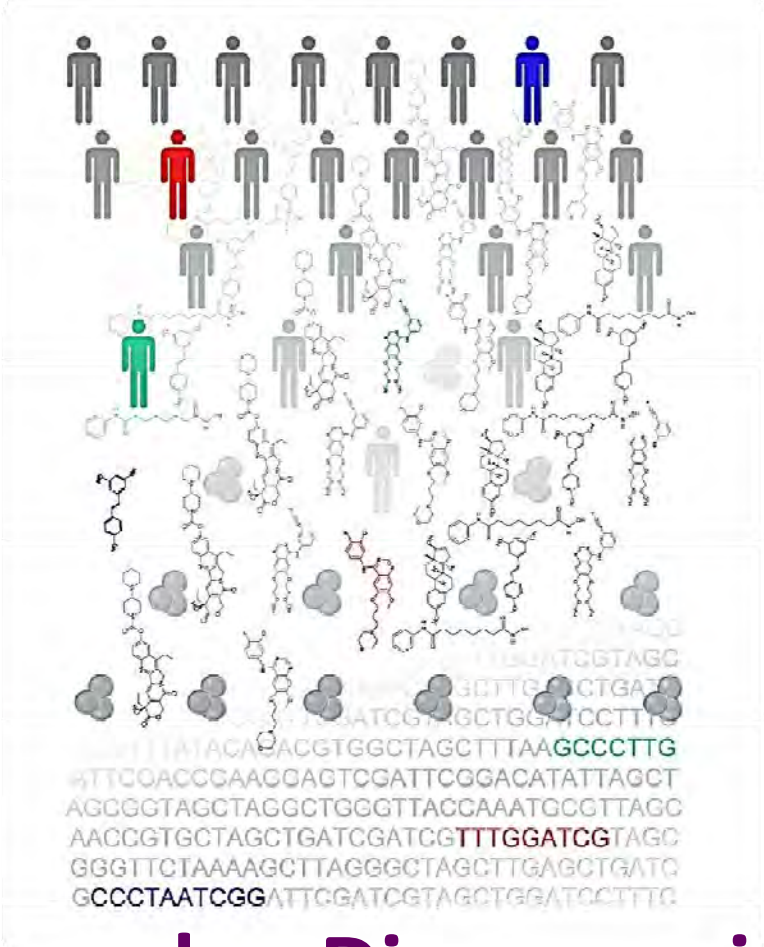


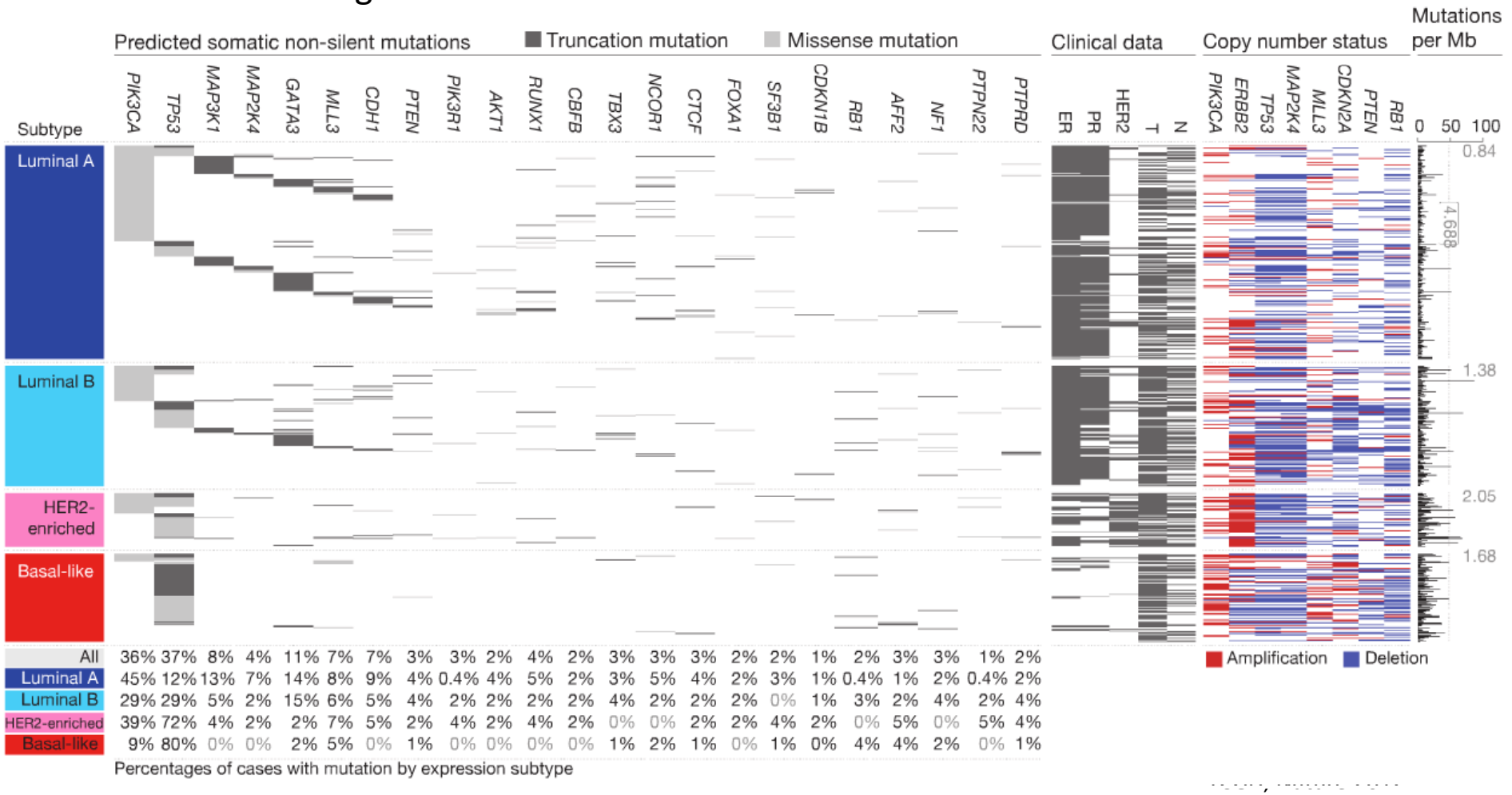
Preclinical Biomarker Discovery in Cancer Cells

Mathew Garnett
Genomics of Drug Sensitivity in Cancer (GDSC)
Wellcome Trust Sanger Institute

SCI, London
15th May 2013

The genomic complexity of cancer

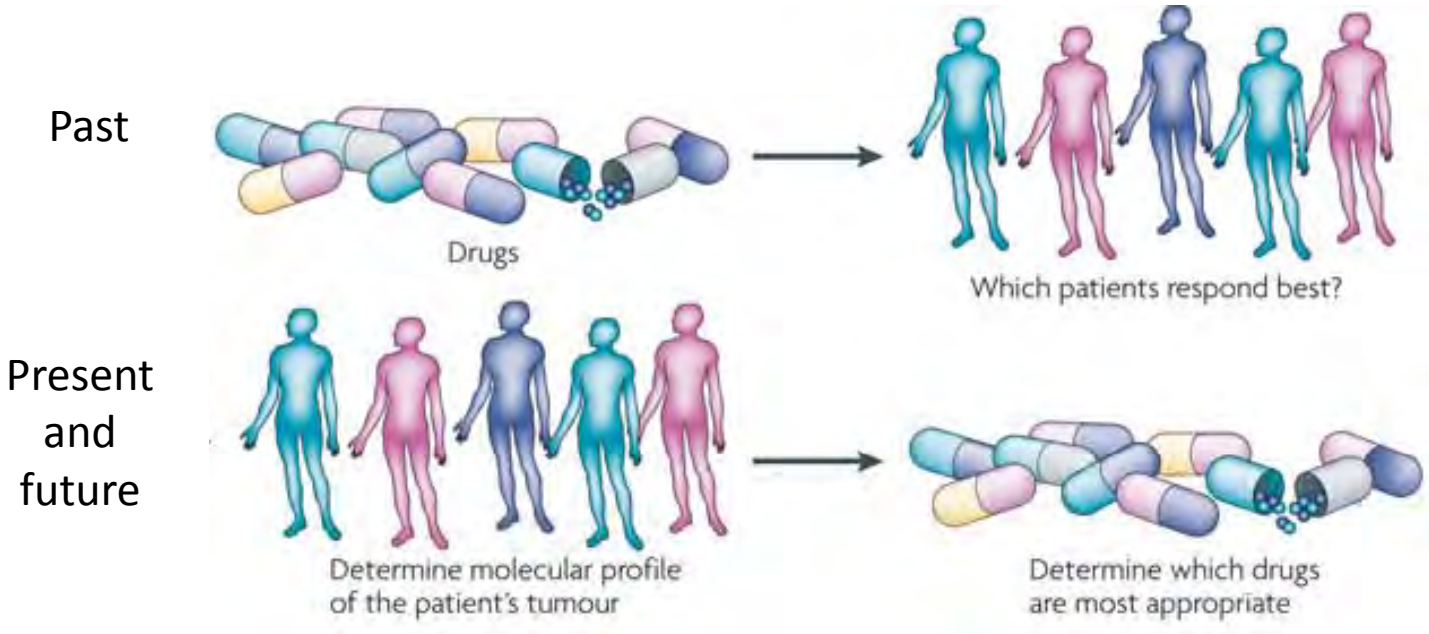
500 breast cancer genomes:



Inter- and intra-tumour heterogeneity

Personalised cancer medicine

Genomic alterations can be used as clinical biomarkers to identify patients most likely to benefit from treatment.



Adapted from Yap et al, Nature Reviews Cancer. 2010

Similarly, to monitor tumour response and clinical relapse.

