Drug Repurposing at NCATS

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IOM GENOMICS-ENABLED DRUG RPEPURPOSING AND REPOSITIONING

NCATS

TRND: Therapeutics for Rare and Neglected Diseases

- Model: Comprehensive drug development collaboration between DPI and extramural labs with disease-area/target expertise
- Projects
  - » May enter at various stages of preclinical development
  - » Disease must meet FDA orphan or WHO neglected tropical disease criteria
  - » Taken to stage needed to attract external organization to adopt to complete clinical development/registration, max 2a
  - » Milestone driven
  - » Therapeutic modalities: small molecules, proteins
  - » Serve to develop new generally applicable platform technologies and paradigms
- Eligible applicants
  - » Academic, non-profit, government lab, biotech/pharma
  - » Ex-U.S. applicants accepted

TRND Portfolio

Therapeutic Area / Disease	Collaborator(s)	Agent	Status
Sickle Cell Disease	Aes-Rx, NHLBI	NME – Small Molecule	Clinical
Chronic Lymphocytic Leukemia	Leukemia & Lymphoma Society, University of Kansas	Repurposed Drug – Small Molecule	Clinical
Hereditary Inclusion Body Myopathy	New Zealand Pharmaceuticals, NHGRI	NME – Small Molecule	Clinical
Niemann-Pick Type C1	Johnson & Johnson, Albert Einstein College of Medicine, Univ. of Pennsylvania, Washington Univ., NICHD , NINDS , NHGRI	Repurposed Drug - Small Molecule	Clinical
Duchenne Muscular Dystrophy	ReveraGen BioPharma	NME – Small Molecule	Preclinical
Cryptococcal Meningitis	Viamet Pharmaceuticals, Inc.	NME - Small Molecule	Preclinical
Core Binding Factor Leukemia	NHGRI	Repurposed Drug - Small Molecule	Preclinical
Neonatal Herpes Simplex	University of Alabama, NIAID	NME – Small Molecule	Preclinical
Autoimmune Pulmonary Alveolar Proteinosis	Cincinnati Children's Hospital	Repurposed Drug - Biologic	Preclinical
Fibrodysplasia Ossificans Progressiva	Massachusetts General Hospital	NME - Small Molecule	Preclinical
Schistosomiasis	CoNCERT Pharmaceuticals	NME – Small Molecule	Preclinical
Creatine Transporter Defect	Lumos Pharma	NME - Small Molecule	Preclinical

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Repurposing Strategies

- Bioinformatics approaches
  - » Search published data on compounds and use that to predict new activities
- Pathway derived
  - » Well understood etiology of disease and known MOA of therapeutic
- Screening based repurposing
  - » Requires a screening set of approved drugs
  - » Allows one to look at synergies with existing standards of care
  - » Capitalize on polypharmacology of existing approved drugs

