Drug Repurposing for Rare Diseases at FDA/NCTR

Zhichao Liu, Ph. D.

Division of Bioinformatics and Biostatistics (DBB),
National Center of Toxicological Research (NCTR),
U.S. Food and Drug Administration (FDA)

Outlines

A brief introduction of rare diseases

In silico drug repurposing at NCTR

Drug repurposing for cystic fibrosis

Drug repurposing of oncologic drugs for rare diseases therapy

Drug repurposing for neuroblastoma by unraveling gene fusions

Bioinformatics Tools Toward Safer Drug Repurposing

Rare Disease Facts

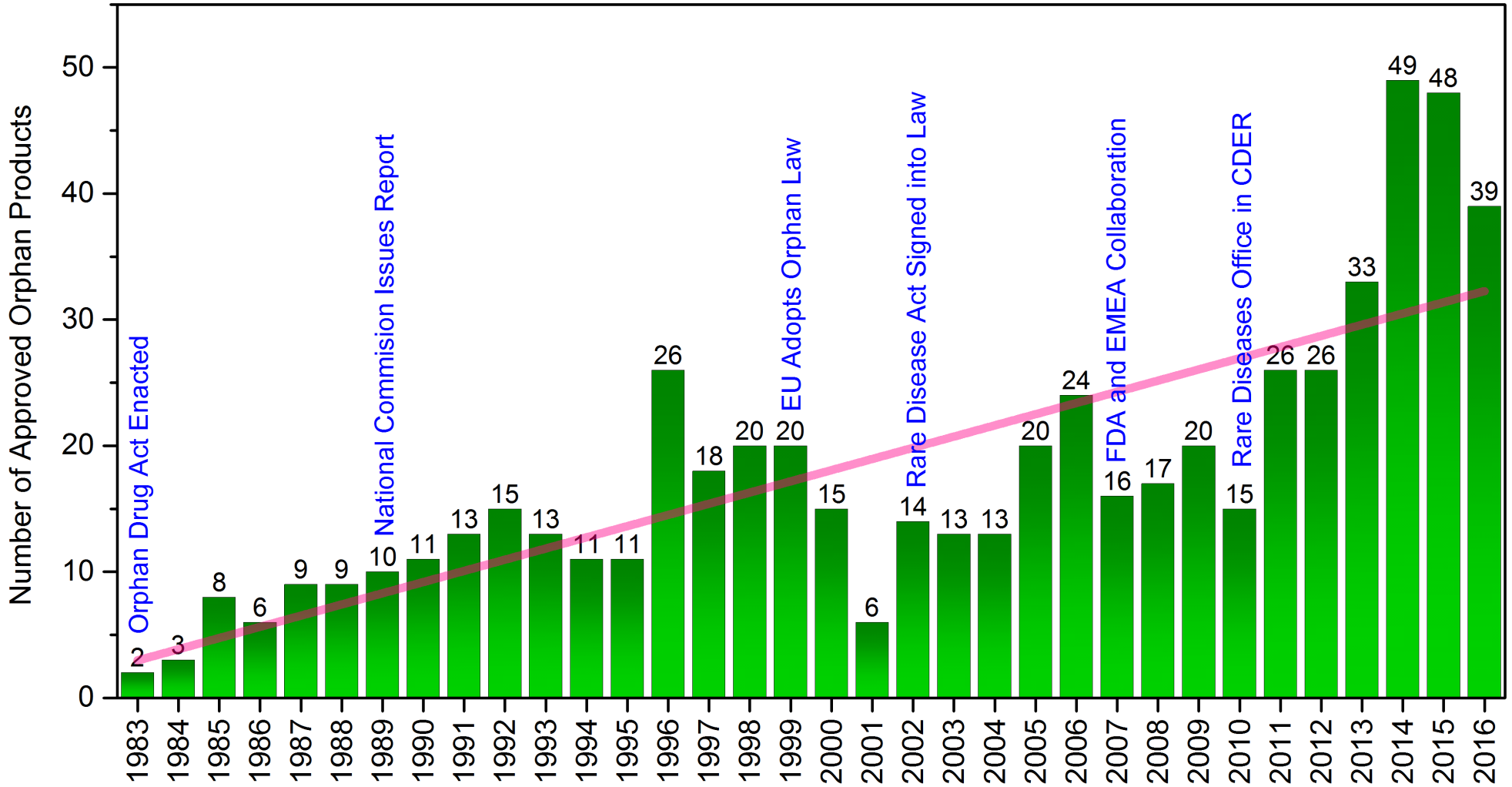
- Affects less than 1/1500 in US or 1/2000 in Europe
- ~ 7000 known rare diseases
- 85 to 90% are chronic, serious or life threatening

Progeria

- 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

http://www.nature.com/news/2011/110627/full/news.2011.387.html

Approved Orphan Product by Year



Only 600 treatment options are available!!!

What is Drug Repurposing?

De Novo drug discovery

Idea!	Target Discovery	Discovery & Screening	Lead Optimization	ADME/T	Development	Registration	Drug
	• Expression analysis • *In vitro* function • *In vivo* validation • Bioinformatics	• *In vitro* • *Ex vivo* • *In vivo* • *In silico* • HTS	• Traditional Med. Chem. • Rational drug design	• Bioavailability • Systemic exposure	• Testing starts at Phase I (Phase I/II for cancer)	• U.S (FDA) • E.U. (EMEA) • Japan (MHLW) • Rest of World	
	2-3 yr	**0.5-1 yr**	**1-3 yr**	**1-2 yr**	**5-6 yr**	**1-2 yr**	

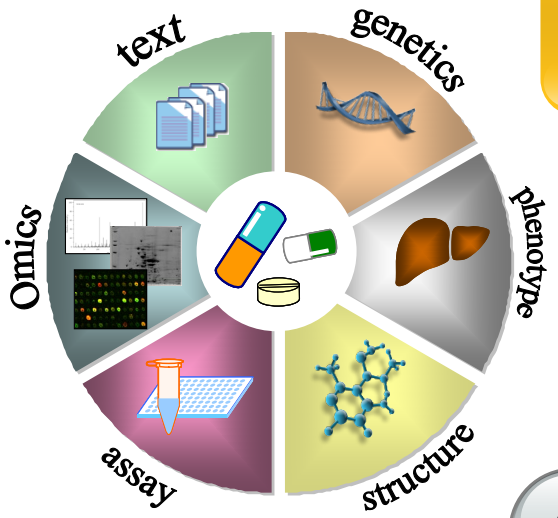
Drug repositioning

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

Identification	Acquisition	Development	Registration	Drug
• Targeted searches • Novel insights • Specialized Screening platforms • Serendipity	• Licensing • Novel I.P. • Both	• May start at Preclinical, Phase I or Phase II • Ability to leverage existing data packages	• U.S (FDA) • E.U. (EMEA) • Japan (MHLW) • Rest of World	
1–2 yr	**0–2 yr**	**1–6 yr**	**1-2 yr**	

Ashburn TT, Thor KB. *Nature Reviews Drug Discovery*, 2004, 3(8): 673-83.

