Drug Repurposing for Rare Diseases at FDA/NCTR

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Outlines

1. A brief introduction of rare diseases
2. *In silico* drug repurposing at NCTR
3. Drug repurposing for cystic fibrosis
4. Drug repurposing of oncologic drugs for rare diseases therapy
5. Drug repurposing for neuroblastoma by unraveling gene fusions
Rare Disease Facts

• Affects less than 1/1500 in US or 1/2000 in Europe
• ~ 7000 known rare diseases
• 85 to 90% are chronic, serious or life threatening

• 80% are genetic
• A doctor in a busy practice would expect to see less than 1 case per year
• Diagnosis often takes years with patients shuffled from one specialist to another
• Costs Can Be Very High

Approved Orphan Product by Year

Only 600 treatment options are available!!!
What is Drug Repurposing?

**De Novo drug discovery**

<table>
<thead>
<tr>
<th>Idea!</th>
<th>Target Discovery</th>
<th>Discovery &amp; Screening</th>
<th>Lead Optimization</th>
<th>ADME/T</th>
<th>Development</th>
<th>Registration</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In vitro validation</td>
<td>In vitro function</td>
<td>Rational drug design</td>
<td>Systemic exposure</td>
<td>(Phase I/II for cancer)</td>
<td>E.U. (EMEA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bioinformatics</td>
<td>In vivo</td>
<td>HTS</td>
<td></td>
<td></td>
<td>Japan (MHLW)</td>
<td></td>
</tr>
</tbody>
</table>

2-3 yr 0.5-1 yr 1-3 yr 1-2 yr 5-6 yr 1-2 yr

**Drug repositioning**

<table>
<thead>
<tr>
<th>Identification</th>
<th>Acquisition</th>
<th>Development</th>
<th>Registration</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted searches</td>
<td>Licensing</td>
<td>May start at Preclinical, Phase I or Phase II</td>
<td>U.S (FDA)</td>
<td></td>
</tr>
<tr>
<td>Novel insights</td>
<td>Novel I.P.</td>
<td>Ability to leverage existing data packages</td>
<td>E.U. (EMEA)</td>
<td></td>
</tr>
<tr>
<td>Specialized Screening platforms</td>
<td>Both</td>
<td></td>
<td>Japan (MHLW)</td>
<td></td>
</tr>
<tr>
<td>Serendipity</td>
<td></td>
<td></td>
<td>Rest of World</td>
<td></td>
</tr>
</tbody>
</table>

1–2 yr 0–2 yr 1–6 yr 1-2 yr

*3-12 year process
• Reduced Safety & PK uncertainty

Prioritize rare diseases regarding their repurposing opportunities

Translate novel genetic finding into drug repurposing framework to facilitate the rare disease therapy

Computational Drug Repositioning for Rare Diseases in the Era of Precision Medicine

Delavan et. al. 2018, Computational drug repositioning for rare diseases in the era of precision medicine, *Drug Discovery Today*, 23 (2), 382-394
Drug Repurposing for Cystic Fibrosis
Cystic Fibrosis (CF) is an inherited chronic (rare) disease that affects the lungs and digestive system. It is caused due to a defect in the gene that produces a protein called cystic fibrosis transmembrane conductance regulator (CFTR). Approximately 30,000 children and adults in the United States (70,000 worldwide) have CF, with around 1,000 new cases per year. The median age of survival is late 30s.

Kalydeco® (VX-770, ivacaftor) - approved by the FDA in 2012 for CF patients aged 12 months and older with G551D mutation in CFTR gene. It was developed with the help of $75mil from the Cystic Fibrosis Foundation.

Symdeco® (tezacaftor 100mg 150 mg ivacaftor) fixed dose combination – approved by FDA in 2018 for CF patients aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.

http://www.cysticfibrosis.net/
Hypothesis to Identify Drug Repurposing Candidates for CF

- 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.

Bioinformatics Approach to Identify Drug Repurposing Candidates for CF

• **Workflow:**
  • Collecting CFTR related genomic data (mRNA, miRNA, etc).
  • Constructing CFTR-specific FFLs with CFTR-specific genes and transcription factors.
  • Identifying drugs with potential to treat CF by interacting with the CF-specific FFL.