Targeted molecular therapies

Mutated cancer gene as biomarkers of drug response:

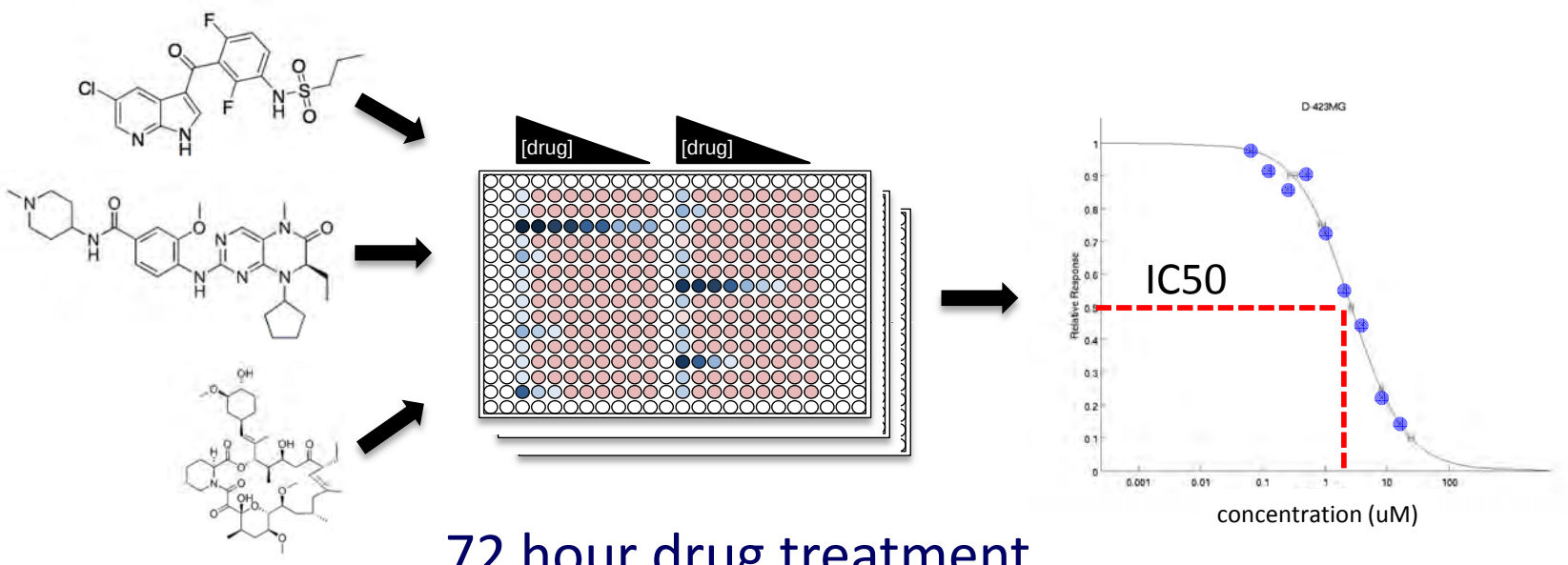
FDA-approved targeted therapies

Molecular biomarker	FDA-approved drug	Clinical indication(s)	Therapeutic target
BCR-ABL	Imatinib, Dasatinib, Nilotinib	CML, AML	ABL1
KIT, PDGFR	Imatinib	Gastrointestinal stromal tumour	KIT, PDGFRA
EGFR	Gefitinib, Erlotinib	Non-small cell lung cancer, pancreatic	EGFR
ERBB2/HER2	Trastuzumab, Lapatinib	HER+ breast cancer	HER2
BRAF	Vemurafinib	melanoma	BRAF
EML4-ALK	Crizotinib	Non-small cell lung cancer	ALK
ER+	Tamoxifen	ER+ breast cancer	ER

Preclinical biomarker discovery

- Genome sequencing is identifying many new cancer targets.
- New compounds and strategies are coming through the pharma pipeline but their effective deployment is challenging.
- Most anti-cancer drugs are not linked to biomarkers that allow patient stratification.
- There are many potential biomarkers that could be used to effectively guide therapy (e.g. mutations, gene amplification or deletion, gene expression, methylation, tissue-type).
- How do we systematically explore pre-clinically the diversity of cancer for biomarkers that predict drug sensitivity?

High-throughput drug sensitivity screening of cancer cell lines



72 hour drug treatment

Fluorescence based viability assay

Use of cancer cell lines as models

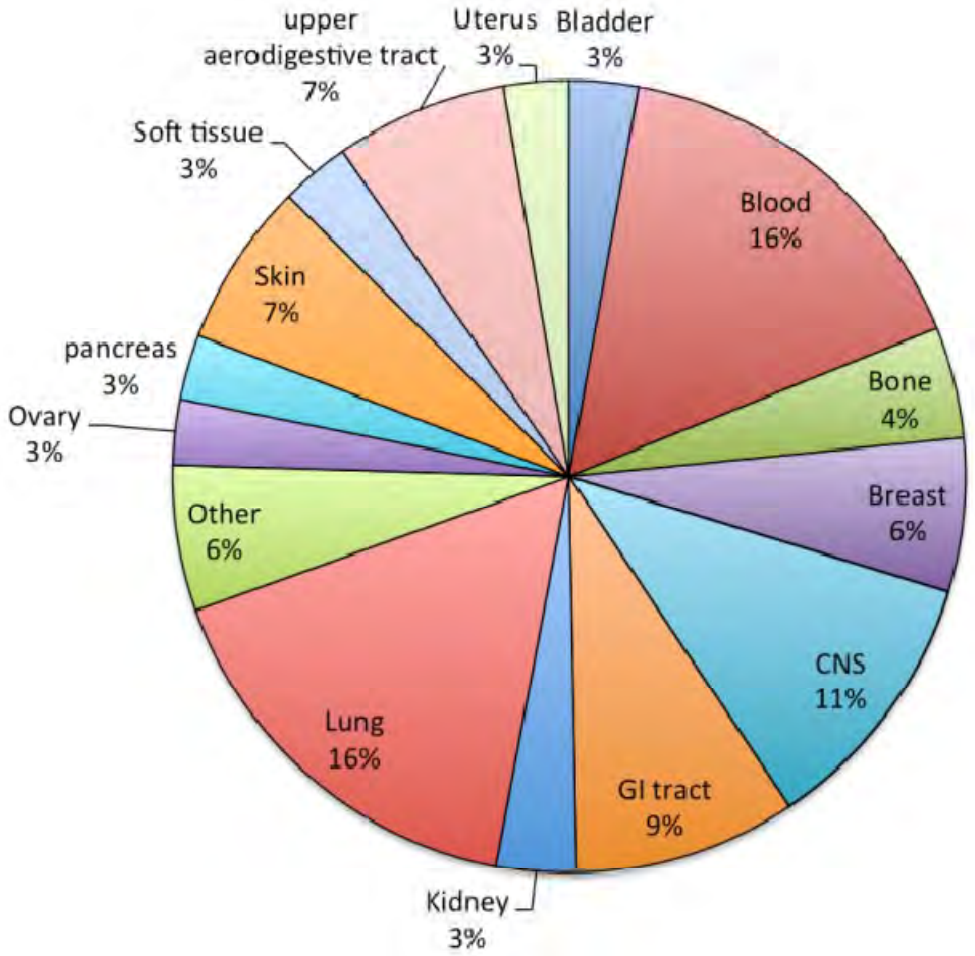
PROS

- Cancer is an intrinsic disease of cells
- Cancer cell lines are derived from naturally occurring human cancers
- Cancer cell line resources capture at least some of the cell-of–origin and mutational diversity of cancer
- Cancer cell lines are routinely used in biological research
- Amenable to high-throughput screens & genetic manipulation