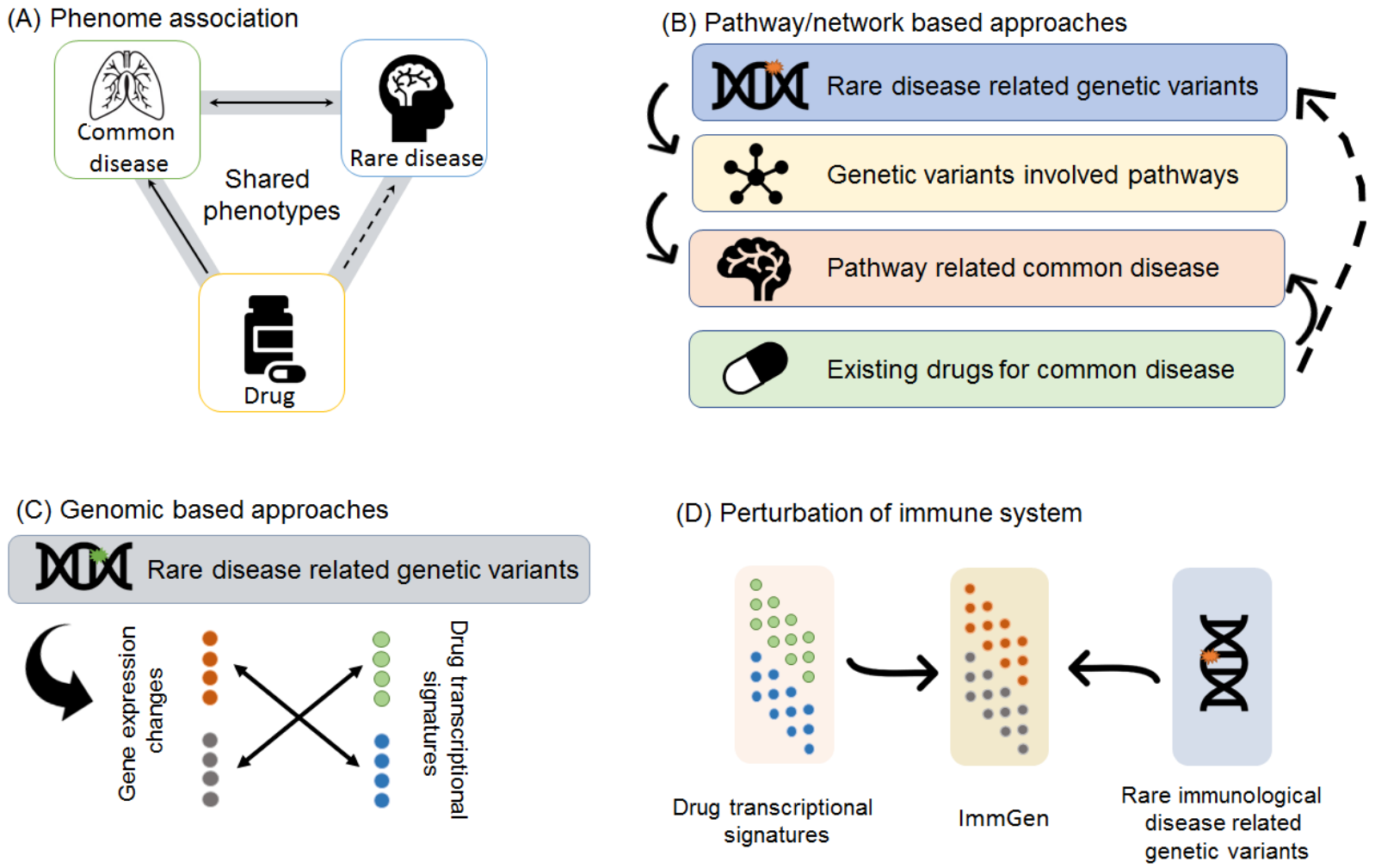
Computational Drug Repositioning at NCTR



1. **P**rovide computational solutions for integrating different data profiles for drug repurposing
2. **P**rioritize rare diseases regarding their repurposing opportunities
3. **T**ranslate novel genetic finding into drug repurposing framework to facilitate the rare disease therapy

Liu et.al. 2013, In silico drug repositioning-what we should know? **Drug Discovery Today**, 18(3-4):110-5.

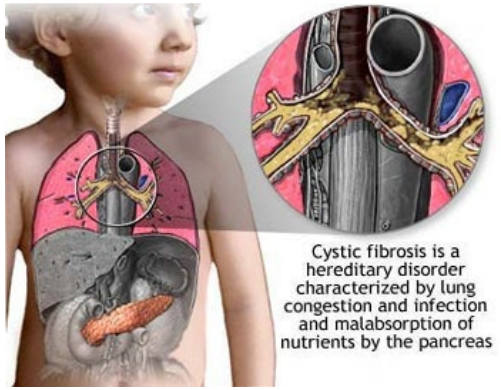
Computational Drug Repositioning for Rare Diseases in the Era of Precision Medicine



Delavan et. al. 2018, Computational drug repositioning for rare diseases in the era of precision medicine, **Drug Discovery Today**, 23 (2), 382-394

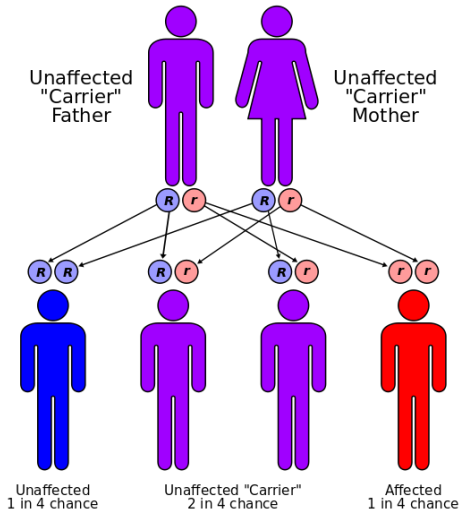
Drug Repurposing for Cystic Fibrosis

Cystic Fibrosis and Approved Drugs



Disease

- Cystic fibrosis (CF) is an inherited chronic (rare) disease that affects the lungs and digestive system.
- Caused due to a defect in the gene that produces a protein called cystic fibrosis transmembrane conductance regulator (CFTR).
- ~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



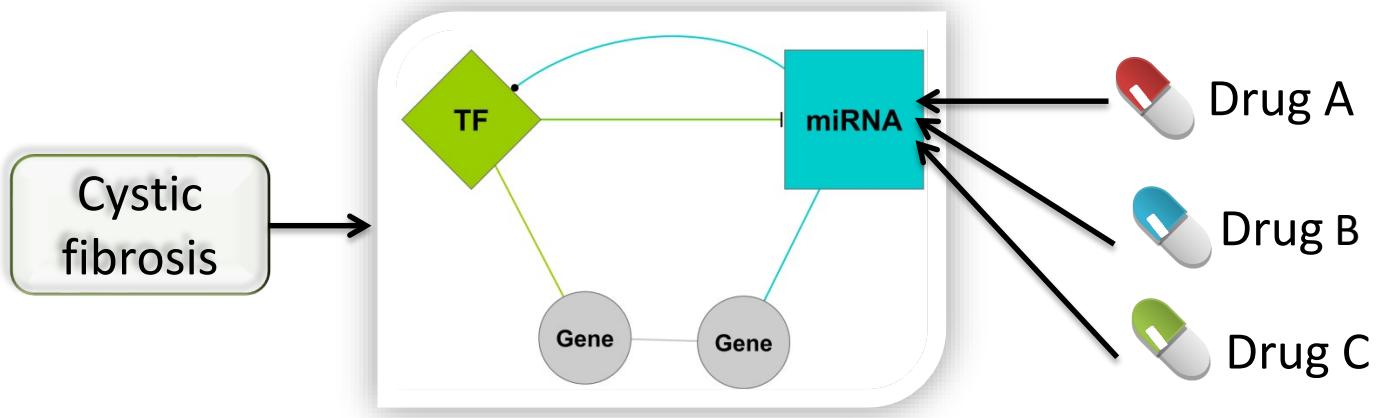
Drug

- Kalydeco ® (VX-770, 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 *CTFR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

http://www.cysticfibrosis.net/
http://rarediseases.info.nih.gov/GARD/Disease.aspx?diseaseID=6233

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.



