Competing & Collaborating to Achieve Successful Drug Repositioning

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NIH Center for Translation Therapeutics

NIH Chemical Genomics Center (NCGC)
• Brings biopharmaceutical technologies to academic/government drug development
• Focus on novel targets, neglected diseases

Therapeutics for Rare and Neglected Diseases (TRND)
• Bridging the gaps in discovery and development for therapeutics of rare and neglected disease
Two approaches to therapeutics for rare and neglected diseases

- >300,000 compounds, 10-15 yrs
- 3000 drugs
- 3 years?

Target Product Profile → Screen → Hit → Lead → Lead Optimization → Preclinical Development → Clinical Trials → FDA approval

3000 drugs
Repurposing in other portfolios

http://www.cff.org/treatments/Pipeline/

http://www.dndi.org/portfolio.html
~30% of TRND applications and projects have some form of repurposing theme, i.e. using existing clinical experience to inform development

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type</th>
<th>Pathology</th>
<th>Collaborators</th>
<th>Compound type</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomiasis, Hookworm</td>
<td>Neglected</td>
<td>Infectious parasite</td>
<td>Extramural</td>
<td>NME</td>
<td>Early (lead optimization)</td>
</tr>
<tr>
<td>Niemann Pick C</td>
<td>Rare</td>
<td>CNS, liver/spleen</td>
<td>Disease Fnd, Extramural, Intramural</td>
<td>Repurposed approved drug</td>
<td>Mid-stage</td>
</tr>
<tr>
<td>HIBM</td>
<td>Rare</td>
<td>Muscle</td>
<td>Biotech, Intramural</td>
<td>Intermediate replacement</td>
<td>Pre-IND</td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
<td>Rare</td>
<td>Blood</td>
<td>Nonprofit, Intramural, Extramural</td>
<td>NME</td>
<td>Mid-stage</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>Rare</td>
<td>Cancer</td>
<td>Disease Fnd, Extramural</td>
<td>Repurposed approved drug</td>
<td>Pre-IND</td>
</tr>
</tbody>
</table>
## How Many Drugs Are There?

<table>
<thead>
<tr>
<th>Term</th>
<th>FDA</th>
<th>Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Product</td>
<td>&gt;140,000</td>
<td>Product with defined package size, dose, formulation of API(s)</td>
</tr>
<tr>
<td>Drug</td>
<td>&gt;19,000</td>
<td>&gt;25,000</td>
</tr>
<tr>
<td>API</td>
<td>4,695</td>
<td>7,980</td>
</tr>
<tr>
<td>Molecular Entity</td>
<td>2,794</td>
<td>4,374</td>
</tr>
<tr>
<td>HTS Suitable</td>
<td>1,822</td>
<td>2,752</td>
</tr>
</tbody>
</table>

- Tylenol, Acetaminophen, Panadol, Datril, Paracetamol
- 103-90-2
**NCGC Pharmaceutical Collection**

<table>
<thead>
<tr>
<th>Drug Source</th>
<th>Current</th>
<th>Remaining</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>US FDA</td>
<td>1635</td>
<td>187</td>
<td>1822</td>
</tr>
<tr>
<td>UK/EU/Japan/Canada</td>
<td>756</td>
<td>174</td>
<td>930</td>
</tr>
<tr>
<td><strong>Total Approved</strong></td>
<td>2391</td>
<td>361</td>
<td>2752</td>
</tr>
<tr>
<td>INN/USAN</td>
<td>928</td>
<td>3932</td>
<td>4860</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3319</td>
<td>4293</td>
<td>7612</td>
</tr>
</tbody>
</table>

**Informatics sources**
- US FDA: Orange Book, OTC, NDC, Green Book, Drugs@FDA
- Britain NHS
- EMEA
- Health Canada
- Japan NHI
- WHO ATC

**Physical sources**
- Procurement from >20 suppliers worldwide
- In-house purification of APIs from marketed forms
- Synthesis

http://tripod.nih.gov/npc/
NCGC Pharmaceutical Collection

http://tripod.nih.gov/npc/
Identifying repurposing opportunities

• Random screening
  – Modest hit rate using phenotypic (cell-based) disease models yields:
    • Novel (off-target) activities of known molecules
    • Intersections of known biology with disease pathways in unexpected ways

• Observational (informatics) approaches
  – Complement screening approaches

• Key is then translating these opportunities (TRND)
Repurposing Development Models
‘The best way to develop a drug is to start with a drug’

• NIH’s goal is to affect public health
  – Ideally, by facilitating commercial development
    • Exclusivity based on patent, orphan, pediatric, product differentiation (route, formulation …)
  – Or not
    • Partnerships to support clinical characterization
    • Registration might not be end goal (oncology off-label compendia)
Repurposing Development Models
‘The best way to develop a drug is to start with a drug’

• Repurposing extends beyond existing products
  – Dose, route, prodrug
  – Clinical candidates (e.g. safe but not efficacious), GRAS, biochemical intermediates, DESI, etc.
  – Drug lead to drug (thalidomide to Revlimid)

Repurposing is not to avoid all costs of filing an IND, but dramatically reduce the cost and risk of development to address unmet needs; re-doing preclinical tox studies is relatively cheap in exchange for overall reduced risk