Polypharmacology – Foe or Friend?

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Introduction

• Polypharmacology is the ability of a compound to interact with and affect multiple targets.

• Aspirin is a well known polypharmacological drug that has been used successfully.

• Due to nonselectivity which lead to drugs’ adverse effects and toxicity, polypharmacology is discouraged by many researchers.

• However, this concept could be beneficial in intentionally designing multitarget drugs for the management of certain diseases by altering different pathways.

What is the Purpose?

To prove that targeted polypharmacology holds opportunities for the discovery of better drugs
In This Paper...

- Safety Panel Screening
  - Unintended *versus* Targeted Polypharmacology

- Promiscuity Predictions
  - Pharmacological Promiscuity Parameters

- Prevalence and Significance for Toxicity and Attrition

- Polypharmacological Drug Discovery
  - Efficacy and Safety Examples
  - Repurposing
  - Combinations of Drugs and Pharmacophores
New Trends in Safety Panel Screening and Promiscuity Prediction

• Adverse drug reactions and preclinical toxicity account for 30% of all drug candidate terminations in clinical trials.

• Many ADRs come from a drug’s unintended activity at an “antitarget”.

• Animal toxicity studies do not reliably predict antitarget-related ADRs in humans due to species differences.

• Thus, safety panel screening has been developed by research organizations in which drug candidates are screened against panels of up to 180 safety-relevant targets.

Table 1. Frequently Encountered Antitargets

<table>
<thead>
<tr>
<th>antitarget</th>
<th>hit rate&lt;sup&gt;a&lt;/sup&gt; (displacement assay) (%)</th>
<th>associated adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>hERG channel</td>
<td>(see text)</td>
<td>arrhythmia</td>
</tr>
<tr>
<td>serotonin 5-HT&lt;sub&gt;2B&lt;/sub&gt; receptor</td>
<td>14</td>
<td>agonists: valvulopathy, pulmonary hypertension</td>
</tr>
<tr>
<td>serotonin 5-HT&lt;sub&gt;2A&lt;/sub&gt; receptor</td>
<td>11</td>
<td>agonists: cognition impairment, hallucination</td>
</tr>
<tr>
<td>α&lt;sub&gt;1A&lt;/sub&gt; adrenergic receptor</td>
<td>10</td>
<td>agonists: arrhythmia; antagonists: orthostatic hypotension</td>
</tr>
<tr>
<td>dopamine D&lt;sub&gt;2&lt;/sub&gt; receptor</td>
<td>9</td>
<td>agonists: confusion, emesis; antagonists: orthostatic hypotension</td>
</tr>
<tr>
<td>histamine H&lt;sub&gt;1&lt;/sub&gt; receptor</td>
<td>6</td>
<td>antagonists: weight gain, sedation, somnolence</td>
</tr>
<tr>
<td>α&lt;sub&gt;2A&lt;/sub&gt; adrenergic receptor</td>
<td>6</td>
<td>agonists: hypotension, sedation</td>
</tr>
<tr>
<td>dopamine D&lt;sub&gt;1&lt;/sub&gt; receptor</td>
<td>5</td>
<td>antagonists: dyskinesia, tremor</td>
</tr>
<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;–&lt;sub&gt;5&lt;/sub&gt; muscarinic receptors</td>
<td>5</td>
<td>multiple cardiovascular and metabolic adverse effects, cognition impairment</td>
</tr>
<tr>
<td>μ-opioid receptor</td>
<td>3</td>
<td>agonists: sedation, respiratory depression, abuse potential</td>
</tr>
</tbody>
</table>

<sup>a</sup>Hit rate: percentage of druglike compounds, which bind to this target with an IC<sub>50</sub> < 1 μM in the BioPrint data set.
Early Safety Screening Criteria

• Assessing off-target activities should be earlier in the drug discovery process.

• Panels should contain only key antitargets and avoid a redundancy of targets.

• Targets with no clear links to ADRs should be omitted from the screening panel.

• Targets with low hit rates can be omitted.

Pharmacological Promiscuity Parameters

• Many molecular properties have shown to be vital in determining pharmacological promiscuity.

• Studies have shown that lipophilic compounds tend to be more promiscuous. *(fig. 1)*

• Basic compounds that are protonated at physiological pH are frequently promiscuous in safety screens.

• MW does not seem to be a useful predictor of promiscuity due to contradictory results.

• Compounds tend to be less promiscuous if they are of high complexity, of little flexibility, or decorated with many side chains.

• Specific structural fragments also play a role in predicting promiscuity. *(chart 1)*
Chart 1. The “Heteroaryl-NH-aryl” Motif Is Predictive of Kinase Activity

Compounds containing the bisarylaniline motif, heteroaryl-NH-aryl, often inhibit a wide variety of kinases.

Promiscuity Prevalence and Toxicity

- Significant percentage of compounds in large databases bind to more than one target.
- The actual prevalence of promiscuity is likely higher than 33–52%.
- Only a quarter of drug withdrawals can be traced back to unintended pharmacological activities.
- However, off-target activities must not be disregarded as an important cause of toxicity.

Drug Withdrawal Reasons

- anti-target related toxicity:
  - hERG blockade (7)
  - 5-HT2B agonism (4)
  - M2 antagonism (1)
  - CYP inhibition (1)
- toxicity mediated through the drug’s therapeutic target (12)
- toxicity related to reactive metabolite formation, BSEP inhibition, or mitochondrial toxicity (24)
- unknown (3)
Polypharmacological Drug Discovery: Examples

- Multikinase anticancer drugs disrupt several signaling processes.
- Sunitinib blocks the receptor kinases of many growth factors associated with cancer.
Table 2. Recently Approved Multi-Kinase Inhibitors as Anticancer Drugs

<table>
<thead>
<tr>
<th>drug</th>
<th>first approval</th>
<th>targets</th>
<th>FDA approval for (status April 2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sorafenib</td>
<td>2005</td>
<td>B-Raf, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-Kit, Fms-like tyrosine kinase 3 (Flt-3), RET</td>
<td>liver cancer, kidney cancer</td>
</tr>
<tr>
<td>sunitinib</td>
<td>2006</td>
<td>VEGFR, PDGFR, c-Kit, Flt-3, RET, colony stimulating factor 1 receptor (CSF-1R)</td>
<td>kidney cancer, gastrointestinal stromal tumors (GIST), pancreatic neuroendocrine tumors</td>
</tr>
<tr>
<td>dasatinib</td>
<td>2006</td>
<td>BCR/ABL, Src, c-Kit, ephrin receptors</td>
<td>chronic myelogenous leukemia (Philadelphia chromosome positive)</td>
</tr>
<tr>
<td>lapatinib</td>
<td>2007</td>
<td>ErbB1, ErbB2, epidermal growth factor receptor (EGFR)</td>
<td>hormone-positive and human epidermal growth factor receptor 2 (HER2) positive advanced breast cancer</td>
</tr>
<tr>
<td>pazopanib</td>
<td>2009</td>
<td>VEGFR, PDGFR, c-Kit</td>
<td>advanced renal cell carcinoma, advanced soft tissue sarcoma</td>
</tr>
<tr>
<td>vandetanib</td>
<td>2011</td>
<td>EGFR, VEGFR, RET, BRK, TIE2, Src, ephrin receptors</td>
<td>unresectable, locally advanced, or metastatic medullary thyroid cancer.</td>
</tr>
<tr>
<td>crizotinib</td>
<td>2011</td>
<td>ALK, Ros-1, hepatocyte growth factor receptor (HGFR)</td>
<td>locally advanced or metastatic non small cell lung cancer (anaplastic lymphoma kinase-positive)</td>
</tr>
<tr>
<td>axitinib</td>
<td>2012</td>
<td>VEGFR, PDGFR, c-Kit</td>
<td>advanced renal cell carcinoma after failure of prior systemic therapy</td>
</tr>
<tr>
<td>bosutinib</td>
<td>2012</td>
<td>BCR/ABL, Src</td>
<td>chronic myelogenous leukemia (Philadelphia chromosome positive)</td>
</tr>
<tr>
<td>regorafenib</td>
<td>2012</td>
<td>VEGFR, PDGFR, fibroblast growth factor receptor (FGFR), TIE-2, B-Raf, c-Kit, RET</td>
<td>advanced gastrointestinal stromal tumors (GIST), previously treated metastatic colorectal cancer</td>
</tr>
<tr>
<td>caboizatinib</td>
<td>2012</td>
<td>RET, MET, VEGFR, c-Kit, Flt-3</td>
<td>progressive, metastatic medullary thyroid cancer</td>
</tr>
<tr>
<td>ponatinib</td>
<td>2012</td>
<td>BCR/ABL, c-Kit, RET, Flt-3</td>
<td>chronic, accelerated or blast-phase chronic myeloid leukemia</td>
</tr>
</tbody>
</table>
Opportunities for Repurposing and for the Discovery of New Drugs