Feed-Forward Loops

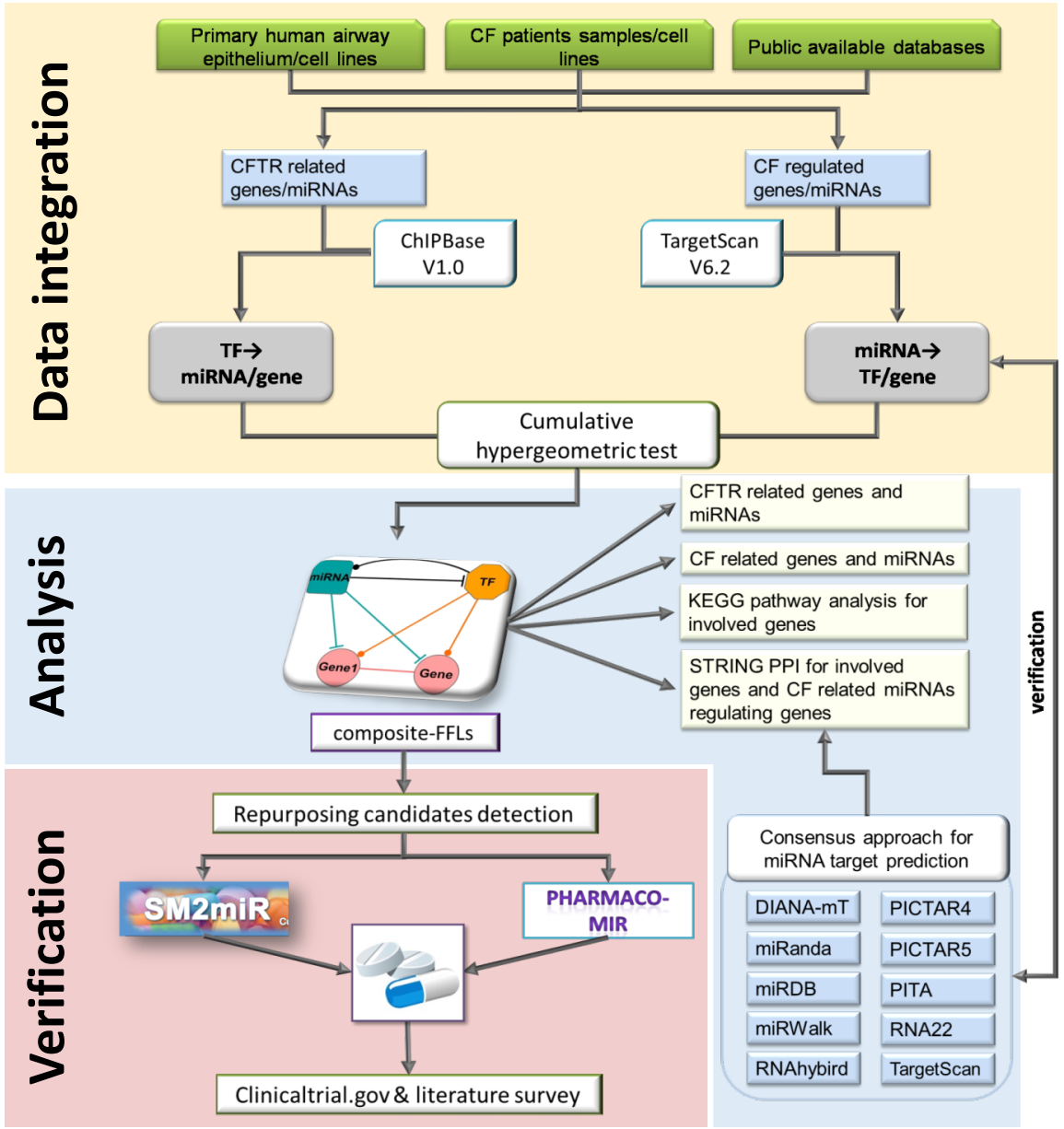
Liu, Z., et al. 2014, "Deciphering miRNA transcription factor feed-forward loops to identify drug repurposing candidates for cystic fibrosis." **Genome Medicine**, 6(12): 94.

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.



Liu, Z., et al. 2014, "Deciphering miRNA transcription factor feed-forward loops to identify drug repurposing candidates for cystic fibrosis." **Genome Medicine**, 6(12): 94.

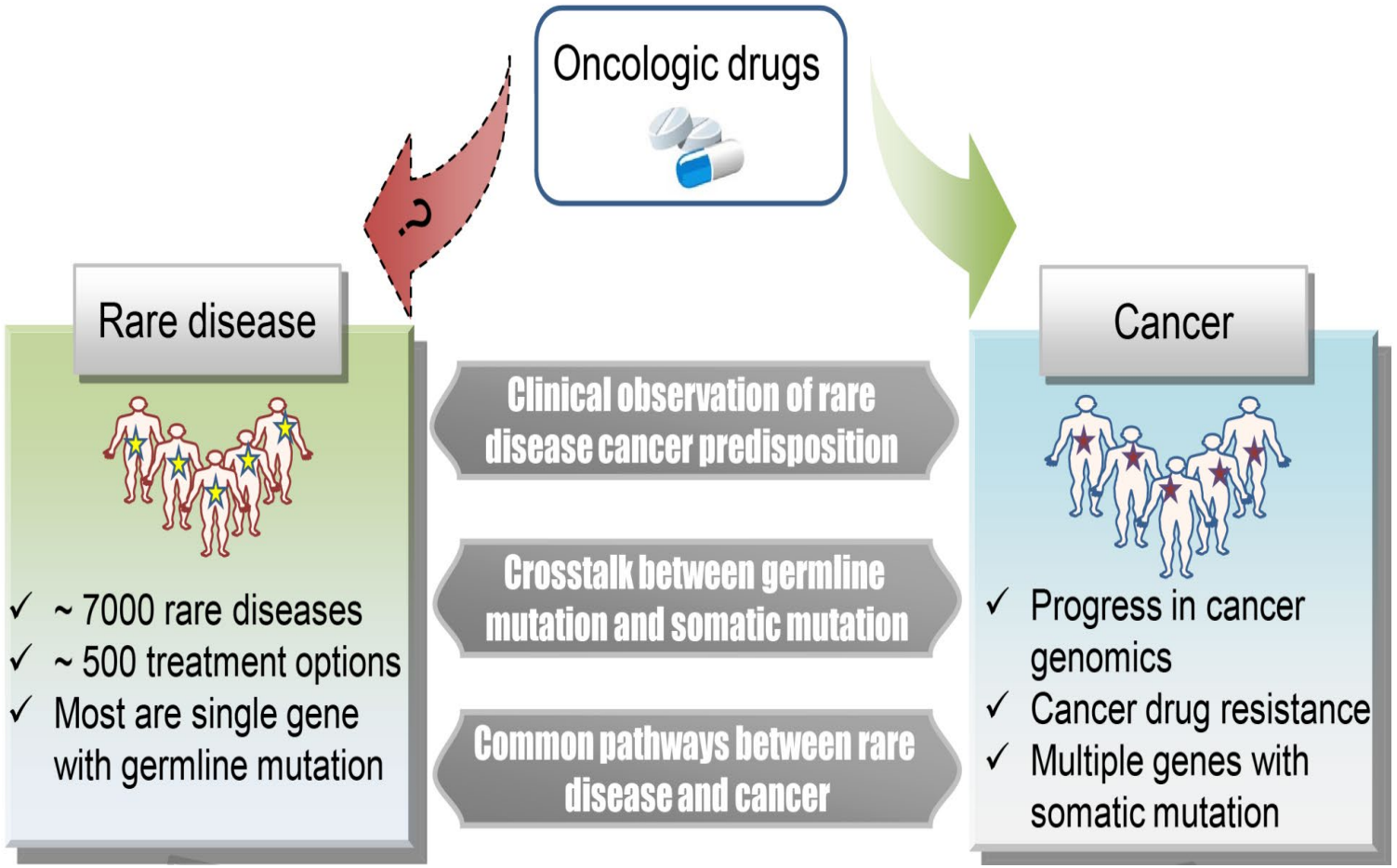
Summary Information of Repurposing Candidates for CF Treatment

