http://ismb.francecentral.cloudapp.azure.com/

BHK LAB

Biomarker Discovery and Machine Learning in Large Pharmacogenomics Datasets

Arvind Singh Mer,
Zhaleh Safikhani,
Petr Smirnov,
Benjamin Haibe-Kains
Princess Margaret Cancer Center,University Health Network
University of Toronto, Canada

UHN Princess Margaret Cancer Centre

VECTOR INSTITUTE

UNIVERSITY OF TORONTO

Objectives

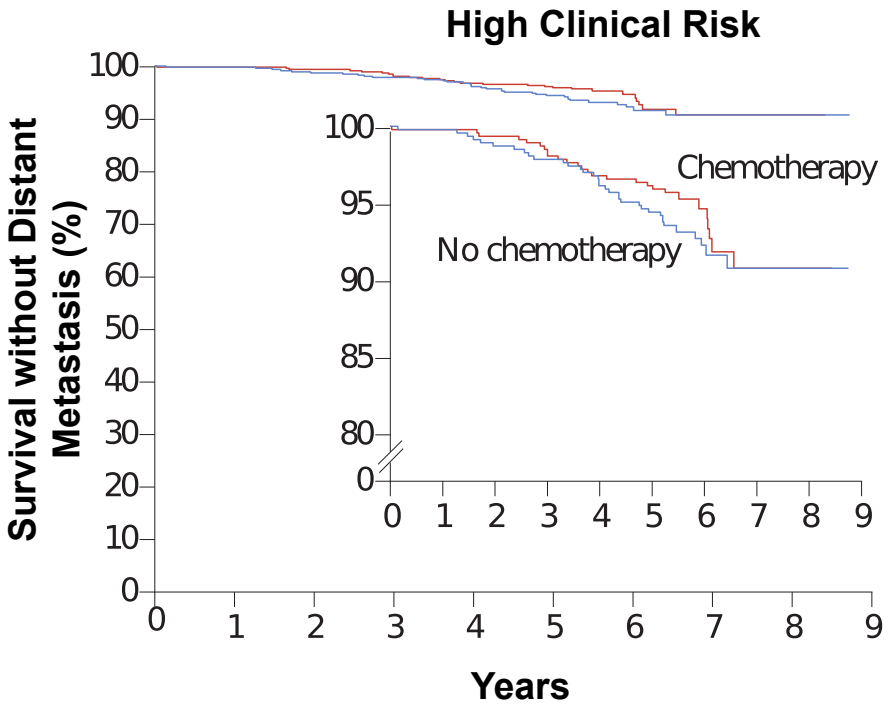
- Know the basics of different preclinical models used in cancer precision medicine
- Understand the role of pharmacogenomics in cancer precision medicine
- Know about different cancer pharmacogenomics datasets and projects
- Perform validation of biomarkers using publically available datasets
- Build machine learning models to predict anticancer drug response

Please don't forget to fill the feedback form!