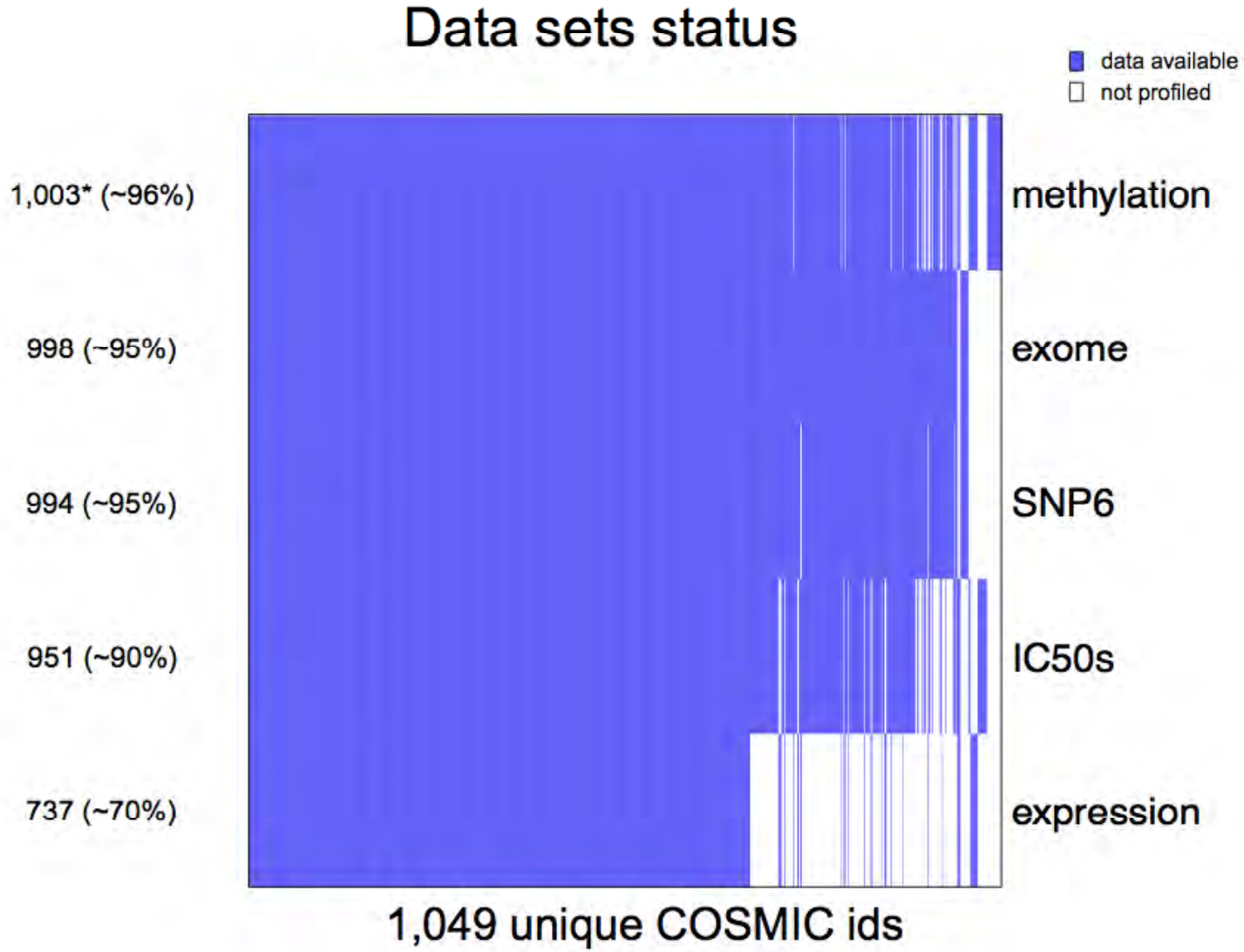
CONS

- Grown *in vitro* for long periods
- Diverse culture histories
- New mutations acquired
- Selection bias
- For many cancer types there are very few lines
- May not fully represent the known driving mutations of that type of cancer
- No normal DNA from the same individual
- 2-D cell culture does not capture immune surveillance, metabolic constraints and tissue interactions