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

Drug Names	Involved FFLs	Original Indication	Boxed Warnings	Price ($)/ tablet	PMID or Clinical.gov ID
Dexamethasone	hsa-mir-26b↔CREBBP	Anti-inflammatory; Oncologic uses; Glucocorticoid resistance; Obstetrics; High altitude illnesses	No	0.29	PMID:15223012
Simvastatin	hsa-miR-200c↔JUN	Hypercholesterolemia	No	1.34	NCT00255242
Levamisole	hsa-mir-26b↔CREBBP and hsa-miR-200c↔JUN	Dukes' stage C colon cancer; Worm infestations	No	0.18	PMID:9609763
Choline	hsa-miR-200c↔JUN and has-miR-29c↔TFAP2C	Dietary shortage or imbalance	No	0.71	NCT01070446
rosiglitazone pioglitazone	hsa-miR-200c↔JUN and has-miR-29c↔TFAP2C	Type 2 diabetes	Yes	1.08/ 1.38	PMID:20154695 NCT00322868

Drug Repurposing of Oncologic Drugs for the Treatment of Rare Diseases

The Relationship between Rare Diseases and Cancers

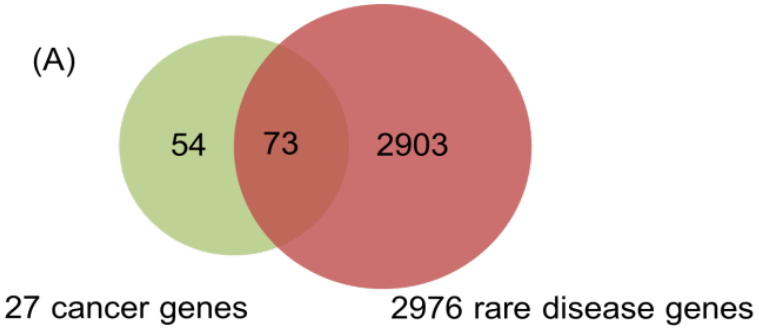


- Some patients with rare diseases are predisposed to develop cancer
- Some genes linked to cancer have also been identified as causative genes for rare diseases
- Rare diseases and cancer could perturb the same biological pathways

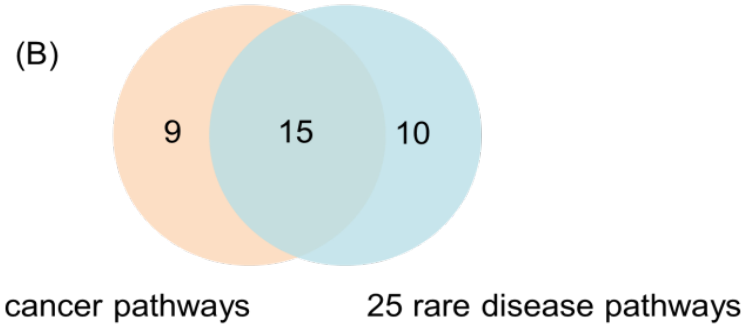
Liu et. al., **Potential reuse of oncologic drugs for the treatment of rare diseases**, *Trends in Pharmacological Sciences*, 2016, 37, 843-857.

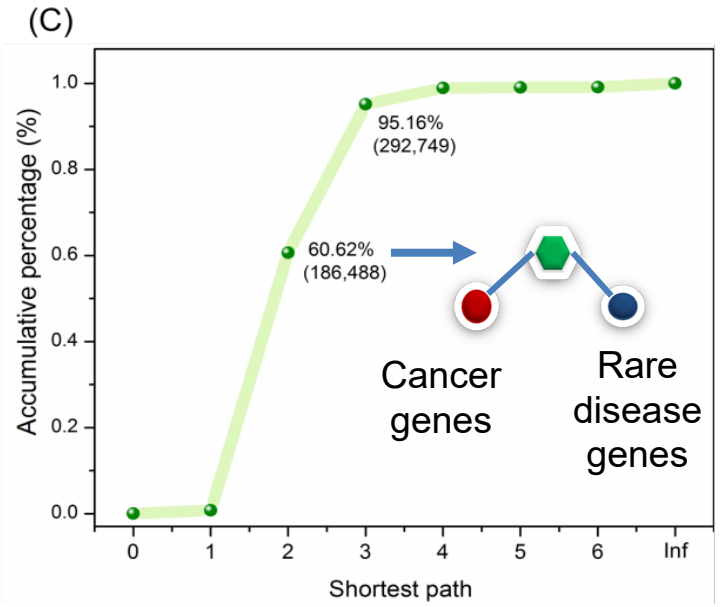
Molecular Association between Cancer and Rare Diseases

Gene overlap



Pathway overlap





Gene-gene distance in a PPI network

(D)

	Total number of drugs	Total number of targets	Number of targets that are also rare disease genes	number of drugs having the targets matched with rare disease genes	p value
Antineoplastic agents	87	97	13	23	3.33E-7
Antibacterials	121	97	7	22	1.70E-5
Cardiac therapy	61	97	8	17	1.35E-4
Antihypertensives	25	97	5	6	0.0034

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

Resources:

