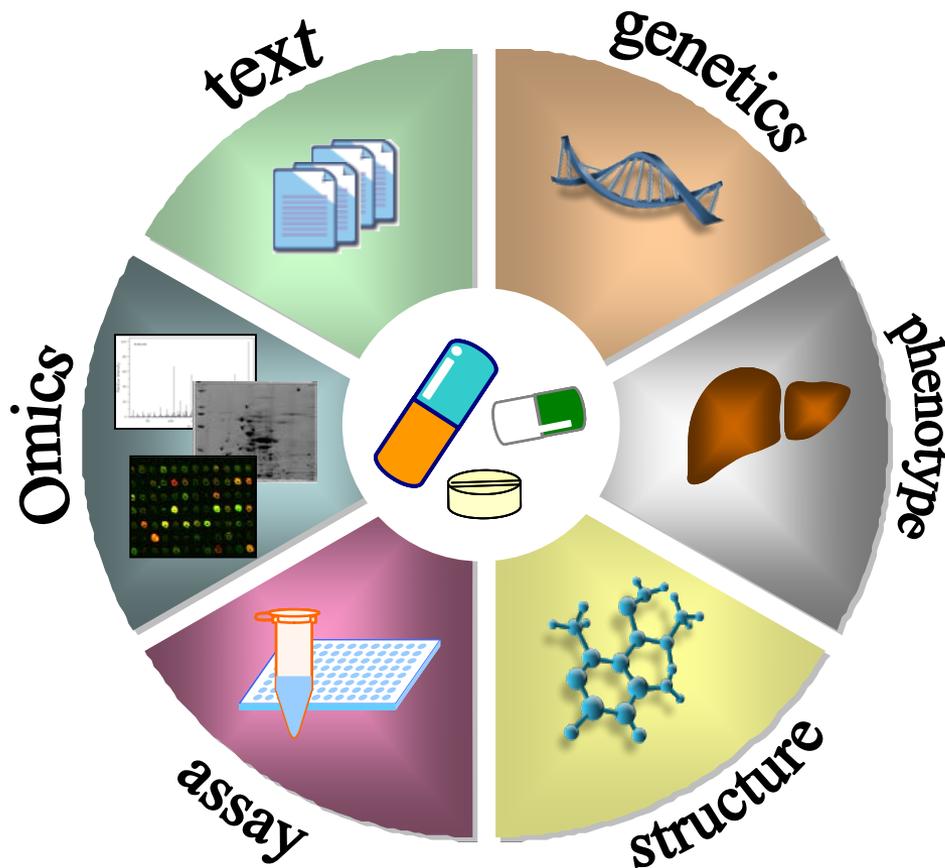


# Drug Repurposing at NCTR/FDA

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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

# 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>
- 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

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

# 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:  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>

# 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

## Drug shortages endanger cancer patients, study finds

Liz Szabo, USA TODAY 8:48 a.m. EDT June 3, 2013



- F

*Most cancer specialists say their patients have been affected by shortages of critical cancer drugs, mostly caused by manufacturing problems at pharmaceutical plants.*

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

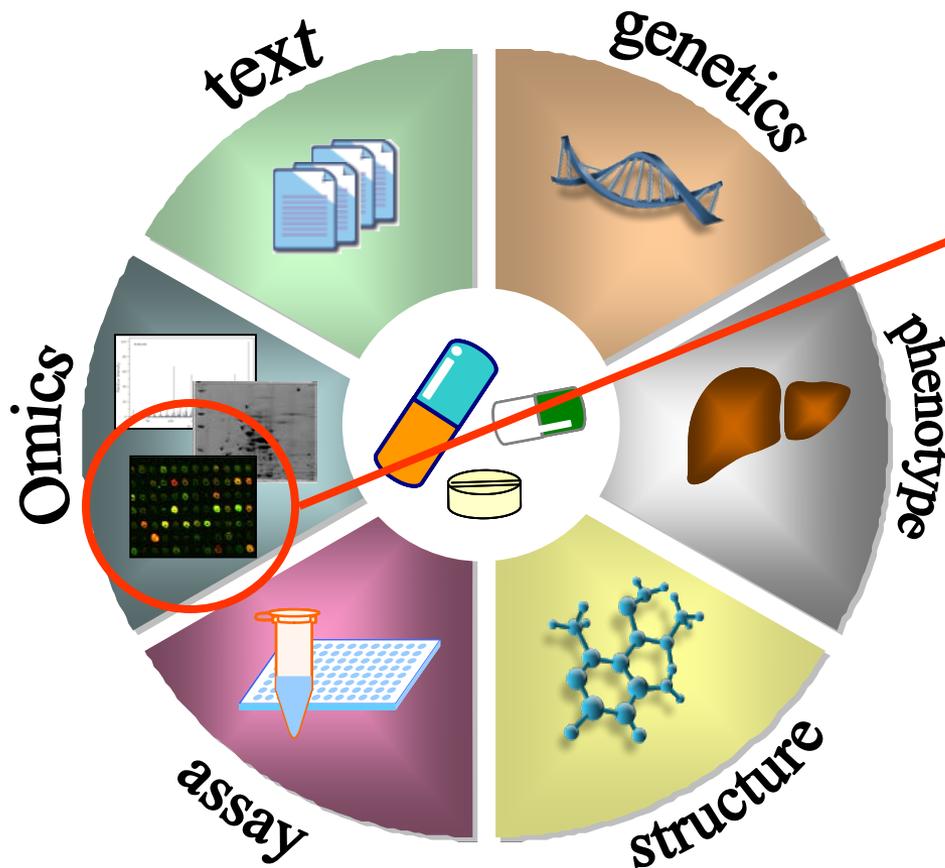
- Available resources:

