Drug Repurposing at NCTR/FDA

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Drug Repositioning with Bioinformatics

• **Goals:** identify new indications of marketed drugs for:
  – Rare and neglected diseases
  – Safer drugs
  – Inexpensive drugs
  – Drug shortage

• **Premises:**
  – “similar drugs” have the same therapeutic effects
  – “similar diseases” can be treated with the same drugs

• **Approach:** “Similarity” is measured with diverse data using bioinformatics

Liu et.al. in silico drug repositioning-what we should know? Drug Discovery Today, 2013, 18(3-4):110-5.
Rare and Neglected Diseases

• ~7000 diseases affect humans with limited therapeutic option
  – Low prevalence, i.e., “rare” (prevalence <200,000 in U.S.)
    • Most are single gene diseases
    • <250 have any pharmacotherapy available.
  – High prevalence but “neglected”
    • Occur mainly in developing nations (treatment costs prohibitive )
    • Most are infectious

• The FDA’s Office of Orphan Products Development (OOPD) aims to advance the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.
  – The Rare Disease Repurposing Database (RDRD) in FDA: [http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm](http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm)

• 33-37% approved drugs for each of the past six years are for rare diseases.
13 out of 39 New Drugs Approved by CDER in 2012 are for Rare Diseases

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Active Ingredient</th>
<th>Review Type</th>
<th>What it’s used for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voraxaze</td>
<td>glucarpidase</td>
<td>P, O</td>
<td>To treat patients with toxic levels of methotrexate in their blood due to kidney failure.</td>
</tr>
<tr>
<td>Kalydeco</td>
<td>ivacaftor</td>
<td>P, O</td>
<td>For the treatment of a rare form of cystic fibrosis (CF) in patients ages 6 years and older who have the specific G551D mutation in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene.</td>
</tr>
<tr>
<td>Elelyso</td>
<td>taliglucerase alfa</td>
<td>S, O</td>
<td>For long-term enzyme replacement therapy to treat a form of Gaucher disease, a rare genetic disorder.</td>
</tr>
<tr>
<td>Kyprolis</td>
<td>carfilzomib</td>
<td>S, O</td>
<td>To treat patients with multiple myeloma who have received at least two prior therapies, including treatment with Velcade (bortezomib) and an immunomodulatory.</td>
</tr>
<tr>
<td>Bosulif</td>
<td>bosutinib</td>
<td>S, O</td>
<td>To treat chronic myelogenous leukemia (CML), a blood and bone marrow disease that usually affects older adults.</td>
</tr>
<tr>
<td>Synribo</td>
<td>omacetaxine mepesuccinate</td>
<td>S, O</td>
<td>To treat adults with chronic myelogenous leukemia (CML), a blood and bone marrow disease.</td>
</tr>
<tr>
<td>Cometria</td>
<td>cabozantinib</td>
<td>P, O</td>
<td>To treat medullary thyroid cancer that has spread to other parts of the body (metastasized).</td>
</tr>
<tr>
<td>Idusia</td>
<td>ponatinib</td>
<td>P, O</td>
<td>To treat adults with chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), two rare blood and bone marrow diseases.</td>
</tr>
<tr>
<td>raxibacumab</td>
<td>raxibacumab</td>
<td>P, O</td>
<td>To treat inhalational anthrax, a form of the infectious disease caused by breathing in the spores of the bacterium Bacillus anthracis.</td>
</tr>
<tr>
<td>Signifor</td>
<td>pasireotide</td>
<td>P, O</td>
<td>To treat Cushing's disease patients who cannot be helped through surgery.</td>
</tr>
<tr>
<td>Gattex</td>
<td>teduglutide</td>
<td>S, O</td>
<td>To treat adults with short bowel syndrome (SBS) who need additional nutrition from intravenous feeding (parenteral) nutrition.</td>
</tr>
<tr>
<td>Juxtapid</td>
<td>lomitapide</td>
<td>S, O</td>
<td>To reduce low-density lipoprotein (LDL) cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein (non-HDL) cholesterol in patients with homozygous familial hypercholesterolemia (HoFH).</td>
</tr>
<tr>
<td>Sirturo</td>
<td>bedaquiline</td>
<td>P, O</td>
<td>As part of combination therapy to treat adults with multi-drug resistant pulmonary tuberculosis (TB) when other alternatives are not available.</td>
</tr>
</tbody>
</table>
Replacing Unsafe Drugs with Safer Ones

• Marketed drugs are one important resources for drug repurposing, however, safety assessment is still a key step.
  – ~ 600 drugs with Boxed Warnings in drug labels.
  – OTC drugs for drug repurposing, e.g.
    • Vitamin E for treatment of nonalcoholic steatohepatitis (NASH)

• U.S. FDA has hierarchical regulatory rules to monitor safety in each phase of drug development, which could facilitate the drug repurposing process.