• “Drug repurposing” or “repositioning” refers to the use of an old drug for a new indication.

• Polypharmacological drugs can be repurposed based on their “off-target” activities.

• Thalidomide is an example of repurposing.

• Polypharmacology-based repurposing also led to the discovery of several important drug classes in the early years of drug discovery. (e.g. Antihistamine)
Repurposing: Examples

• **Indication:** morning sickness
• **ADR:** birth defects

• **Indication:** treatment of erythema nodosum leprosum

• **Indication:** multiple myeloma
Repurposing: Examples

- Promethazine was the starting point to develop antipsychotic drugs which led eventually to the discovery of tricyclic antidepressants.

- Although the discovered drugs retained antihistamine activity, they showed an increase in potency toward their specific targets.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Target for ...</th>
<th>$\text{IC}_{50}$ (radioligand binding, $\mu$M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_1$</td>
<td>allergy</td>
<td>0.0054</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td>$D_2$</td>
<td>schizophrenia</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>5-HT$_{2A}$</td>
<td>schizophrenia</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0034</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>SERT</td>
<td>depression</td>
<td>7.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0035</td>
</tr>
</tbody>
</table>
Repurposing: Examples

- Sulfacarbamide was an important sulfonamide antibacterial after WWII but suffered from a short halflife.

- Loranil (1) was a follow-up compound with a longer half-life, but produced hypoglycemia.

- Carbutamide was then developed as an antibiotic and as a hypoglycemic drug for the treatment of Type-2 diabetes.

- Carbutamide was not approved in the U.S. It was therefore followed up by tolbutamide, an antidiabetic with no antibacterial activity.
Combinations of Drugs and Pharmacophores

• Polypharmacological drug research has not been widely embraced.

• The combination of individual single-target drugs is an alternative to polypharmacological drug discovery.

• However, drug–drug interactions or poor compliance due to complex dosing regimens might be encountered.
Combinations of Drugs and Pharmacophores

- Polypharmacological leads can be designed by a combination of known pharmacophores into a single compound.

- However, this strategy leads often to a high MW and extreme lipophilicity with a little success.

Example: The betablocker pindolol was connected to the angiotensin-converting enzyme (ACE) inhibitor enalaprilat to give the dual-target 2.

Combinations of Drugs and Pharmacophores

- Similar pharmacophores, although may overlap in a single molecule successfully.

- For example, naphtylpiperazine and dopamine were merged into (3).

- Further optimization resulted in ziprasidone, which was successfully developed as an antipsychotic.

SUMMARY

• Unintended polypharmacology must be avoided.

• Early screening of compounds against small panels of frequently hit antitargets is recommended.

• The opportunities of polypharmacological drug discovery are increasingly being appreciated.

• The gap between theoretical network concepts and practical discovery of polypharmacological drugs should be resolved.
Thank You
Early Alerts of Potential Polypharmacology

![Graph showing hit rate against ClogP](image)

- **Green dots**: neutrals, incl. weak bases / acids ($pK_a < 7$)
- **Blue dots**: bases ($pK_a[B] \geq 7$)
- **Black dots**: permanently positively charged compounds
- **Red dots**: acids ($pK_a[A] \geq 7$)
- **Yellow dots**: zwitterionic compounds

Dependence of pharmacological promiscuity (off-target hits) on the lipophilicity of marketed beta-blockers. Lipophilic beta-blockers tend to be more promiscuous.