https://goo.gl/forms/0sR1kfVO6nj4X8bO2

Introduction

- Treatment efficacy of anticancer drugs is low



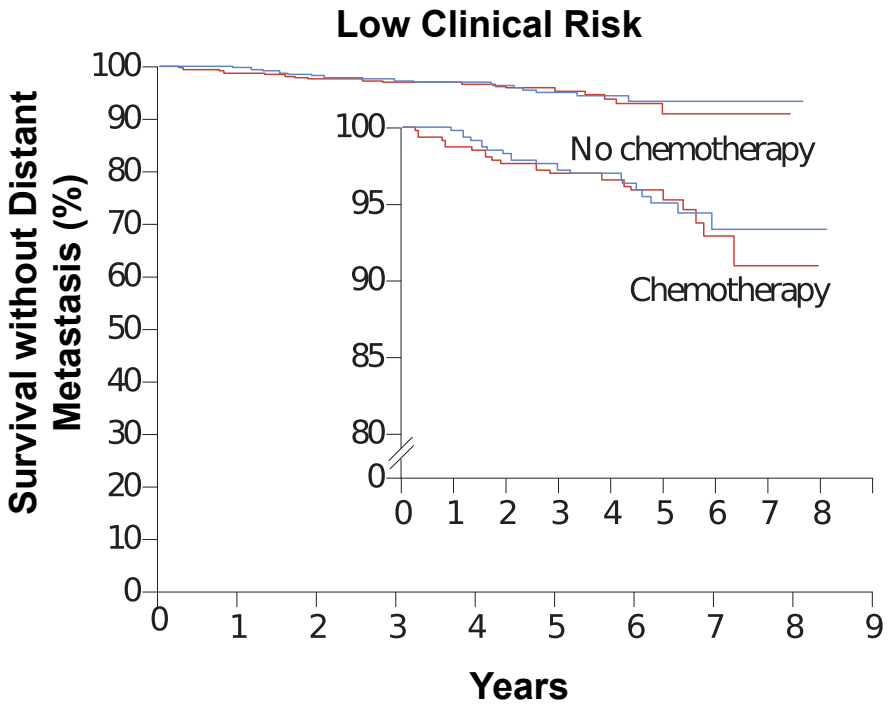
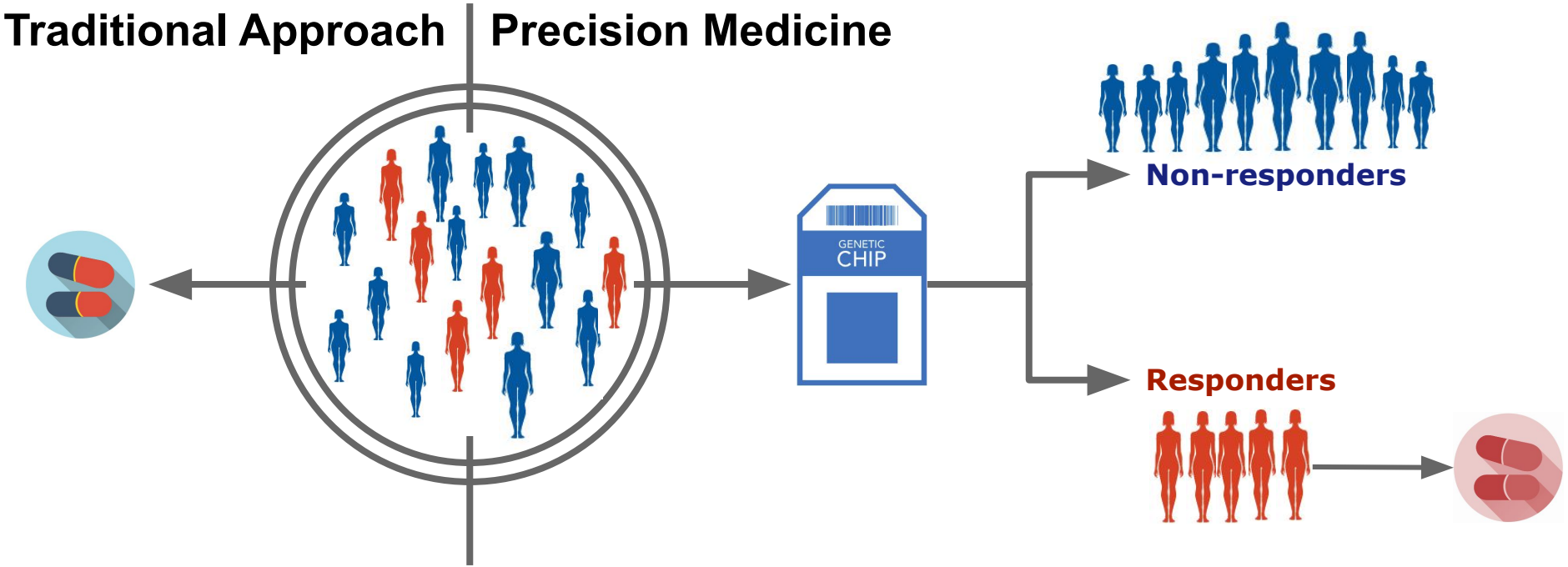


*Figure from Cardoso, Fatima, et al., *New England Journal of Medicine* 375.8 (2016): 717-729.

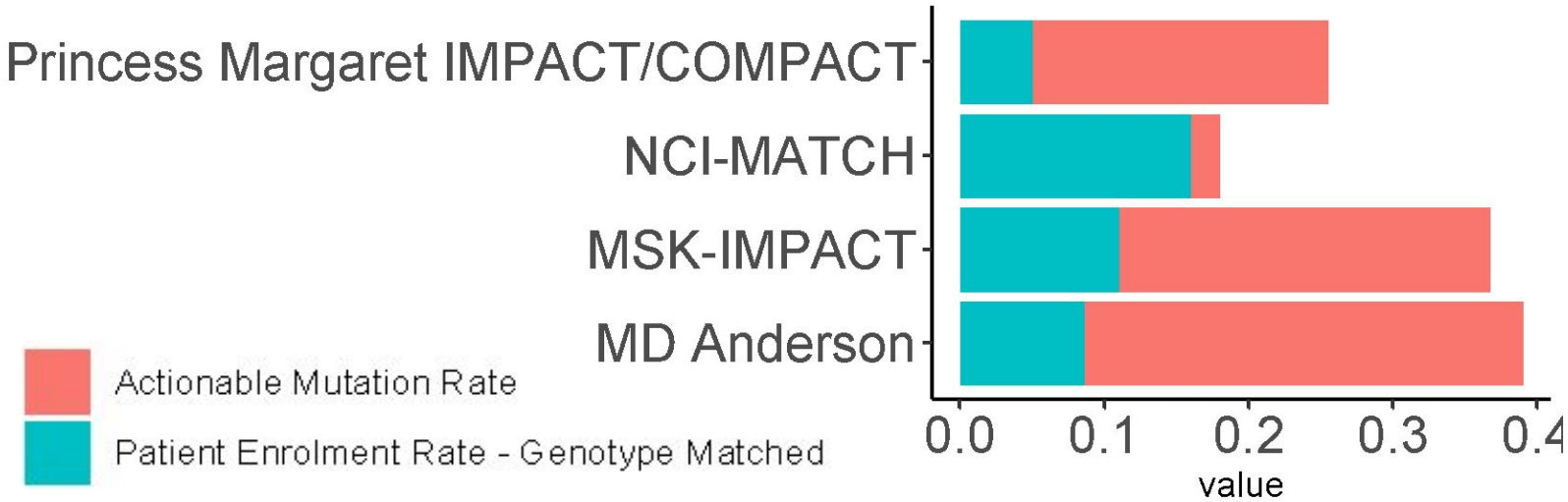
Precision Medicine



➢ Precision Medicine: Patient-Drug matching using genomic profiling

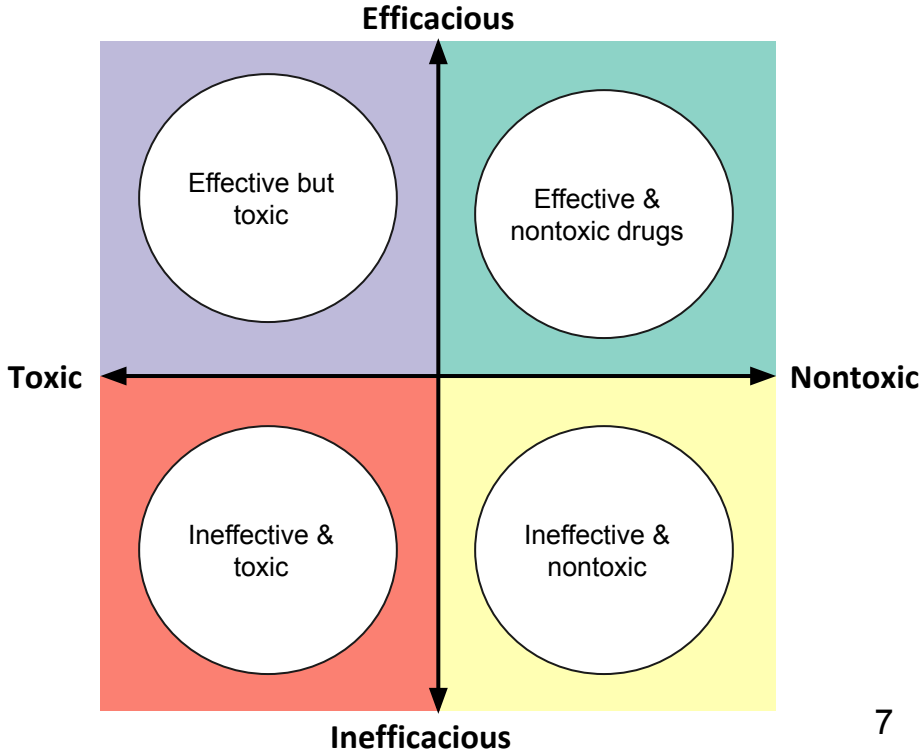
Challenges

- Matching rate is low (only 7% in breast cancer)
- Only a small panel of mutations is used to match patient to drugs
- Only 18-39% patients can be matched to clinical trials based on targeted sequencing

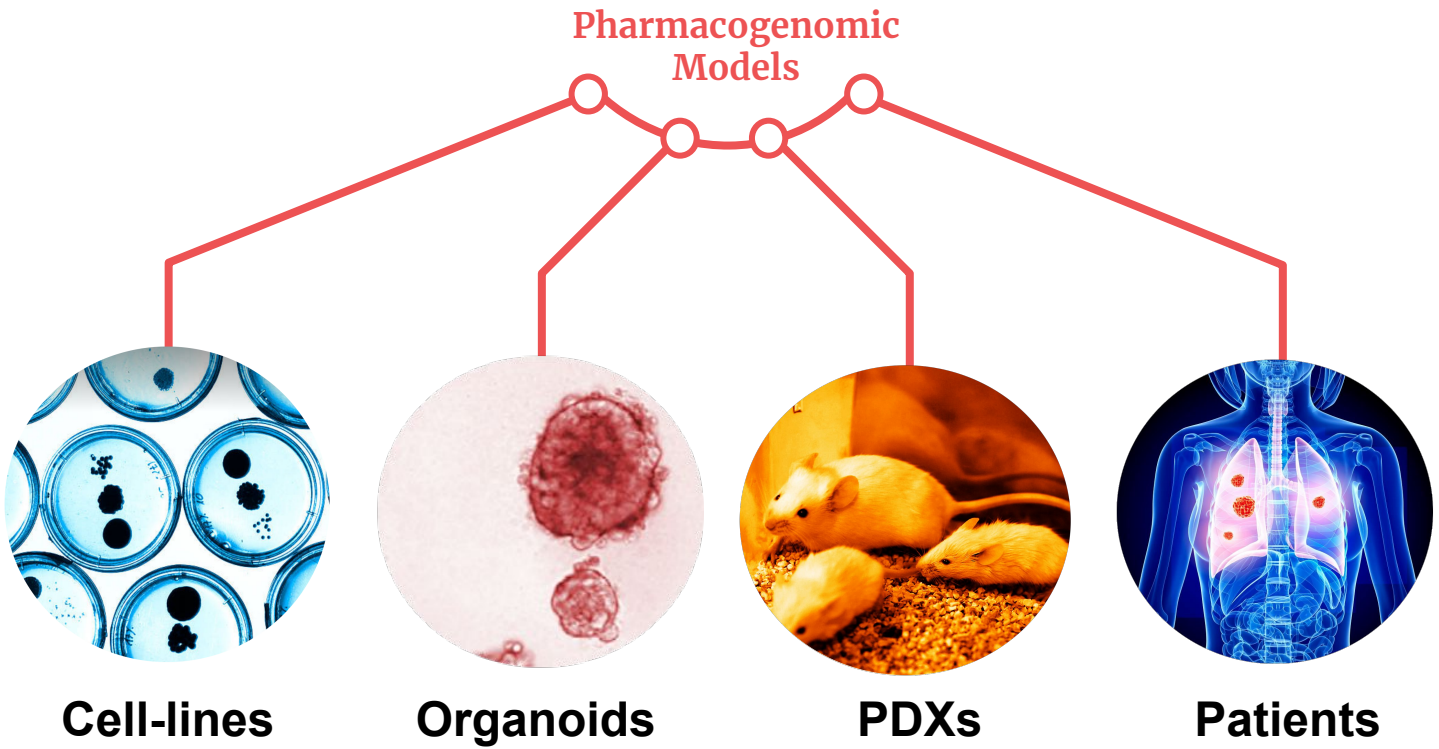


Pharmacogenomics

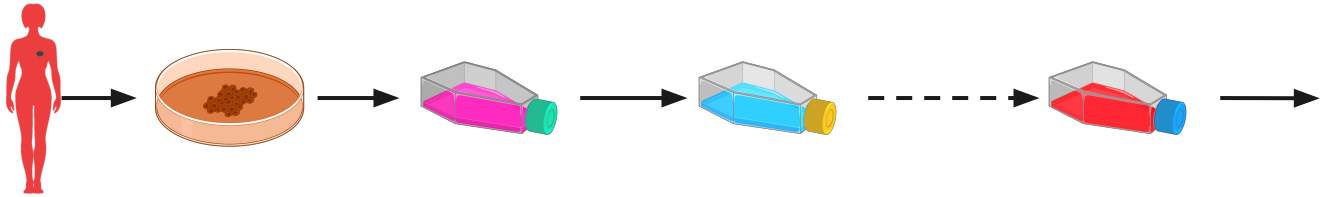
- Pharmaco + Genomics = Pharmacogenomics
- Pharmacogenomics is the study of how genes affect response to drugs
- It aims to:
  - Maximize drug efficacy
  - Minimize drug toxicity
  - Improve patient to drug matching
  - Aid drug development
  - Accelerate precision medicine