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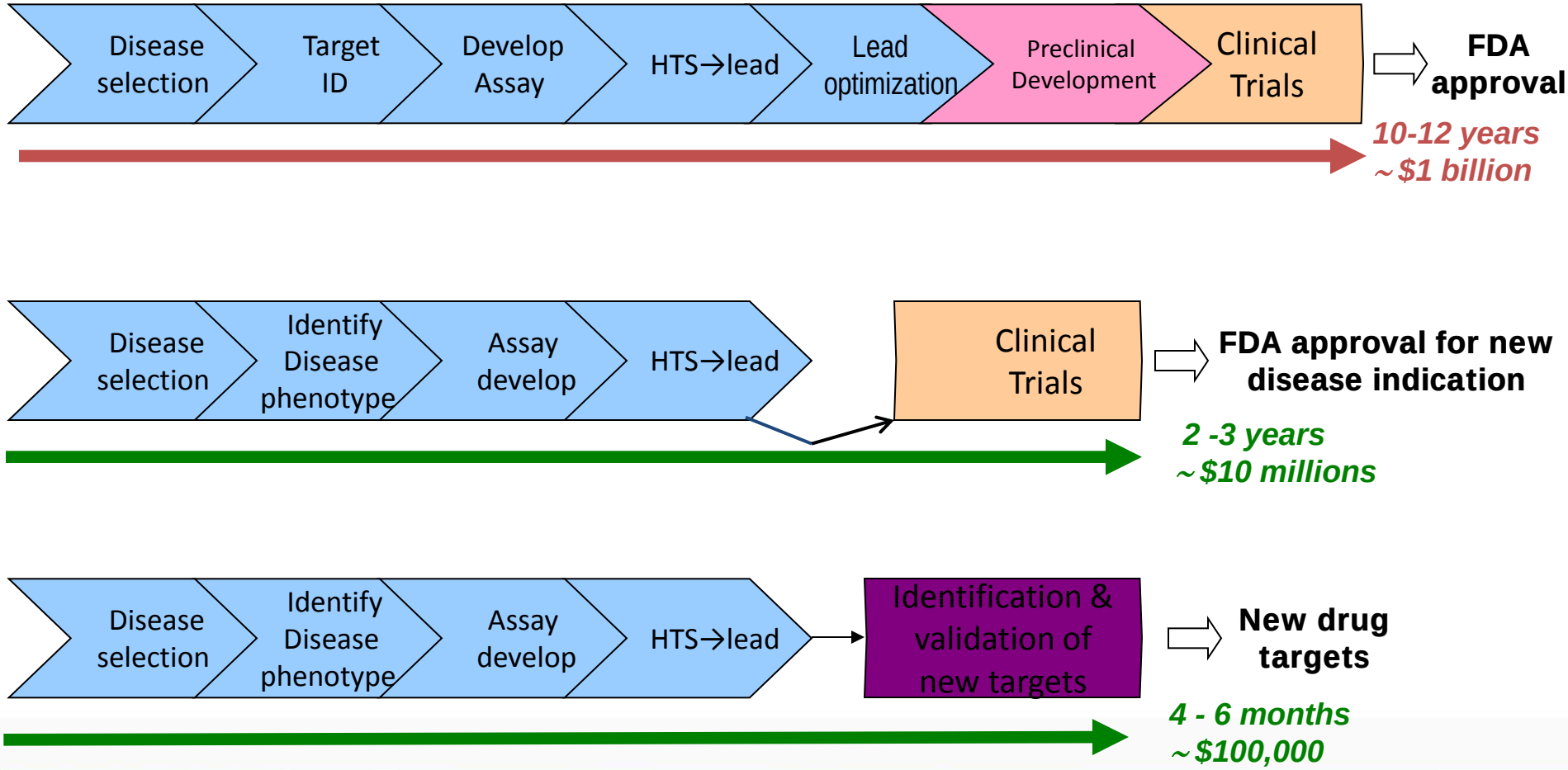
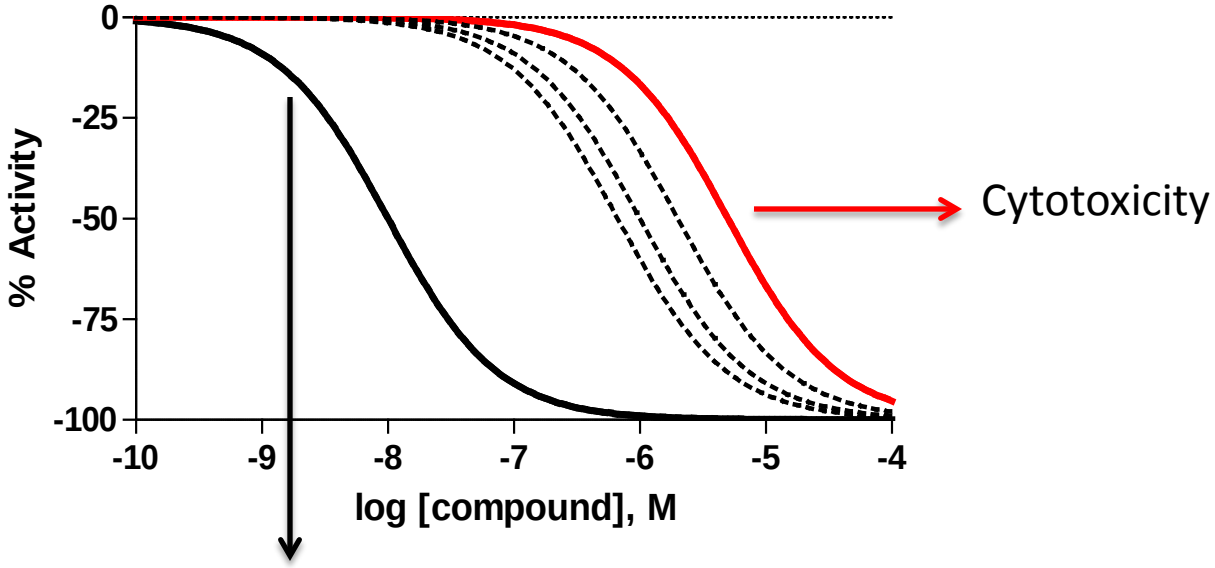
Potential Benefits of Repurposing