• Available resources:
  – FDAlabel™:
    http://www.fda.gov/ScienceResearch/BioinformaticsTools/ucm289739.htm
  – FAERS:
Finding Affordable Alternatives

• Specialty Drugs
  – Very expensive: Kalydeco for cystic fibrosis: $297,000/year (~$5700 per week)
  – Treat the health conditions that often have few or no other alternative treatments
  – Generally require special handling
  – Often prescribed for chronic, complex, or rare health conditions
    • E.g., cancer, hepatitis C, hemophilia, rheumatoid arthritis, cystic fibrosis, infertility, HIV, or multiple sclerosis

• Specialty drugs will account for 50% of all drug costs by 2018

• In 2010, the Affordable Care Act (ACA 6004) was signed into law to ensure that specialty drugs meet the FDA’s standards of safety and efficacy.

• Available resources:
  – DrugBank: http://www.drugbank.ca/
  – GoodPx: http://www.goodrx.com/
Drug Availability Is Also An Issue

• In 2010, there were 178 drug shortages reported to the FDA and the number increased to 251 in 2011.

• FDA takes great efforts to address and prevent drug shortages.

• The shortage can occur for many reasons, including manufacturing and quality problems, delays, and discontinuations.

• Available resources:
  – American Society of Health System Pharmacists (ASHP): http://www.ashp.org/
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What’s Cystic Fibrosis?

- Cystic fibrosis is an inherited chronic disease (rare disease) that affects the lungs and digestive system.

- ~30,000 children and adults in the United States (70,000 worldwide)
  - ~1,000 new cases per year
  - The median age of survival is late 30s

- Kalydeco (VX-770) was developed with the help of $75mil from the Cystic Fibrosis Foundation and was approved by the FDA in 2012.

- Only for people with CF ages 6 and older with G551D mutation of CF

- Very expensive!

http://www.cysticfibrosis.net/
Hypotheses

• Cystic fibrosis (CF) is regulated by a set of feed-forward loops (FFLs) that contains genes-TF-miRNA
• Drugs interfering the CF specific FFLs can treat CF
The composite feed-forward loops (FFLs) for cystic fibrosis

the green diamond nodes, the blue rectangle and the gray ellipse denote transcription factors (TFs), miRNAs and genes, respectively. The t-shape edge and circle-shape edge and gray solid line represent repression of miRNAs to genes/TF, regulation of TFs to genes/miRNAs, and protein-protein interaction, respectively.
# Repurposing candidates for cystic fibrosis

<table>
<thead>
<tr>
<th>Drug Names</th>
<th>Involved FFLs</th>
<th>Original Indication</th>
<th>Boxed Warnings</th>
<th>Price ($)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>dexamethasone</td>
<td>hsa-mir-26b↔CREBBP</td>
<td>Anti-inflammatory; Oncologic uses; glucocorticoid resistance; Obstetrics; High altitude illnesses</td>
<td>No</td>
<td>48.76</td>
</tr>
<tr>
<td>simvastatin</td>
<td>hsa-miR-200c↔JUN</td>
<td>hypercholesterolemia</td>
<td>No</td>
<td>3.50</td>
</tr>
<tr>
<td>levamisole</td>
<td>hsa-miR-26b↔CREBBP and hsa-miR-200c↔JUN</td>
<td>Dukes' stage C colon cancer; worm infestations</td>
<td>No</td>
<td>7.5</td>
</tr>
<tr>
<td>Choline</td>
<td>hsa-miR-200c↔JUN and has-miR-29c↔TFAP2C</td>
<td>dietary shortage or imbalance</td>
<td>No</td>
<td>4.38</td>
</tr>
</tbody>
</table>

*Price ($)*
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