GDSC 1000 cancer cell line resource

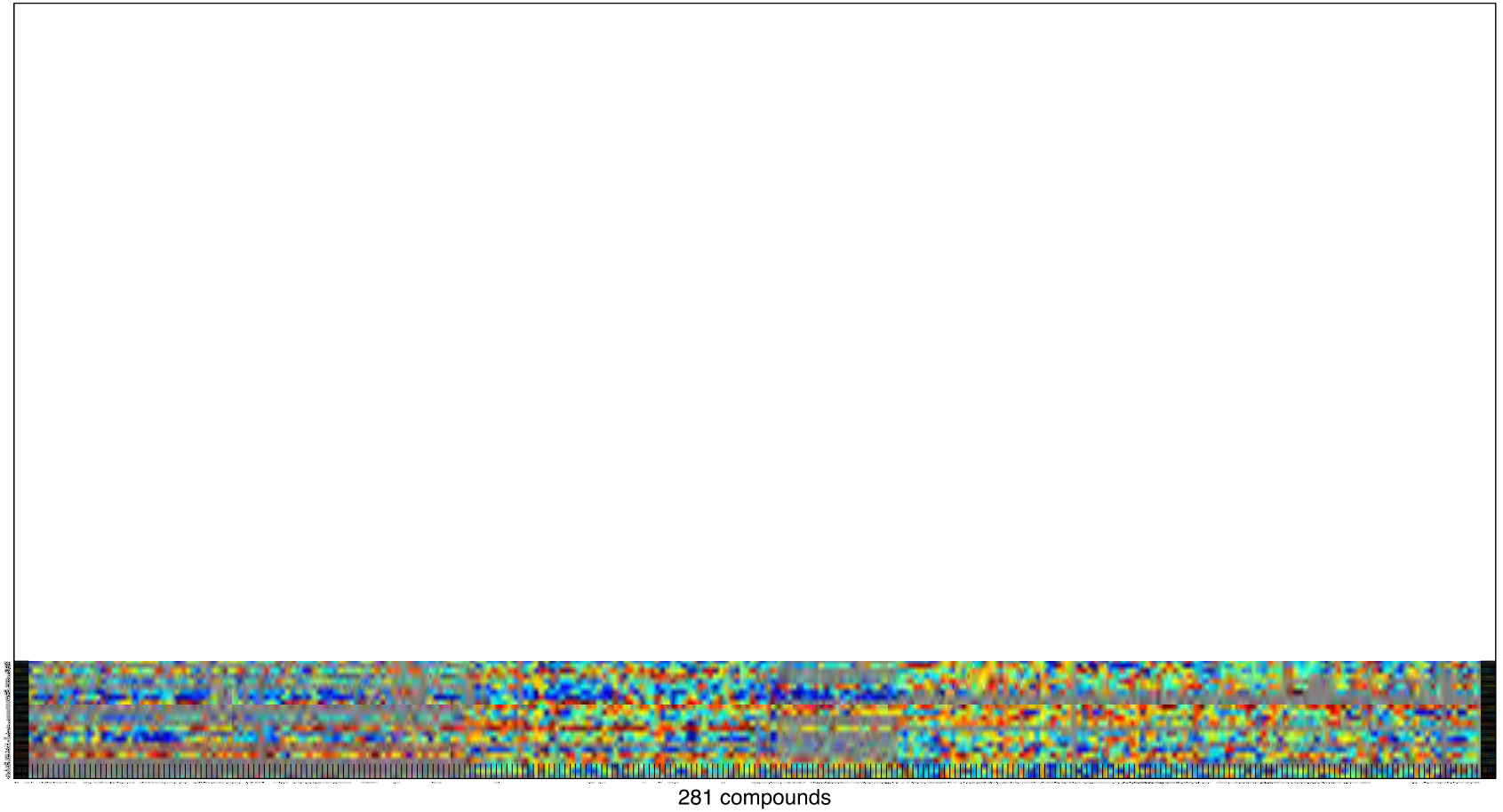


Pharmacogenomic characterisation of GDSC 1000



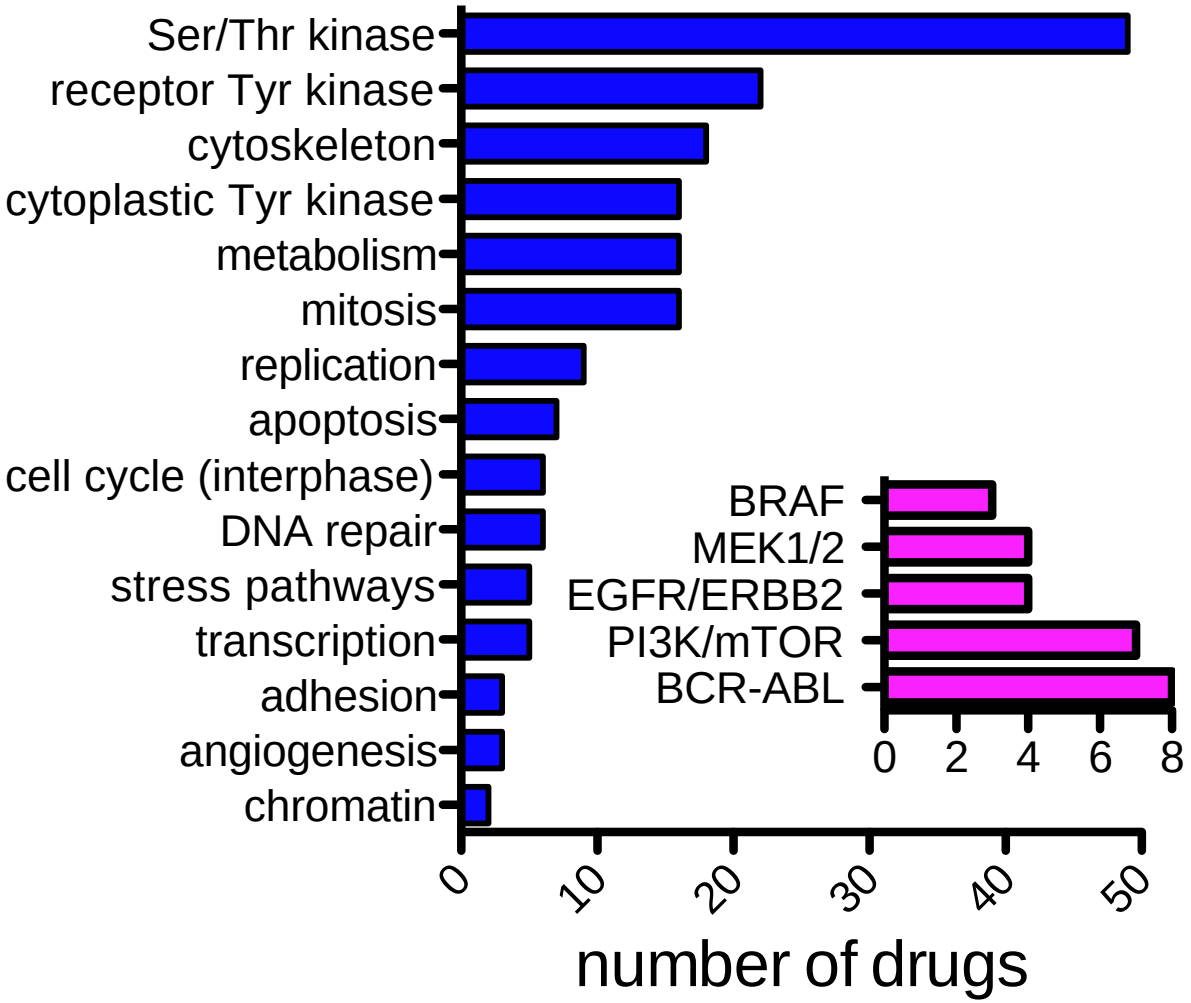
Systematic analysis of drug sensitivity

IC50 value heatmap



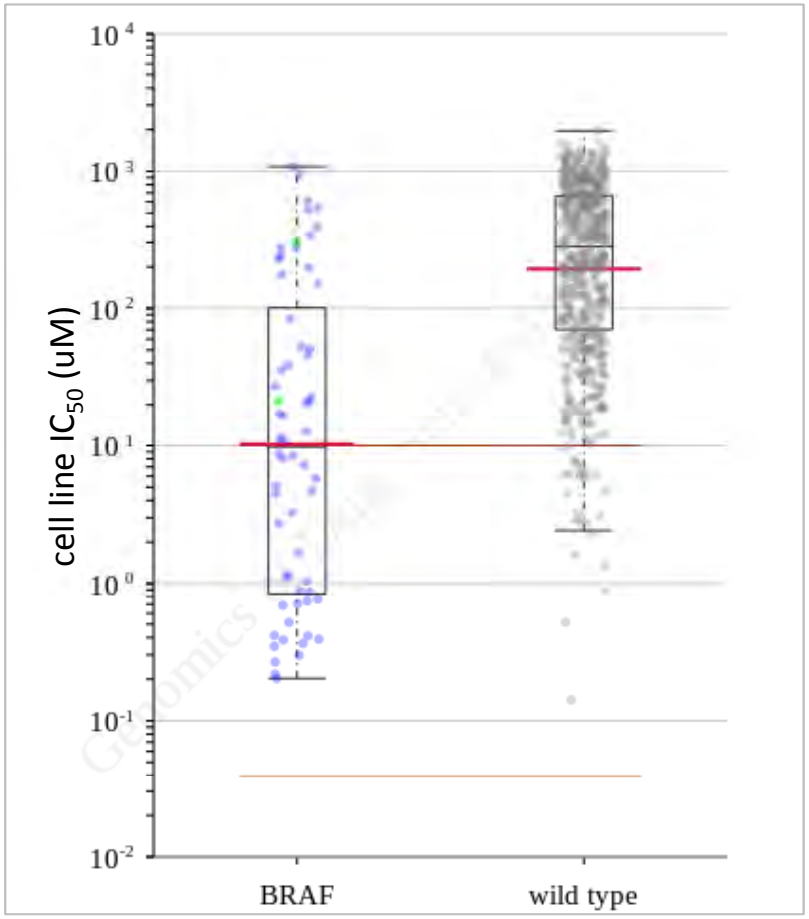
Current dataset includes 550 drugs (~300,000 IC50 values)

Target space of screening compounds in study



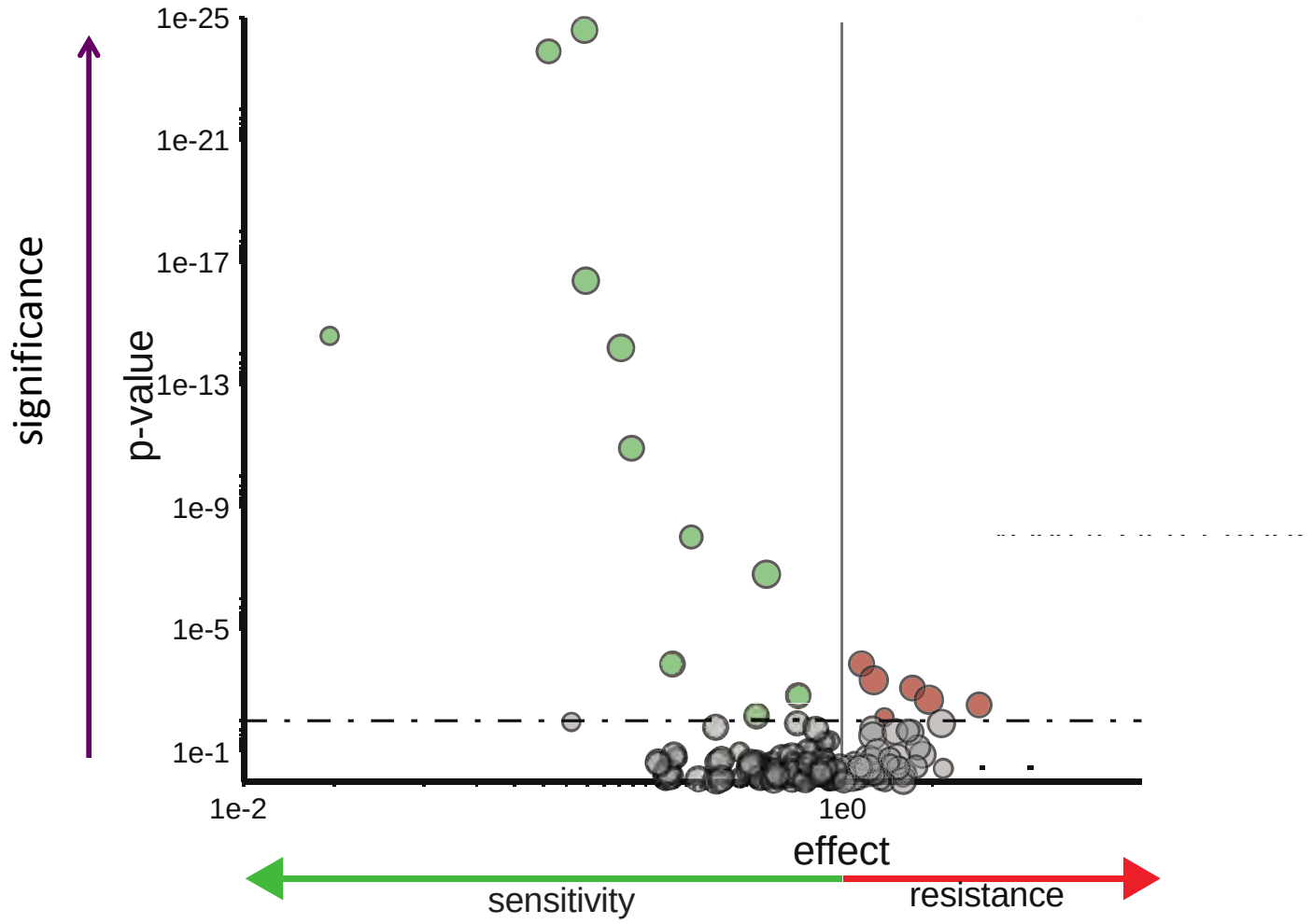
Drug sensitivity associated with *BRAF* mutation

BRAF inhibitor PLX4720



n = 51 *n* = 511

Drug sensitivity associated with *BRAF* mutation



Cell line models capture clinical markers of drug sensitivity

FDA-approved targeted therapies

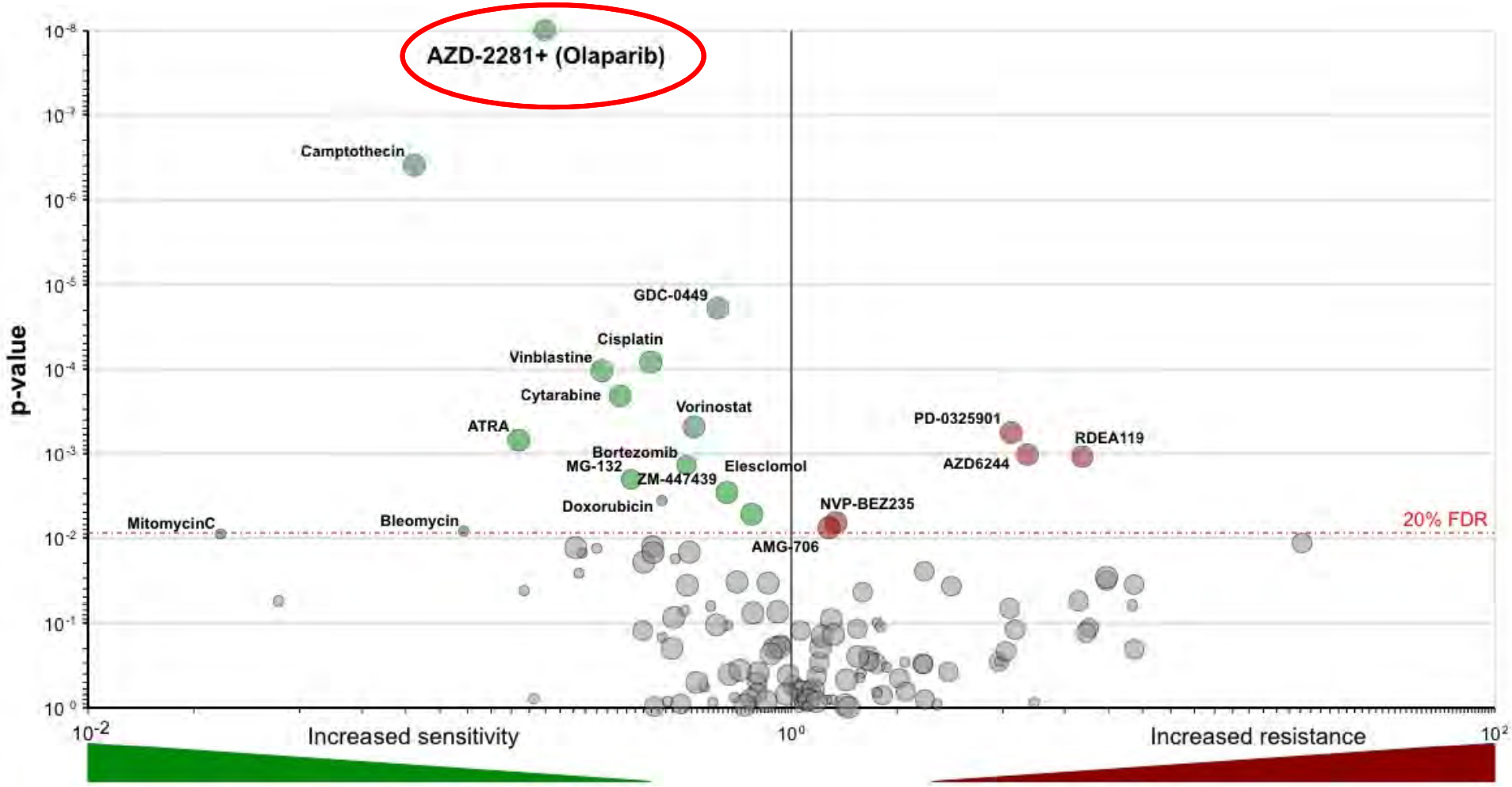
Molecular biomarker	FDA-approved drug	Clinical indication(s)	Therapeutic target	
BCR-ABL	Imatinib, Dasatinib, Nilotinib	CML, AML	ABL1	✔
KIT, PDGFR	Imatinib	Gastrointestinal stromal tumour	KIT, PDGFRA	ND
EGFR	Gefitinib, Erlotinib	Non-small cell lung cancer, pancreatic	EGFR	✔
ERBB2/HER2	Trastuzumab, Lapatinib	HER+ breast cancer	HER2	✔
BRAF	Vemurafinib	melanoma	BRAF	✔
EML4-ALK	Crizotinib	Non-small cell lung cancer	ALK	7
ER+	Tamoxifen	ER+ breast cancer	ER	✔