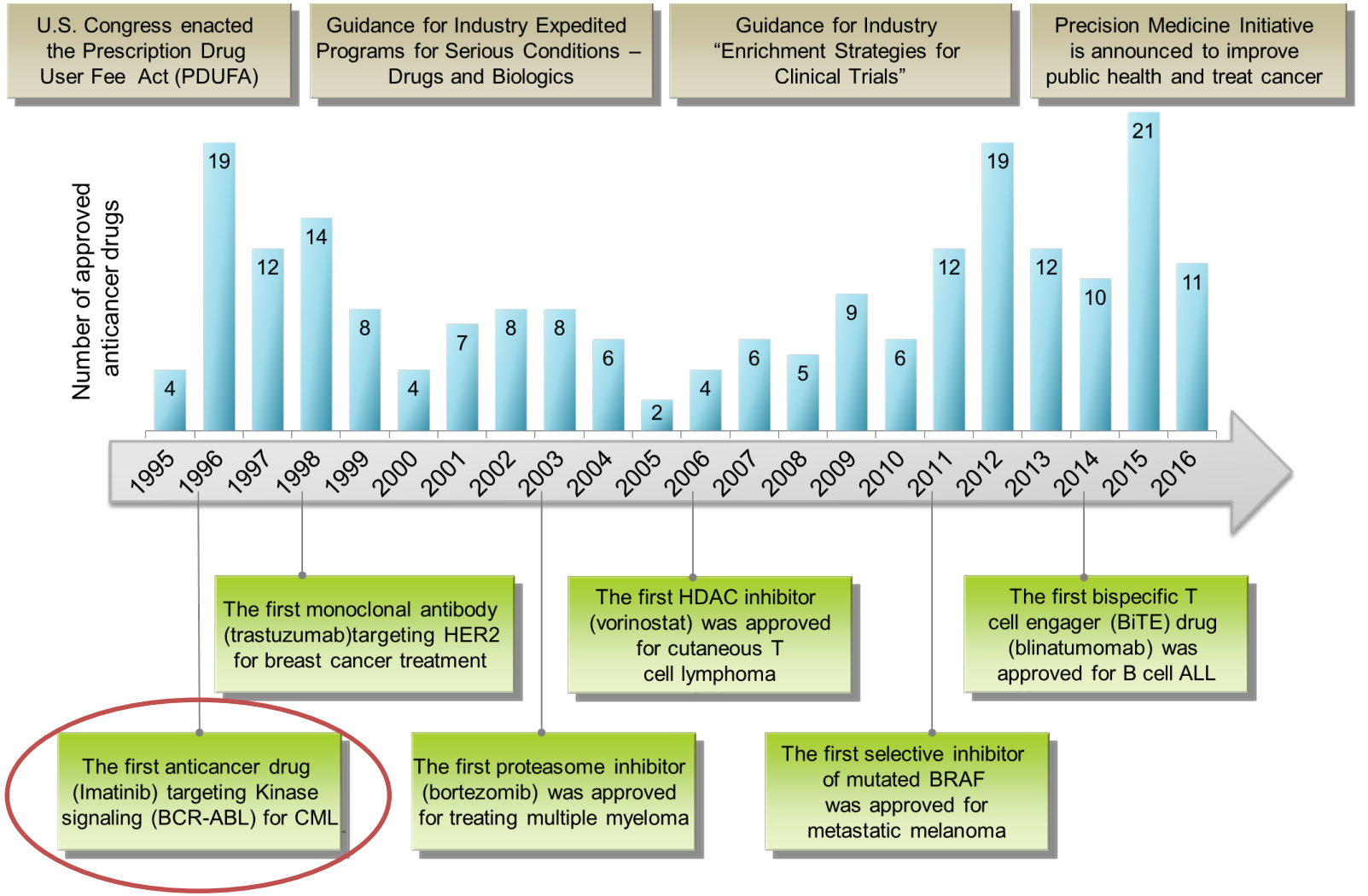
- Gene-rare disease relationships are curated from Orphanet
- Cancer genes are curated from TCGA pan-cancer data sets
- PPI are based on STRING v11.0 database
- Drug-target relationships are extracted from Therapeutic Target Database (TTD)

Rare Diseases that Could be Treated with Oncologic Drugs Evidence from Clinical Trials (clinicaltrials.gov) or the Literature

Orphanet ID	Rare disease	Evidences	Categories
117	Behcet disease	Cli, Lit	Rare skin disease
500	**LEOPARD syndrome**	**Lit/Exp**	
2884	Piebaldism	Lit	
774	Rendu-Osler-Weber disease	Cli	
3444	Watson syndrome	Lit	
670	PIBIDS syndrome		
284973	Marfan syndrome type 2		Rare circulatory system disease
88636	Aortic dilatation - joint hypermobility - arterial tortuosity		
140944	CLOVE syndrome		
1340	Cardiofaciocutaneous syndrome	Lit	Rare cardiac disease
79315	D-2-hydroxyglutaric aciduria	Lit	Rare neurologic disease

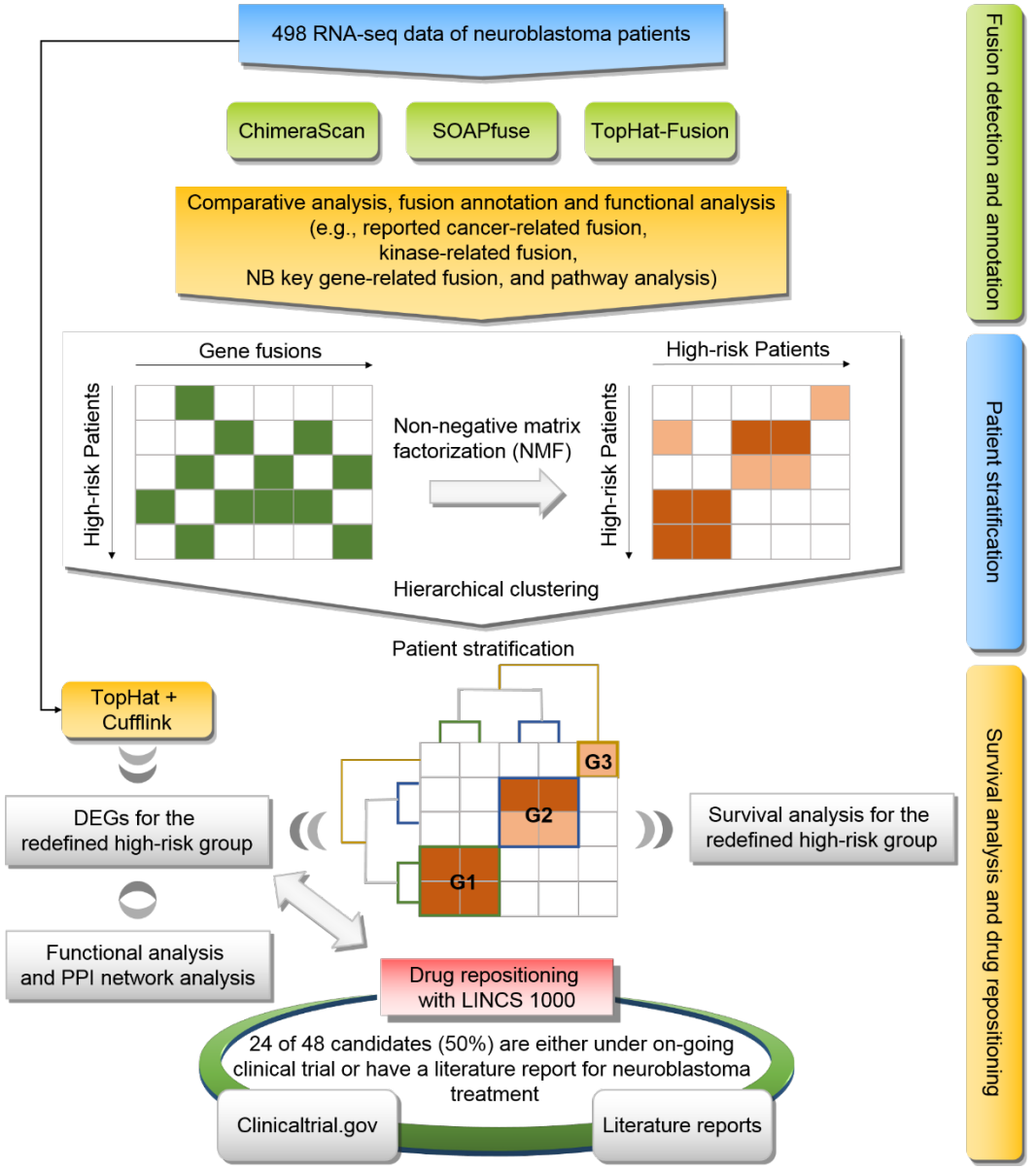
Drug Repurposing for Neuroblastoma by Unraveling Gene Fusion Events