- Drug shortages in FDA:

<http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>

- American Society of Health System Pharmacists (ASHP): <http://www.ashp.org/>

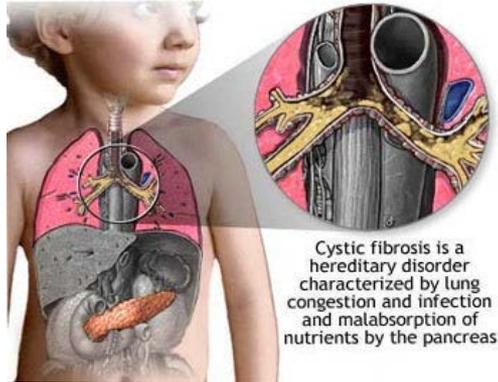
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# What's Cystic Fibrosis?

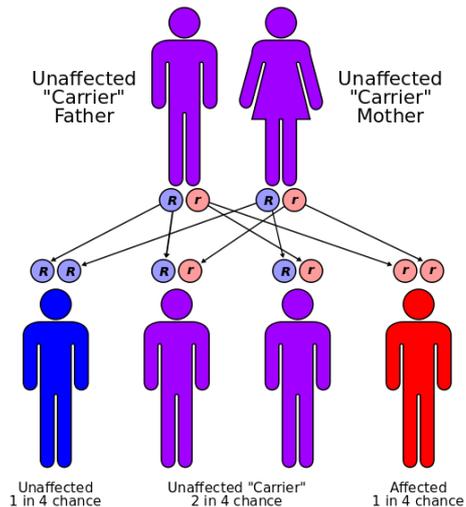
## Disease



- 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

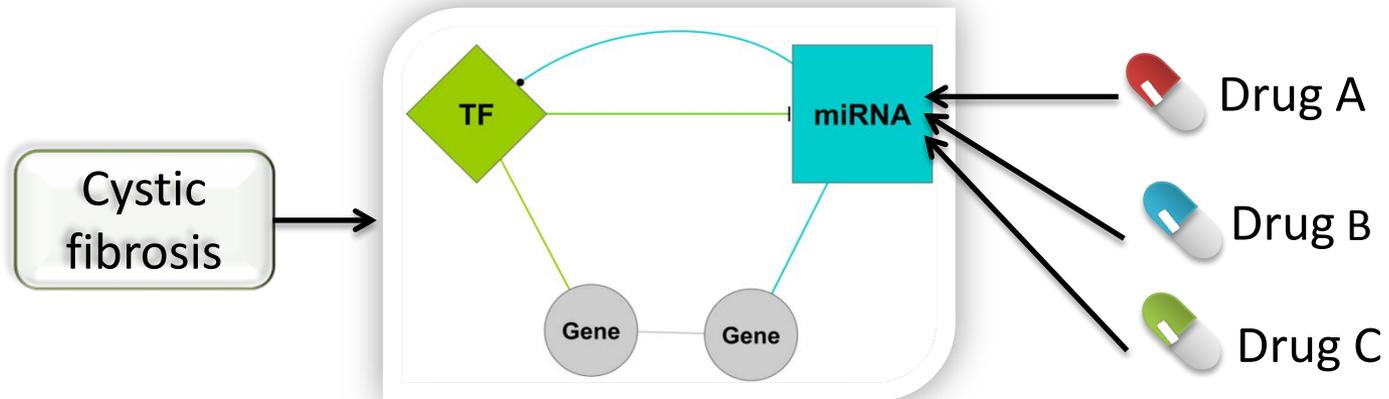
## Drug

- 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!



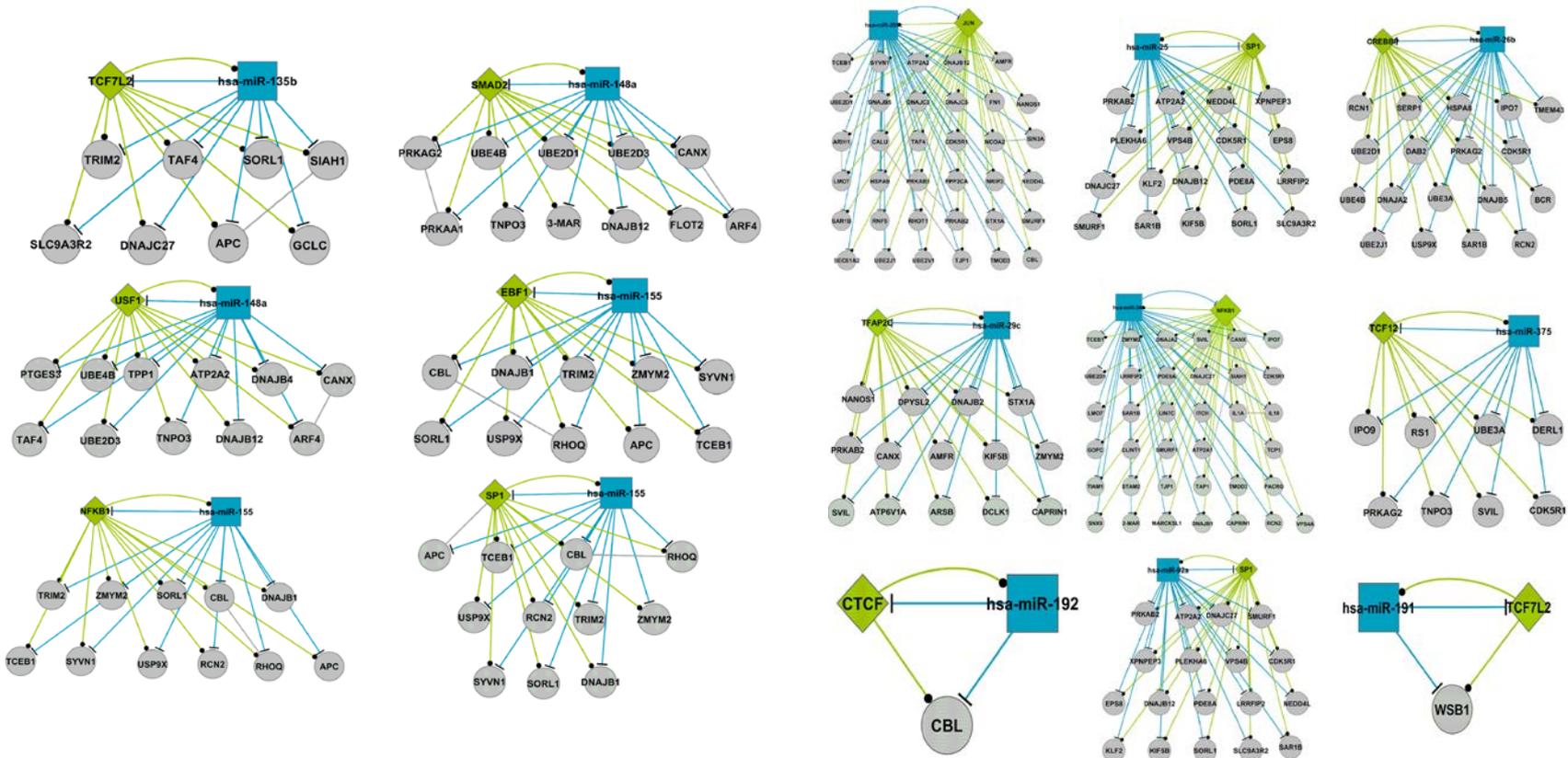
# Hypotheses

- 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



Feed-Forward Loops

# 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

Drug Names	Involved FFLs	Original Indication	Boxed Warnings	Price (\$)*
<b>dexamethasone</b>	hsa-mir-26b↔CREBBP	Anti-inflammatory; Oncologic uses; glucocorticoid resistance; Obstetrics; High altitude illnesses	No	48.76
<b>simvastatin</b>	hsa-miR-200c↔JUN	hypercholesterolemia	No	3.50
<b>levamisole</b>	hsa-mir-26b↔CREBBP and hsa-miR-200c↔JUN	Dukes' stage C colon cancer; worm infestations	No	7.5
<b>Choline</b>	hsa-miR-200c↔JUN and has-miR-29c↔TFAP2C	dietary shortage or imbalance	No	4.38
	hsa-miR-			12

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