Targeted therapies in clinical development

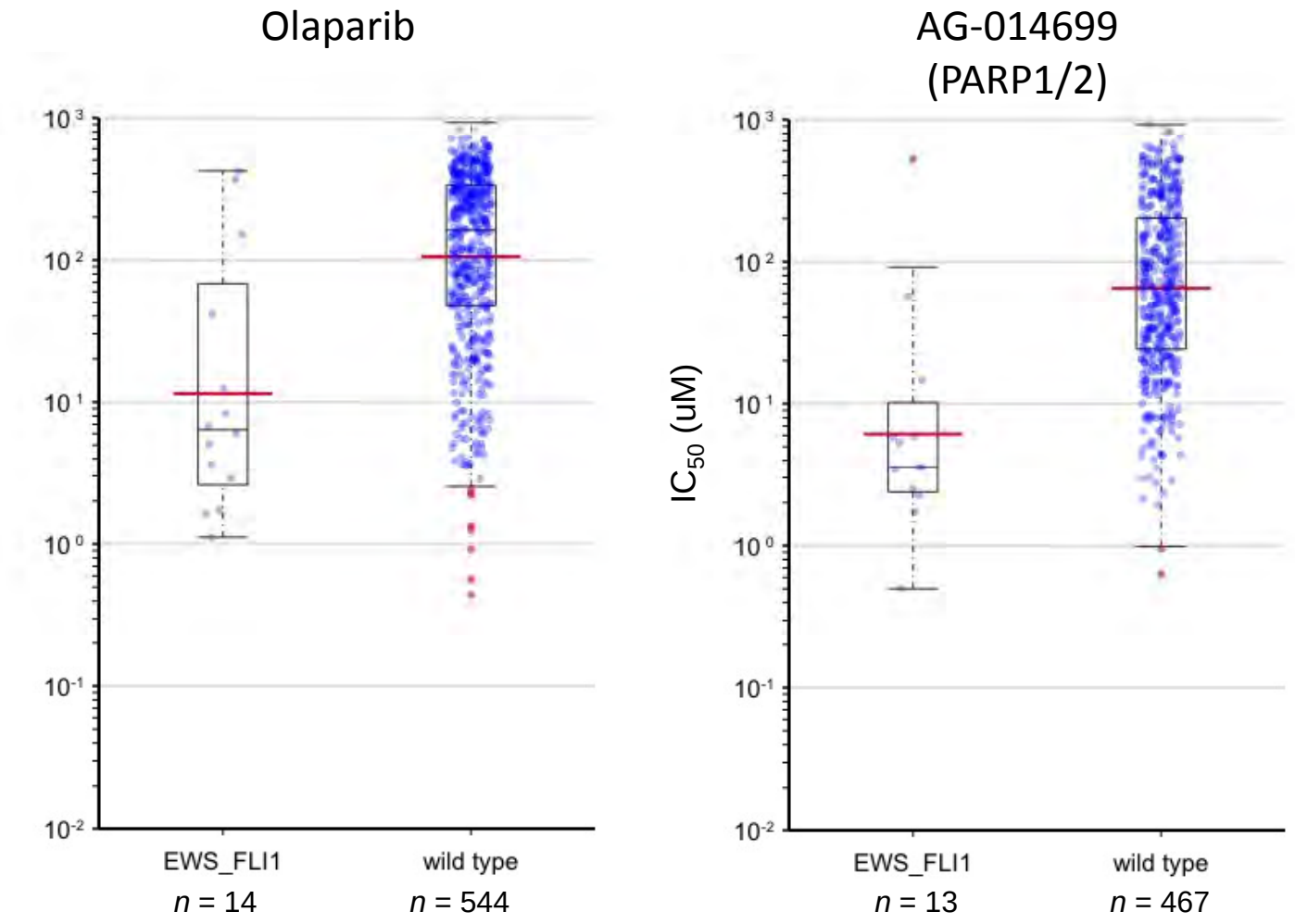
Molecular biomarker	Drugs in clinical development	Clinical indication(s)	Therapeutic target	
BRAF	e.g. PD0325907	melanoma, NSCLC	MEK	✔
KRAS	e.g. PD0325908	NSCLC	MEK	✔
NRAS	e.g. PD0325909	melanoma	MEK	✔
FGFR2	e.g. PD173074		FGFR	✔
PIK3CA	e.g. AZD6482		PI3K	✔
PIK3CA	e.g. AKT inhibitor VIII		AKT	✔
FLT3	e.g. sunitinib		FLT3	✔
BRCA1/2	e.g. Olaparib	Breast, ovarian	PARP	✔7

Ewing sarcoma cell lines with the EWS-FLI1 translocation are sensitive to PARP inhibitors

Drug sensitivity associated with the EWS-FLI1 fusion gene:



EWS-FLI1 mutated cell are sensitive to PARP inhibitors

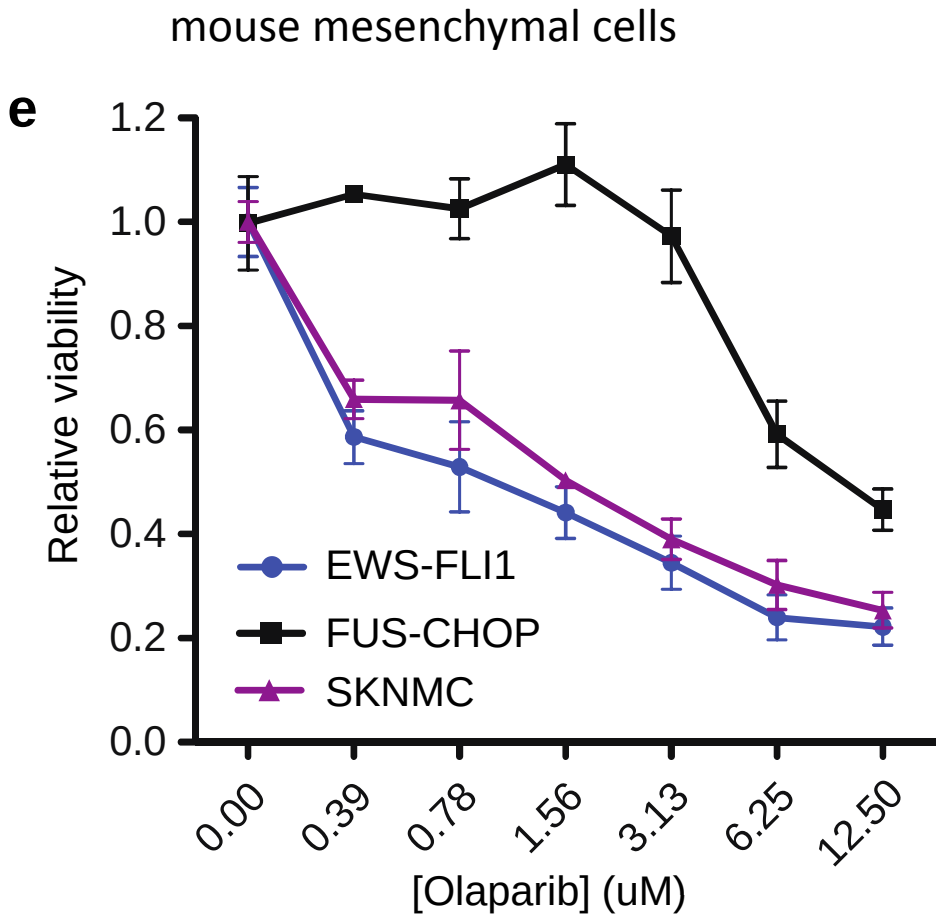


Mutations of *BRCA1* or *BRCA2* are not present in these *EWS-FLI1* mutated cell lines