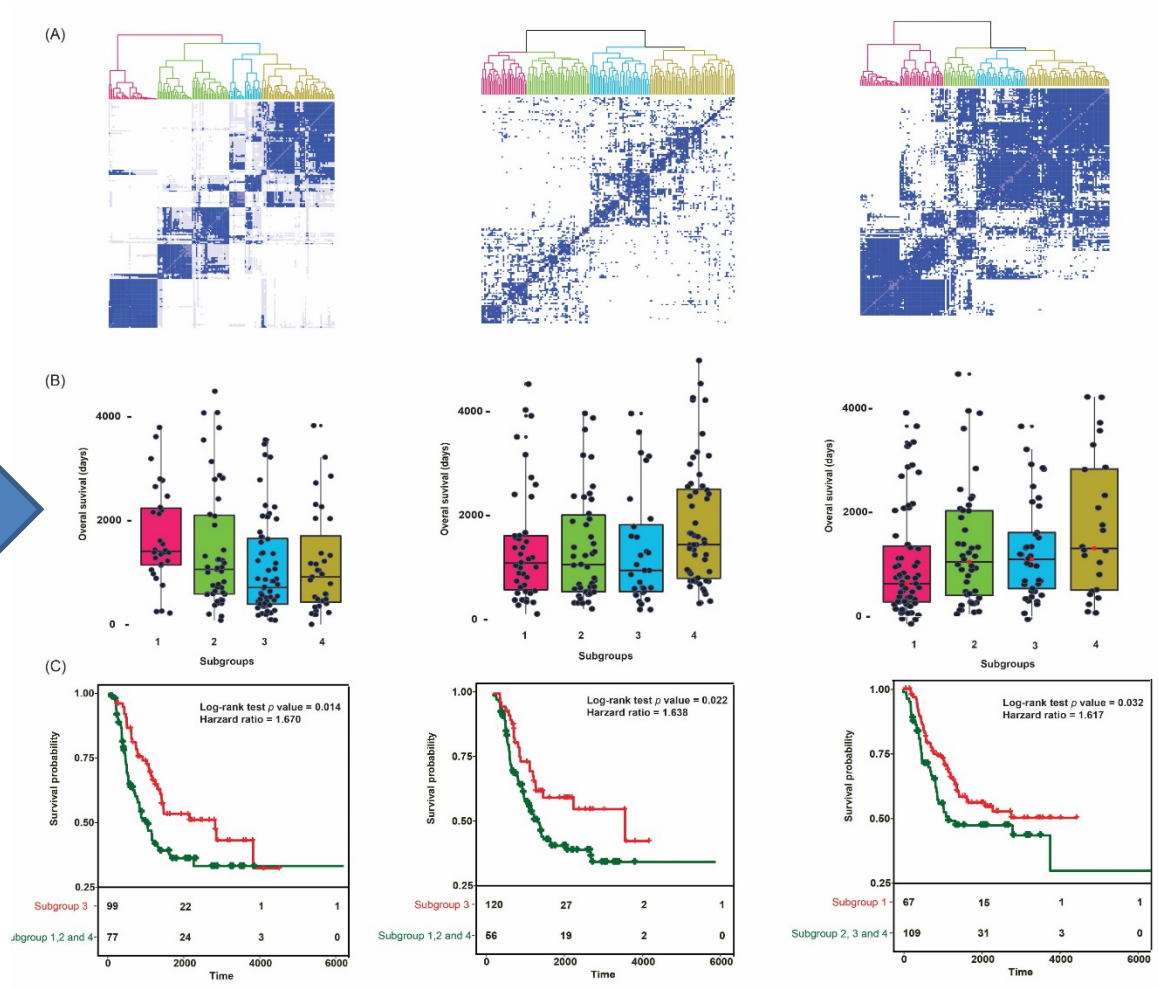
Gene Fusion for Anticancer Drug Development



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

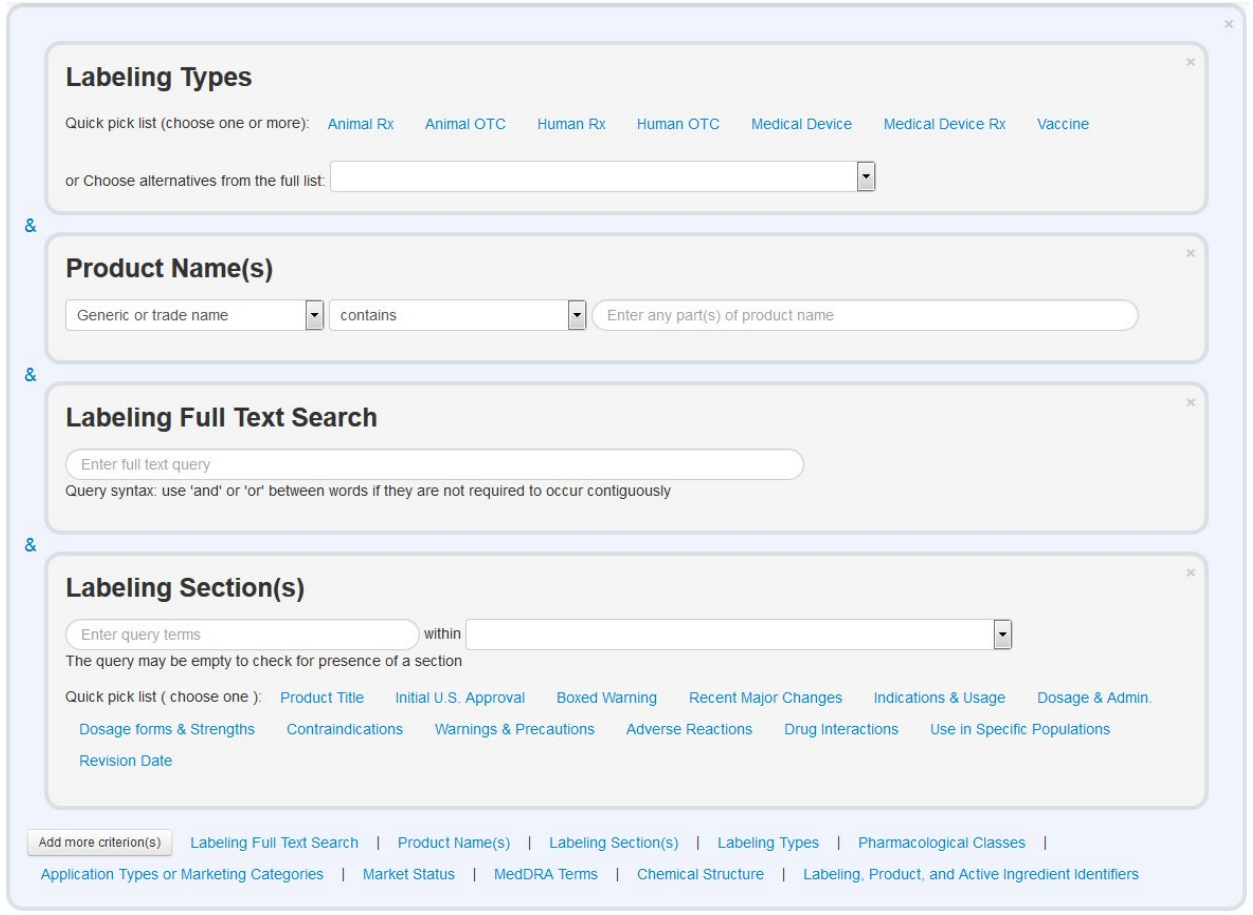
Preliminary Results of Drug Repurposing for Neuroblastoma





