Will the Drugs of the Future Analyze like the Drugs of the Past?

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The bottom line message

• Chemistry structures for oral drugs are constrained by fundamental principles
• Expect small molecule chemistry to be like the past
• Or maybe more topologically interesting and chiral
Aqueous Solubility and Permeability Data Must be Provided to Chemistry as Early as Possible to Avoid Oral Absorption Problems
Minimum Acceptable Solubility in ug/mL Bars shows the minimum solubility for low, medium and high permeability \((Ka)\) at a clinical dose.

Distribution Parameters for 7483 INN/USAN Drugs Define the 90% Limits Corresponding to Properties Unfavorable for Oral Drug Absorption.
The “rule of five” mnemonic

• Poor absorption or permeation are more likely when there are:
• More than 5 H-bond donors.
• The MWT is over 500.
• The CLog P is over 5 (or MLOGP is over 4.15).
• The sum of N’s and O’s is over 10.
• Substrates for transporters and natural products are exceptions.
Rules and common sense

- Rules play to the probability
- Exceptions will always exist
- For non orally active compounds

The molecular properties and most commonly occurring structural elements are statistically analyzed to capture the differences between routes of administration.
Today’s reality in oral drugs

• Properties are worse in early discovery
• Approved drug properties are stable
• Properties improve through clinical
• Average MWT at approval is 350
Some targets are better than others

• Better
  — kinases
  — ion channels
  — aminergic GPCR’s

• Worse
  — proteases
  — phosphatases
  — protein protein interactions
Leads at Pfizer changed towards higher molecular weight and lipophilicity with the advent of high throughput screening.
What is new in screening

- Fragment screening
- MWT 175 – 225
- Optimizable by medicinal chemistry
- Rule of 3
- Screen at 100 um – 5 mM
- NMR, x-ray, MS
- **Bottom line - no trend to poor properties**
Upwards molecular weight trend in Merck advanced candidates
Upwards molecular weight trend in Pfizer, Groton early candidates
No increase in lipophilicity with time in Merck advanced candidates
Upwards lipophilicity trend with time in Pfizer, Groton early candidates
Increasing hydrogen bond acceptor trend with time in Merck candidates
No hydrogen bond acceptor trend with time in Pfizer, Groton candidates
Potency and delivery options

• 80% of oral IND’s are 1 mg/kg potency
• 10% of oral IND’s are 0.1 mg/kg potency
• Dose is the key factor
• 20 mg dose allows delivery options
  — pulmonary
  — dermal
  — sublingual
  — oral via low capacity transporters
Why high in-vivo potency is difficult

• In-vitro and in-vivo activity
  — do not scale linearly

• Low dose in-vivo
  — transporters are not saturated
  — compounds clear rapidly

• So excellent in-vitro
  — but not so good in-vivo
High in-vivo potency is luck

• Planning high in-vivo potency is impossible
• Transporters are not understood
• Technically difficult screening
  — double transfectants
  — 10 years in the future
• No chemistry guidance
• Assays needed to solve a problem
Funky strange compounds

- Don’t expect many strange structures that deviate from the “rule of 5”
- Unless a miracle happens and the transporter problem is solved soon
- Unless something happens to make discovery of high in-vivo potency possible
Poor intestinal permeability

• Unsolvable in formulation
  —“academic” science 10 years from reality
• Solvable in chemistry with pro-drugs
  —technically difficult
• Solvable in chemistry by structure changes
  —intramolecular H-bond
  —often limited by target biology limitations
Peptidomimetics increasing?

• Pro -
  – more protease targets in the human proteome than we expected

• Con
  – proteases are at the fringes of druggability
  – permeability issues are unsolvable in formulation
Historically few “innovator” targets / year

<table>
<thead>
<tr>
<th>CHEMISTRY</th>
<th>CAS</th>
<th>NAME</th>
<th>YEAR</th>
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<td>Precose</td>
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<td>Fosamax</td>
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<td>CellCept</td>
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<td>Plavix</td>
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<td>Tracleer</td>
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<td>Natrecor</td>
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<td>Kineret</td>
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<td>Xigris</td>
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<td>Recombinant activated protein C</td>
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</tbody>
</table>

24 New Ligands in 8 Years Across Everybody
Non combichem innovator drugs

Glucophage

Precose

Rapamune

Integrilin
Decline of natural products

• Similar decision across most of Pharma
  – pragmatic, based on results
  – chemistry complexity is no advantage unless needed

• Decline coincident with:
  – rise of automated chemistry
  – demise of phenotypic screening
  – decline of infectious disease research

• Resurrection:
  – watch for reversal of the above three trends
Nucleotide targets?

- Protein targets:
  - hydrophobic binding
- Nucleotide targets
  - ionic, H-bonding binding
- Where would you find a library for screening against nucleotide targets?
Space in screening and ligands

• Mechanistic screening
  – narrow target opportunity space

• Phenotypic screening
  – broad target opportunity space

• Typical medicinal chemistry compounds
  – broad chemistry space

• Natural products and diversity oriented synthesis
  – narrow chemistry space
Matching targets and ligand space

• Natural products and DOS
  – phenotypic targets - good
  – mechanistic targets – poor

• Typical medicinal chemistry
  – phenotypic targets – excellent: BUT
    • mechanism deciphering is tough
  – Mechanistic targets – good
    • mechanism is known so not an issue
Success rate in protein-protein interactions

Size of colored graphic = screening success at Pharmacopeia

Protein protein interactions

• Normal combichem does not work
• Natural products or DOS?
• Fragment screening on allostERIC sites??
Skeletal diversity in DOS Infinity libraries
DOS, the big experiment

- DOS works on protein protein interactions
  - big change in chemistry
  - topologically complex, chiral compounds

- DOS fails on protein protein interactions
  - business as usual in analytical chemistry