EWS-FLI1

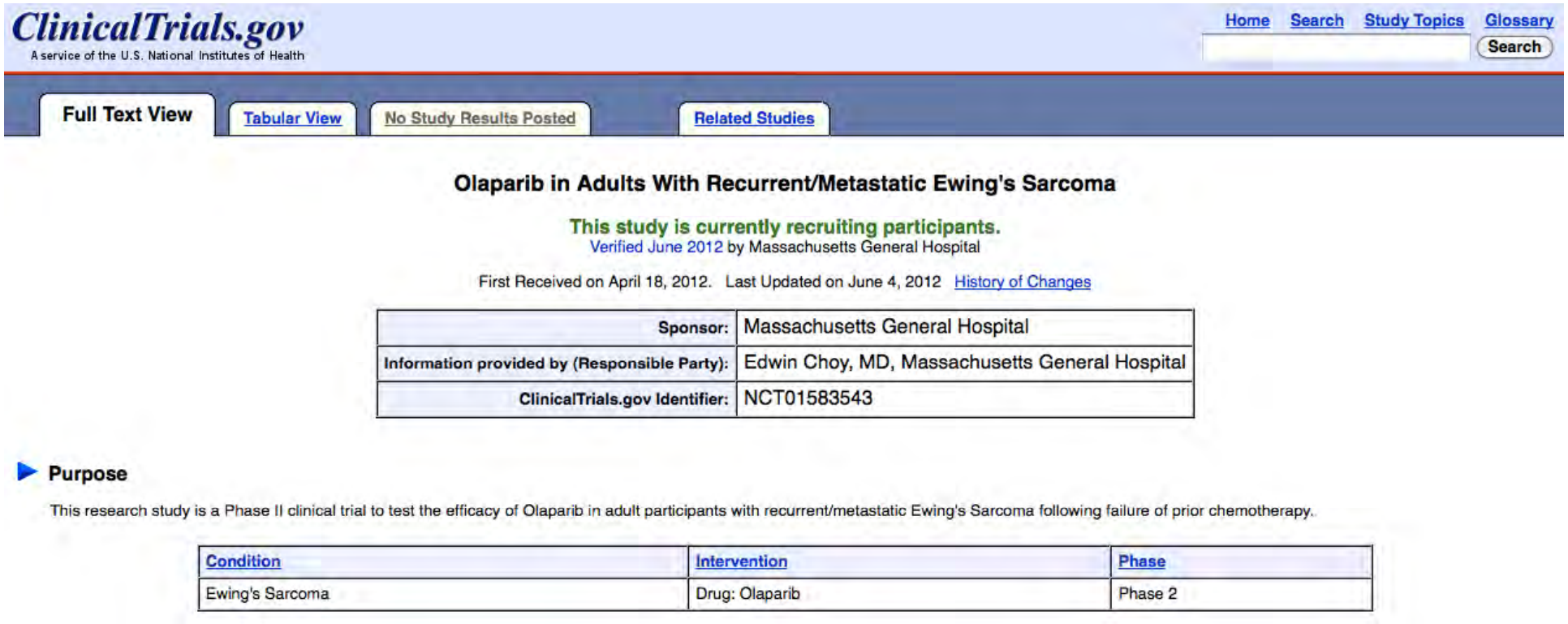
- Characteristic of Ewing's sarcoma, a malignant bone tumour that affects children.
- A chromosomal translocation (11:22)(q24;q12) fusing the EWSR1 gene to the FLI1 gene.
- Fusion proteins act as aberrant transcription factors that bind DNA through their ETS DNA binding domain.
- Current treatment is aggressive chemotherapy, surgery and radiotherapy.
- Poor prognosis in the 15-25% of patients with metastatic or recurrent disease.

Is PARP inhibitor sensitivity is dependent on the EWS-FLI1 translocation?



We are actively working to understand the mechanism of PARP inhibitor sensitivity.

Clinical trials for PARPi in Ewing's Sarcoma patients



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Olaparib in Adults With Recurrent/Metastatic Ewing's Sarcoma

This study is currently recruiting participants.
Verified June 2012 by Massachusetts General Hospital

First Received on April 18, 2012. Last Updated on June 4, 2012 History of Changes

Sponsor:	Massachusetts General Hospital
Information provided by (Responsible Party):	Edwin Choy, MD, Massachusetts General Hospital
ClinicalTrials.gov Identifier:	NCT01583543

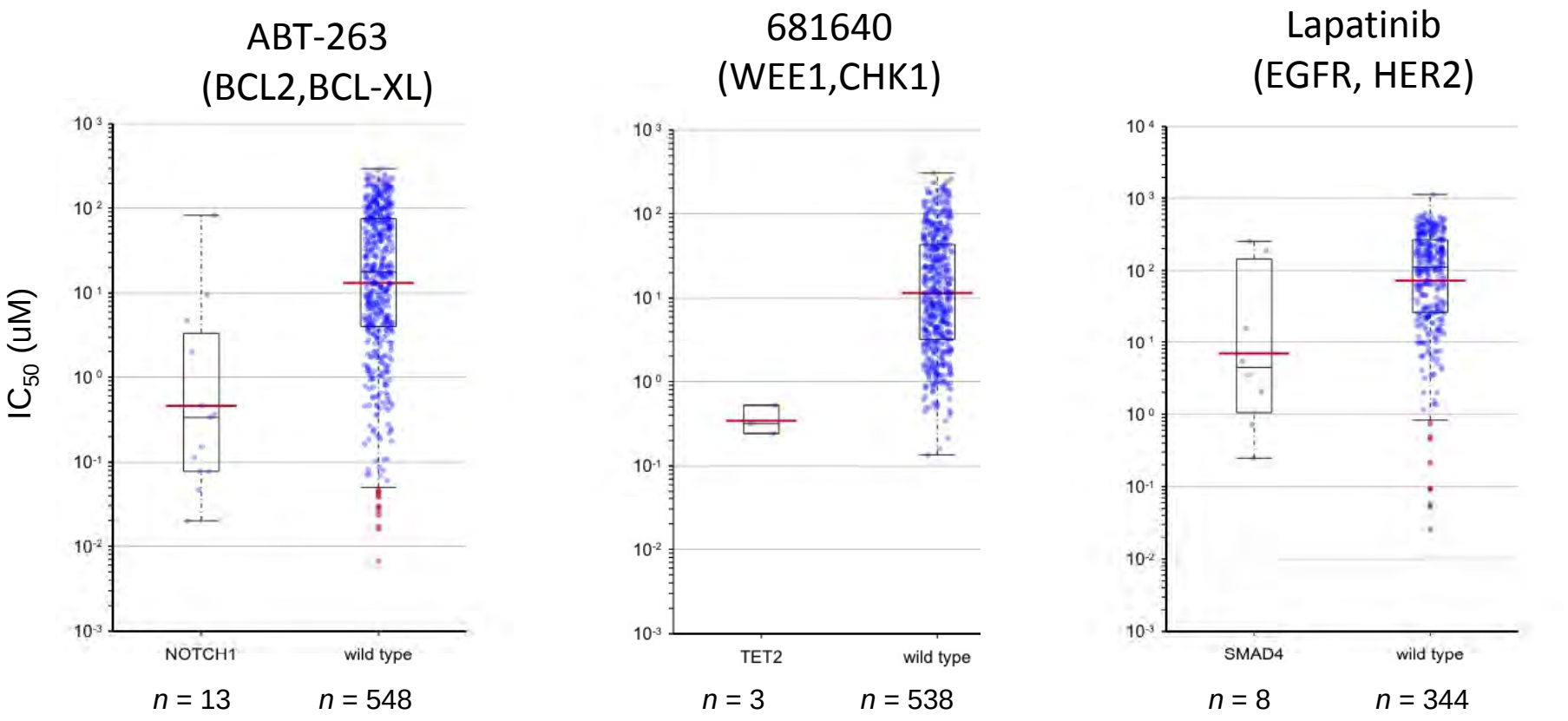
Purpose

This research study is a Phase II clinical trial to test the efficacy of Olaparib in adult participants with recurrent/metastatic Ewing's Sarcoma following failure of prior chemotherapy.

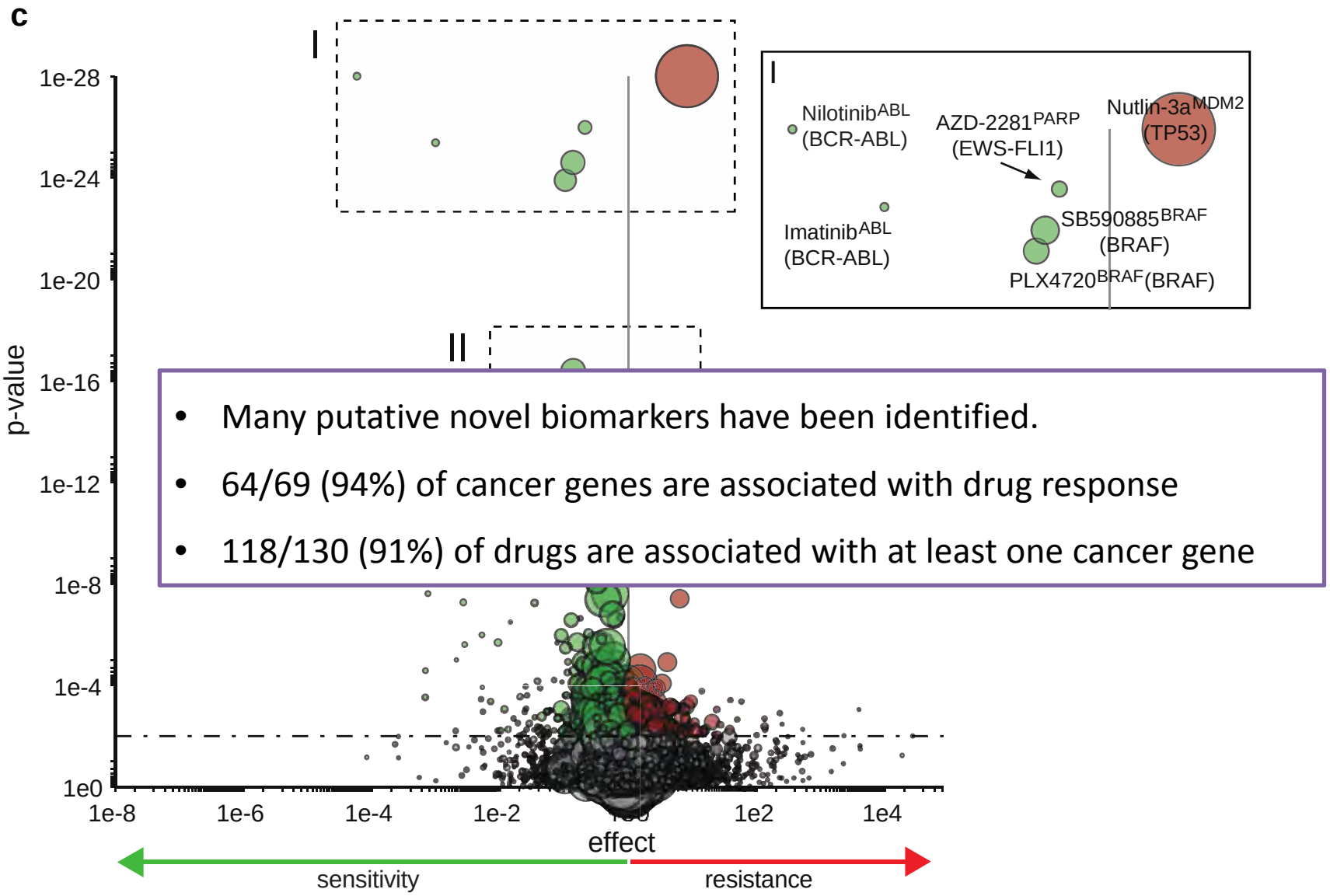
Condition	Intervention	Phase
Ewing's Sarcoma	Drug: Olaparib	Phase 2

Second trial: phase 1 for BMN-673

Many putative therapeutic biomarkers have been identified

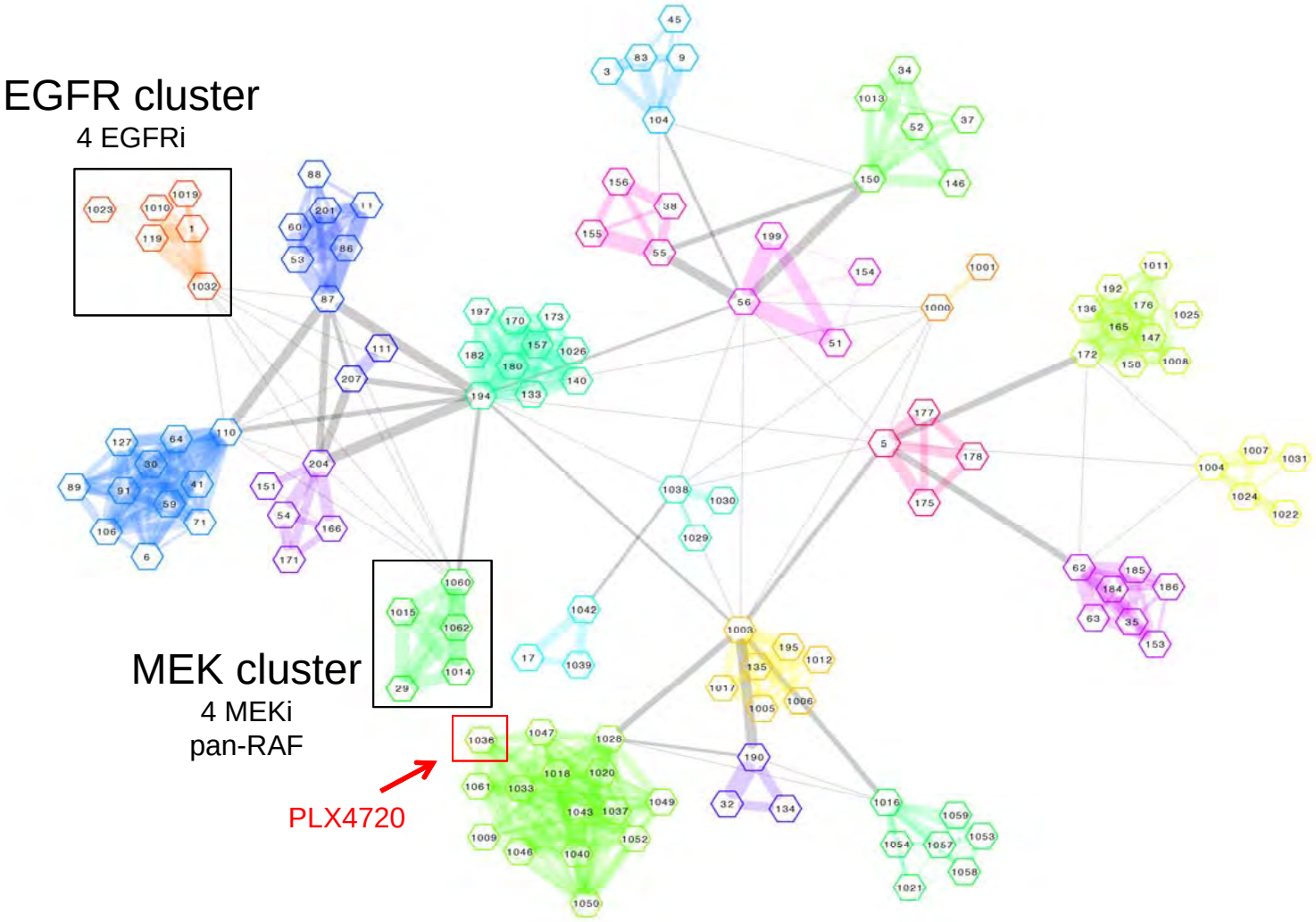


Landscape of drug sensitivity in cancer



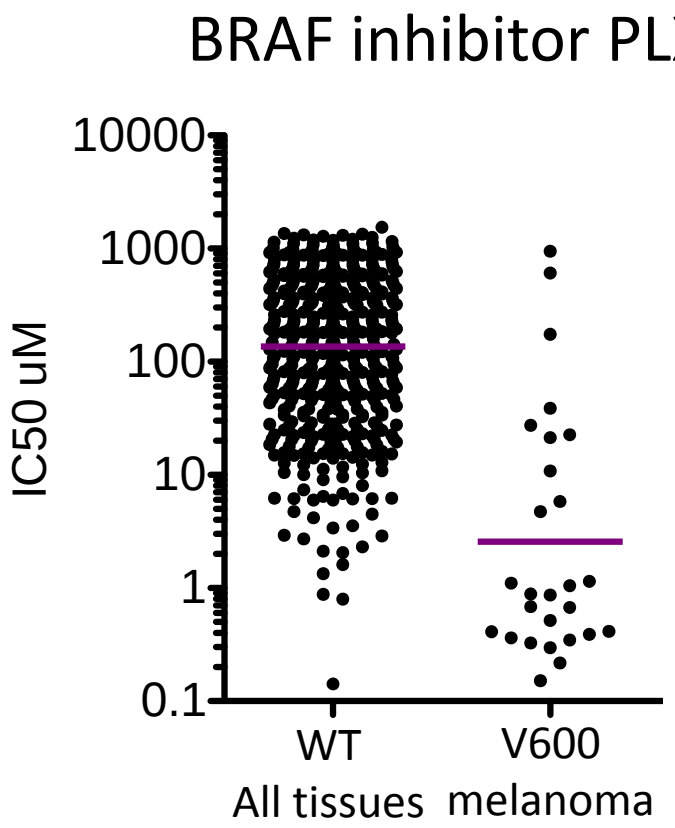
- Many putative novel biomarkers have been identified.
- 64/69 (94%) of cancer genes are associated with drug response
- 118/130 (91%) of drugs are associated with at least one cancer gene

Target validation and discovery: clustering of drugs based on IC50 values



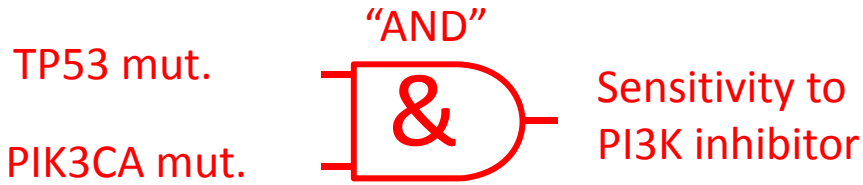
Complex signatures of drug response

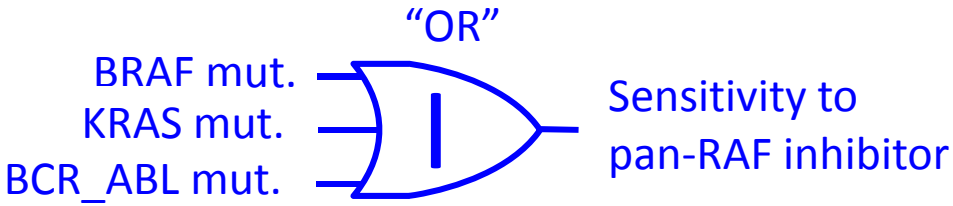
- Single gene mutations rarely explain the range of drug sensitivities observed.



Drug response as a logic combination of genomic markers

Models that explain sensitivity as logic combination of mutations, CNV, gene expression, methylation and tissue.

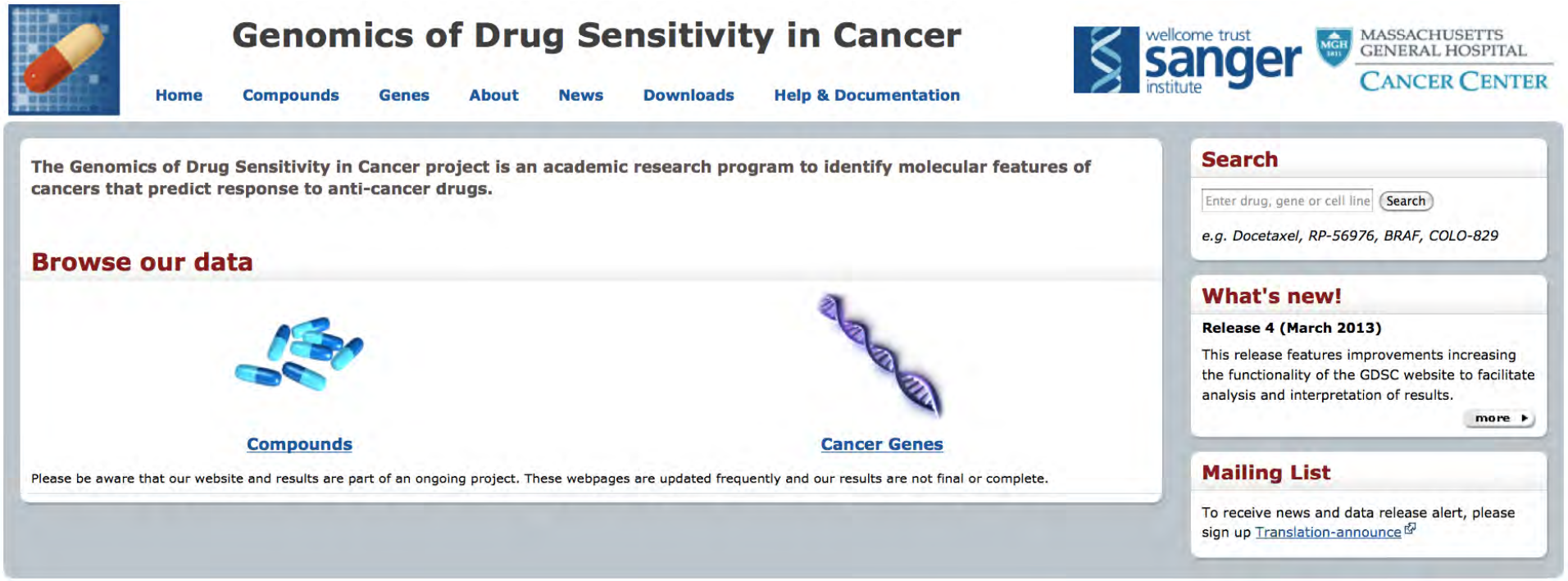




Explain more of the variation in drug response.

Lodewyk Wessels, NKI

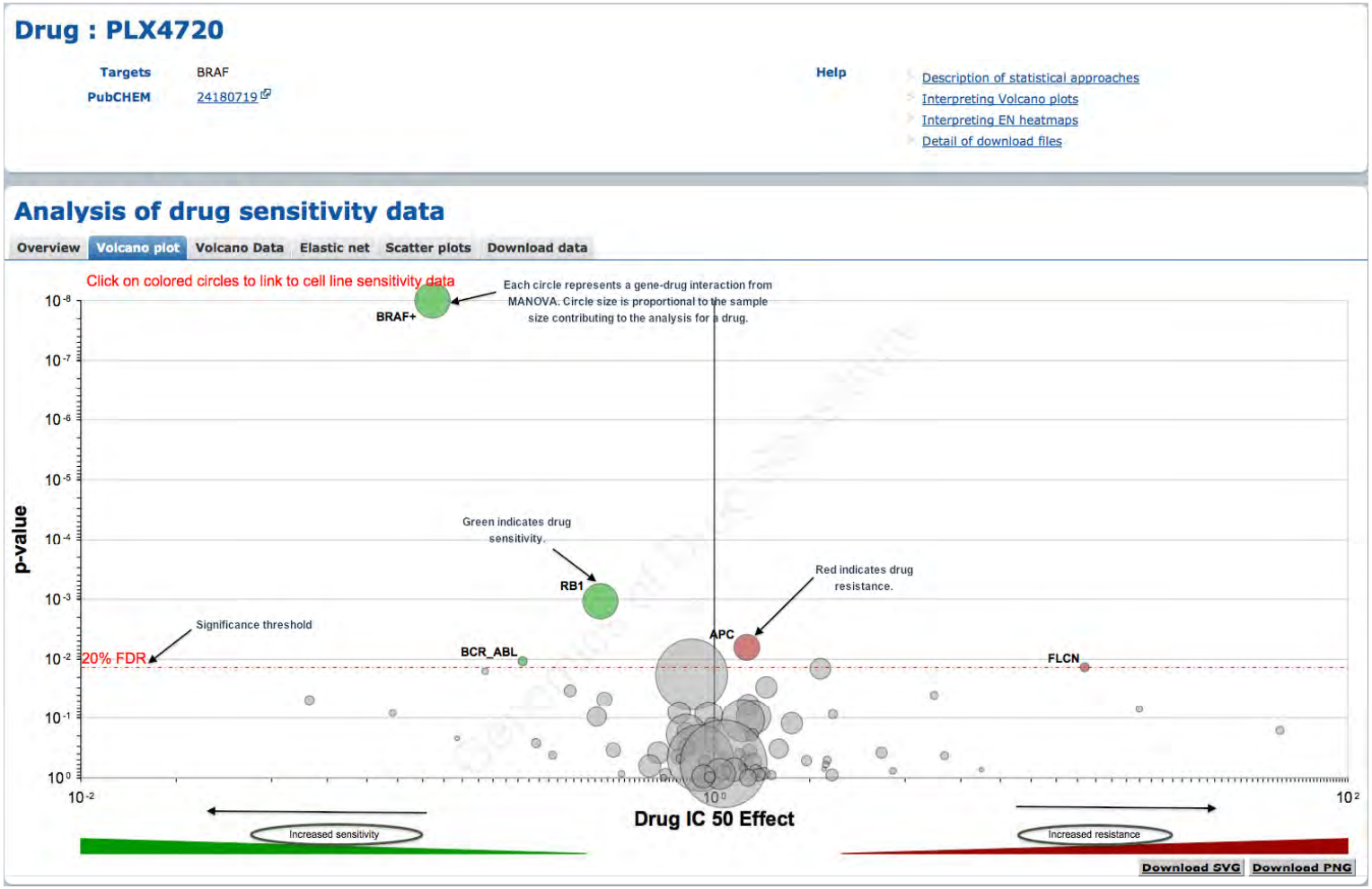
www.cancerRxgene.org



Web release 4 (March 2013):

- 142 drugs
- 78,000 IC50 values
- 714 cell lines
- All drug sensitivity and genomic data are freely available

www.cancerRxgene.org

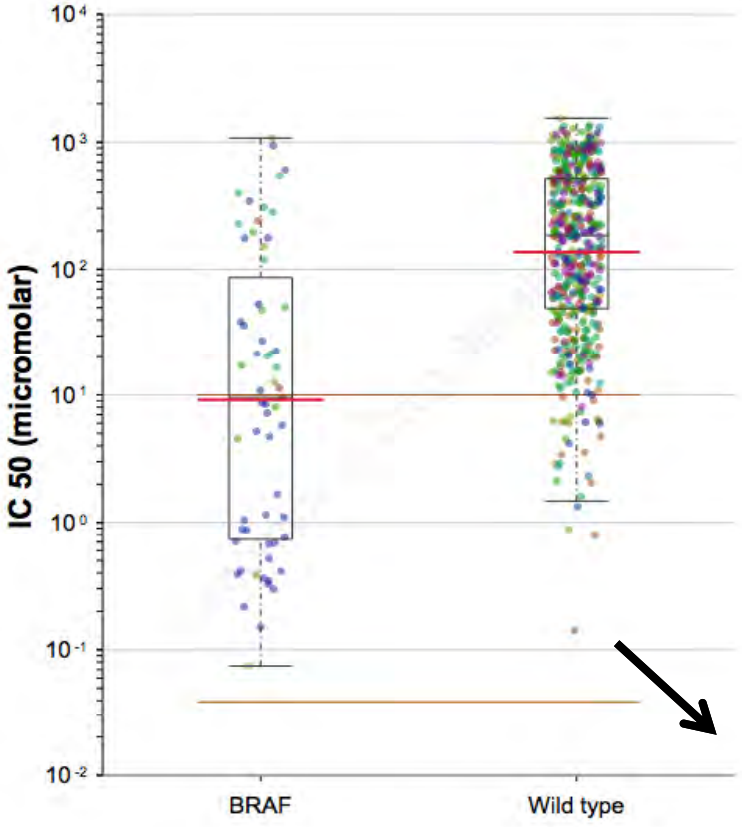


www.cancerRxgene.org

PLX4720

By mutation type | By tissue type

Click on circles to link to cell line information



Download SVG | Download PNG

Screening concentration: 0.039062 (lower brown line) - 10.000 (upper brown line)

	BRAF	Wild type	Selected
Number of cell lines	61 of 61	511 of 511	
Upper quartile	86.161	510.76	
Median	9.5697	183.75	
Geometric mean (red line)	9.1569	136.24	
Lower quartile	0.73425	49.299	
Non-parametric test Probability			2.7716e-14
#Bladder	0	17	☑
#Blood	2	57	☑
#Bone	0	27	☑
#Breast	2	33	☑
#Central Nervous System	4	68	☑
#Gastro-intestinal tract	5	49	☑
#Kidney	0	21	☑
#Lung	9	94	☑
#Ovary	0	18	☑
#Other tissue type	1	18	☑

Check all | Clear all

COSMIC
Catalogue of somatic mutations in cancer

Summary

- Clinically relevant association between drugs and cancer genes can be detected in high-throughput cell line screens.
- Many novel gene-drug associations have been identified, including sensitivity of Ewing's cells to PARP inhibitors.
- Most cancer genes influence drug response and, conversely, most drugs are influenced by cancer genes.
- For most drugs, single cancer genes do not explain the range of observed drug responses.

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SESSIONS

- Cancer Genomics
- Drugging the Cancer Genome
- Experimental and pre-clinical therapeutic models
- Combating drug resistance
- Molecular biomarkers in the clinic

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