Bioinformatics Tools Toward Safer Drug Repurposing

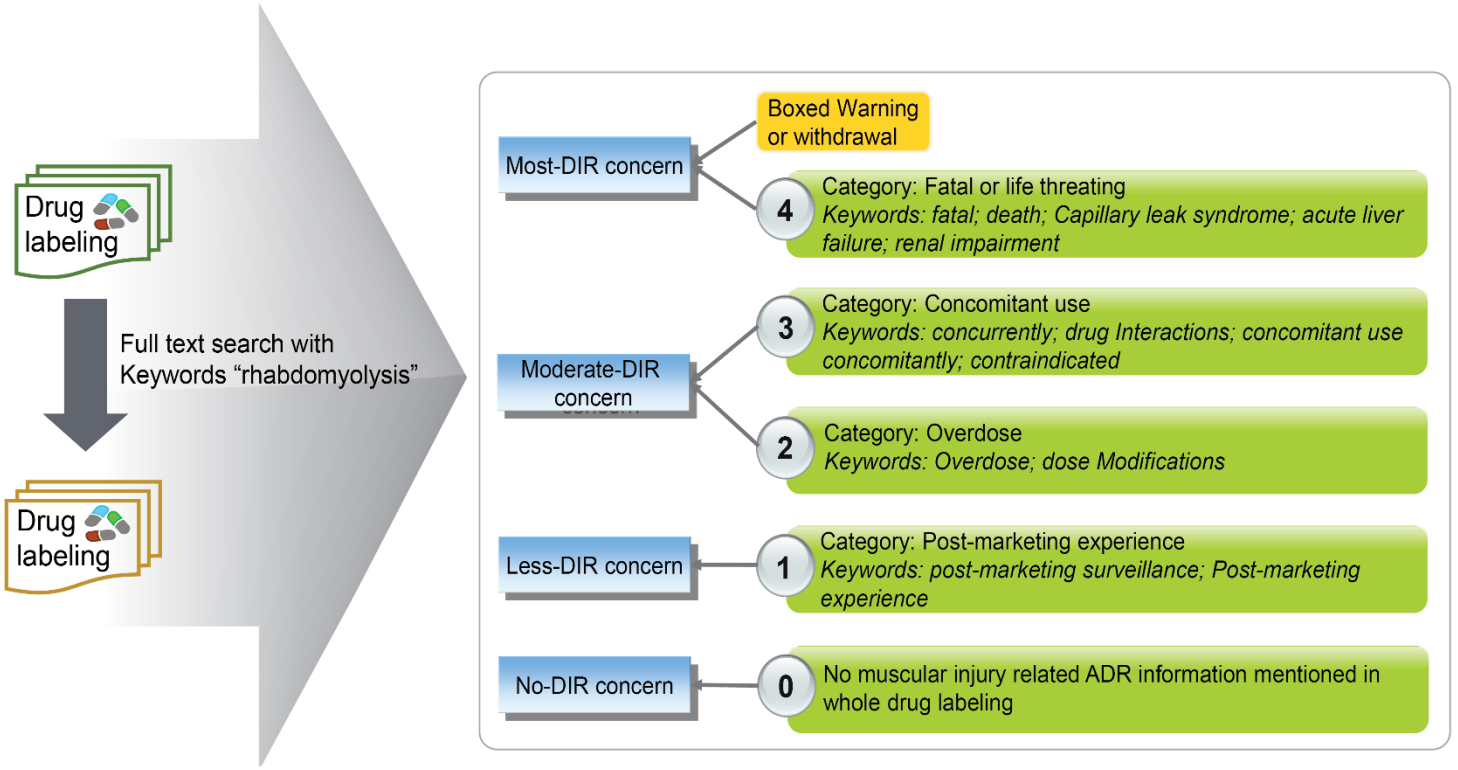
FDALabel – an Amazon Cloud Version



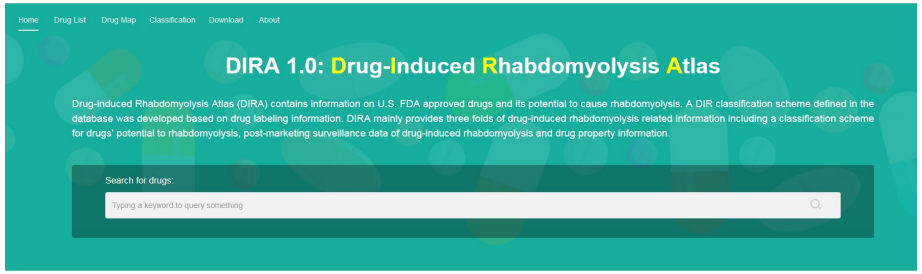
- A web-based application
- Customizable searches of over 100,000 labeling documents (RX, OTC, etc)
- One stop solution for FDA approved drug labeling information

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/

Wen et al., Drug-Induced Rhabdomyolysis Atlas (DIRA) for idiosyncratic adverse drug reaction management, Drug Discovery Today, 2019, 24(1), 9-15.