Pharmacogenomic Models

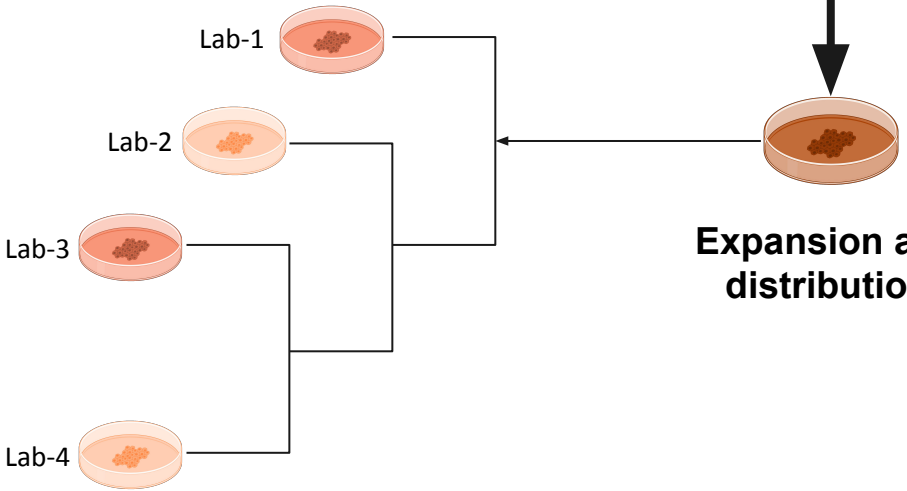


Cell Lines



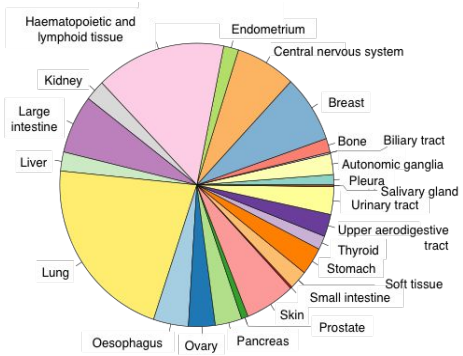
Expansion and Immortalization

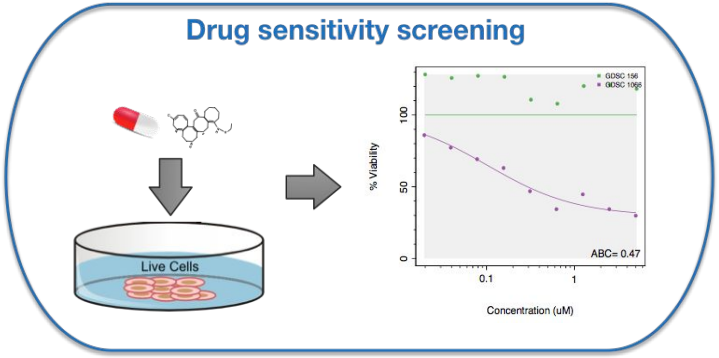
Cryopreservation & storage



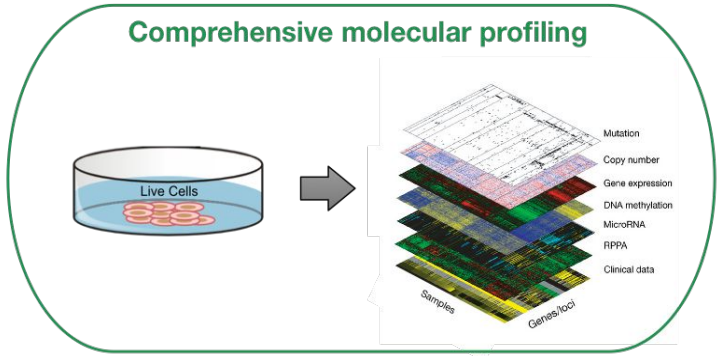
Expansion and distribution

Cell line-based (in vitro) Pharmacogenomic





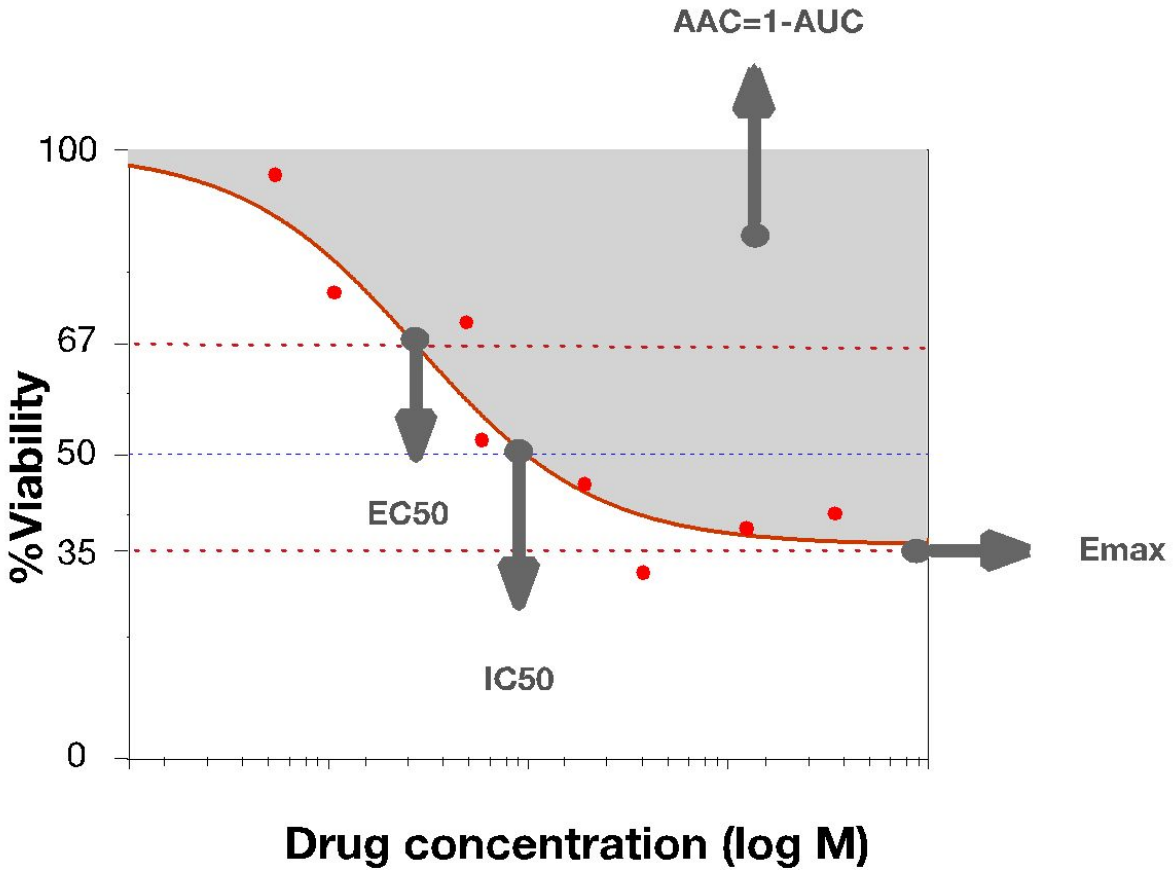
Biomarker discovery



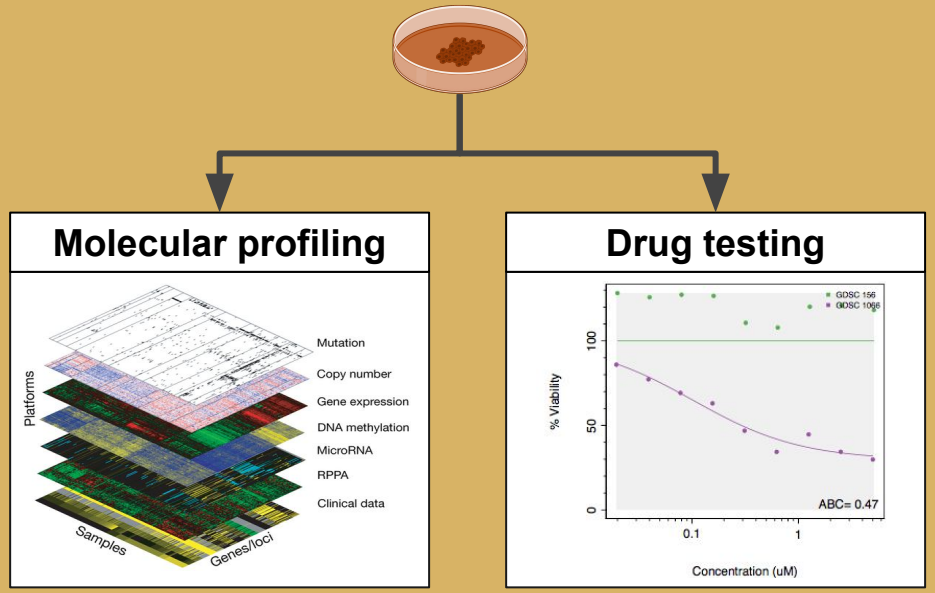