Screening Outcomes

- Tool compound to probe disease pharmacology/new targets
- Hit to use as a starting point for a med chem optimization program
  - » Weigh how this compares to starting with HTS campaign hits
- Approved drug that can be tested directly in patients in the clinic
  - » Same route of administration
  - » Sufficient toxicology to cover efficacious exposures in new indication
  - » Access to drug master file
  - » Similar target tissue (peripheral vs. central)
  - » Dosing regime (chronic vs. acute)
- Weigh existing data and IP options to decide path forward
  - » Weakly potent molecule that will require much additional data to augment existing DMF
  - » Can method of treatments claims or other IP patents be filed?

Screening Outcomes



TRND Screening Strategies

- Phenotypic cell based assays most useful tools for panning the collection
  - » Best tool to capitalize on the polypharmacology of the approved drug collection
- Use primary patient derived cells in the initial screen
  - » Cells must express the disease phenotype
- Beginning to use IPS Cells derived from patients differentiated to appropriate cell types
  - » When possible this represents the best resources to examine in vitro the potential of a compound

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The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang,* Noel Southall,* Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen, Christopher P. Austin†

Small-molecule compounds approved for use as drugs may be "repurposed" for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.

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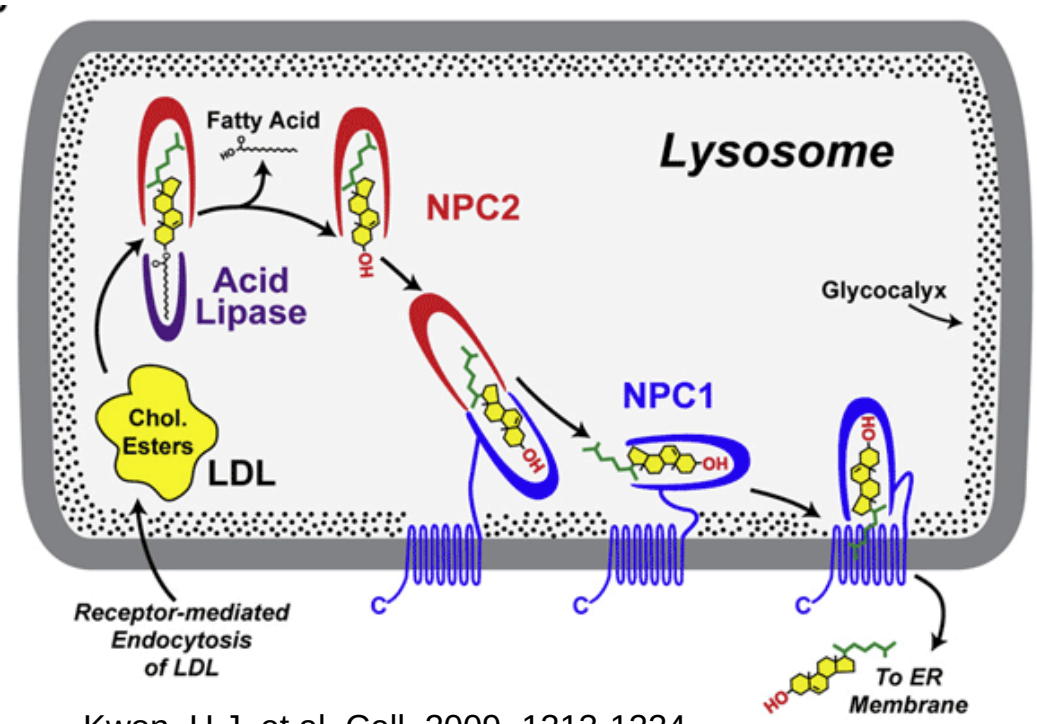
Niemann Pick Type C Disease

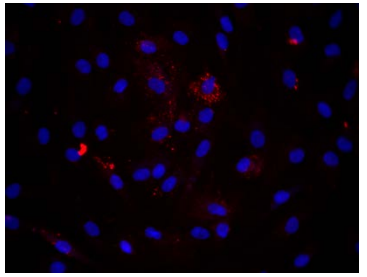
- Autosomal recessive disease: mutated genes are NPC1 (95%) and NPC2 (5%)
- Prevelance: 1/150,000, ~ 50% of cases have symptoms before 10 years of age
- Defects in NPC-1 or NPC-2 proteins cause cholesterol accumulation in lysosomes
- Clinical manifestations
  - » Enlargement of the spleen (splenomegaly) and liver (hepatomegaly)
  - » Progressive neurological disorders including cerebellar ataxia, dysarthria, dysphagia,tremor, epilepsy etc.
- Treatment
  - » No FDA approved therapies
  - » Miglustat, a glucosylceramide synthase inhibitor, has been approved in Europe but it is not a target specific treatment

LSD with a Defect in Cholesterol Trafficking

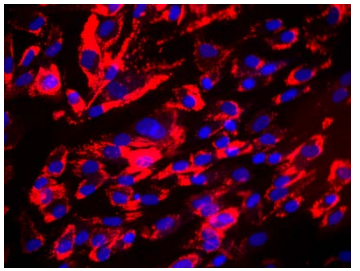


Kwon, H.J. et.al. Cell, 2009, 1213-1224

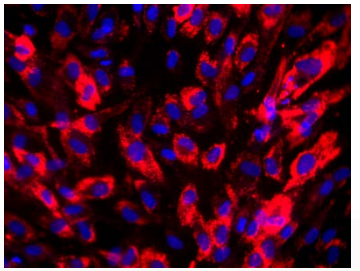
Wild type



NPC1 mutation



NPC2 mutation



Lysosome size enlarged in NPC1 and NPC2 cells. Red: lysosome Blue: nuclei

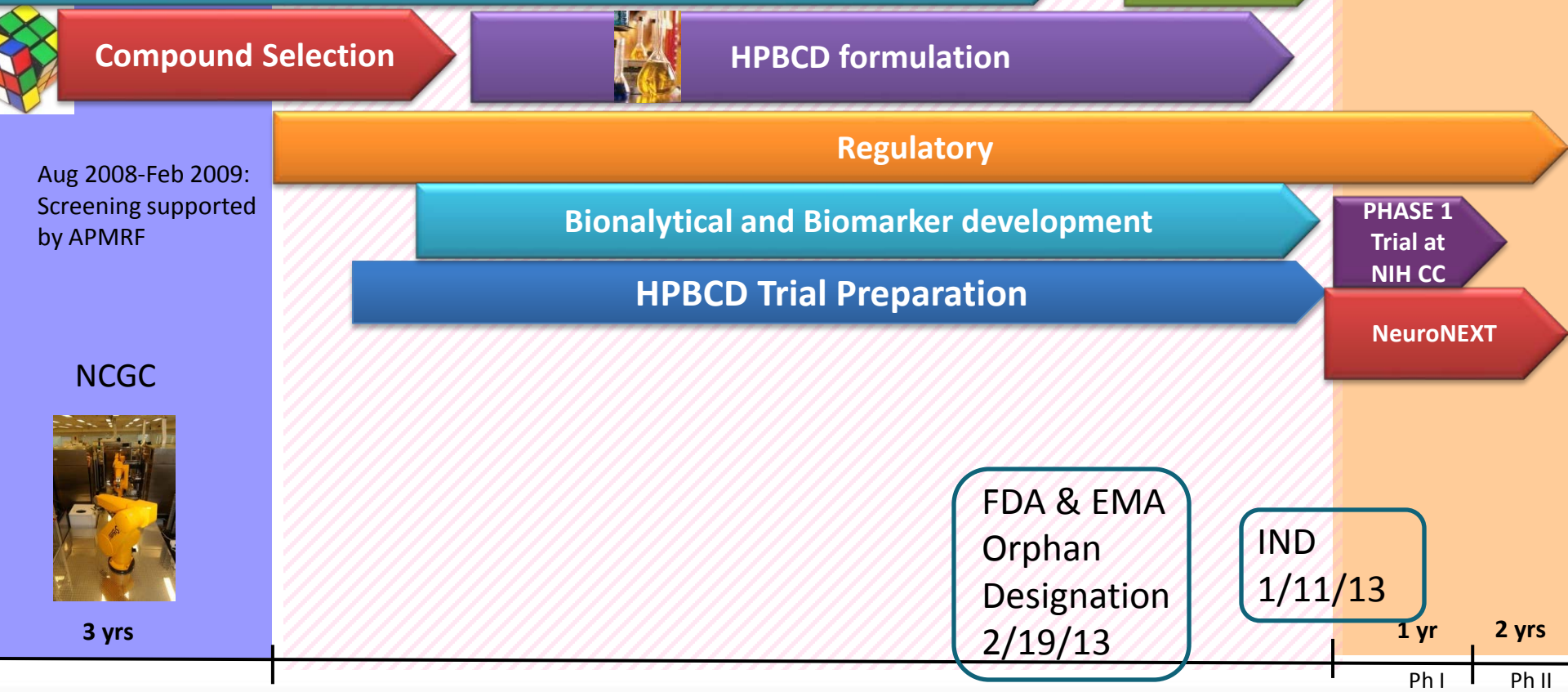
Tools to Find Potential Therapeutics

- Funding and Screening Collection
  - Grant from Ara Parseghian Medical Research Foundation to perform a screen
  - 60 reported potential “drugs” to be included
  - NCGC’s repurposing collection

- Cells
  - 58 patient derived NPC-1 cell lines from skin biopsy
  - Each line genotyped: know the defect causing disease