**Bioinformatics Approach:**
• Takes drug safety and affordability into consideration.
• Can be used for drug repurposing for rare diseases in general.

## Summary Information of Repurposing Candidates for CF Treatment

### Evidence from Clinical Trials (clinicaltrials.gov) or the Literature

<table>
<thead>
<tr>
<th>Drug Names</th>
<th>Involved FFLs</th>
<th>Original Indication</th>
<th>Boxed Warnings</th>
<th>Price ($) / tablet</th>
<th>PMID or Clinical.gov ID</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>0.29</td>
<td>PMID:15223012</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>hsa-miR-200c↔JUN</td>
<td>Hypercholesterolemia</td>
<td>No</td>
<td>1.34</td>
<td>NCT00255242</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>0.18</td>
<td>PMID:9609763</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>0.71</td>
<td>NCT01070446</td>
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<tr>
<td>Rosiglitazone</td>
<td>hsa-miR-200c↔JUN and has-miR-29c↔TFAP2C</td>
<td>Type 2 diabetes</td>
<td>Yes</td>
<td>1.08/1.38</td>
<td>PMID:20154695 / NCT00322868</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>hsa-miR-200c↔JUN and has-miR-29c↔TFAP2C</td>
<td>Type 2 diabetes</td>
<td>Yes</td>
<td>1.08/1.38</td>
<td>PMID:20154695 / NCT00322868</td>
</tr>
</tbody>
</table>
Drug Repurposing of Oncologic Drugs for the Treatment of Rare Diseases
The Relationship between Rare Diseases and Cancers

- Some patients with rare diseases are predisposed to develop cancer
- Some genes linked to cancer have also been identified as causative genes for rare diseases
- Rare diseases and cancer could perturb the same biological pathways

Molecular Association between Cancer and Rare Diseases

Gene-gene distance in a PPI network

The relationship of the targets of oncologic drugs and rare disease genes

Resources:
- Gene-rare disease relationships are curated from Orphanet
- Cancer genes are curated from TCGA pan-cancer data sets
- PPI are based on STRING v11.0 database
- Drug-target relationships are extracted from Therapeutic Target Database (TTD)
<table>
<thead>
<tr>
<th>Orphanet ID</th>
<th>Rare disease</th>
<th>Evidences</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>117</td>
<td>Behcet disease</td>
<td>Cli, Lit</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td><strong>LEOPARD syndrome</strong></td>
<td>Lit/Exp</td>
<td></td>
</tr>
<tr>
<td>2884</td>
<td>Piebaldism</td>
<td>Lit</td>
<td>Rare skin disease</td>
</tr>
<tr>
<td>774</td>
<td>Rendu-Osler-Weber disease</td>
<td>Cli</td>
<td></td>
</tr>
<tr>
<td>3444</td>
<td>Watson syndrome</td>
<td>Lit</td>
<td></td>
</tr>
<tr>
<td>670</td>
<td>PIBIDS syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>284973</td>
<td>Marfan syndrome type 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>88636</td>
<td>Aortic dilatation - joint hypermobility - arterial tortuosity</td>
<td></td>
<td>Rare circulatory system disease</td>
</tr>
<tr>
<td>140944</td>
<td>CLOVE syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1340</td>
<td>Cardiofaciocutaneous syndrome</td>
<td>Lit</td>
<td>Rare cardiac disease</td>
</tr>
<tr>
<td>79315</td>
<td>D-2-hydroxyglutaric aciduria</td>
<td>Lit</td>
<td>Rare neurologic disease</td>
</tr>
</tbody>
</table>
Drug Repurposing for Neuroblastoma
by Unraveling Gene Fusion Events
Gene Fusion for Anticancer Drug Development

Liu et al., 2017, Lessons Learned from Two Decades of Anticancer Drugs, *Trend in Pharmacological Sciences*, 38 (10), 852-872.
Preliminary Results of Drug Repurposing for Neuroblastoma