$Y = f(X)$

X

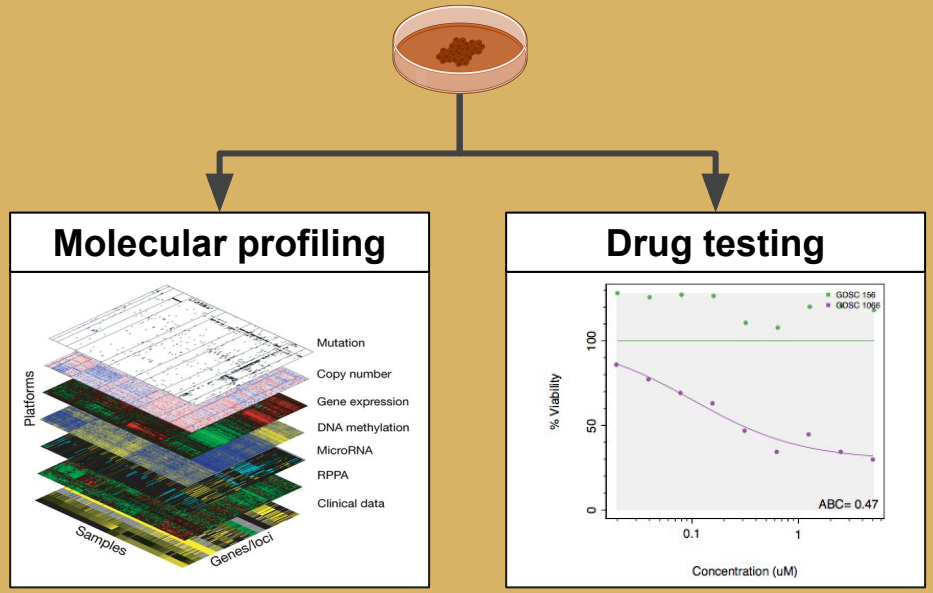
Drug Dose Response Curves

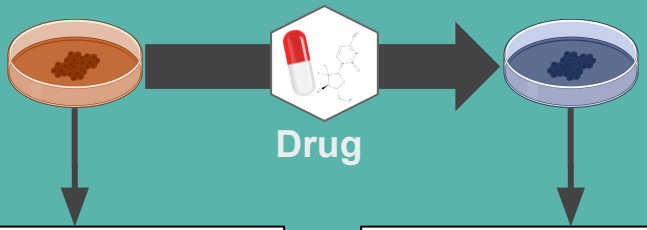


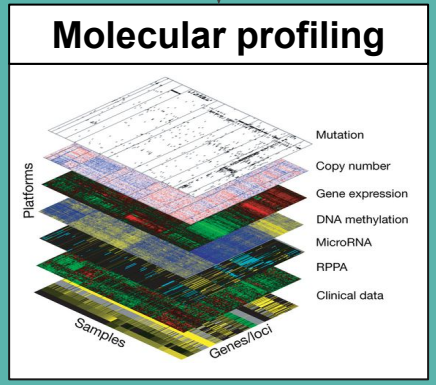
Sensitivity vs. Perturbation

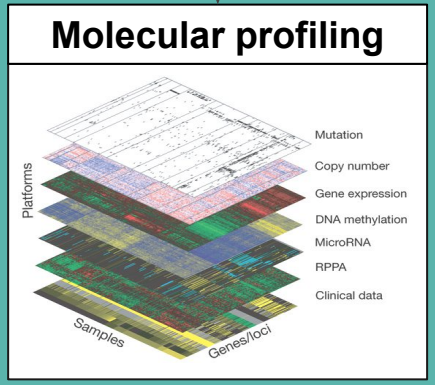


Sensitivity vs. Perturbation









Cell Lines

Advantage

- Widely used
- No ethical issues
- Comparatively low cost
- Easy to manage and manipulate
- High-throughput screening
- Many datasets are available

