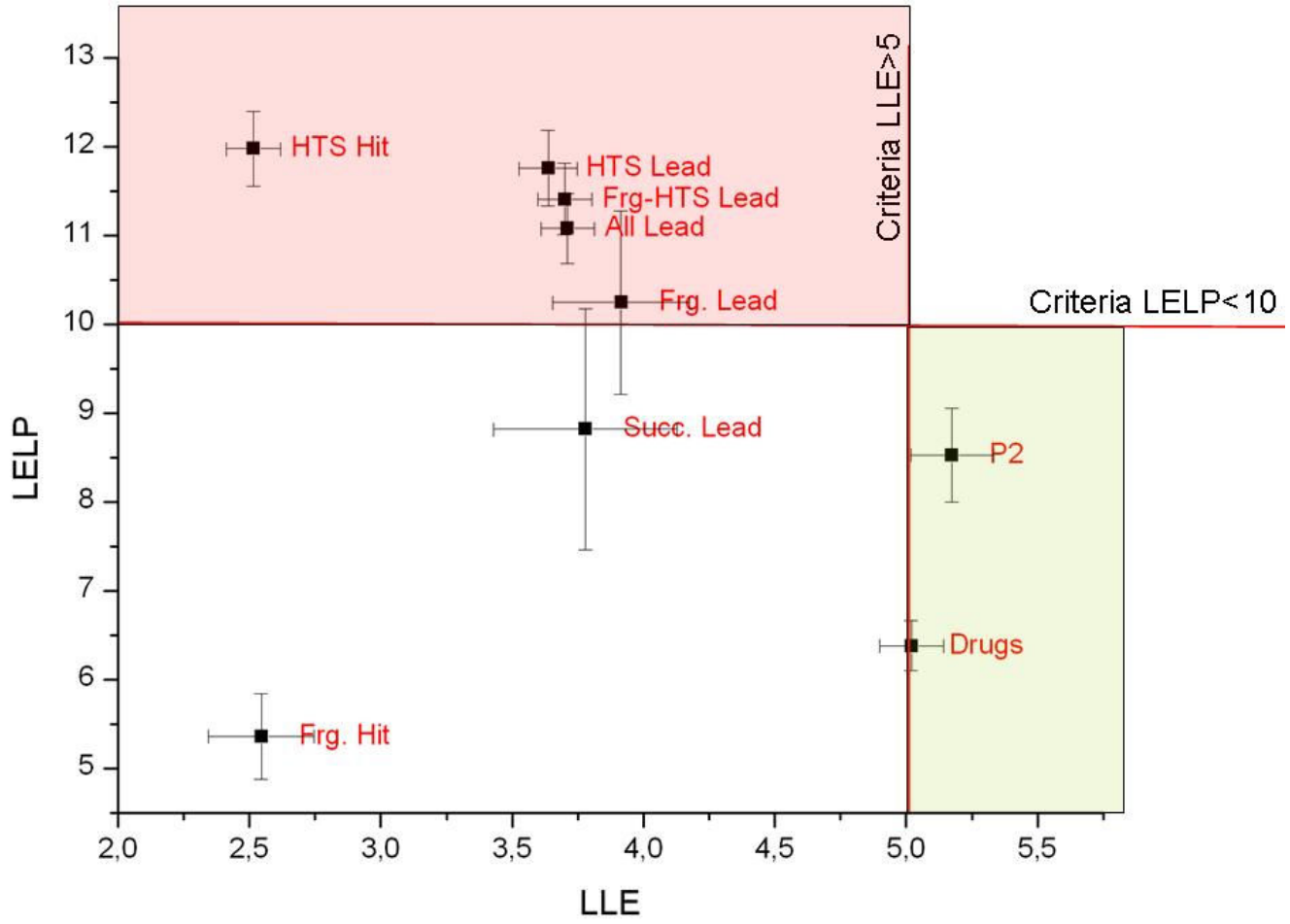
http://www.nature.com/nrd/journal/v11/n5/extref/***nrd3701-s1***.pdf

Acknowledgement

- György Ferenczy ex SANOFI
- Mike Hann and Paul Leeson GlaxoSmithKline
- Greg Makara ex MERCK
- Glyn Williams astex
- Chuck Reynolds ex Johnson & Johnson


Thank you for your attention

Lipophilic efficiency metrics separate development stages



Keserű et al, JMC 2012