- 498 RNA-seq data of neuroblastoma patients
- Comparative analysis, fusion annotation and functional analysis (e.g., reported cancer-related fusion, kinase-related fusion, NB key gene-related fusion, and pathway analysis)

Gene fusions

High-risk Patients

Non-negative matrix factorization (NMF)

Hierarchical clustering

Patient stratification

TopHat + Cufflink

DEGs for the redefined high-risk group

Functional analysis and PPI network analysis

Drug repositioning with LINCS 1000

24 of 48 candidates (50%) are either under on-going clinical trial or have a literature report for neuroblastoma treatment

Clinicaltrial.gov

Literature reports

Survival analysis and drug repositioning

Survival analysis for the redefined high-risk group

Subgroups: G1, G2, G3

Oncogenes and tumor suppressors

Drug repurposing with LINCS 1000

Clinical trial data

Literature reports

19
Bioinformatics Tools Toward Safer Drug Repurposing
FDALabel – an Amazon Cloud Version

- A web-based application
- Customizable searches of over 100,000 labeling documents (RX, OTC, etc)
- One stop solution for FDA approved drug labeling information

https://nctr-crs.fda.gov/fdalabel/ui/search
Drug Induced Rhabdomyolysis Atlas (DIRA)

• Statin drugs are one of popular repurposing therapeutic categories
• Safety concerns for statin drugs and how to manage
• We developed a Drug Induced Rhabdomyolysis Atlas (DIRA)

DIRA mainly provides three folds of drug-induced rhabdomyolysis related information including a classification scheme, post-marketing surveillance, and drug property information.

http://www.adratlas.com/dira/

Thank you for your attention!!!

Any suggestion is very welcome. We are looking forward to different level of collaboration.
please contact me via Zhichao.liu@fda.hhs.gov
Acknowledgement

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- Wenjun Bao (SAS)

**NIH**
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- Jean Yuan (OD)
- George Santangelo (OD)
Backup slides
Better Understanding of Data and Methodologies

Methodology
- Machine learning
- Statistical models
- Text Mining
- AI

Data profiles
- -omics
- IVIVE
- Free text

Drug Repurposing

An established framework for applying our research results and tools development to impact the review process

Reproducibility

Rare disease
- Prioritization
- Regulatory needs

Data Quality
Potential Drug Repositioning Resources at FDA

**Rare diseases**
- Office of Orphan Products Development
- Rare Disease Repurposing Database (RDRD)
- Funding opportunity and Grants

**Drug safety**
- MedWatch
- FAERS
- VAERS
- FDALabel
- Drug@FDA
- Orange Book

**Drug review**
- PharmaPendium
- Patient Narratives
- FDA's Sentinel Initiative
- Biomarker Qualification Program

**Clinical repositories**

[https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm](https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm)
# Programs Under FDA Office of Orphan Products Development

<table>
<thead>
<tr>
<th>Programs</th>
<th>Program Descriptions</th>
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<tbody>
<tr>
<td>Orphan Drug Designation</td>
<td>Orphan status for drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders.</td>
</tr>
<tr>
<td>Humanitarian Use Device (HUD)</td>
<td>Designates medical devices that are intended to benefit patients in the treatment or diagnosing a disease or condition.</td>
</tr>
<tr>
<td>Rare Pediatric Disease Priority Review Voucher Program</td>
<td>A sponsor who receives an approval for a drug or biologic for a &quot;rare pediatric disease&quot; may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product.</td>
</tr>
<tr>
<td>Orphan Products Grants Program</td>
<td>Funding for clinical research that tests the safety and efficacy of drugs, biologics, medical devices and medical foods in rare diseases or conditions.</td>
</tr>
<tr>
<td>Pediatric Device Consortia (PDC) Grants Program</td>
<td>Funding to develop nonprofit consortia to facilitate pediatric medical device development.</td>
</tr>
<tr>
<td>Orphan Products Natural History Grants Program</td>
<td>Support studies that advance rare disease medical product development through characterization of the natural history of rare diseases/conditions.</td>
</tr>
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</table>

[https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm](https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm)