Thermodynamics guided lead discovery and optimization

György M. Keserű
Head of Discovery Chemistry
Gedeon Richter
Property inflation in medicinal chemistry

- Dr. 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=\text{logP}/\text{LE})

- Main development risks:
  - Pharmacokinetics
  - Promiscuity, non-specific interactions, side effects
  - Toxicology
It is less dependent on the target

- Property changes in 1680 medicinal chemistry optimizations

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

- Molecular obesity might have cultural and strategic background
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

<table>
<thead>
<tr>
<th>Process</th>
<th>pPot change</th>
<th>MW change</th>
<th>logP change</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early opt.</td>
<td>1.39</td>
<td>51.5</td>
<td>0.27</td>
<td>Keserű et al. Nature Rev Drug Disc 2009</td>
</tr>
<tr>
<td>Lead opt.</td>
<td></td>
<td>42.0</td>
<td>0.5</td>
<td>Hann et al. J. Chem Inf Sci 2001</td>
</tr>
<tr>
<td>(average)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead opt.</td>
<td>2.08</td>
<td>89.9</td>
<td>0.05</td>
<td>Perola J Med Chem 2010</td>
</tr>
<tr>
<td>(successful)</td>
<td></td>
<td></td>
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</table>
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
The primary objective of optimization is increasing affinity

\[ RT \ln K_d = \Delta G_{\text{binding}} = \Delta H - T \Delta S \]

The optimization challenge is overriding enthalpy-entropy compensation

Optimization strategies
- Enthalpic optimization: decreasing \( \Delta H \)
- Entropic optimization: increasing \( \Delta S \)
- Combined optimization

Ferenczy, Keserű DDT 2010
Enthalpic optimization

- Decrease in $\Delta H$ 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 $\Delta H$ reward
  - These new heteroatoms disfavor desolution resulting $\Delta S$ penalty
  - New interactions reduce flexibility resulting $\Delta S$ penalty
- Gain in $\Delta H$ could easily be compensated by $\Delta S$ penalty from multiple sources

Ferenczy, Keserű DDT 2010
Entropic optimization

- Increase in $\Delta S$ from ligand side could be achieved by
  - Increasing the lipophilicity
  - Decreasing flexibility
- Entropic optimization is less difficult
  - More lipohlypic compounds desolvate easily resulting significant reward in $\Delta S$
  - Lipophilic compounds replace water at lipophilic binding sites resulting further reward in $\Delta S$
  - Chain-ring strategies decrease $\Delta S_{\text{conf}}$ penalty
- Gain in $\Delta S$ could hardly be compensated by $\Delta H$ penalty

Ferenczy, Keserű DDT 2010
Physchem profile of high affinity and high enthalpy compounds

<table>
<thead>
<tr>
<th>Physicochemical property</th>
<th>High affinity (p$K_d$ &gt; 8, n = 172)</th>
<th>High entropy (p$K_s$ &gt; 8, n = 123)</th>
<th>High enthalpy (p$K_H$ &gt; 8, n = 188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p$K_d$</td>
<td>9.19</td>
<td>8.07</td>
<td>6.66</td>
</tr>
<tr>
<td>Molecular mass</td>
<td>557.30</td>
<td>596.60</td>
<td>384.99</td>
</tr>
<tr>
<td>LogP</td>
<td>3.36</td>
<td>3.29</td>
<td>1.56</td>
</tr>
<tr>
<td>Number of non-hydrogen atoms</td>
<td>39.56</td>
<td>42.47</td>
<td>26.72</td>
</tr>
<tr>
<td>Number of rotatable bonds</td>
<td>11.26</td>
<td>12.59</td>
<td>7.44</td>
</tr>
<tr>
<td>Number of charged atoms</td>
<td>0.08</td>
<td>0.10</td>
<td>0.30</td>
</tr>
<tr>
<td>Number of hydrogen-bond acceptors</td>
<td>6.44</td>
<td>6.84</td>
<td>6.59</td>
</tr>
<tr>
<td>Number of hydrogen-bond donors</td>
<td>3.95</td>
<td>4.56</td>
<td>3.34</td>
</tr>
<tr>
<td>Apolar surface area</td>
<td>404.55</td>
<td>444.58</td>
<td>240.86</td>
</tr>
</tbody>
</table>

Hann, Keserű NRDD2012
Enthalpic optimization is not always straightforward

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

- 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
  - $\text{MW} \leq 300 \ (N_{\text{heavy}} \leq 22)$
  - $\text{Log P} \leq 3$
  - H-donors $\leq 3$
  - H-acceptors $\leq 3$
  - Number of rotational bonds $\leq 6$
  - Polar surface $\leq 130 \text{ Å}^2$
  - 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?

Average potency: pPot ~8

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
  - $LE = \Delta G / N_{\text{hev}}$ and derivatives
  - $SILE = \Delta G / (N_{\text{hev}})^{0.3}$
- Lipophilic efficiency efficiency metrics
  - $LLE = pPot - \log P$
  - $LELP = \log P / LE$ (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

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

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

- Waring logP low
- uM pot. logP
- Waring logP high
- Gleeson logP
- Lipinski logP

Lipinski MW, Gleeson MW, uM potency MW

Hann, Keserű NRDD 2012
How to reach the sweet spot?

- Pick up enthalpic leads
- This provides a suitable starting 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
Finding the sweet spot: the role of nature and nurture in medicinal chemistry

Michael M. Hann and György M. Keserü

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

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- Greg Makara ex MERCK
- Glyn Williams ex astex
- Chuck Reynolds ex Johnson & Johnson
Thank you for your attention.
Lipophilic efficiency metrics separate development stages

Keserű et al, JMC 2012