Cell Lines

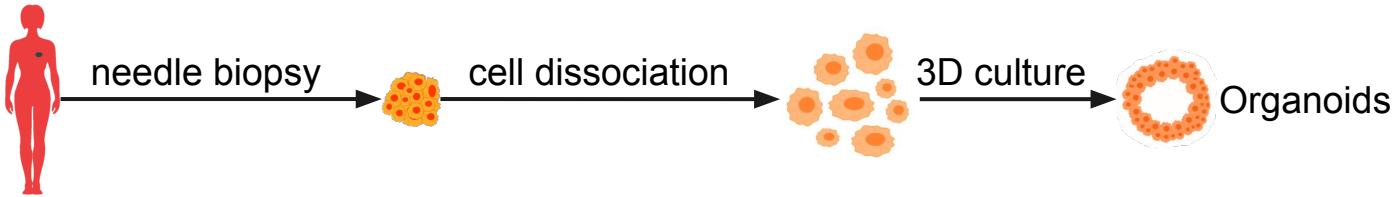
Advantage

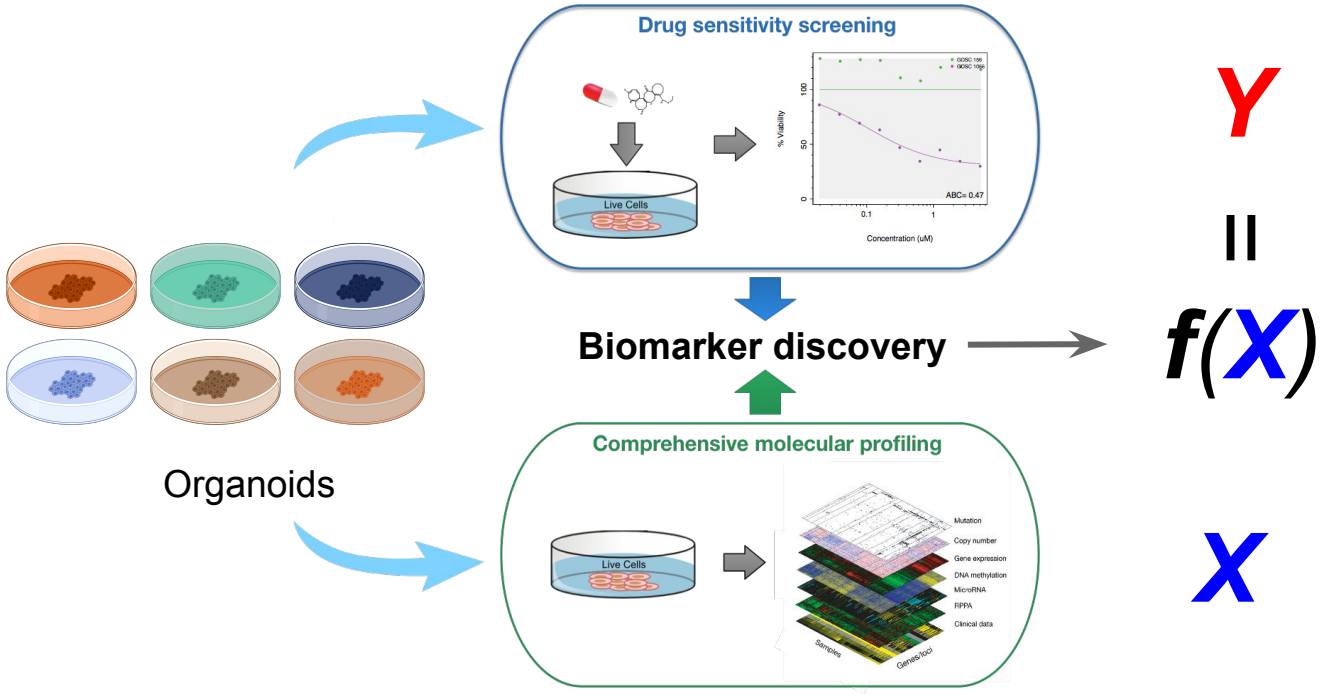
- Widely used
- No ethical issues
- Comparatively low cost
- Easy to manage and manipulate
- High-throughput screening
- Many datasets are available

Disadvantage

- Do not fully recapitulate human cancer
- Lack many features of tumors
- Sensitive to culture conditions
- Different strains can produce different results
- Contamination is frequent

Organoids


needle biopsy
cell dissociation
3D culture
Organoids


Drug sensitivity screening
Live Cells
% Viability
Concentration (uM)
ABC= 0.47
Y
=
f(X)
Biomarker discovery
Organoids
Comprehensive molecular profiling
Live Cells
Mutation
Copy number
Gene expression
DNA methylation
MicroRNA
RPPA
Clinical data
Samples
Genes/loci
X

Organoids

Advantage

- 3D model of tumor
- Better recapitulate tumor biology
- Less ethical issues
- Easy high-throughput screening

Organoids

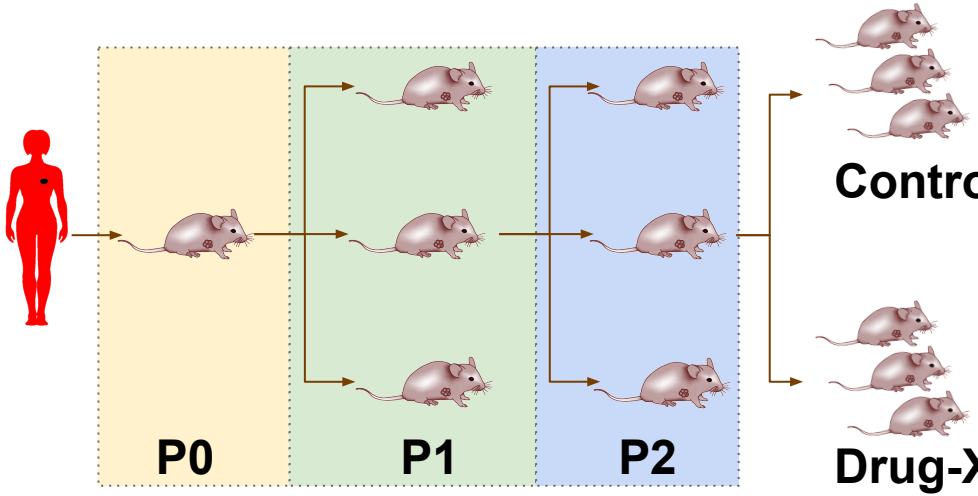
Advantage

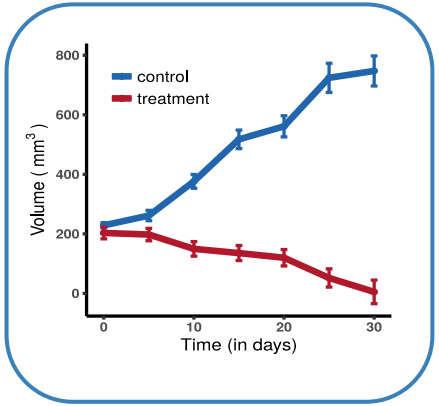
- 3D model of tumor
- Better recapitulate tumor biology
- Less ethical issues
- Easy high-throughput screening

Disadvantage

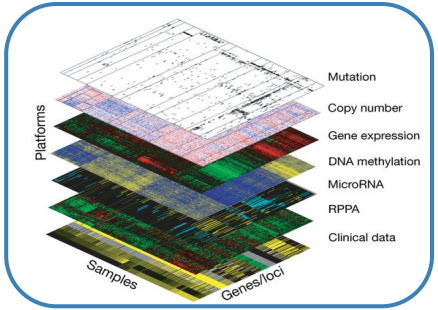
- Difficult to derive and immortalize
- Do not recapitulate the microenvironment of the tumors
- Medium-throughput drug screening platform

PDX





Biomarker discovery



PDX

Advantage

- *In Vivo* model of tumor
- Better recapitulate tumor biology
- Recapitulate many in vivo features
- Can be used for tumor microenvironment study

PDX

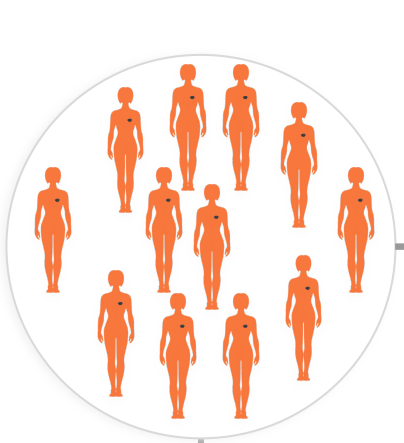
Advantage

- *In Vivo* model of tumor
- Better recapitulate tumor biology
- Recapitulate many in vivo features
- Can be used for tumor microenvironment study

Disadvantage

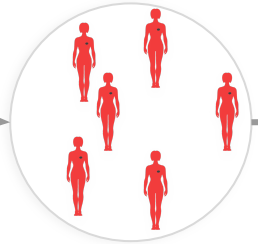
- Difficult to establish
- Expensive
- High-throughput screening is difficult

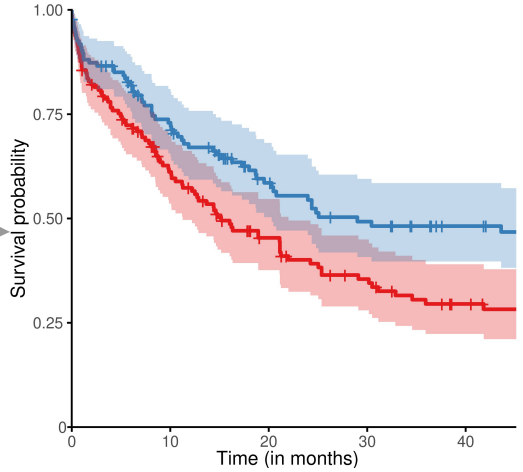
Patients



Drug-X

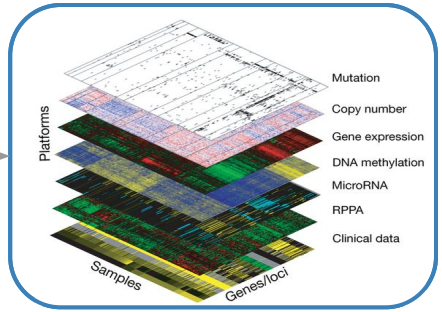
Standard drug





needle biopsy

Biomarker discovery



BHK LAB

Patients

Advantage

- Gold standard for drug response
- Direct translational research
- Explicit assessment of toxicity

Patients

Advantage

- Gold standard for drug response
- Direct translational research
- Explicit assessment of toxicity

Disadvantage

- Very expensive
- Several ethical issues
- Many confounding factors
- High-throughput screening is difficult

Questions

Please don't forget to fill the feedback form!

https://goo.gl/forms/0sR1kfVO6nj4X8bO2

Arvind Mer	a.mer@utoronto.ca	@ArvidMer
Zhaleh Safikhani	zhaleh.safikhani@utoronto.ca	@Zhaleh_julie
Petr Smirnov	petr.smirnov@mail.utoronto.ca	@ _psmirnov