  - Multiple patient cell lines used for screening

- Phenotypic Assays
  - Amplex-red cholesterol assay (primary screen)
  - Filipin staining assay – accumulated cholesterol
  - Lysotracker assay - enlarged size of lysosome

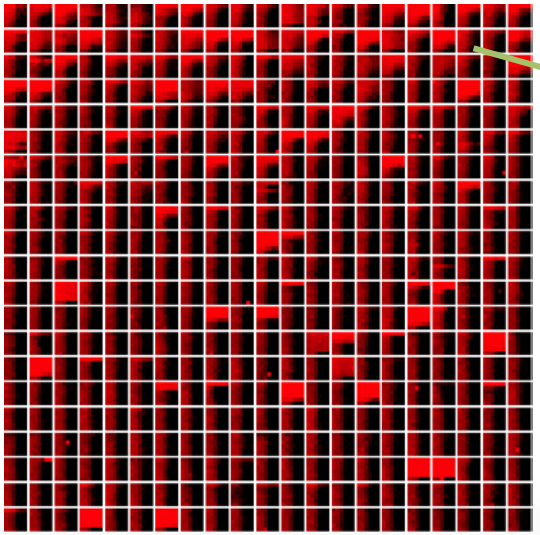
NPC Timeline



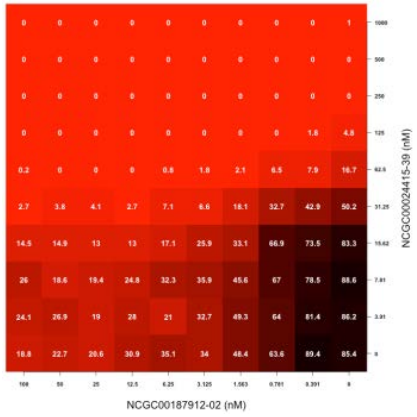
Personalized Repurposing

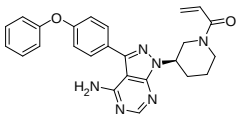
- "Mechanism Interrogation Plates" (MIPes): High-precision combination screening of known-mechanism compounds
- Enabled by acoustic dispensing technology and informatics advances

A compilation of all 6X6 matrices for the ibrutinib and MIPE experiment versus the ABC subtype of diffuse large B-cell lymphoma.

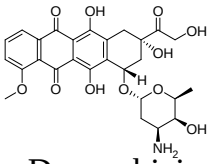


An example of a synergistic 10X10 matrix heatmap between ibrutinib and doxorubicin versus the ABC subtype of diffuse large B-cell lymphoma.





Ibrutinib
NCGC00187912



Doxorubicin
NCGC00024415

Issues

- Screening collection is expensive to create and maintain
  - » Unable to give out plates, must work through collaboration
- Challenging to find incentives to move a generic compound through enough clinical study to effect a label change
- Costs of some repurposing candidates prohibitive if originator is not willing to participate

Further Information

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