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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NIH

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Other collaborators

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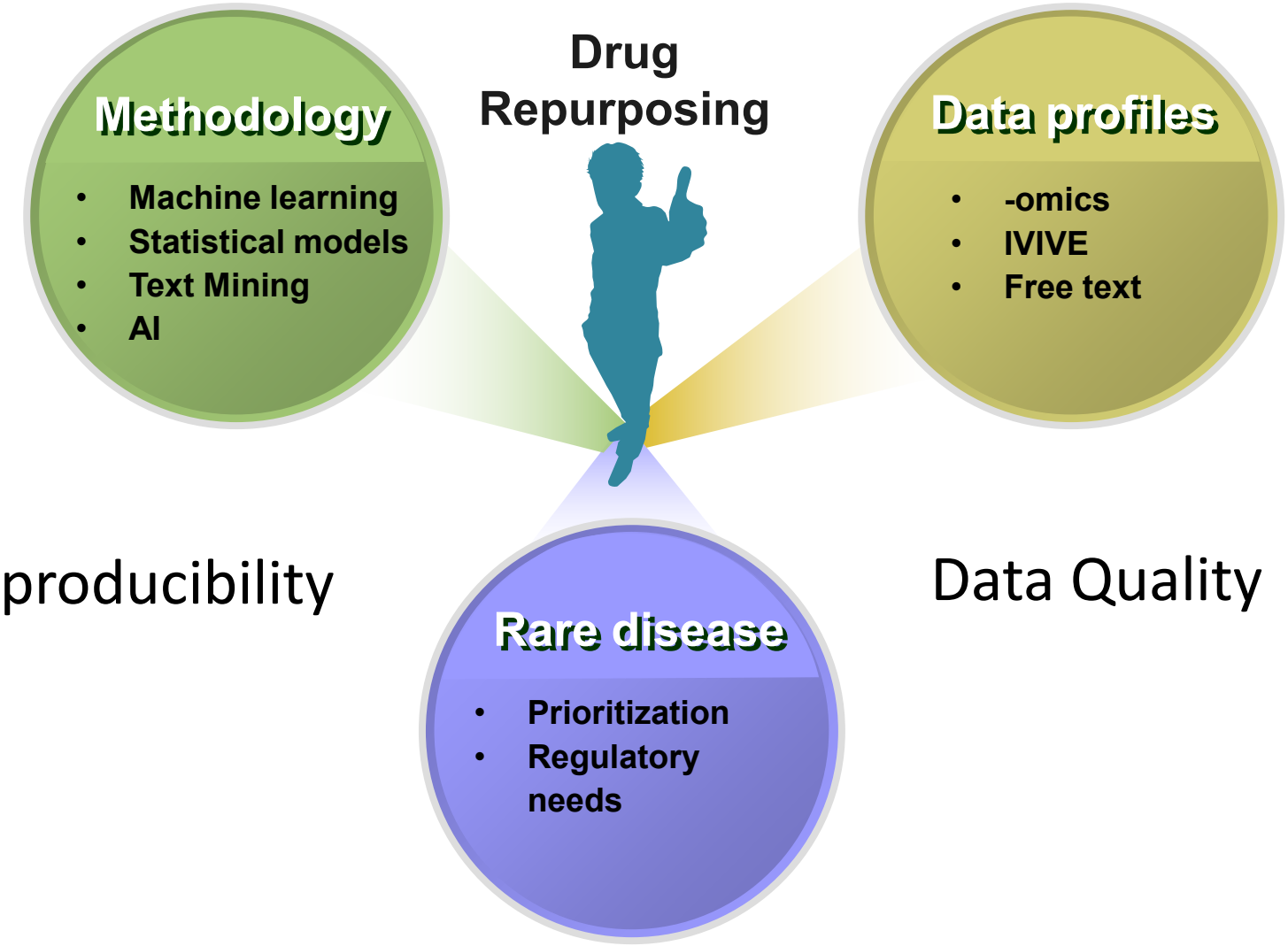
- Ruth Roberts (ApconiX)
- Jurgen Borlak (Hannover Medical School)
- Junguk Hur (University of North Dakota)
- Halil Bisgin (University of Michigan)
- Wenjun Bao (SAS)

Backup slides

Better Understanding of Data and Methodologies

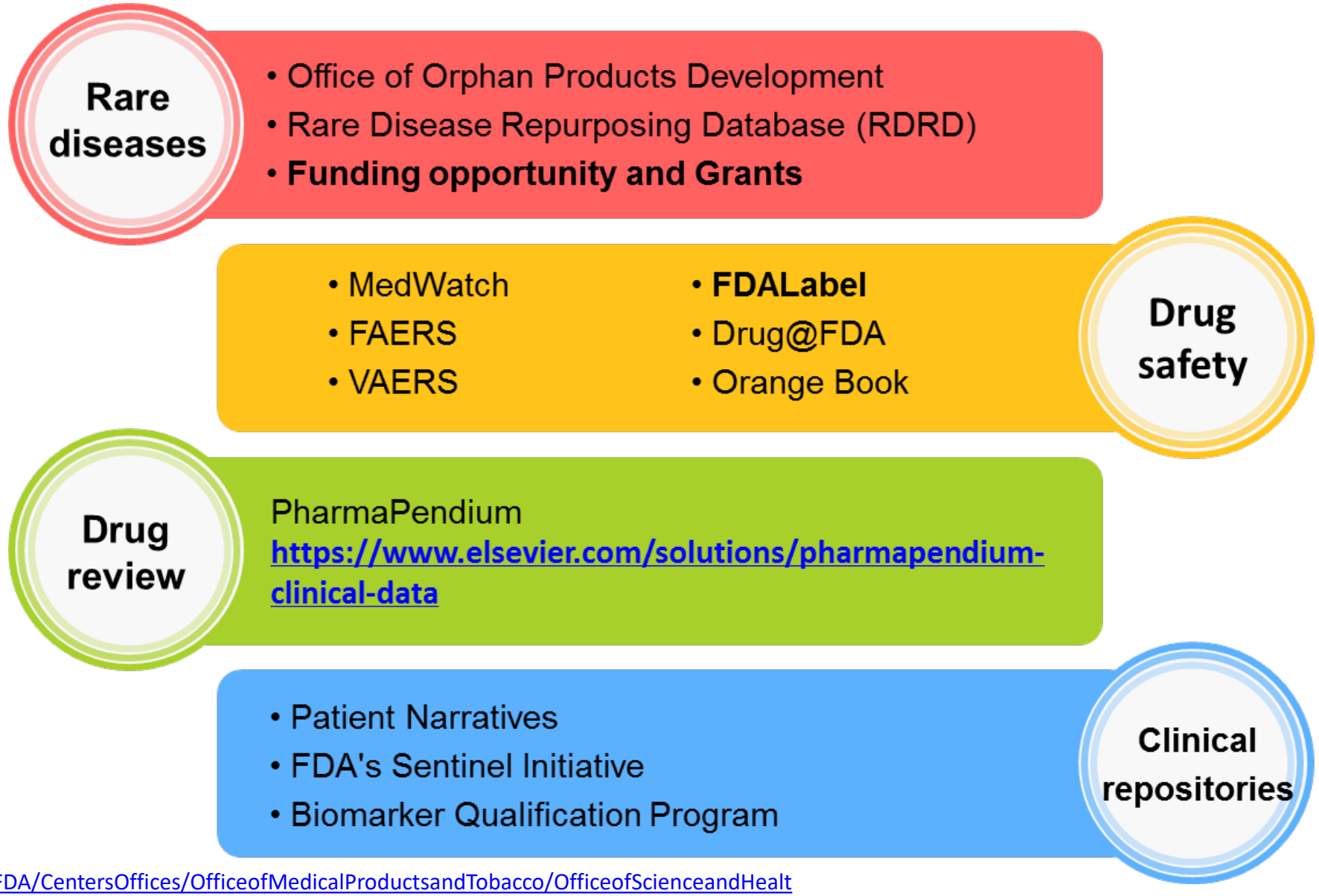


Reproducibility

Data Quality

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

Potential Drug Repositioning Resources at FDA



https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm

Programs Under FDA Office of Orphan Products Development

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

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm