Precision medicine in hepatocellular carcinoma:

From cell lines to patients

Zhixin Qiu, Hong Li, Yixue Li, Lijian Hui, et.al.

Shanghai Institutes for Biological Sciences
Chinese Academy of Sciences
Shanghai Center for Bioinformation Technology
Shanghai Academy of Science&Technology

The concept of "precision medicine"

- Precision Medicine refers to the tailoring of medical treatment to the individual characteristics of each patient.
- It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease.
- Precision medicine often involves the application of panomic analysis and systems biology to analyze the cause of an individual patient's disease at the molecular level and then to utilize targeted treatments (possibly in combination) to address that individual patient's disease process.
- Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

The National Research Council, USA

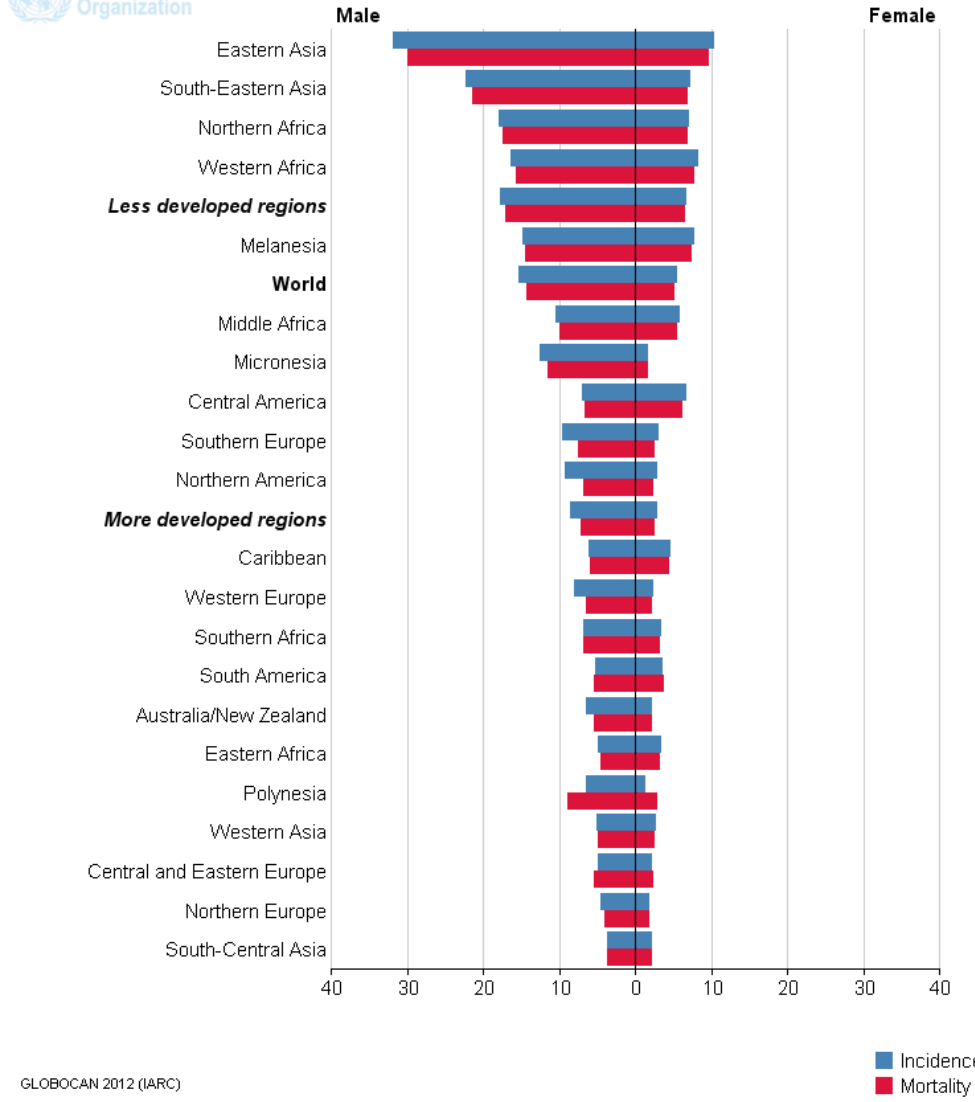
Main content of the work

Over the past few years we have built the world's largest cell bank of liver cancer cell lines, **Liver Cancer Model Repository** (LIMORE) with our collaboration partners.

We established a corresponding "dry“ and "wet" combined database, and based on LIMORE Cell Bank, we have screened out a number of potential disease related biomarkers, which can be used for the evaluation of the efficacy and prognosis of anti-liver cancer drugs.

For the precise treatment of the liver cancer we have successfully used the LIMORE system to discover a disease biomarker, which is a **secreted protein**, and can be used as a companion to the diagnosis of Sorafenib's prognosis and efficacy.

Hepatocellular carcinoma(HCC) is a major health problem globally and especially in China



The fifth most common cancer

55% in China

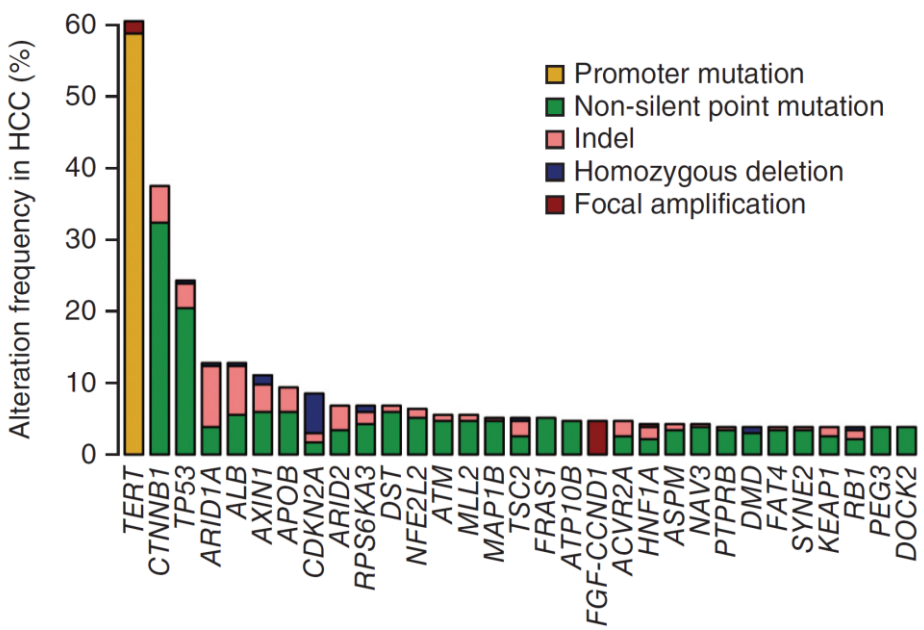
The second leading cause of cancer

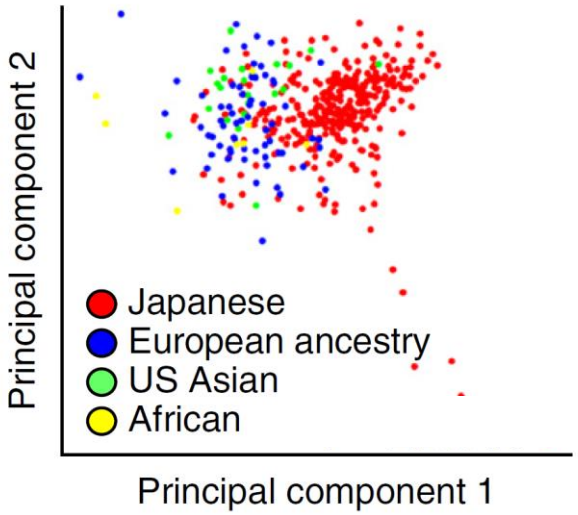
Five year survival rate is only 8.9%

50% in China

Hepatocellular carcinoma (HCC) is a worldwide disease problem. In Asia, especially China, the incidence and mortality of liver cancer are the highest. More than 50% of new cases and deaths occur in China every year, which brings great burden to China's health.

HCC genetic heterogeneity among patients



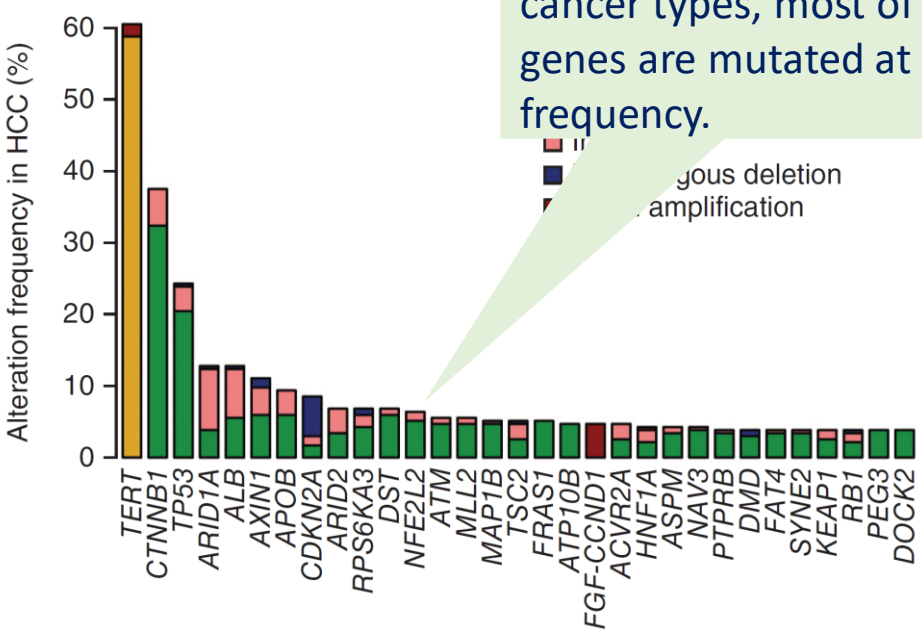


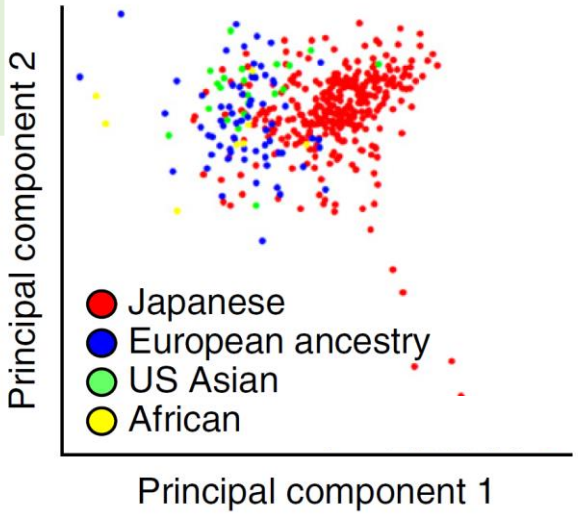
Genetic heterogeneity complicates the prediction of cancer prognosis

Totoki Y et al. *Nature Genetics*. 2014
Schulze K et al. *Nature Genetics*. 2015

HCC genetic heterogeneity among patients

Liver cancer is a heterogeneous disease. But compared to other cancer types, most of the genes are mutated at a low frequency.



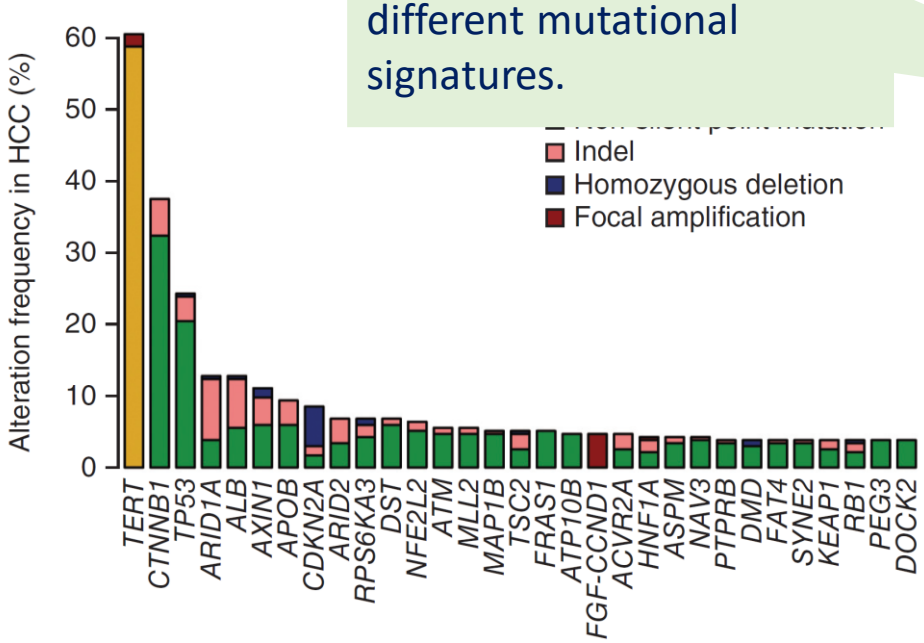


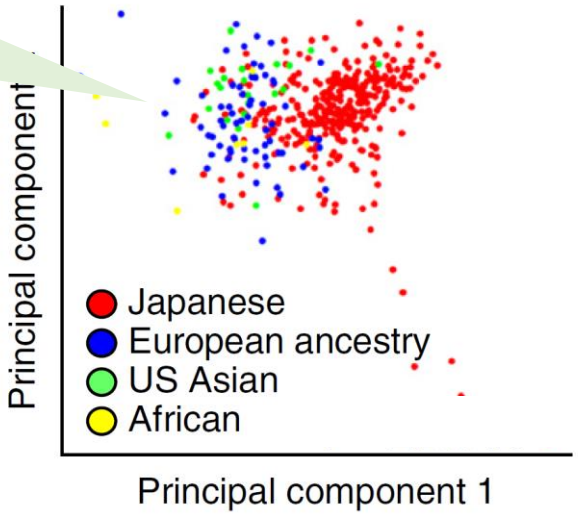
Genetic heterogeneity complicates the prediction of cancer prognosis

Totoki Y et al. *Nature Genetics*. 2014
Schulze K et al. *Nature Genetics*. 2015

HCC genetic heterogeneity among patients

Previous study has also shown that patients from different ancestries have different mutational signatures.



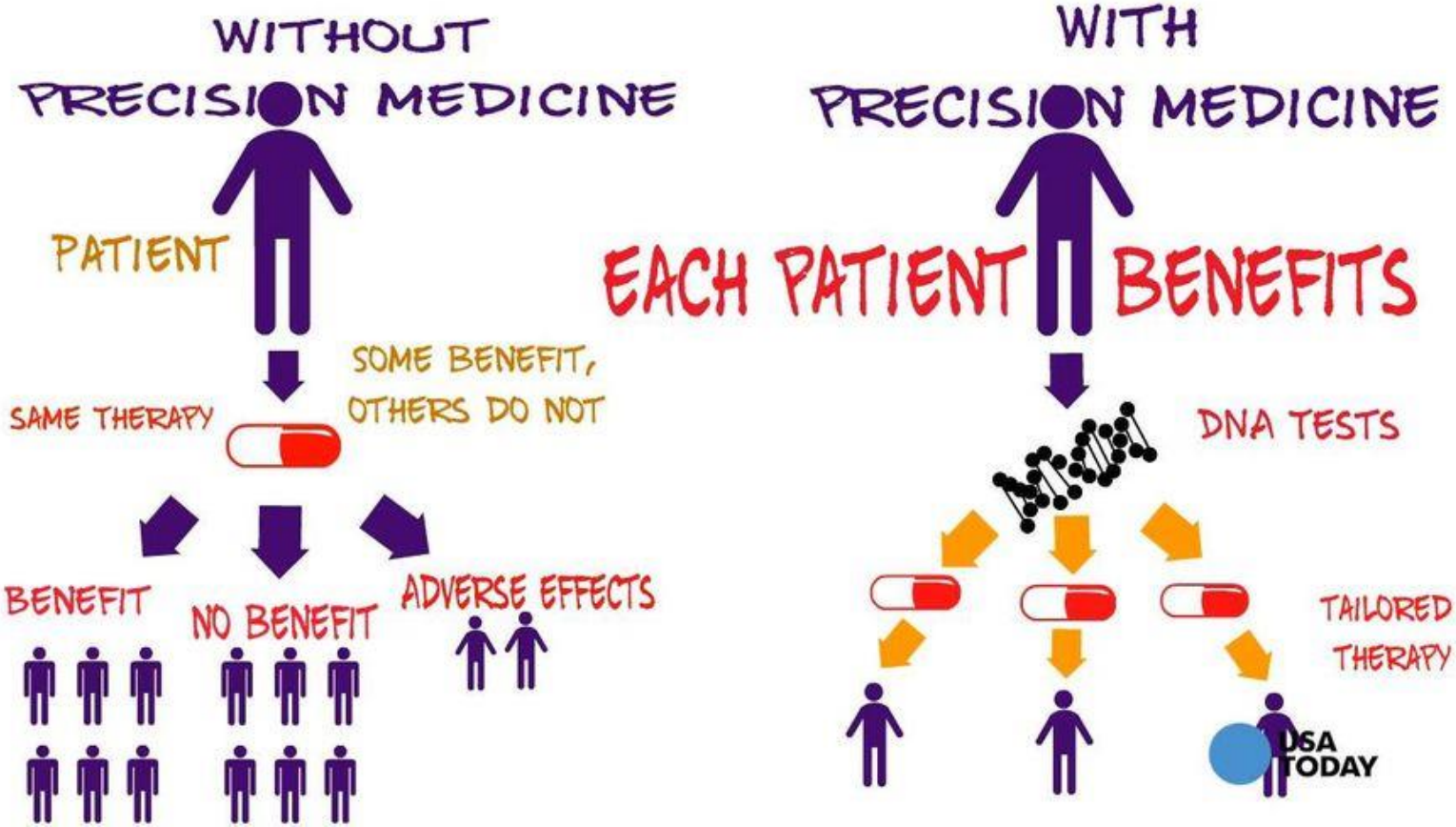


Genetic heterogeneity complicates the prediction of cancer prognosis.

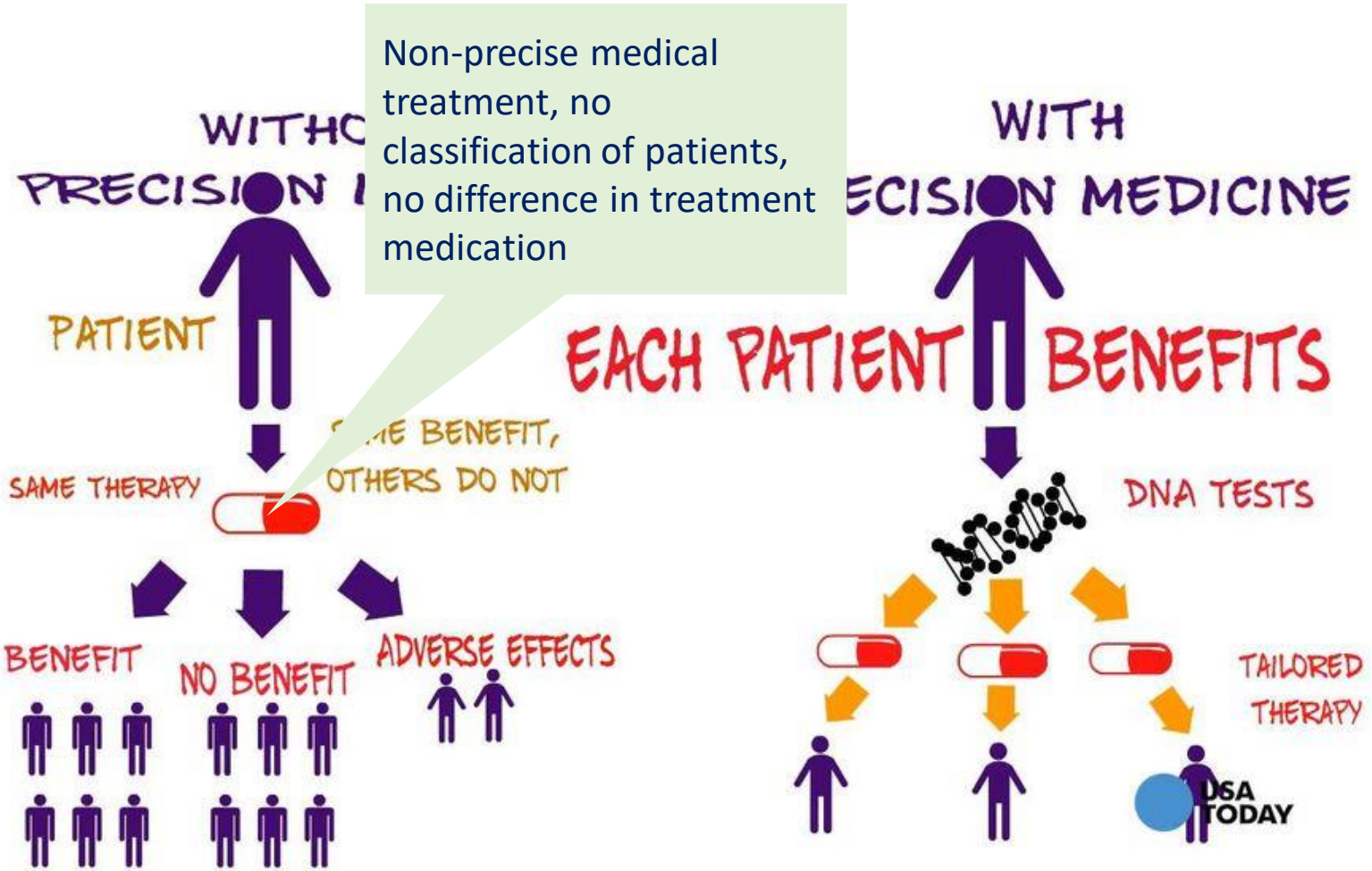
Therefore, Motivated by these studies, we aim to establish a large panel of liver cancer cell lines from different ancestries to better represent the genetic heterogeneity of liver cancer.

Totoki Y et al. *Nature Genetics*. 2014
Schulze K et al. *Nature Genetics*. 2015

In the Era of Precision Medicine

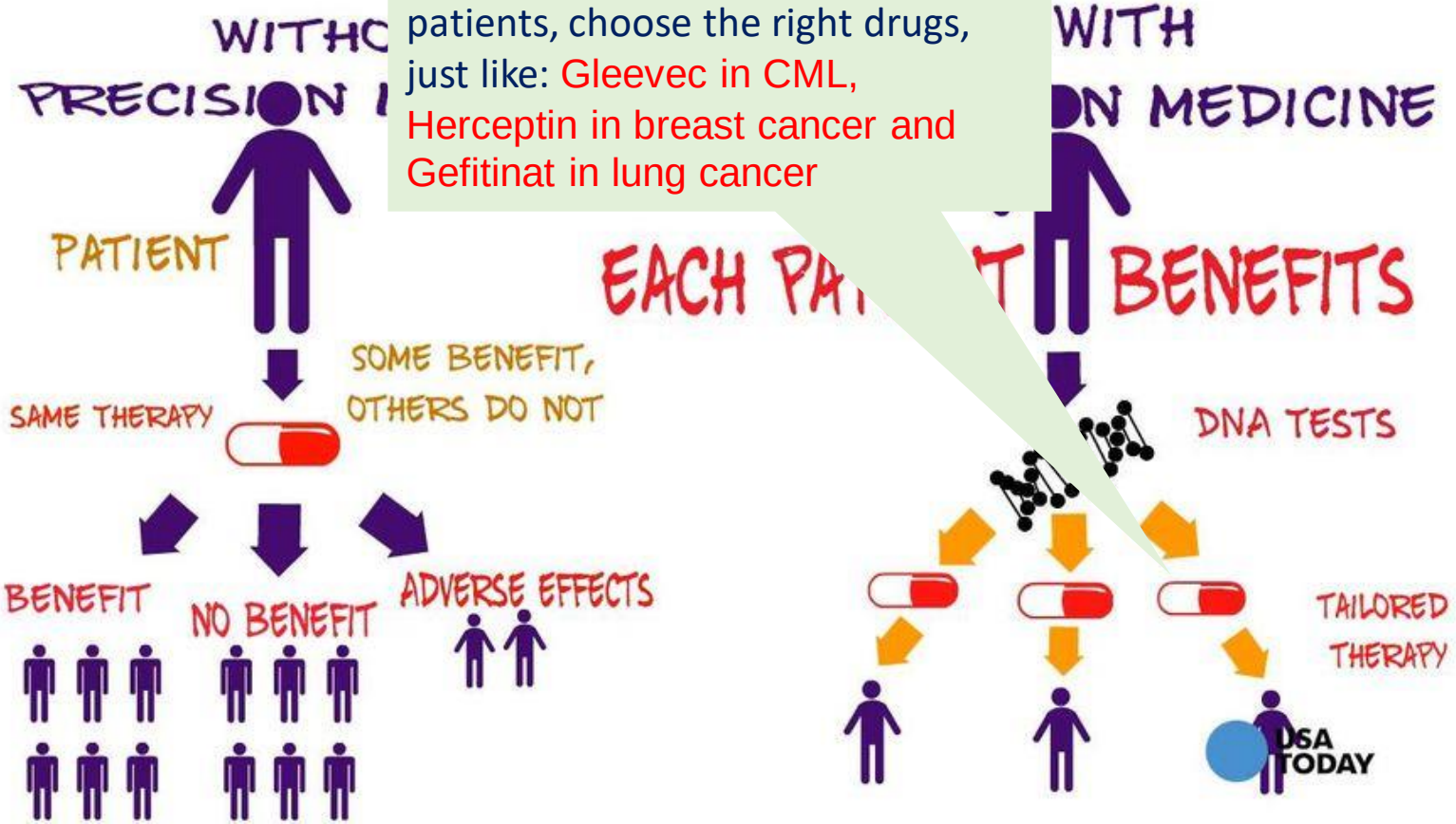


In the Era of Precision Medicine



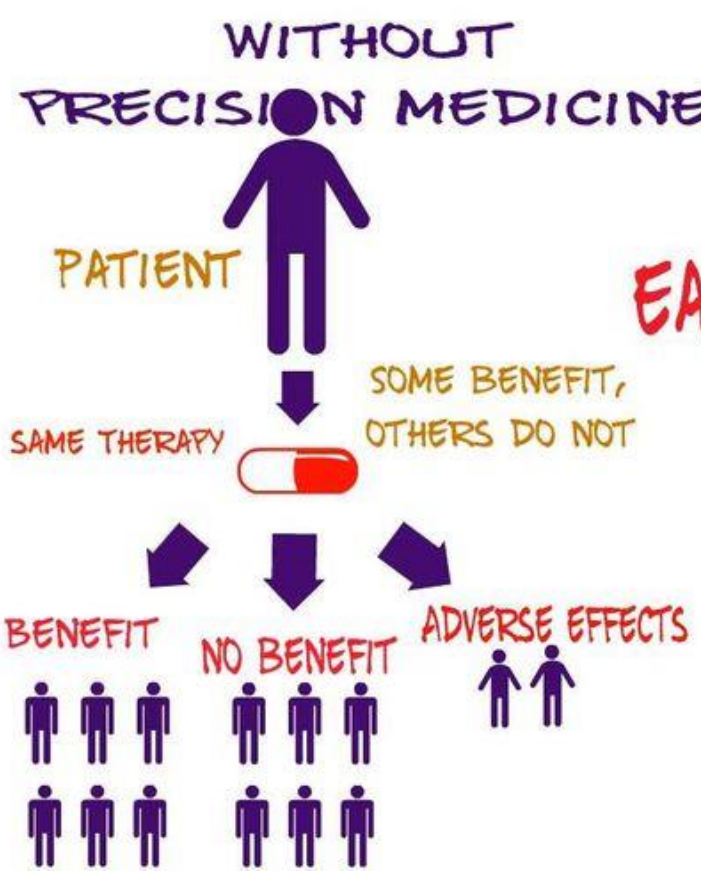
In the Era of Precision Medicine

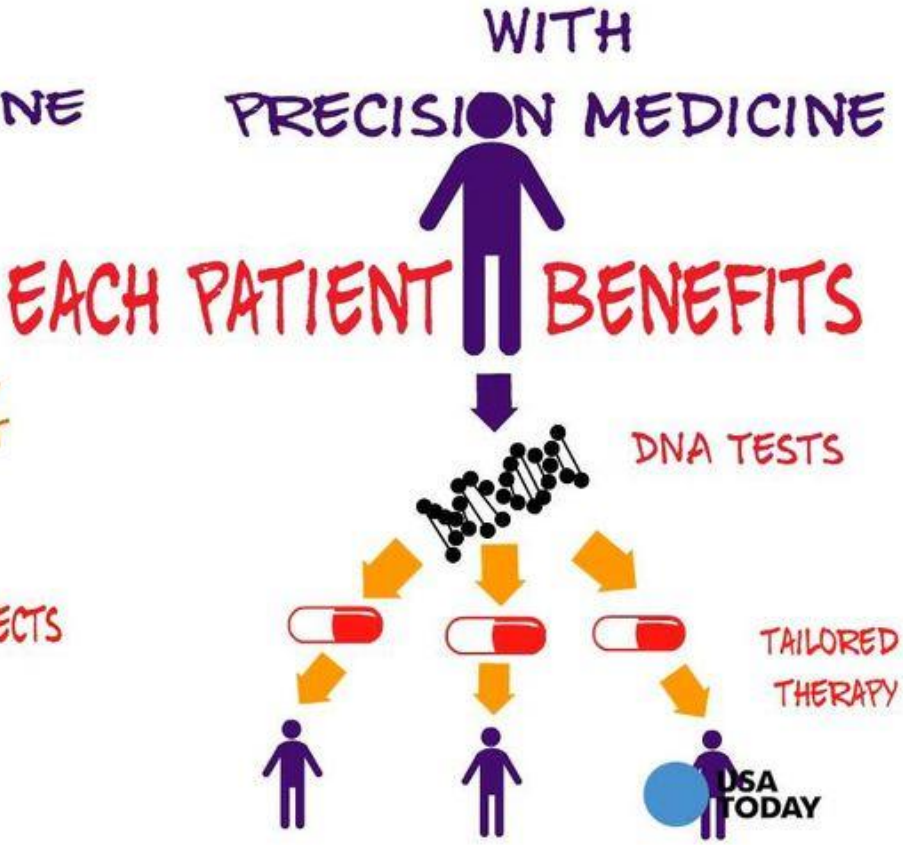
Precision medical treatment according to mutations to genotype patients, choose the right drugs, just like: Gleevec in CML, Herceptin in breast cancer and Gefitinat in lung cancer



Gleevec in chronic myelogenous leukemia
Herceptin in breast cancer
Tarceva in lung cancer

In the Era of Precision Medicine

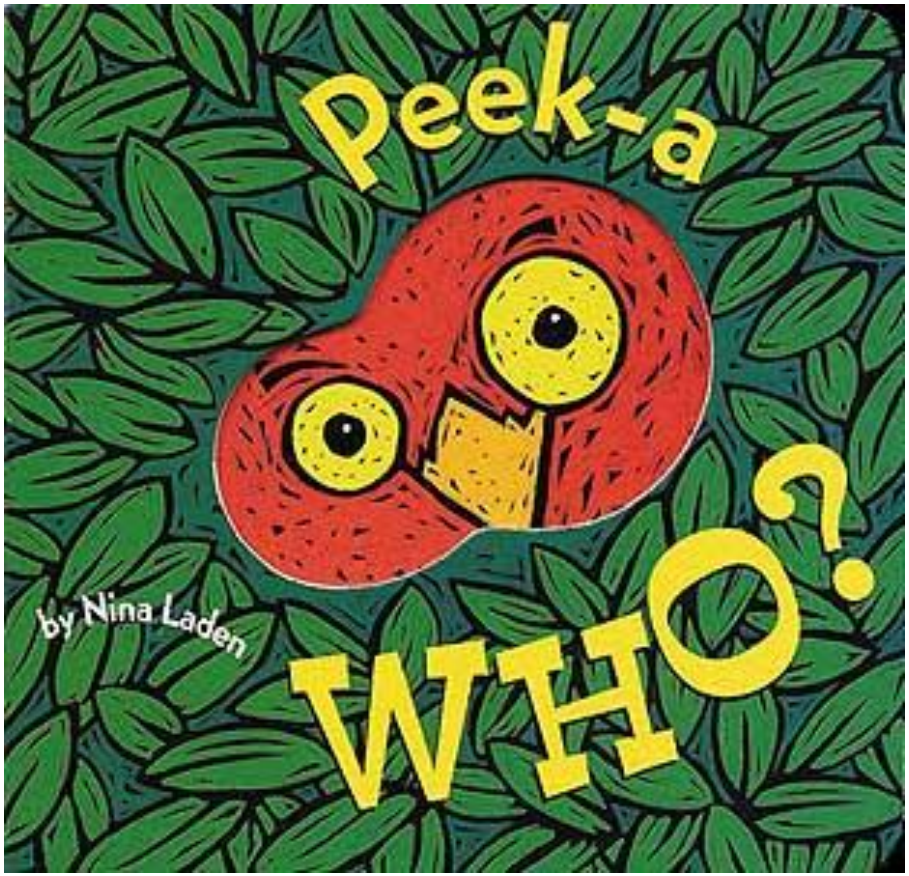




In the era of precision medicine, people have a new understanding of the treatment of diseases.

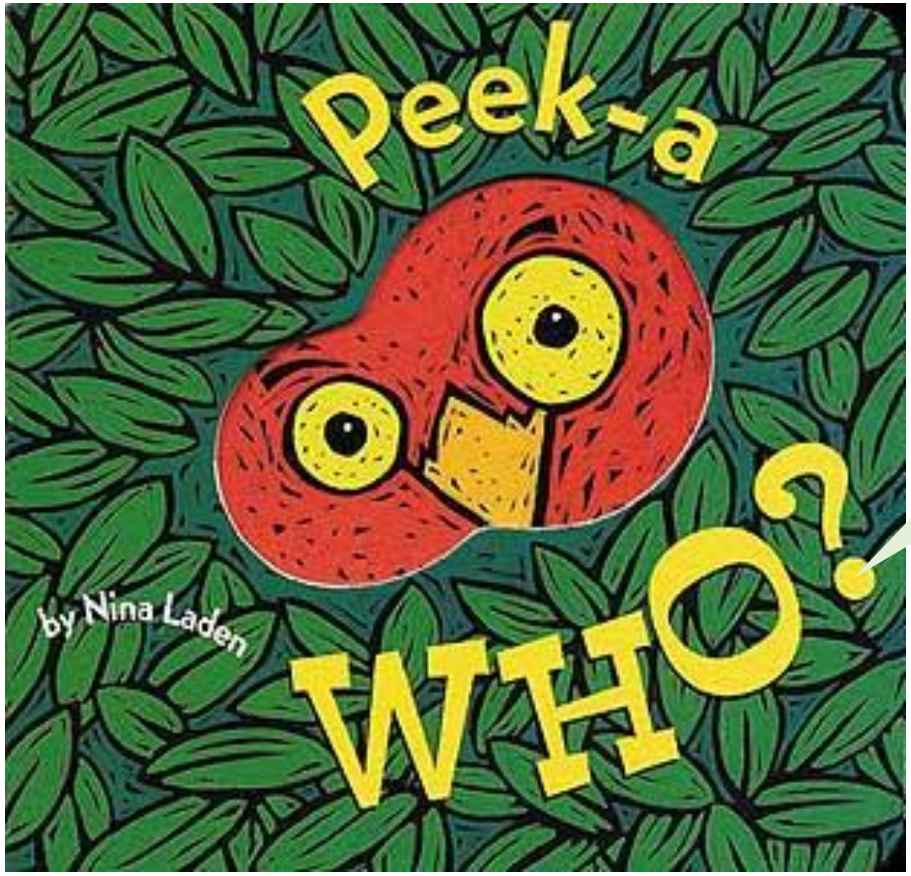
Gleevec in chronic myelogenous leukemia
Herceptin in breast cancer
Tarceva in lung cancer

Precision medicine: Peek-a-WHO



Models! Models! Models!

Precision medicine: Peek-a-WHO



Our works is: Rapid establishment of a gene-drug knowledge base through large-scale analysis in models, then we can peek who will be a right patient for give a right treatments.

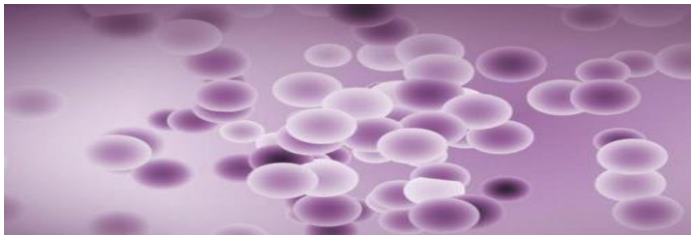
Models! Models! Models!

Models must reflect genetic heterogeneity

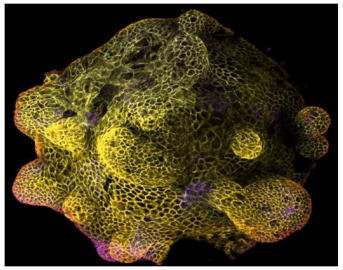
Genetic Heterogeneity → Drug response

Patient **D**erived **X**enografts — PDX

Patient **D**erived **C**ancer **C**ell — Cancer cell line (PDC)



Patient **D**erived **O**rganoid — Organoid (PDO)



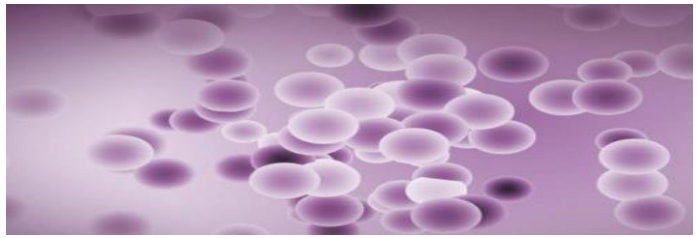
Models to reflect genetic heterogeneity

Patient derived xenografts (**PDX**) are models of cancer where the tissue or cells from a patient's tumor are implanted into an immuno-deficient or humanized mouse. PDX models are used to create an environment that allows for the natural growth of cancer, its monitoring, and corresponding treatment evaluations for the original patient.

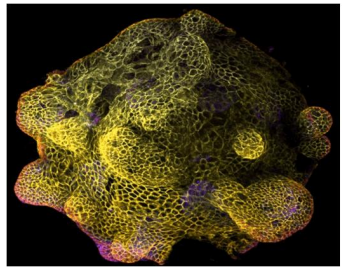
He ... sponse

Patient Derived Xenografts — PDX

Patient Derived Cancer Cell — Cancer cell line (PDC)



Patient Derived Organoid — Organoid (PDO)



Models to reflect genetic heterogeneity

Genetic

He

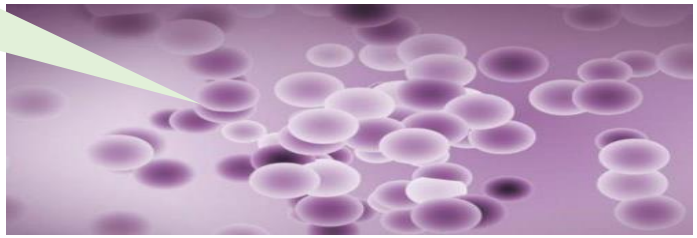
sponse

Patient derived Cancer Cell (**PDC**) are models of cancer where the cells from a patient's tumor are implanted into a petri dish and stay alive. PDC cell line are used to monitoring, and corresponding treatment evaluations for the original patient.

Patient Derived Xer

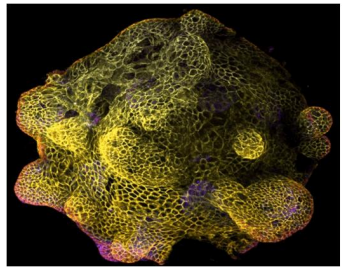
Patient Derived Cancer Cell

Cancer cell line (PDC)



Patient Derived Organoid

Organoid (PDO)



Models to reflect genetic heterogeneity

Genetic Heterogeneity → Drug response

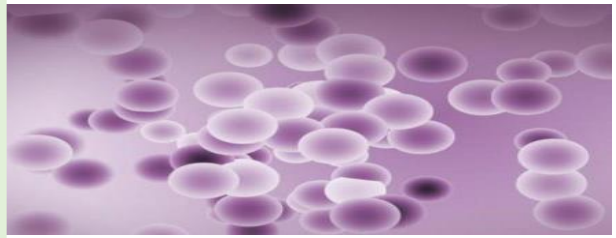
Patient **D**erived **X**er

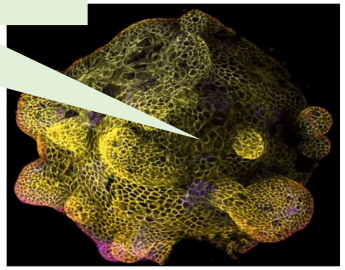
Patient **D**erived **C**ar

Patient **D**erived **O**rganoid

Patient derived Organoid (**PDO**) are models of cancer where the tissue or cells from a patient's tumor are implanted into a special petri dish and stay alive. PDO contains a local tumor microenvironment, can be used to monitoring, and corresponding treatment evaluations for the original patient.

Organoid (PDO)

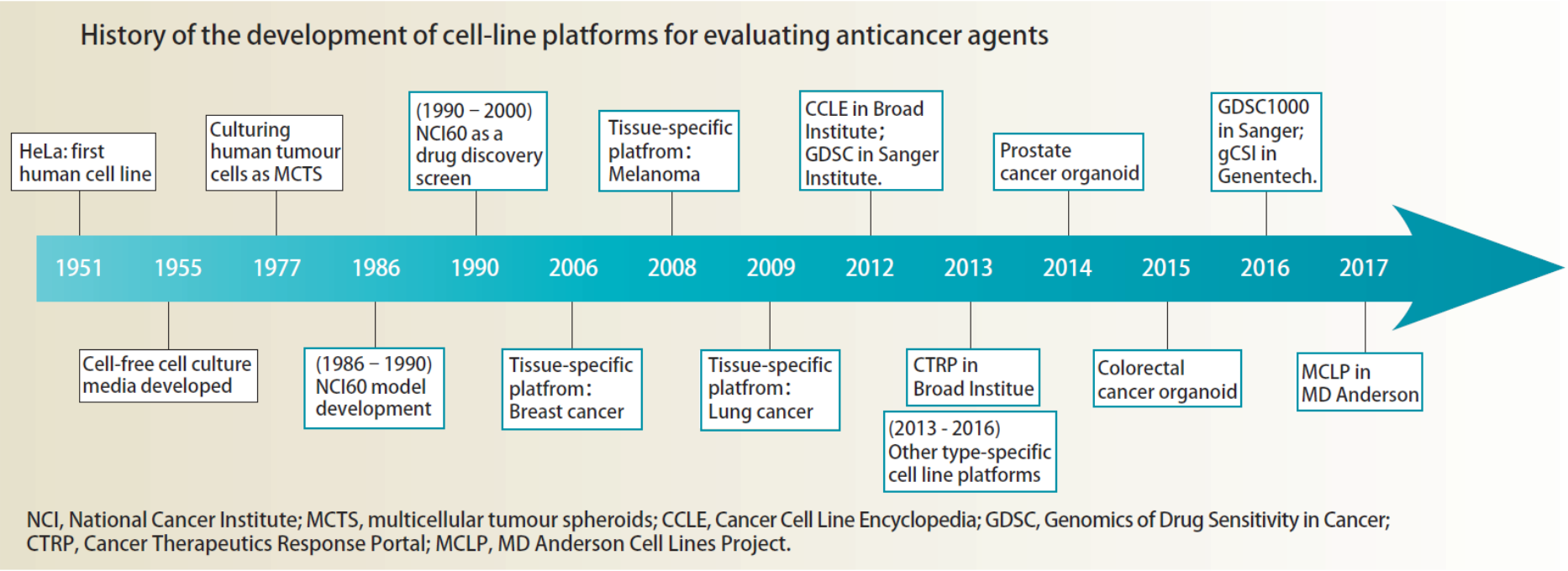




These three models are very good, but they are expensive and Time consuming. Is there any other choice?

Again Cell Line?

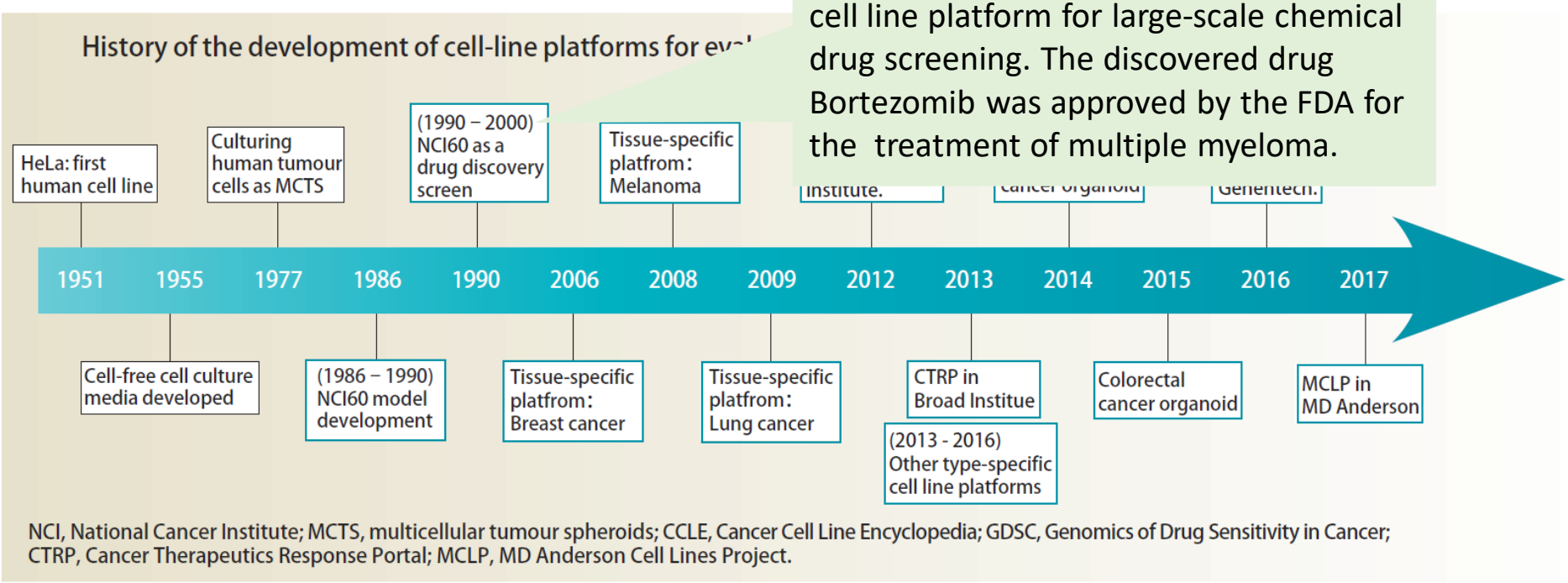
History of cancer cell line-based platforms



Sharma SV et al. *Nature Review Cancer*. 2010.

History of cancer cell line-based platforms

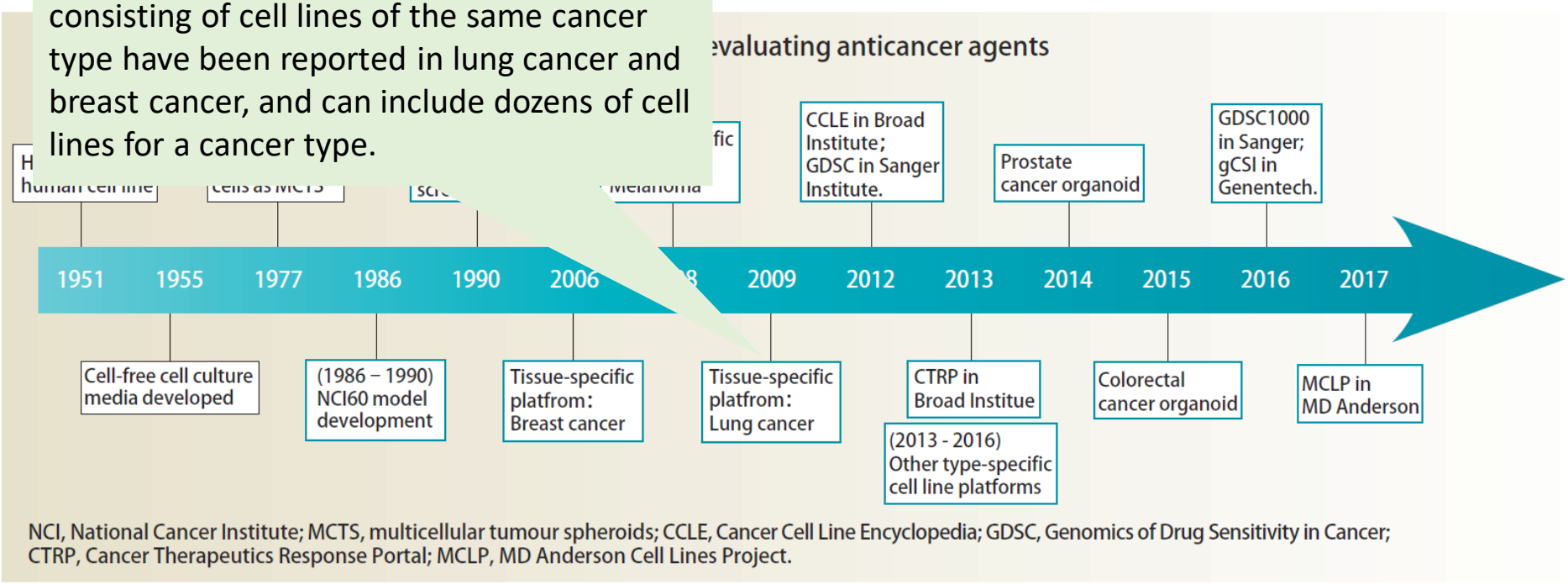
The earliest cell line platform dates back to the 1980s. The National Cancer Institute collected 60 cell lines from different cancer types to form the NCI60 cell line platform for large-scale chemical drug screening. The discovered drug Bortezomib was approved by the FDA for the treatment of multiple myeloma.



Sharma SV et al. *Nature Review Cancer*. 2010.

ell line-based platforms

With the understanding of cancer heterogeneity, NCI60 has been unable to meet the needs of the analysis. Beginning in 2006, tissue-specific cell line platforms consisting of cell lines of the same cancer type have been reported in lung cancer and breast cancer, and can include dozens of cell lines for a cancer type.



NCI, National Cancer Institute; MCTS, multicellular tumour spheroids; CCLE, Cancer Cell Line Encyclopedia; GDSC, Genomics of Drug Sensitivity in Cancer; CTRP, Cancer Therapeutics Response Portal; MCLP, MD Anderson Cell Lines Project.

Sharma SV et al. *Nature Review Cancer*. 2010.

So far, we have not found a suitable cell line platform for liver cancer research. Can a large panel of liver cancer cell lines facilitate to address the challenges?

Establishment of Liver Cancer Model Repository (LIMORE)

1, Establishment of cell line is of low efficiency

2, Cell lines gain similar mutations

3, Represent genetic heterogeneity and drug response

4, Database of LIMORE cell bank

Establishment of Liver Cancer Model Repository (LIMORE)

1, Establishment of cell line is of low efficiency

2, Cell lines gain similar mutations

3, Represent genetic heterogeneity and drug response

4, Database of LIMORE cell bank

Establishment of HCC cell lines

Public cell banks

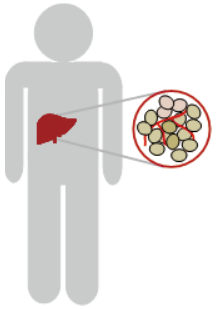
Korean Cell Line Bank

ATCC NIBIO JCRB Cell Bank

SGST.CN 上海研发公共服务平台

31 collected cell lines

Liver cancer patients

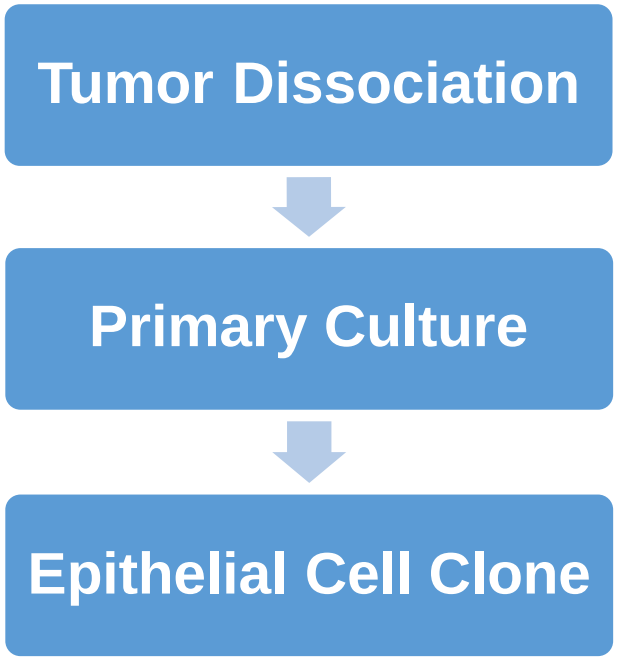


Surgically removed

Primary and long-term culture

45 newly generated cell lines

Establishment of HCC cell lines from Chinese patients



Fresh samples & optimized enzymatic dissociation

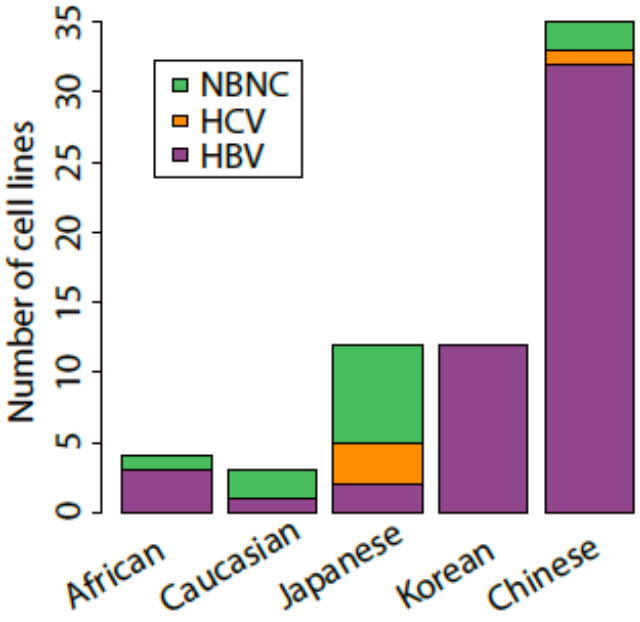
Optimized medium with growth factors, hormones, and FBS

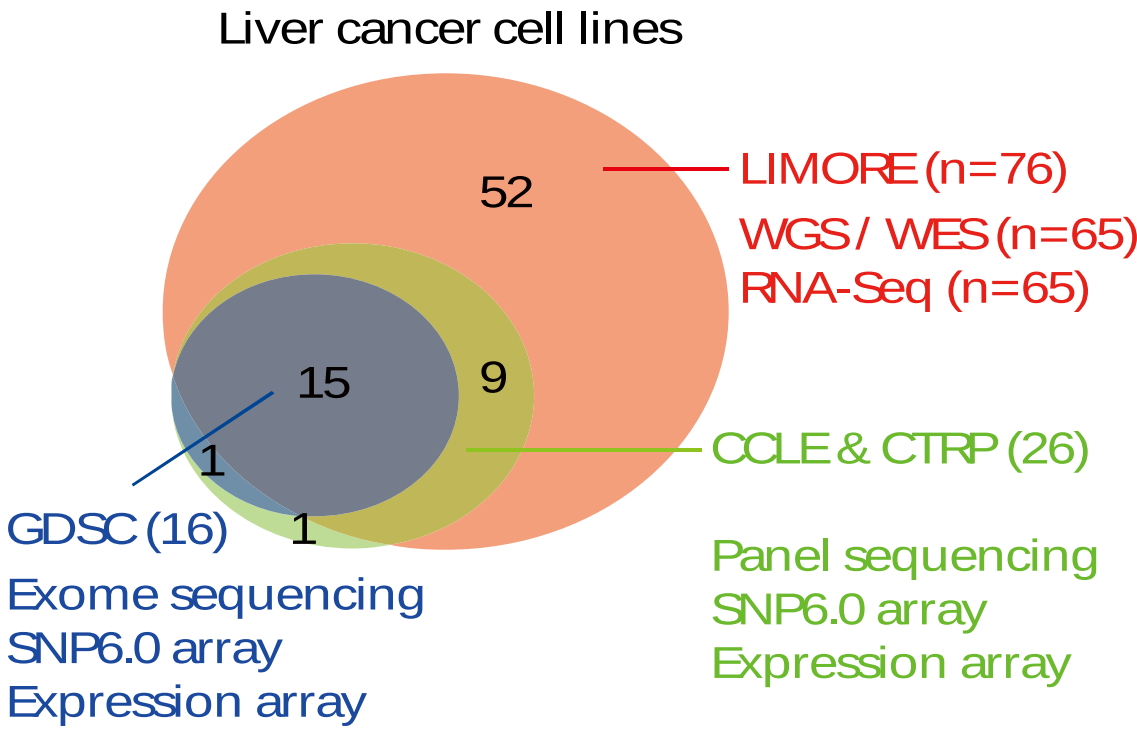
Clone picking up

45 new liver cancer cell lines

The success rate of cell culture : ~50%

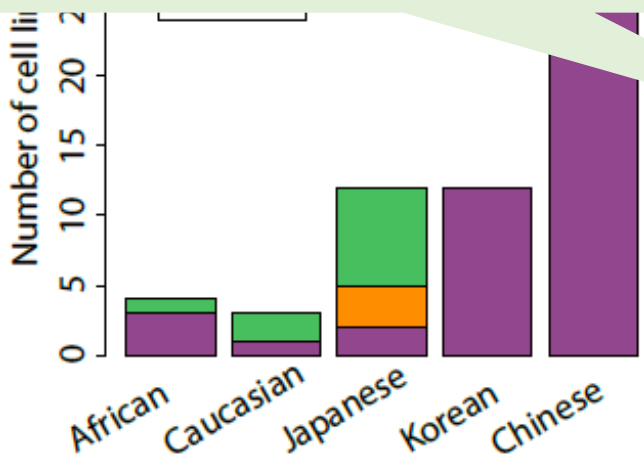
Liver Cancer Model Repository (LIMORE)

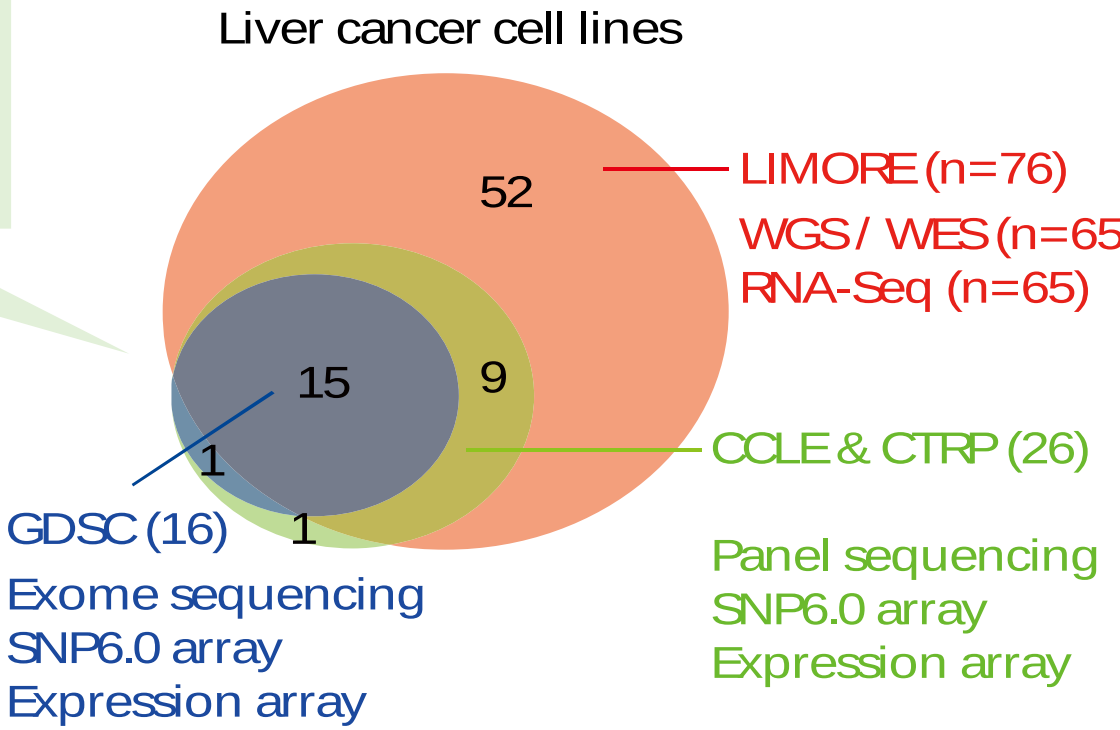




del Repository (LIMORE)

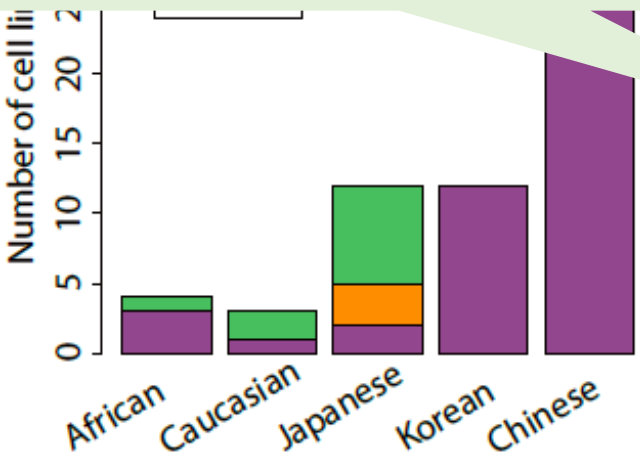
Finally, we have a total of 76 liver cancer cell lines. This is far more than CCLE in liver cancer. These liver cancer cell lines and data would be a great platform for liver cancer research. About half of them are from Chinese. 70% are from HBV positive patients.

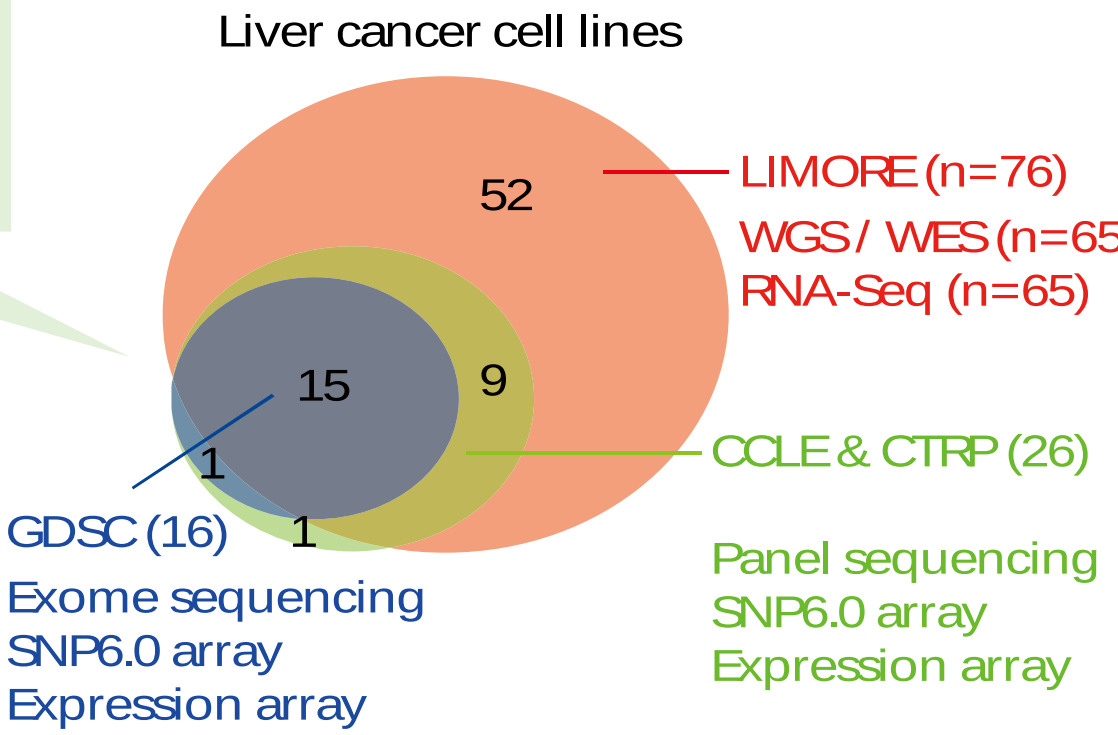




Finally, we have a total of 76 liver cancer cell lines. This is far more than CCLE in liver cancer. These liver cancer cell lines and data would be a great platform for liver cancer research. About half of them are from Chinese. 70% are from HBV positive patients.

del Repository (LIMORE)





Do HCC cell lines retain mutation landscape of primary HCCs?

Establishment of Liver Cancer Model Repository (LIMORE)

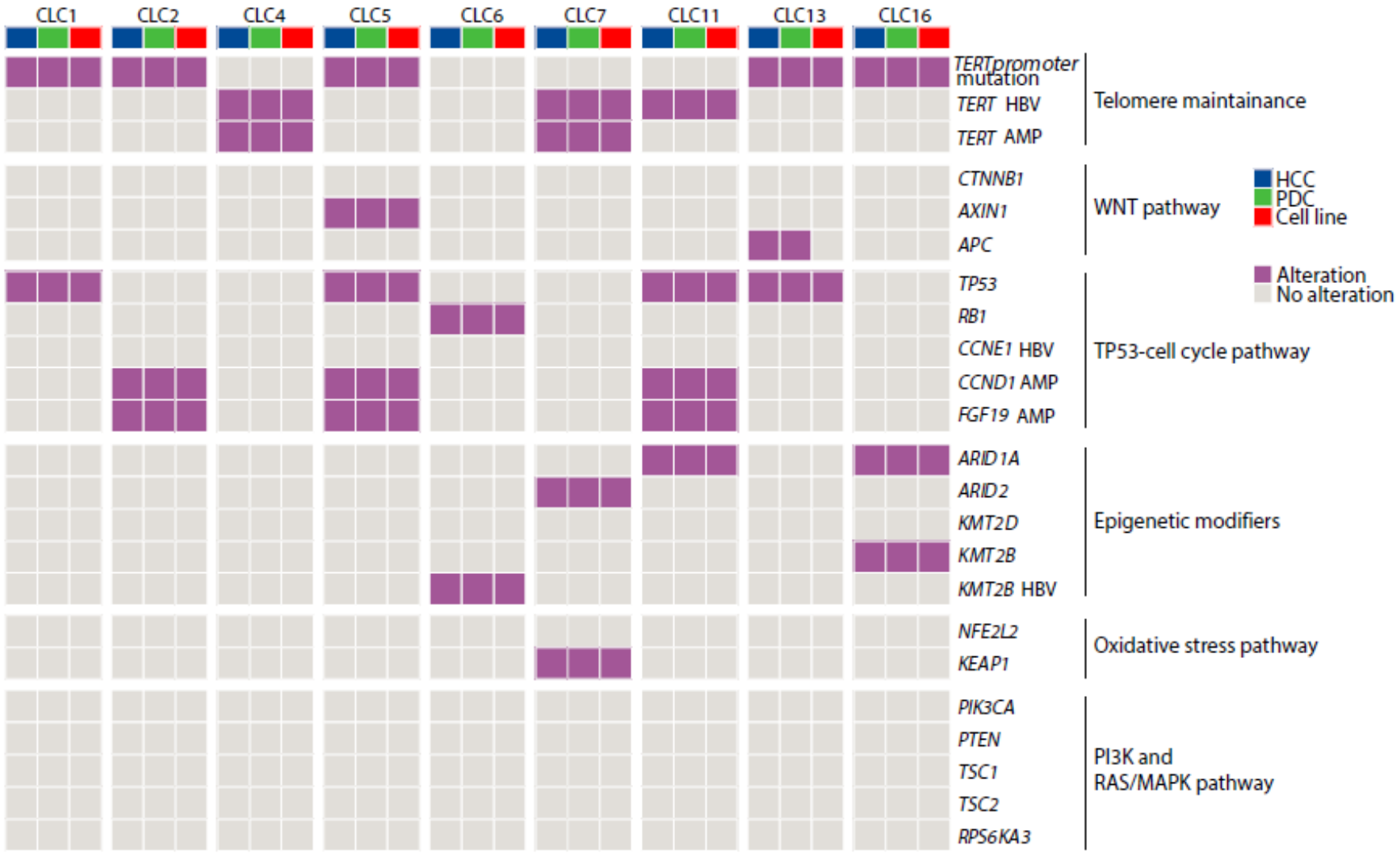
1, Establishment of cell line is of low efficiency

2, Cell lines gain similar mutations

3, Represent genetic heterogeneity and drug response

4, Database of LIMORE cell bank

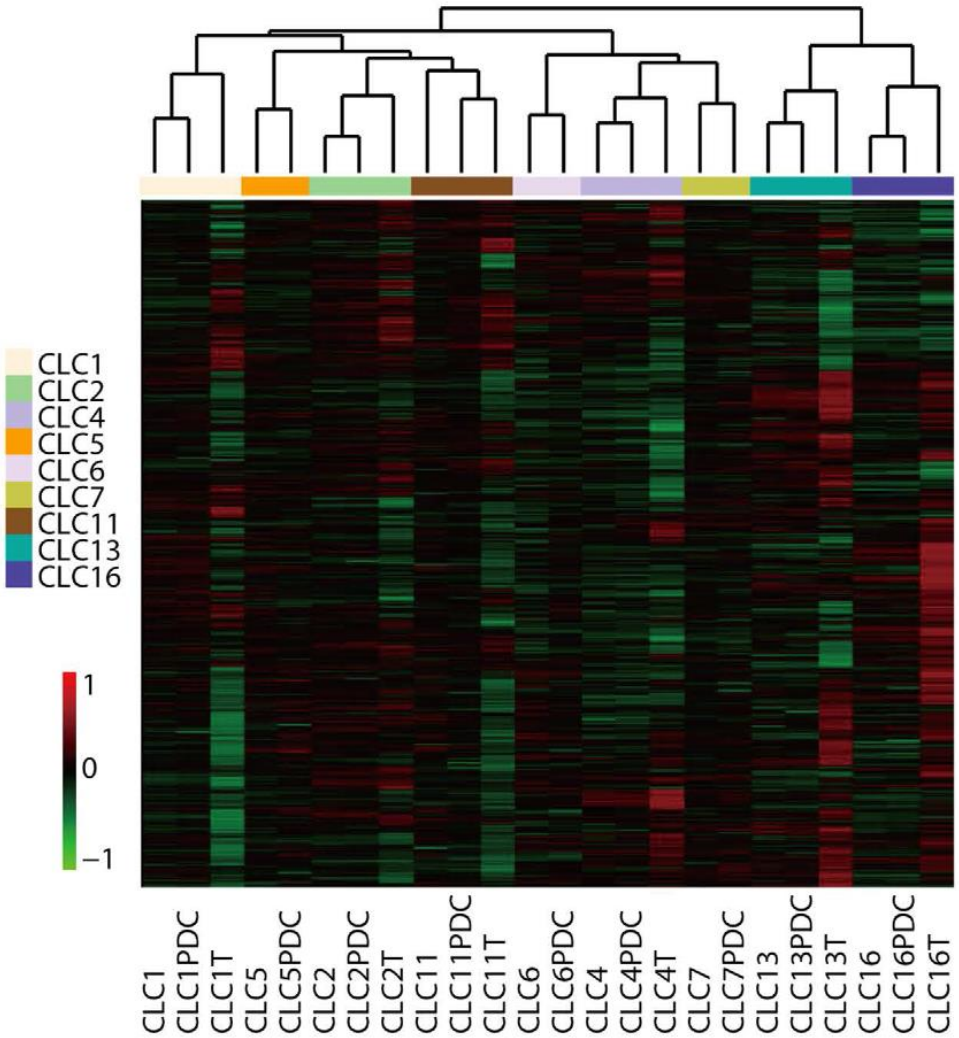
Cell lines retain genomic alterations of primary HCCs



Cell li ic alterations of primary HCCs

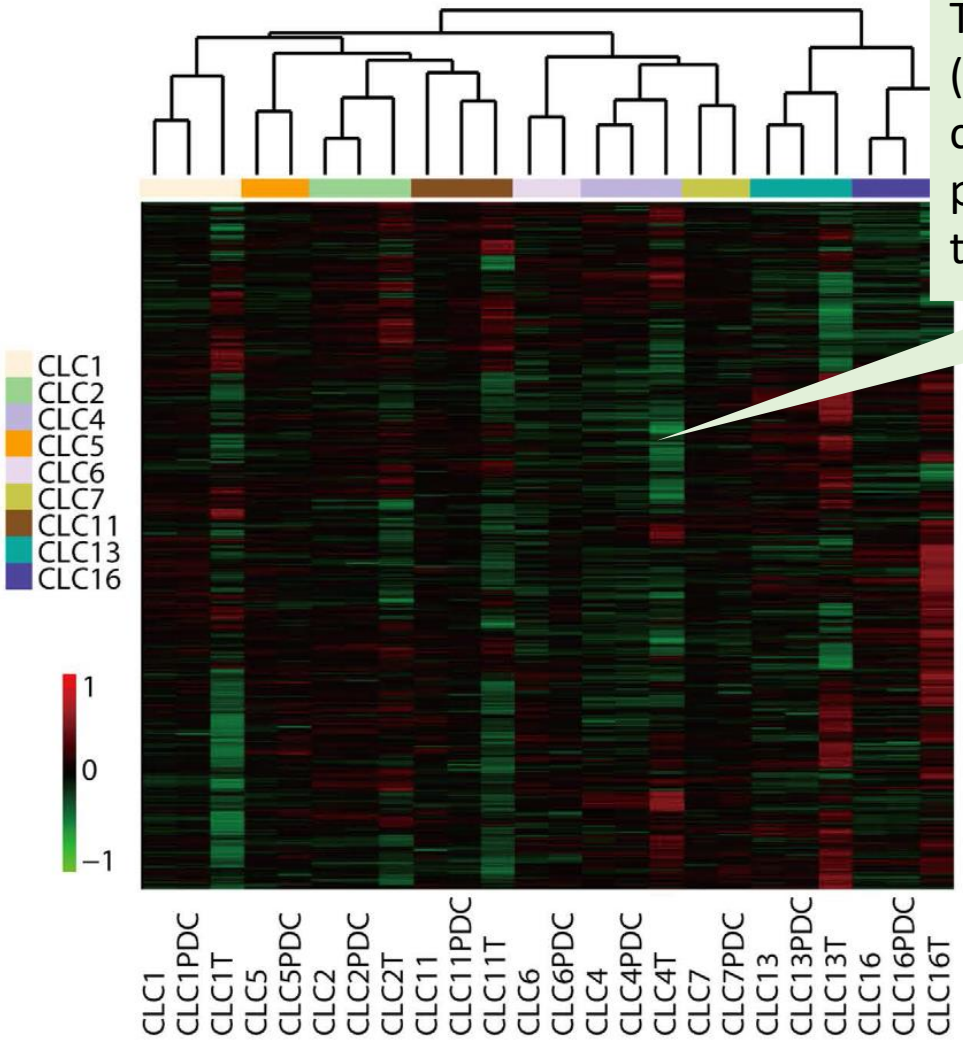
In the corresponding groups (tissue, PDC, cell line) ,the driven gene mutations were completely identical.

Cell lines also retain expression profiles of primary HCCs



Qiu et al *Sci Rep* 2016 July

Cell lines also retain expression profiles of primary HCCs



The corresponding groups (tissue, PDC, cell line) have completely similar expression patterns and are clustered together.

Qiu et al *Sci Rep* 2016 July

TOP 100 – READ ARTICLES – 2016
OFFICIAL AUTHOR
SCIENTIFIC REPORTS

Establishment of Liver Cancer Model Repository (LIMORE)

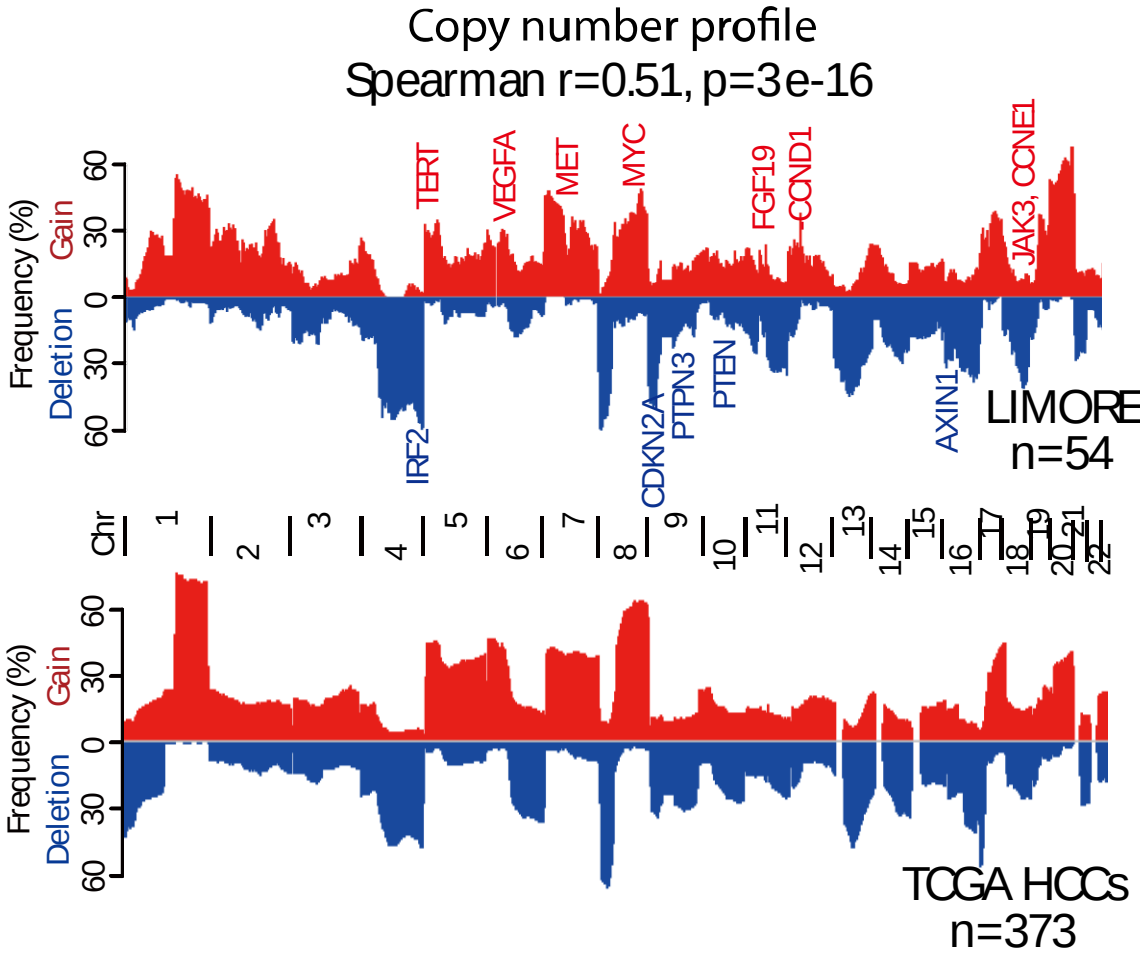
1, Establishment of cell line is of low efficiency

2, Cell lines gain similar mutations

3, Represent genetic heterogeneity and drug response

4, Database of LIMORE cell bank

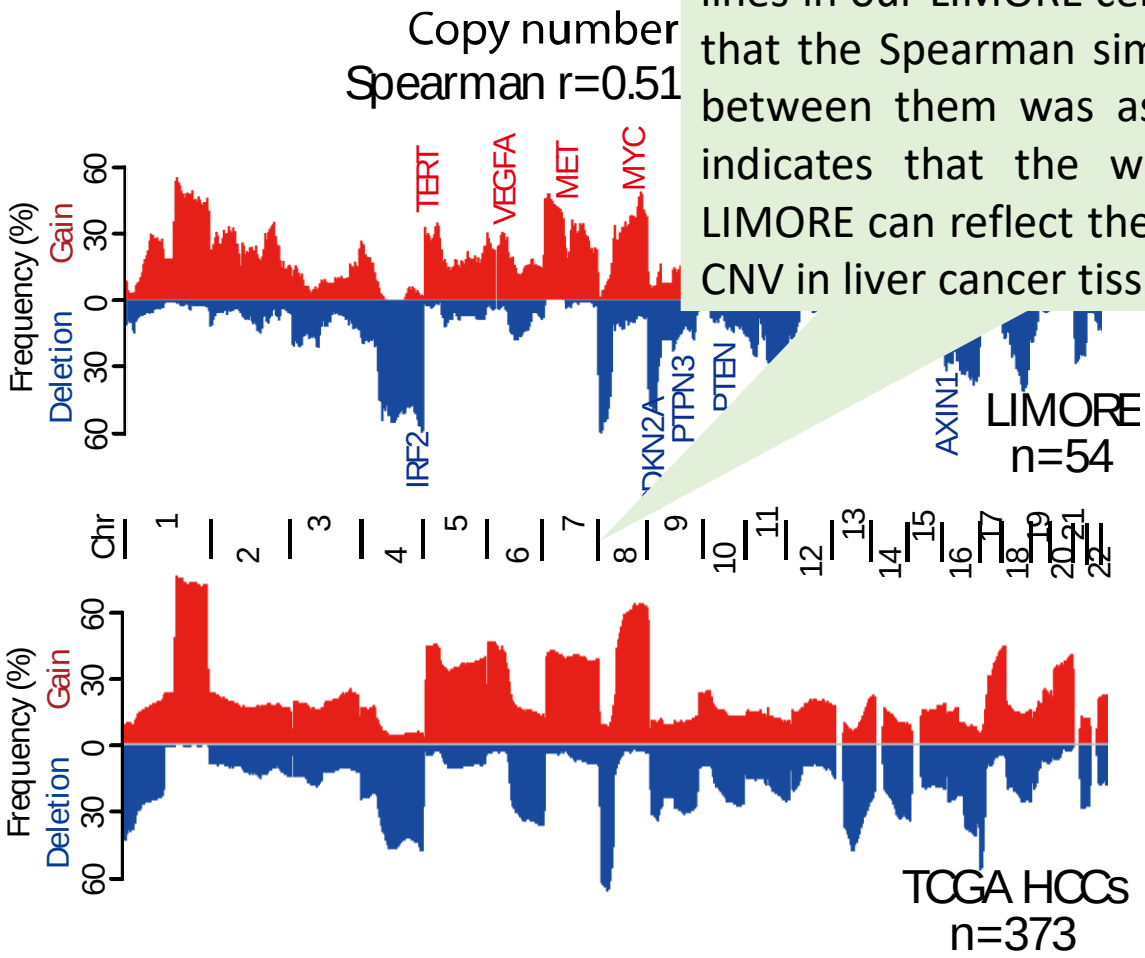
Cell lines vs. HCC: CNV heterogeneity



Schulze K et al. *Nature Genetics*. 2015

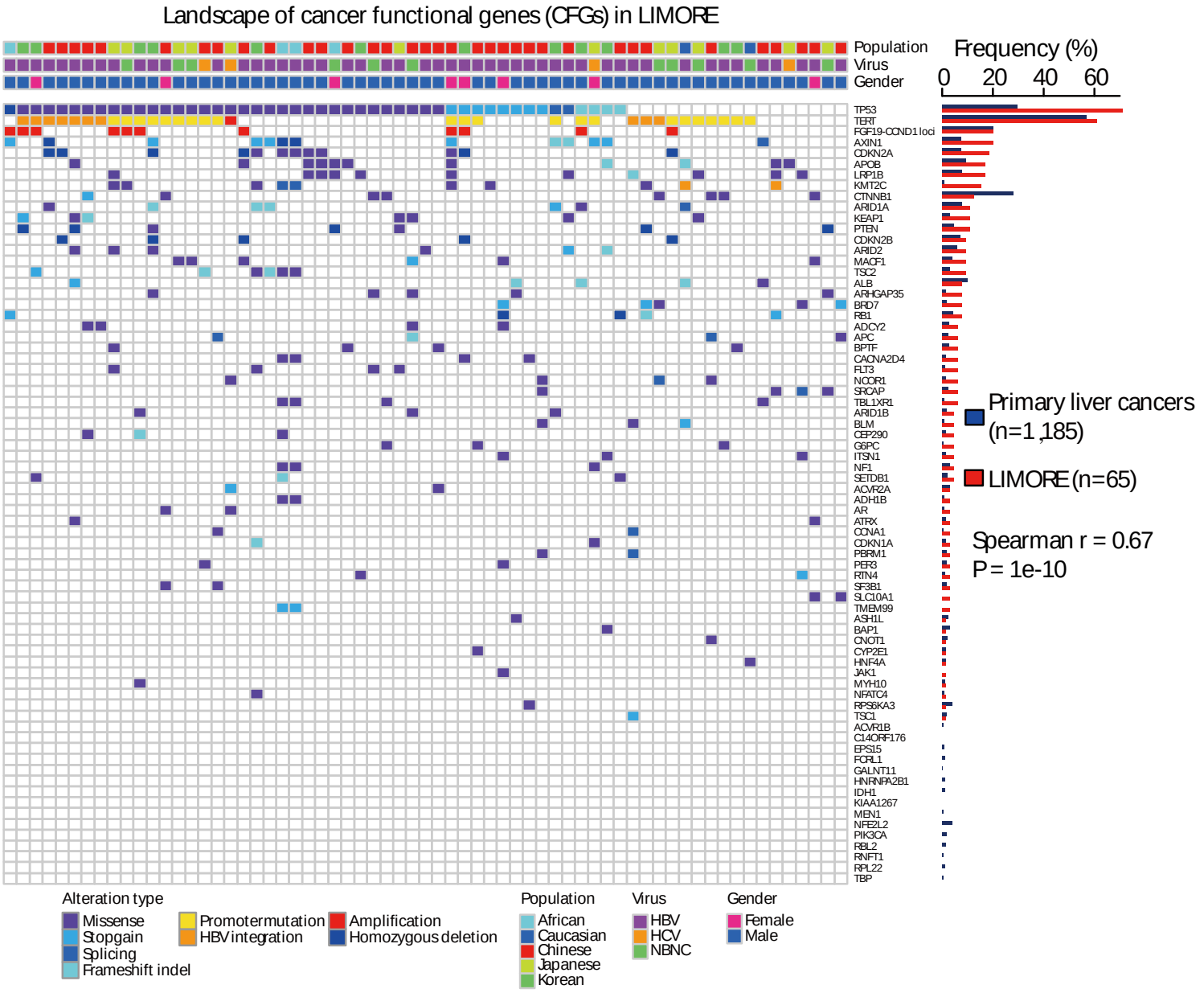
Cell lines vs. HCC: CNV

We compared the profiles of CNV variation in all 373 samples in TCGA with the profiles of CNV variation in 54 cell lines in our LIMORE cell bank, and found that the Spearman similarity coefficient between them was as high as 0.51. It indicates that the whole cell line in LIMORE can reflect the heterogeneity of CNV in liver cancer tissues.

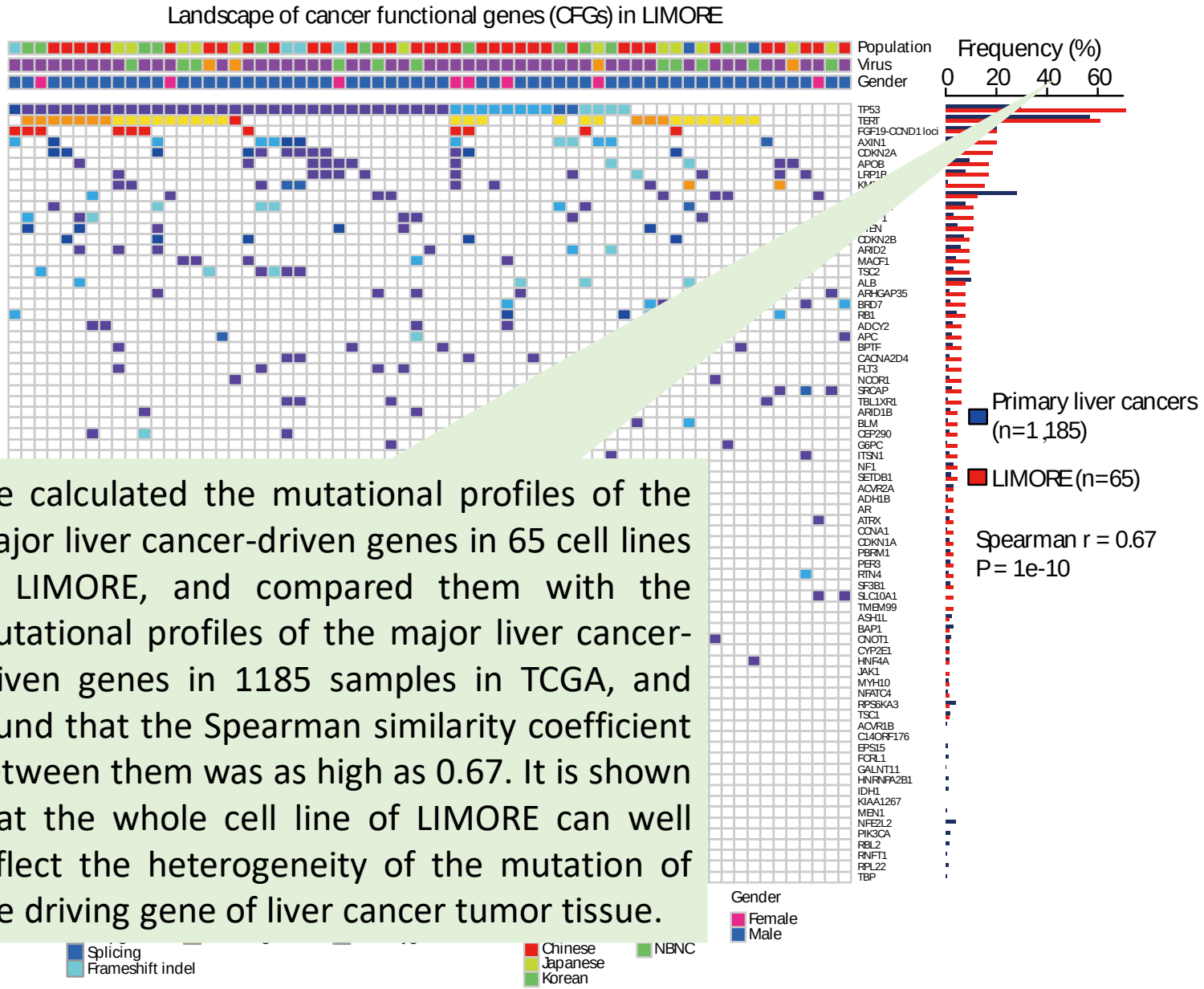


Schulze K et al. *Nature Genetics*. 2015

Cell lines vs. HCC: Driver alteration heterogeneity

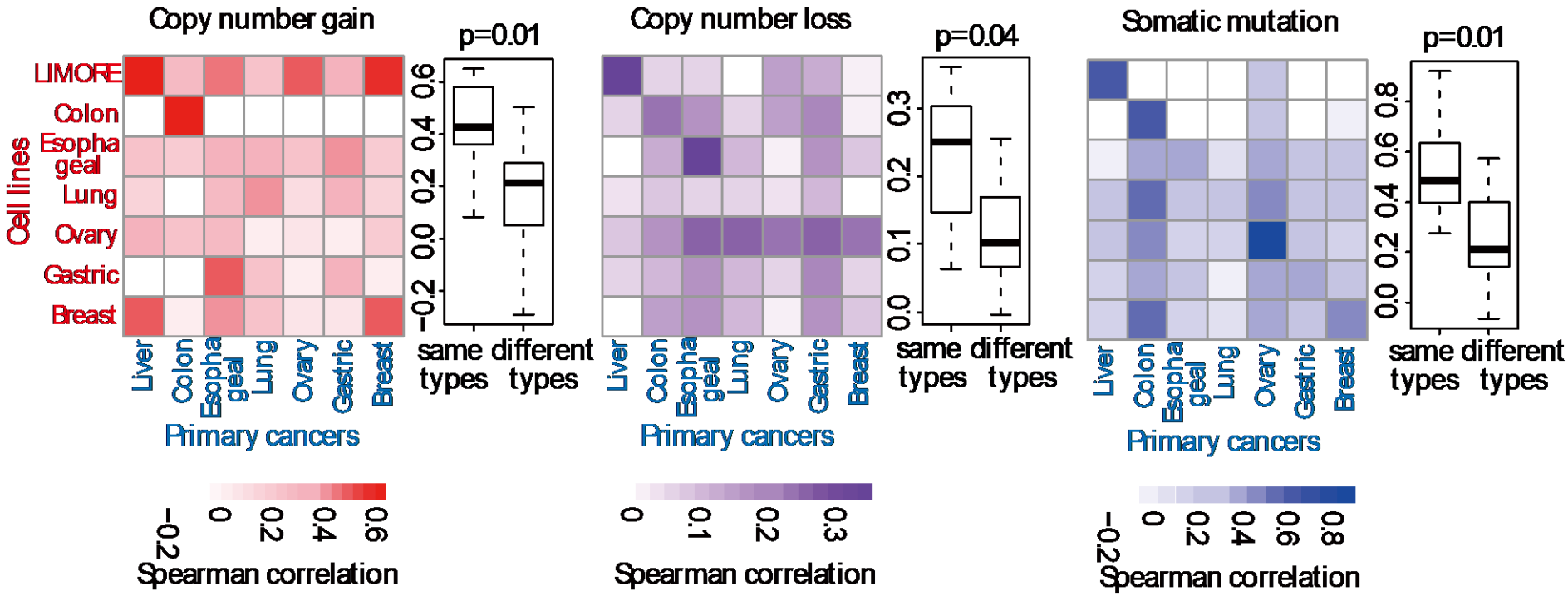


Cell lines vs. HCC: Driver alteration heterogeneity



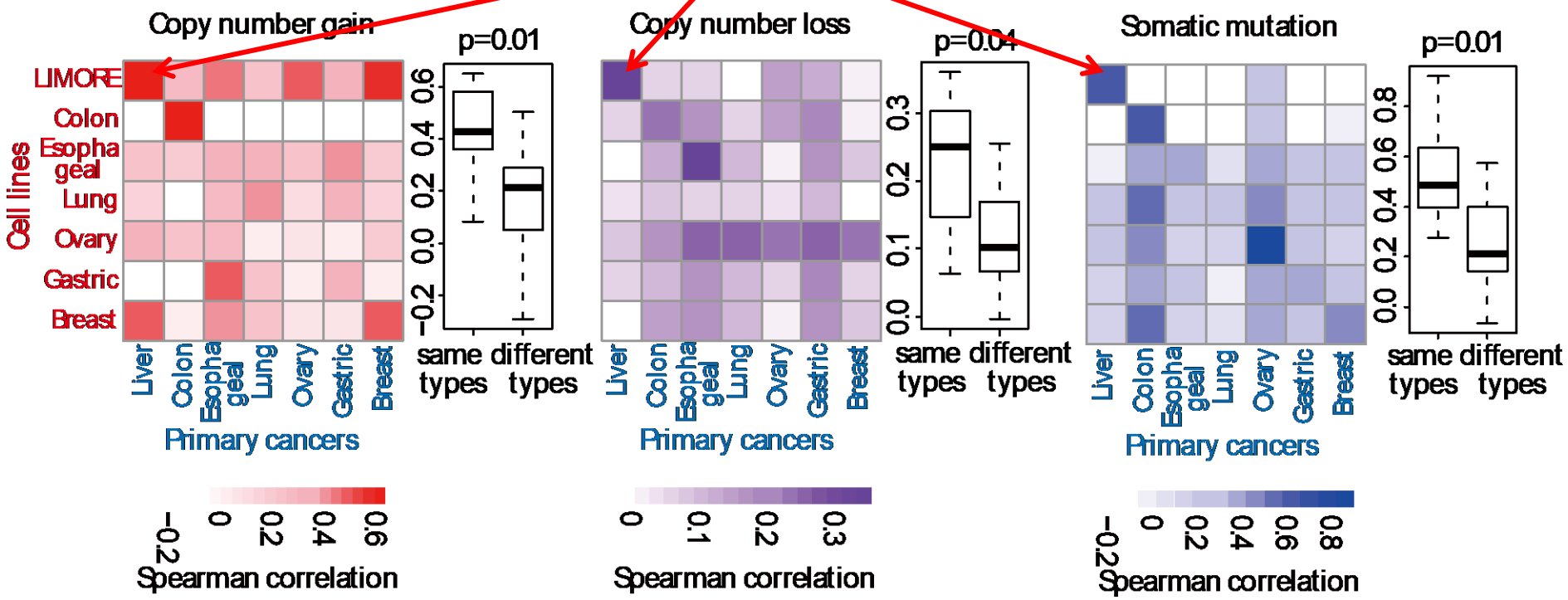
We calculated the mutational profiles of the major liver cancer-driven genes in 65 cell lines in LIMORE, and compared them with the mutational profiles of the major liver cancer-driven genes in 1185 samples in TCGA, and found that the Spearman similarity coefficient between them was as high as 0.67. It is shown that the whole cell line of LIMORE can well reflect the heterogeneity of the mutation of the driving gene of liver cancer tumor tissue.

Cancer type comparison



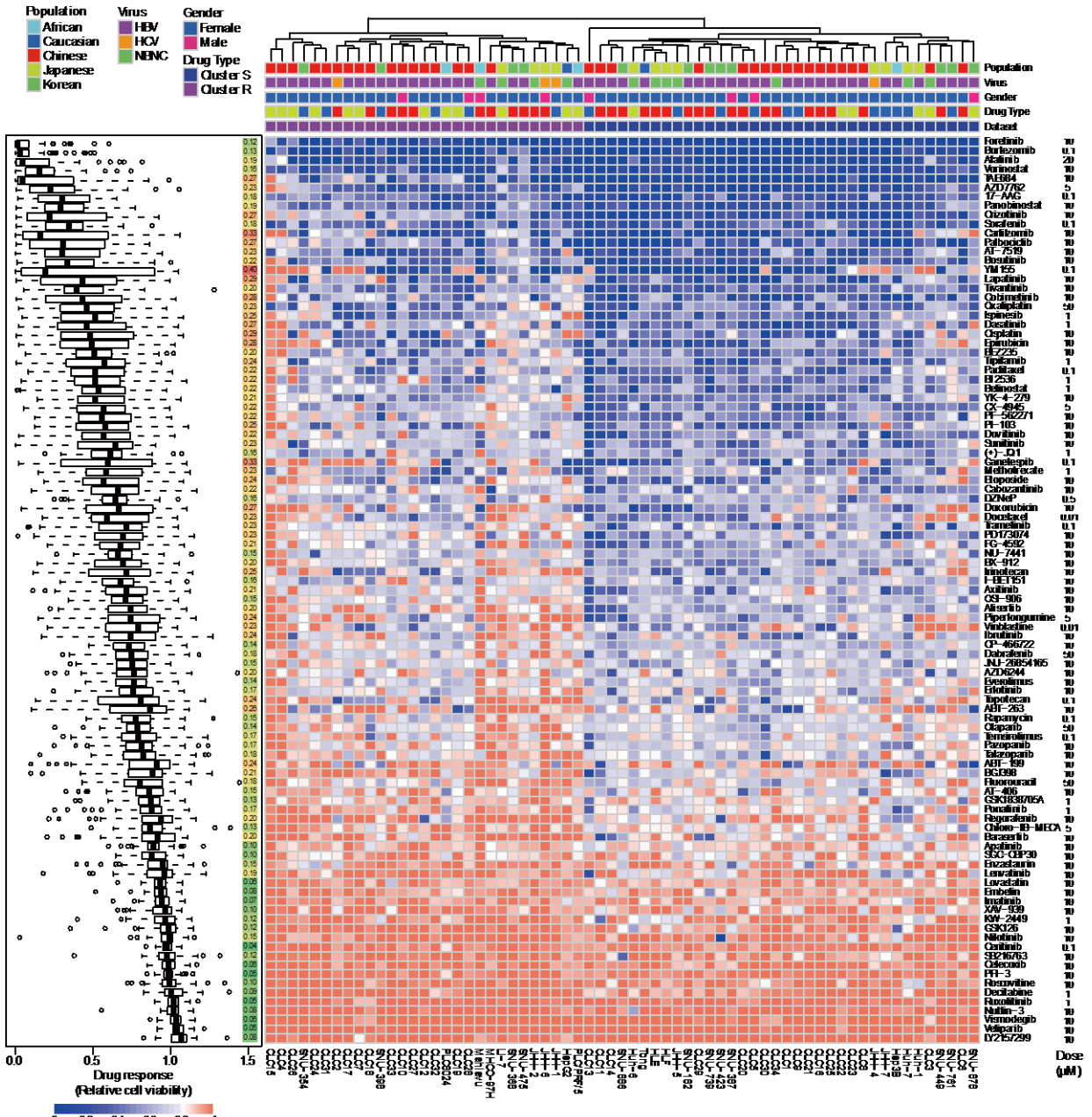
Cancer type compa

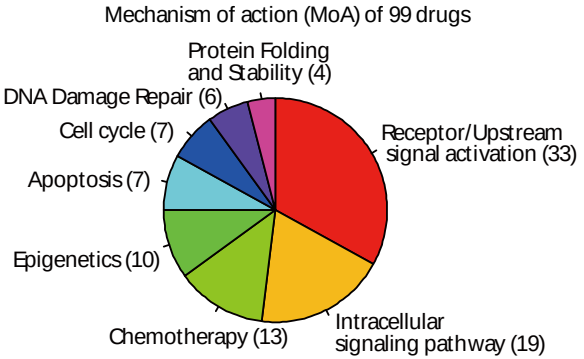
We used different tumor cell lines to describe tumor heterogeneity. It can be seen that LIMORE shows the closest similarity to liver tumor tissue.



LIMORE system is a completely new cell line system that comprehensively reflects the heterogeneity of liver cancer, and is a good and simple model system for studying liver cancer.

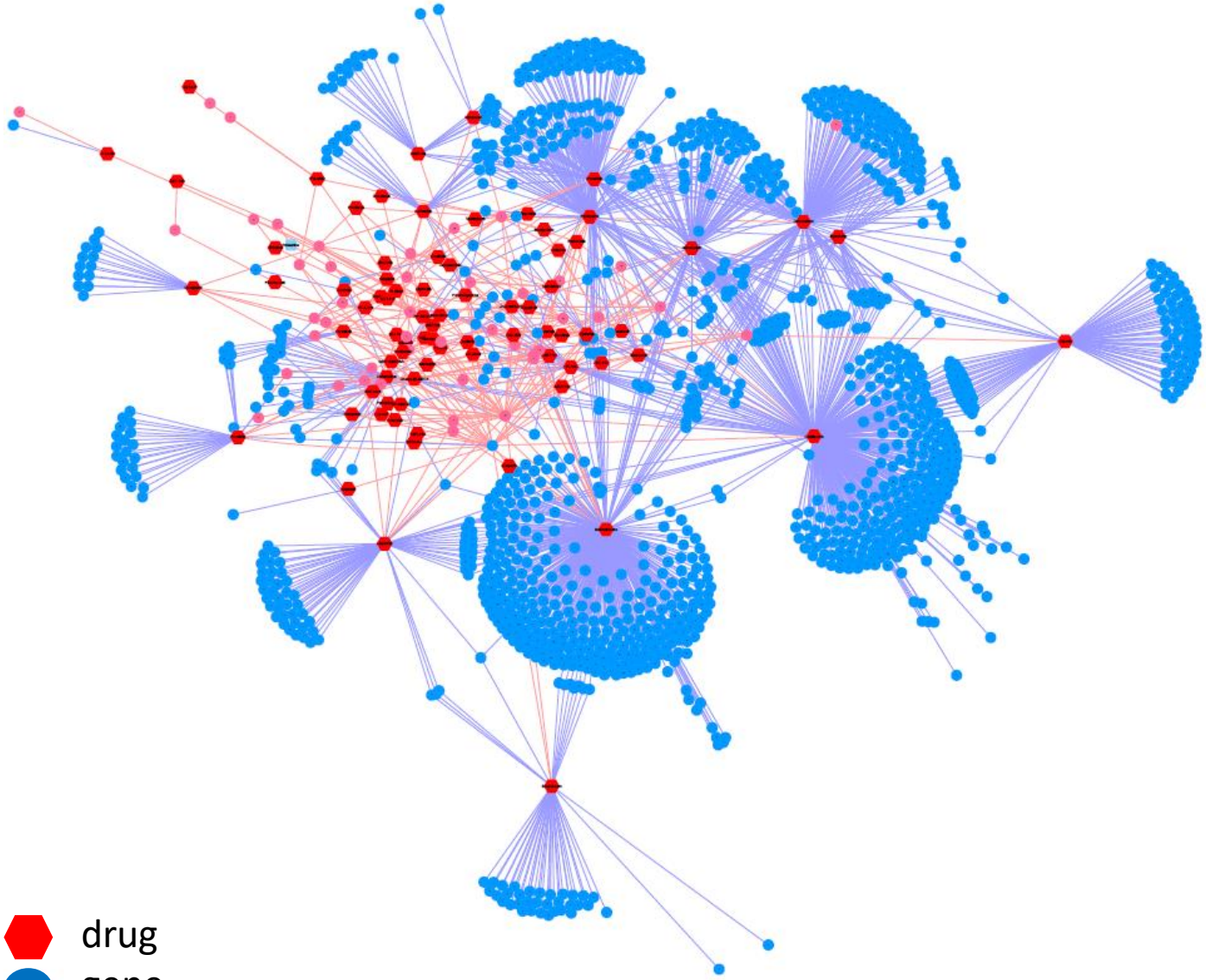
Sensitivities of liver cancer cell lines to 99 anti-cancer drugs





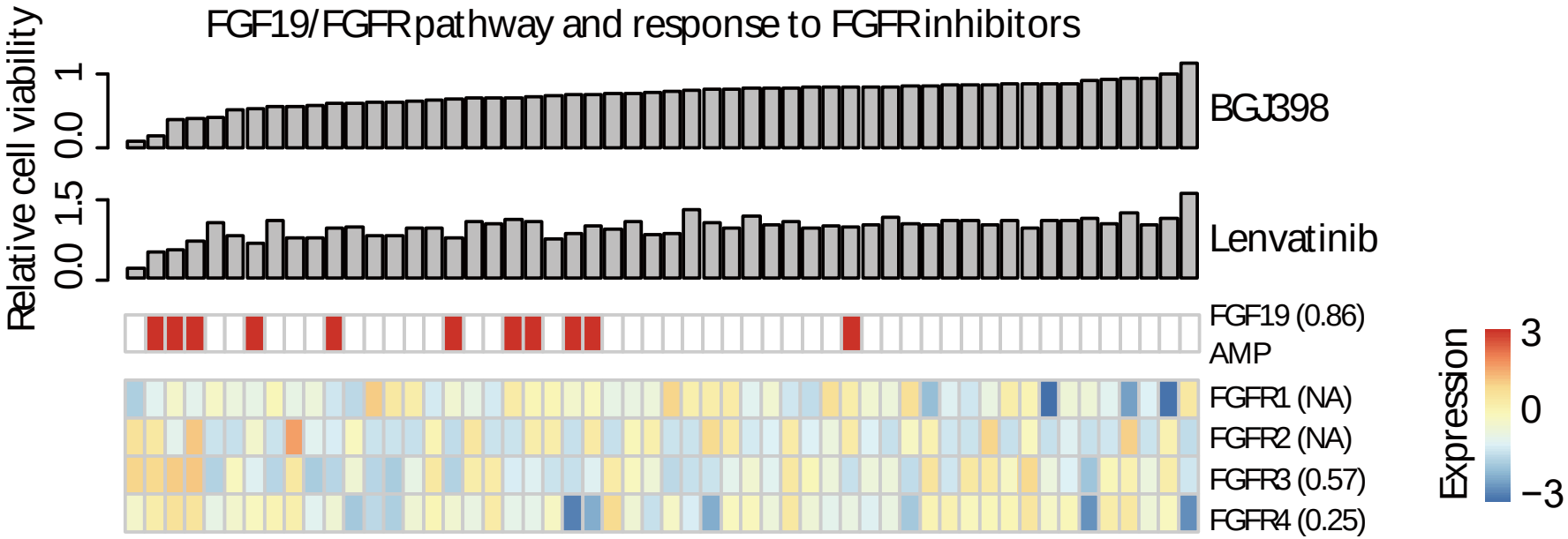
We performed 99 anti-cancer drug susceptibility experiments on 66 liver cancer cell lines in LIMORE. By integrating the genetic information of the cell line with the drug sensitivity analysis, a number of potential molecular biomarkers indicating drug susceptibility could be identified.

Overview of pharmacogenomic landscape
Elastic net regression



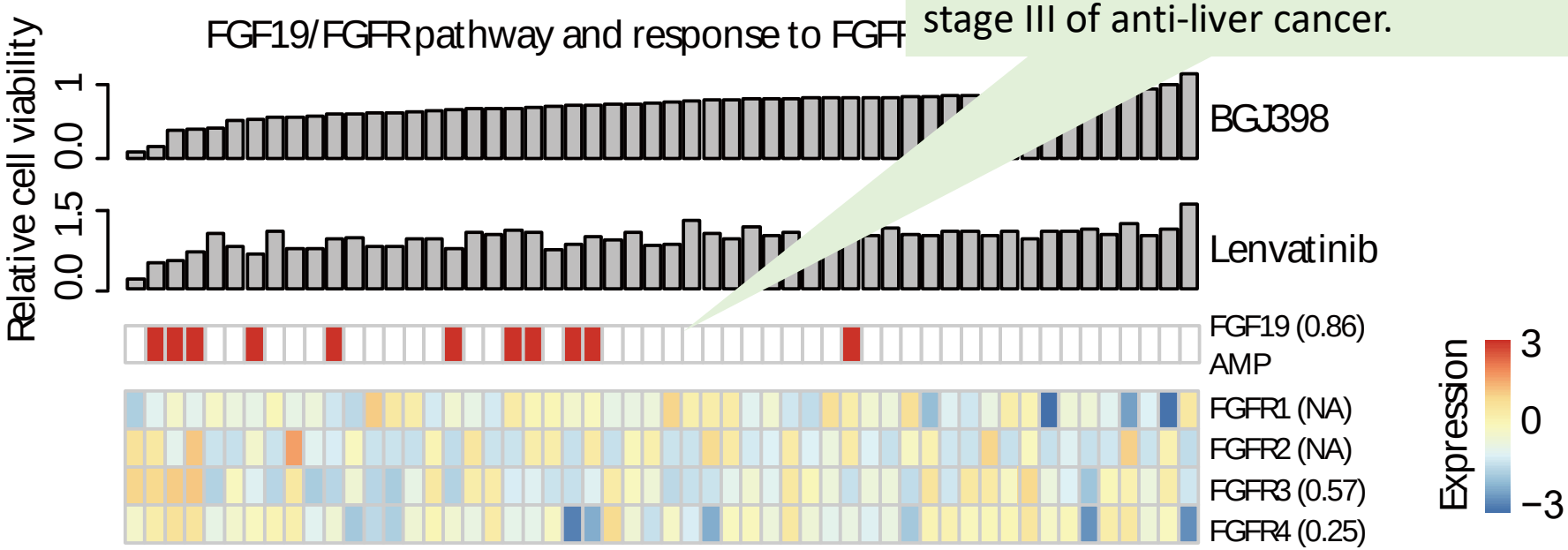
We use ***elastic net regression model*** to build our pharmaco-genomic landscape, here small red hexagons are drugs, small blue dots are genes. This map links the drug-acting phenotype of each individual cell line with the gene expression and gene mutation patterns of the cell line under the action of the drug.

FGF19 alterations and FGFR inhibitors

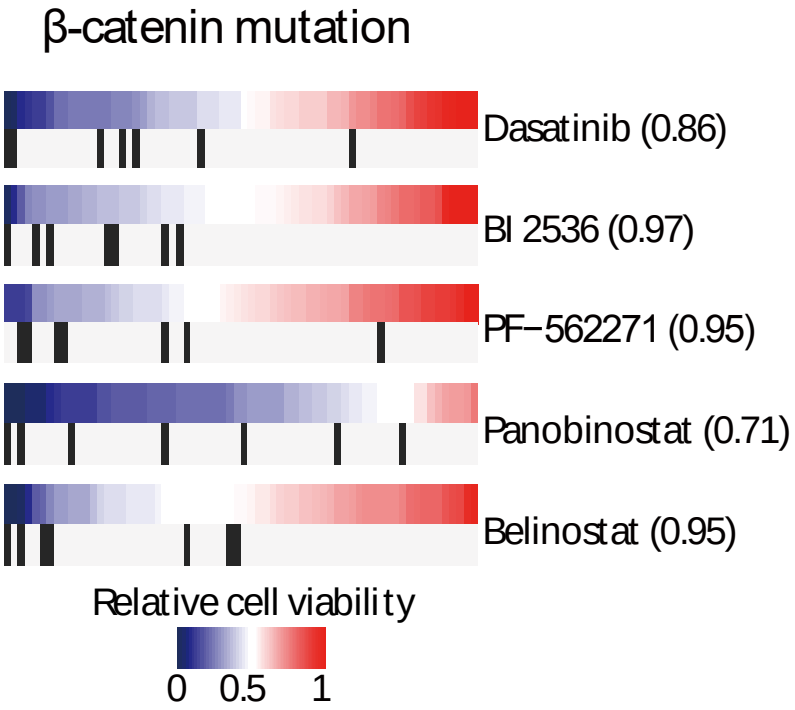


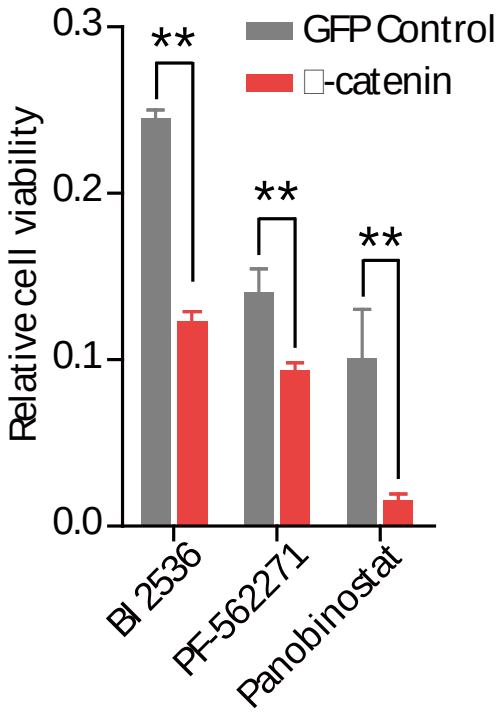
FGF19 alterations and

In our experiments we found that FGF19 gene amplification and overexpression are associated with its receptor FGFR and the Inhibition of FGFR. Lenvatinib is FGFR inhibitor and a drug in the clinical stage III of anti-liver cancer.



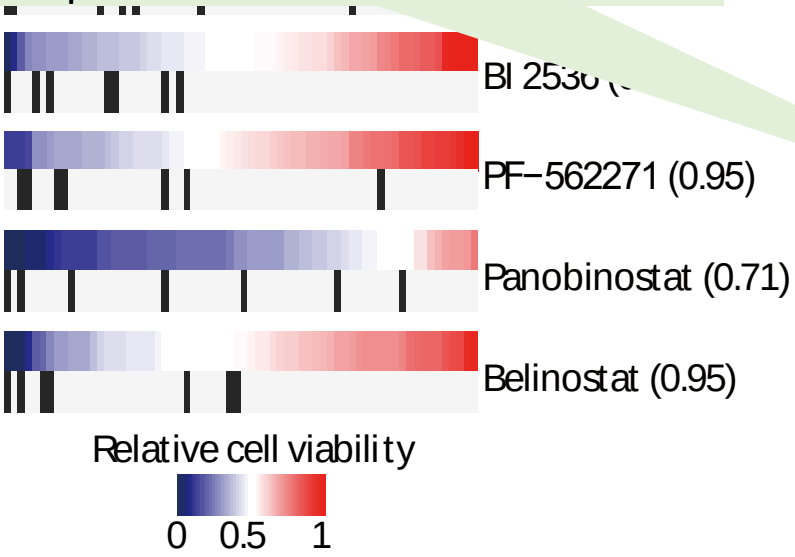
CTNNB1 activating mutations and drug sensitivities

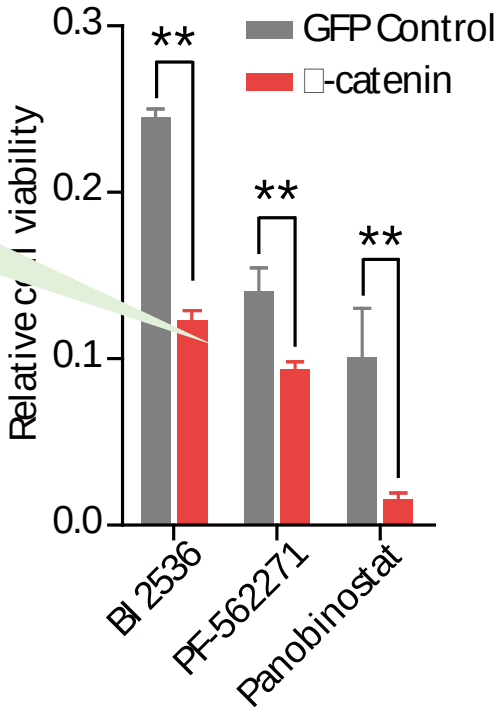




CT ons and drug sensitivities

In the susceptibility test to the LIMORE cell line, we found that the activating mutations in CTNNB1 are associated with three drug-sensitive enhancements, bi2536 (PLK inhibitor), PF562271 (FAK inhibitor), panobinostat (HDAC inhibitor) Here, the CTNNB1 gene encodes the protein β-catenin.





Sorafenib for Advanced Hepatocellular Carcinoma

- A multi-kinase inhibitor, c-Raf, b-Raf, VEGFR, PDGFR…
- The only approved drug for advanced HCC.
- Patients' response is low.

How to improve sorafenib response?

1. patient stratification
2. combination therapy

	Sorafenib group (n=150)	Placebo group (n=76)
Complete response	0 (0)	0 (0)
Partial response	5 (3·3)	1 (1·3)
Stable disease	81 (54·0)	21 (27·6)
Progressive disease	46 (30·7)	41 (54·0)
Not assessable	18 (12·0)	13 (17·1)

NEJM, 2008, *Lancet Oncology*, 2009

Sorafenib for Advanced Hepato

- **A multi-kinase inhibitor, c-Raf, b-Raf, VE**
- **The only approved drug for advanced HC**
- **Patients' response is low.**

The efficacy of liver cancer patients for Sorafenib drug treatment is relatively poor. Patients' response is low. Even comparing with placebo is not much better.

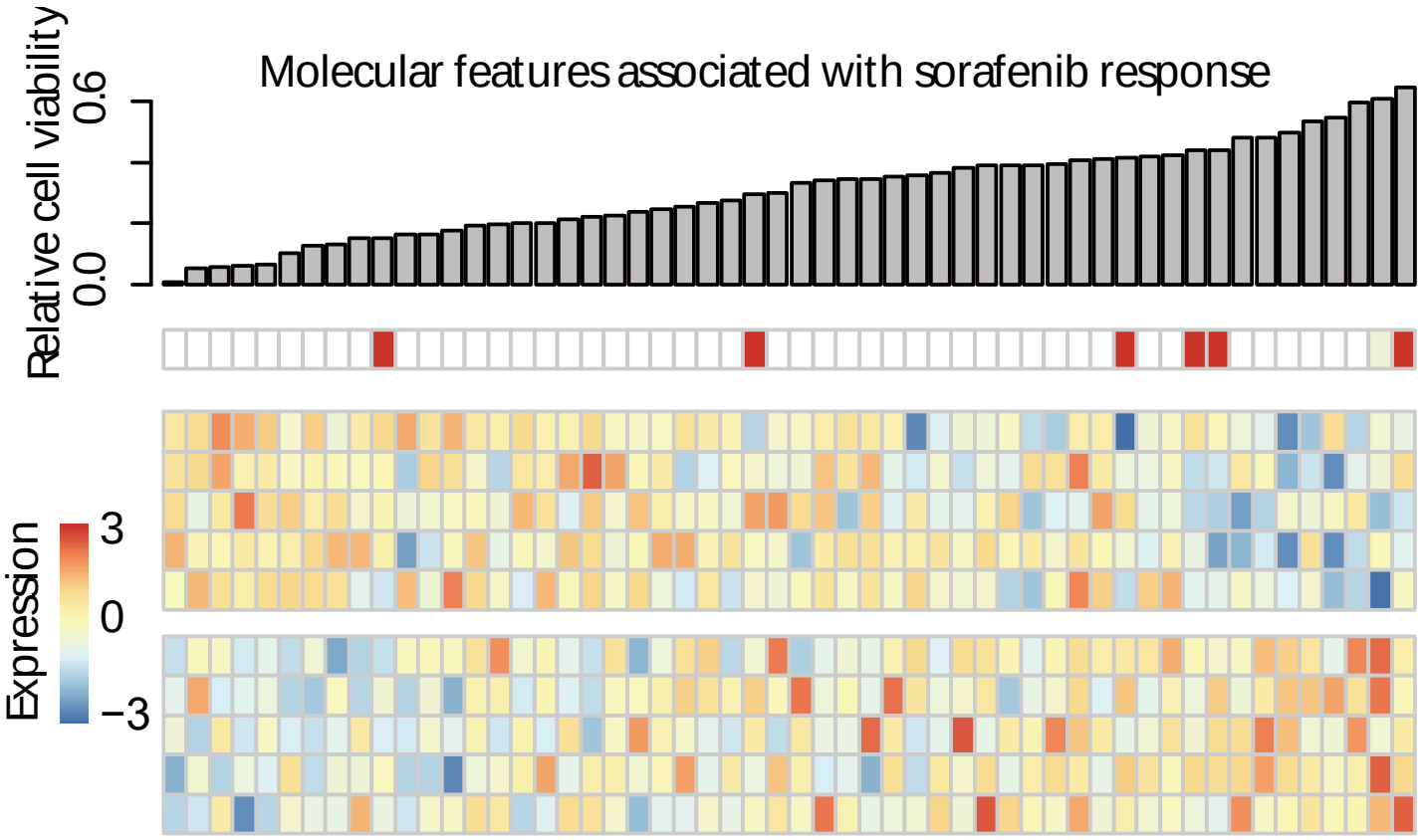
How to improve sorafenib respon

1. **patient stratification**
2. **combination therapy**

	Sorafenib group (n=150)	Placebo group (n=76)
Complete response	0 (0)	0 (0)
Partial response	5 (3·3)	1 (1·3)
Stable disease	81 (54·0)	21 (27·6)
Progressive disease	46 (30·7)	41 (54·0)
Not assessable	18 (12·0)	13 (17·1)

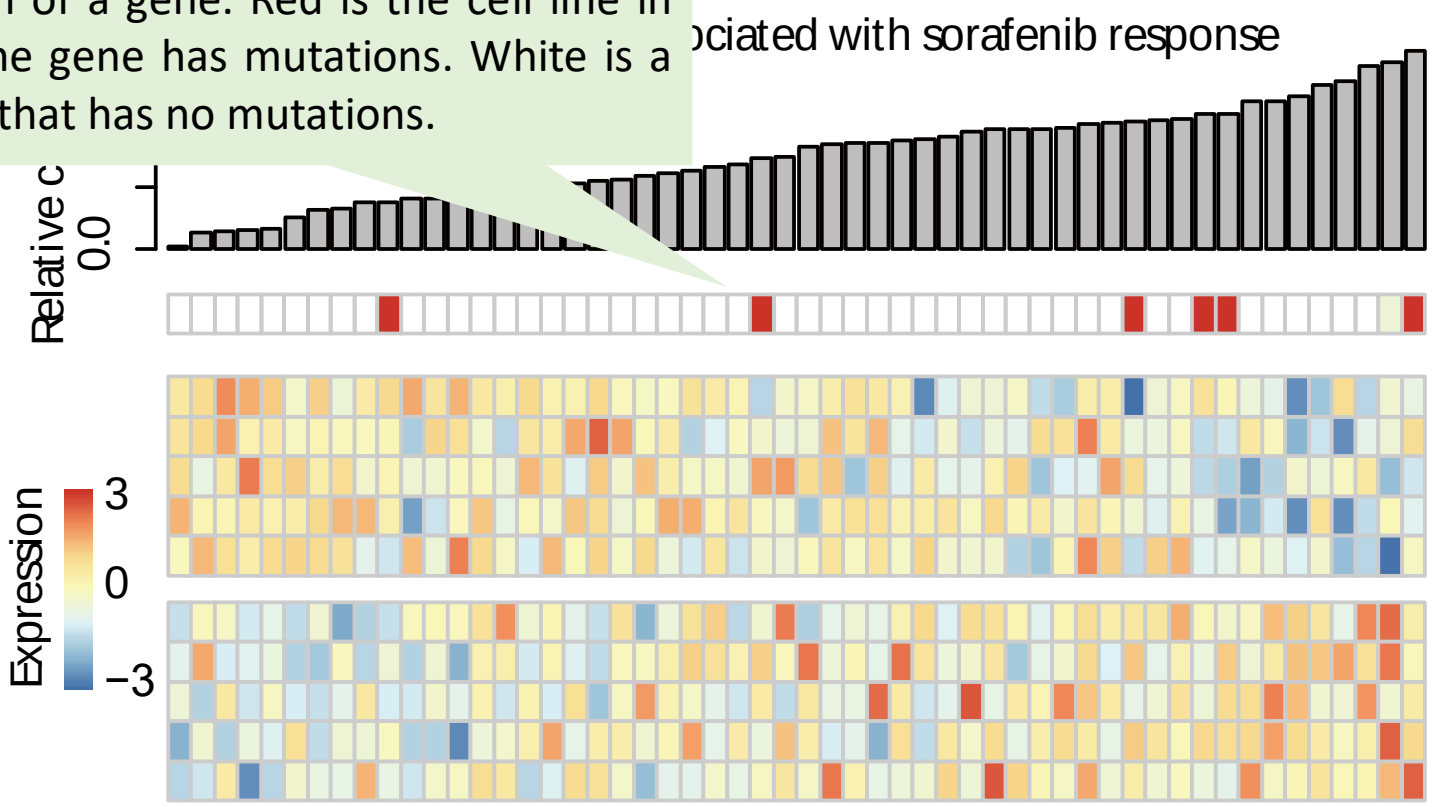
***NEJM*, 2008, *Lancet Oncology*, 2009**

Improving sorafenib efficacy: 1) patient stratification



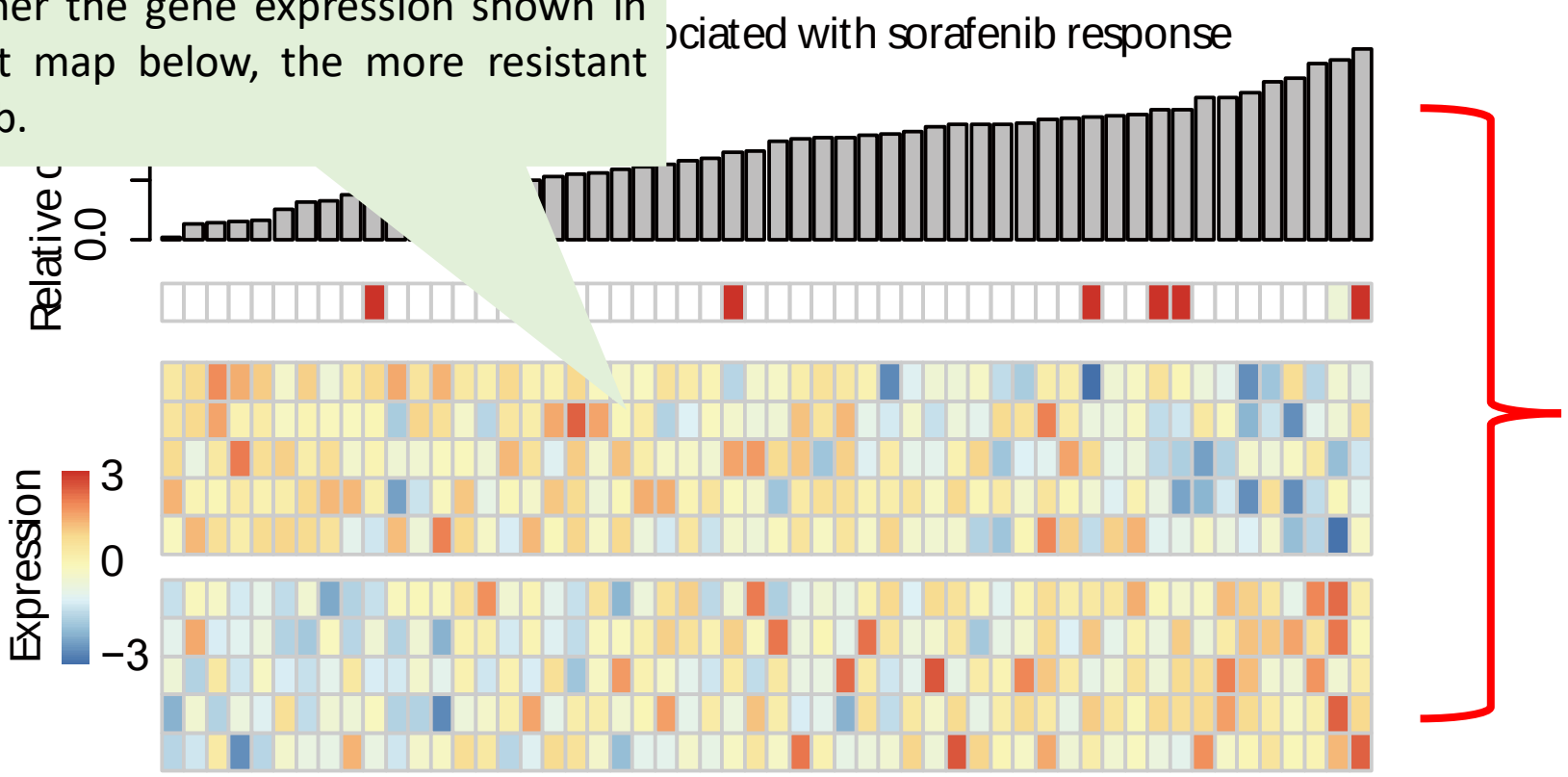
The vertical axis of this histogram reflects the sensitivity of the cell line to Sorafenib. The smaller the value, the more cells are killed and the more sensitive. Each column is a cell line. The bottom row shows the mutation of a gene. Red is the cell line in which the gene has mutations. White is a cell line that has no mutations.

cacy: 1) patient stratification



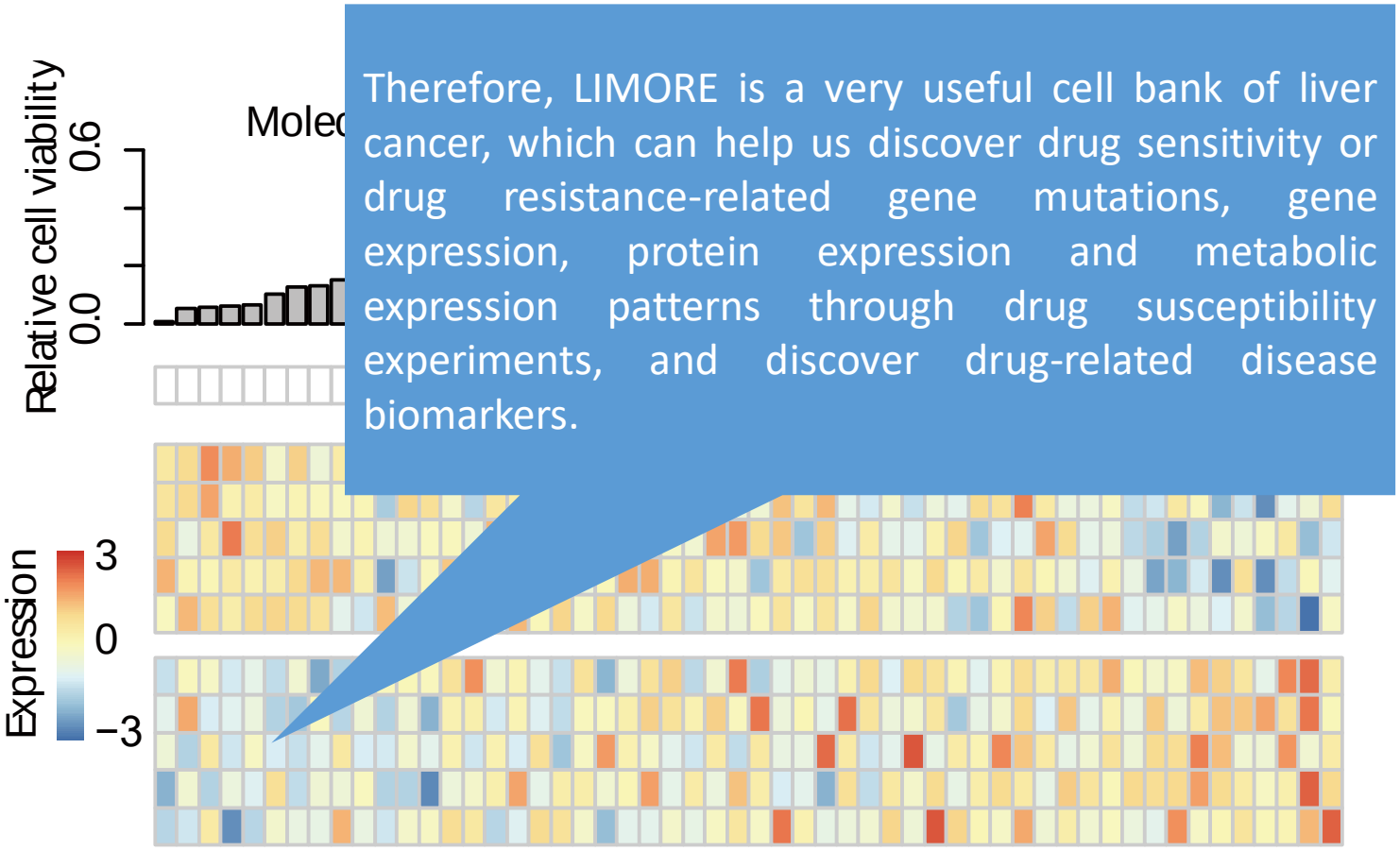
cacy: 1) patient stratification

These two heat maps show genes associated with sensitivity and resistance to Sorafenib. The higher the gene expression shown in the heat map above (red-yellow), the more sensitive Sorafenib. The higher the gene expression shown in the heat map below, the more resistant sorafenib.



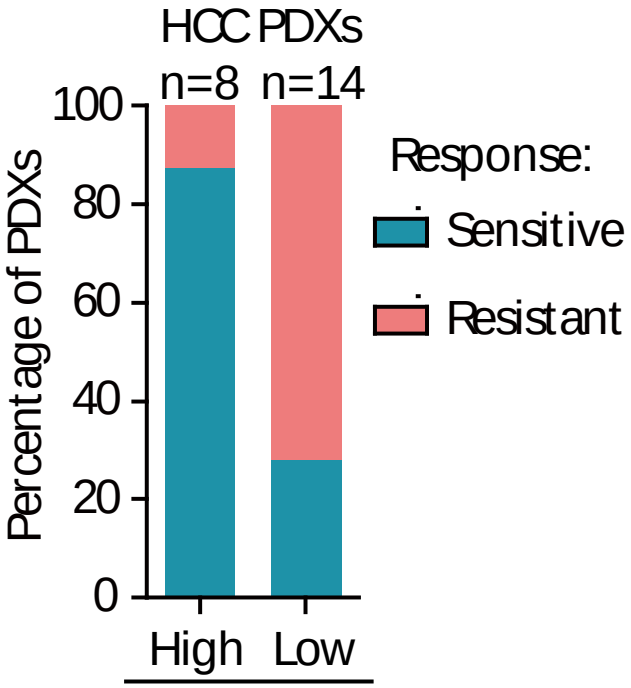
From these calculations, we found some genes related to the efficacy of Sorafenib. Among these genes, we chose a gene with high scores and secreted into the blood to study whether this gene can be used as an evaluation of Sorafenib. a pharmacological prognostic biomarker.

Improving sorafenib efficacy: 1) patient stratification

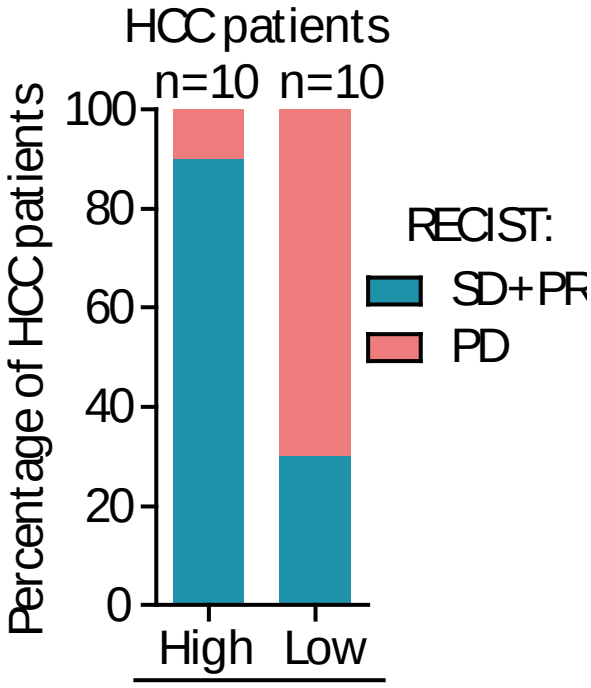


Improving sorafenib efficacy: 1) patient stratification

serum biomarker



TMM cutoff: 21.22
p=0.02 by Fisher's exact test



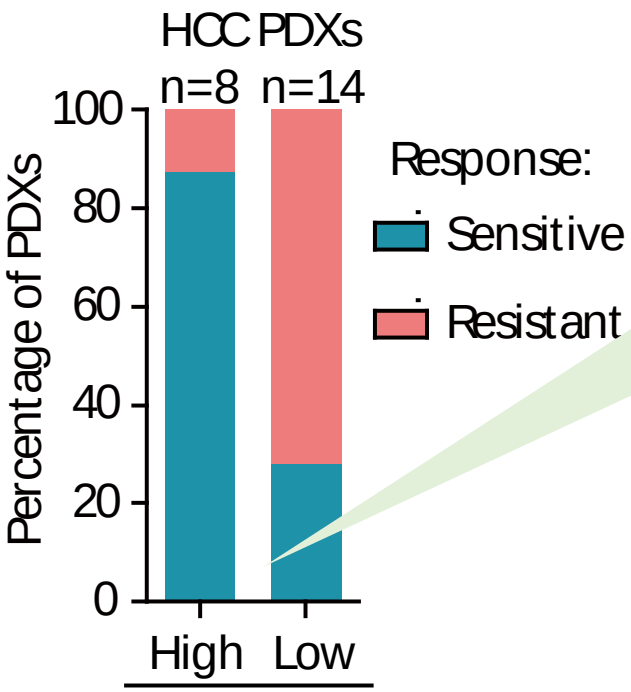
serum cutoff: 0.96 ng/mL
p=0.02 by Fisher's exact test

The last slide found some genes related to the efficacy of Sorafenib. Among these genes, we selected a gene with high scores and **secreted into the blood**, validated in PDX and patients, The results of the validation are consistent with the results in the cell line. So this gene can be used as a biomarker to evaluate the efficacy of Sorafenib.

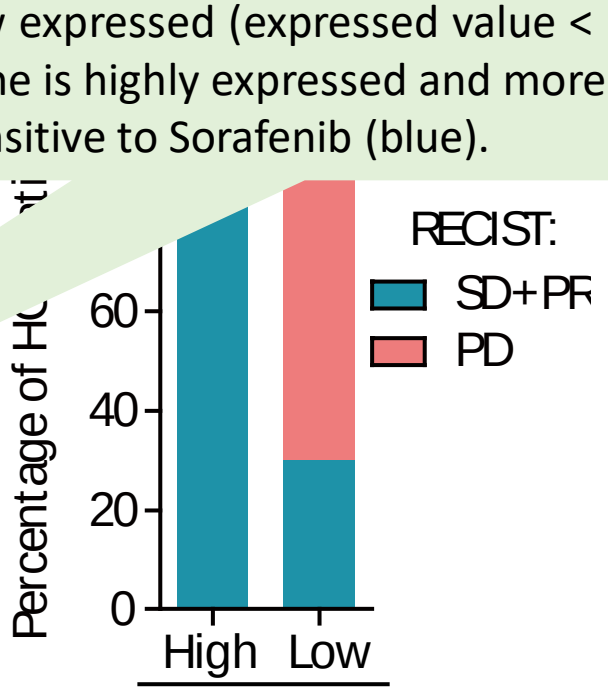
Improving sorafenib efficac

serum b

We observed the expression of the genes found in the patient's PDX model, and the results of the validation in the PDX model are as follows. Two columns indicate that the gene is high (expressed value > 21.22) and low expressed (expressed value < 21.22). The gene is highly expressed and more likely to be sensitive to Sorafenib (blue).



TMM cutoff: 21.22
p=0.02 by Fisher's exact test

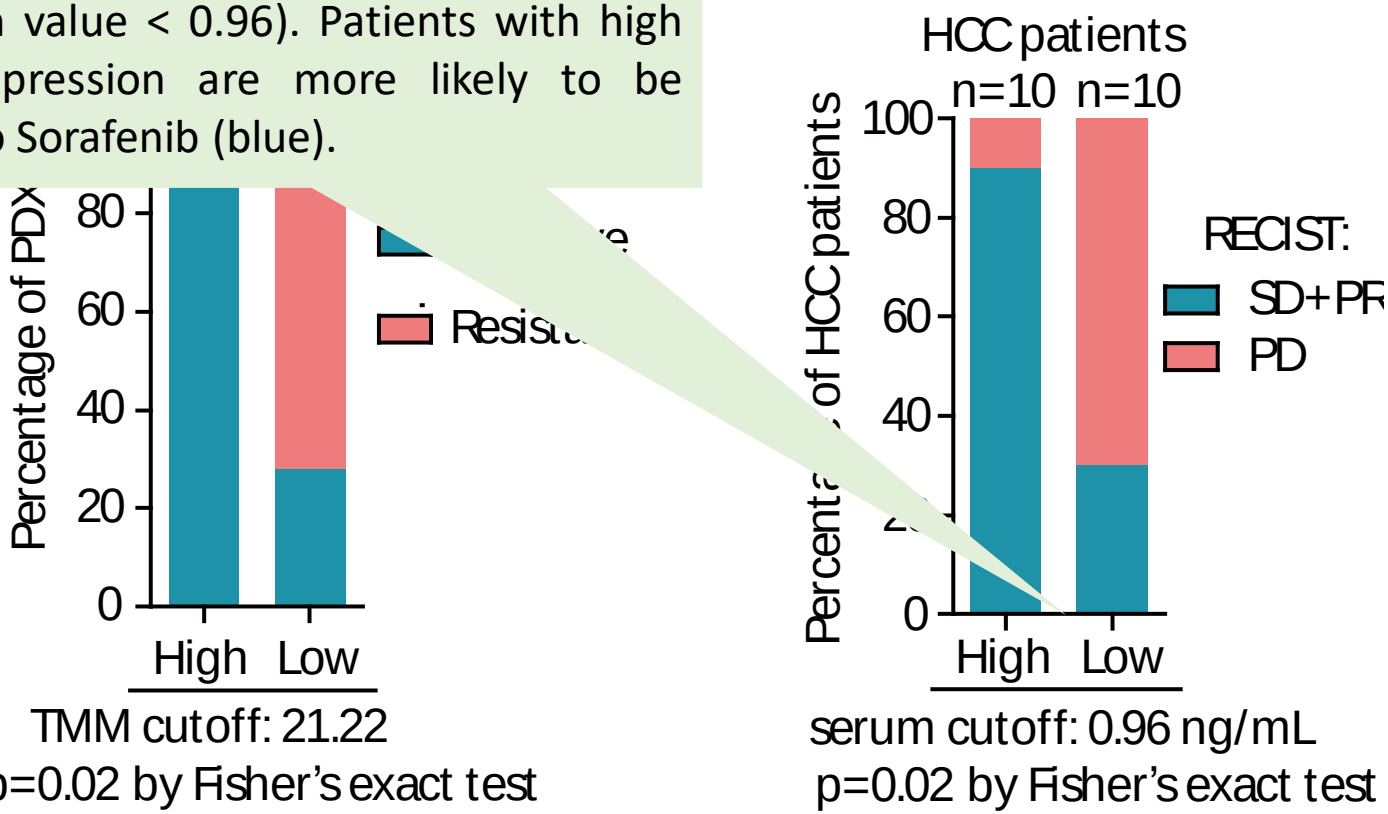


serum cutoff: 0.96 ng/mL
p=0.02 by Fisher's exact test

The protein expression of the genes we observed in the patients was verified here. Two columns indicate that the protein of the gene is highly expressed in the blood (protein expression value > 0.96) and low expression (expression value < 0.96). Patients with high protein expression are more likely to be sensitive to Sorafenib (blue).

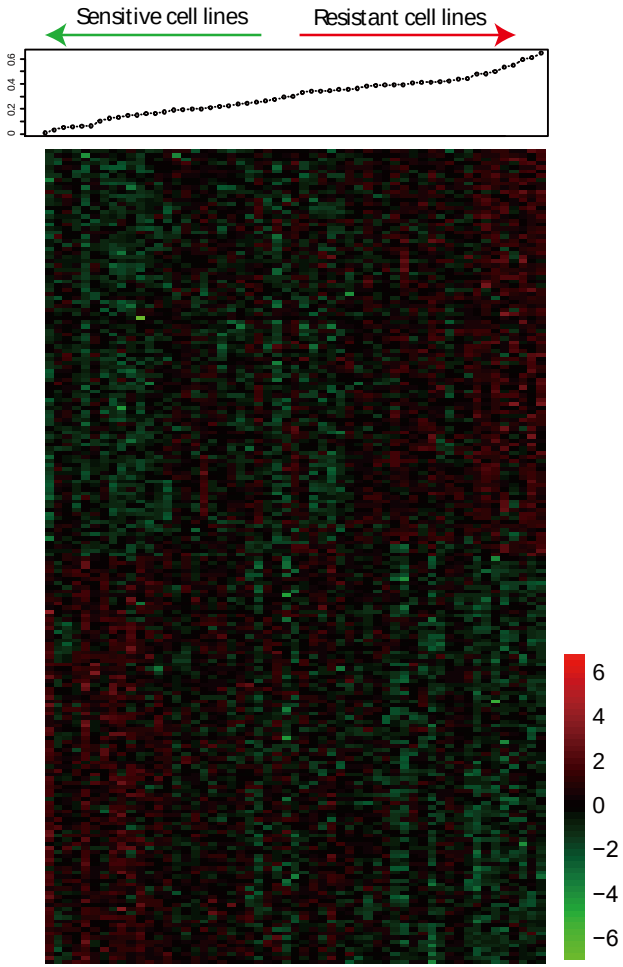
cy: 1) patient stratification

iomarker



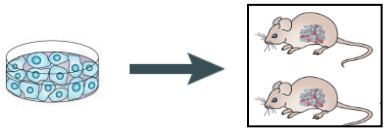
We successfully identified a secreted protein using the LIMORE system, which can be used as a biomarker for the accompanying diagnosis of anti-liver cancer treatment of Sorafenib and evaluates the therapeutic effect and prognosis.

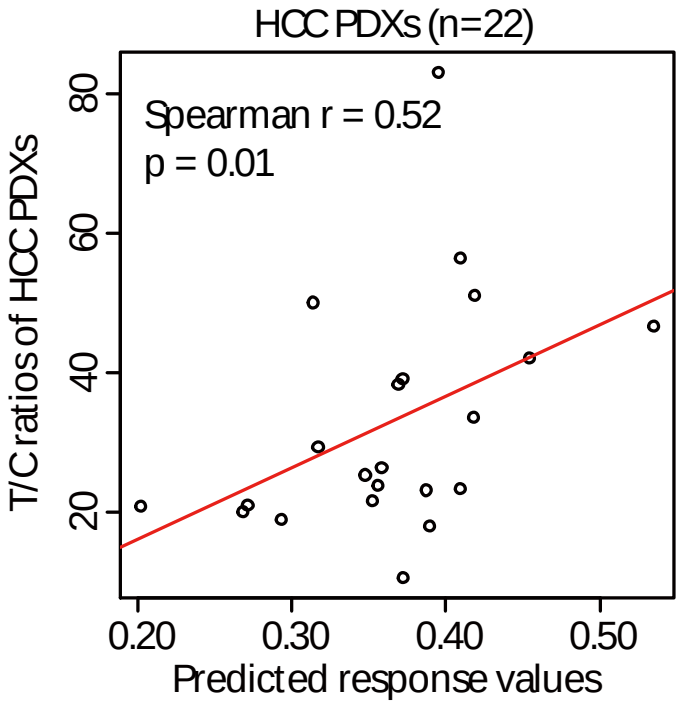
Improving sorafenib efficacy: 1) patient stratification



Heat maps of all genes associated with sorafenib susceptibility in 11 cell lines

Prediction model



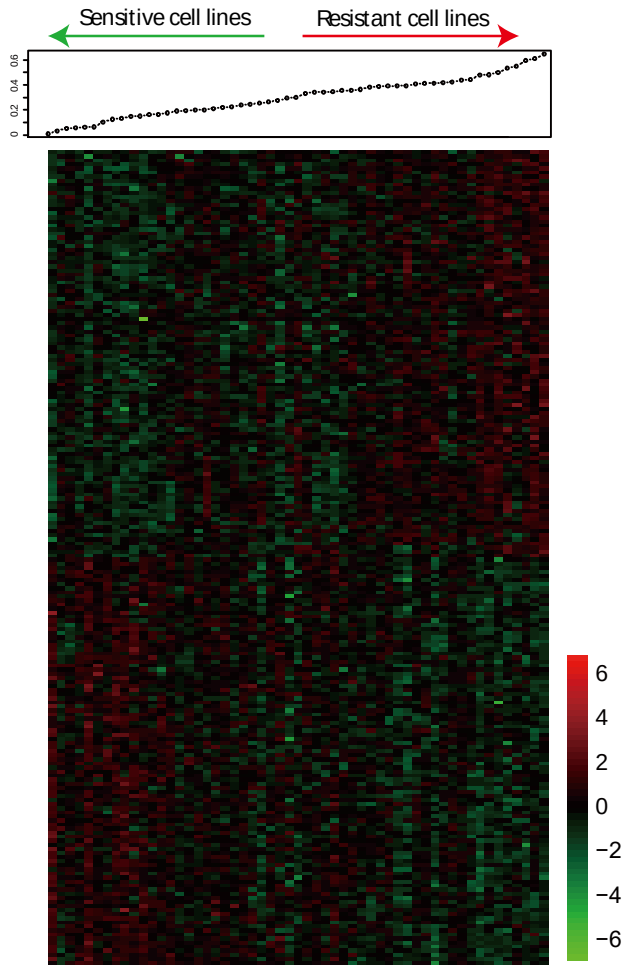


The figure shows the results of the prediction model on 22 PDXs. The horizontal axis is the predicted value and the vertical axis is the actual value of the experimental test. Both are very relevant

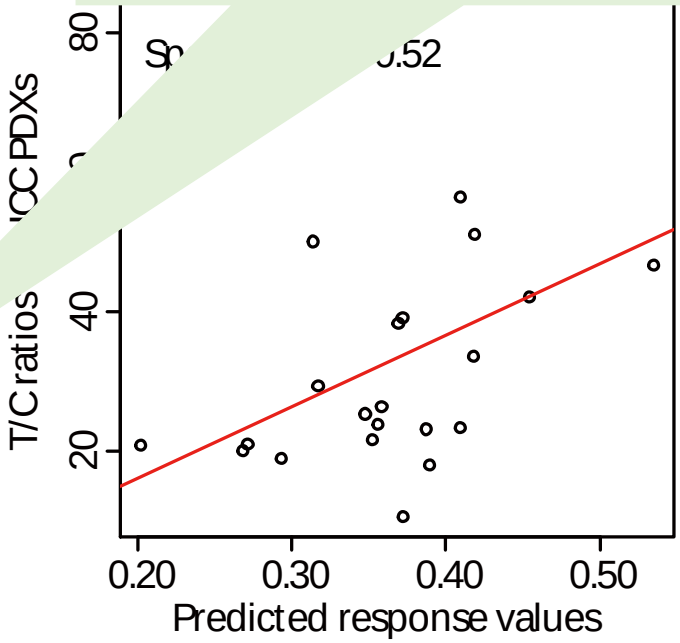
Improving sorafenib effica

Predict

Our analysis found many genes related to the sensitivity of Sorafenib, and one of them was selected and verified in the last slide. Based on these related genes, we used the Eletric Net Regression algorithm to establish a predictive model, and then evaluated whether the model could predict the efficacy of Sorafenib well on 11 independent cell lines and 22 PDX.

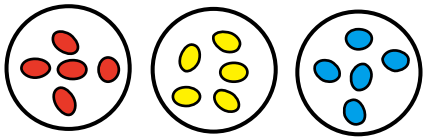


Heat maps of all genes associated with sorafenib susceptibility in 11 cell lines



The figure shows the results of the prediction model on 22 PDXs. The horizontal axis is the predicted value and the vertical axis is the actual value of the experimental test. Both are very relevant

Improving Sorafenib efficacy: 2) combination therapy



Drug A: Sorafenib
Drug B: 55 different drugs

72h treatment

Cell viability (CV)
by CellTiter Glo assay

Coefficient of drug interaction
in a cell line, CDI

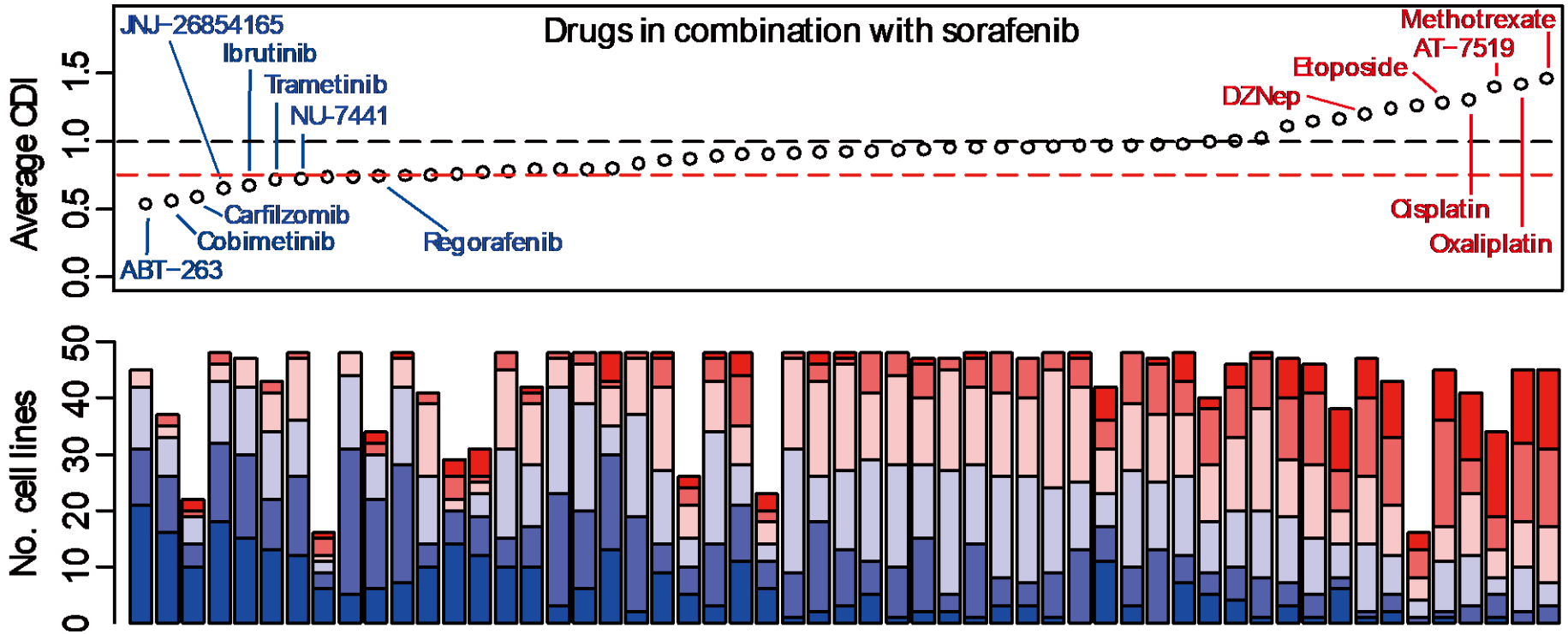
$$CDI = \frac{CV_{AB}}{CV_A \cdot CV_B}$$

Now we can also study CDI, a drug interactions with LIMORE Cell Bank.

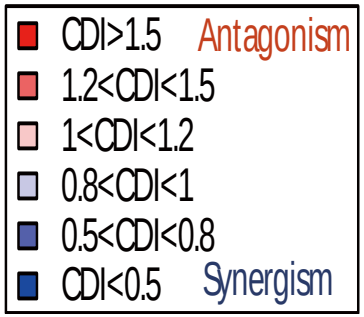
- CDI>1.5
- 1.2<CDI<1.5
- 1<CDI<1.2
- 0.8<CDI<1
- 0.5<CDI<0.8
- CDI<0.5

CDI: The efficacy of a combination of a drug and Sorafenib. The smaller this value, the more effective the combination.

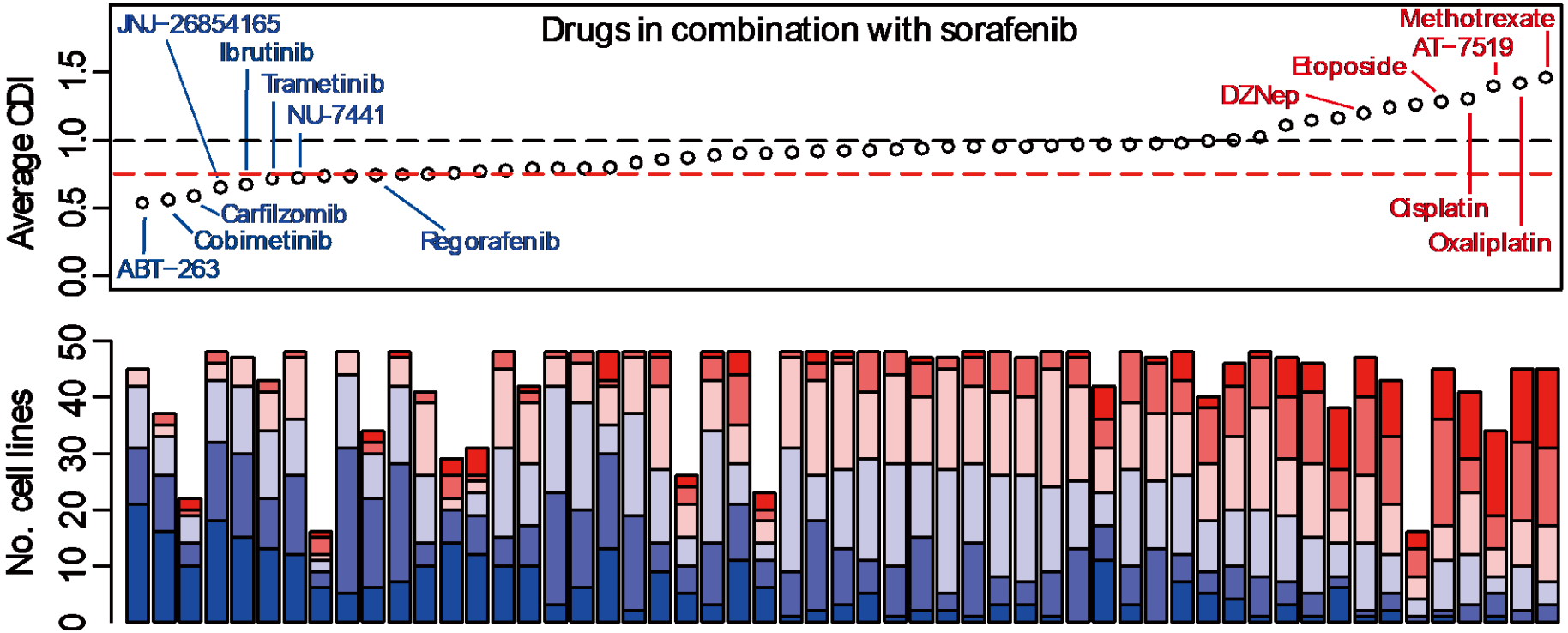
Improving sorafenib efficacy: 2) combination therapy



The last few slides were all about the efficacy of Sorafenib when used alone. This slide shows the efficacy of Sorafenib in combination with other drugs.

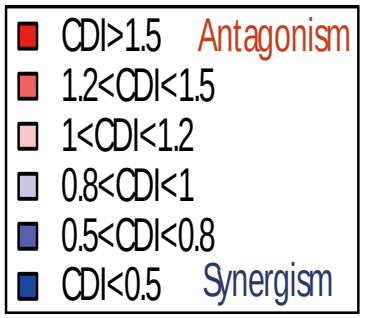


Improving sorafenib efficacy: 2) combination therapy



In the above graph, each point is a drug, and the vertical axis represents the average CDI of all the cell lines after the combination of the drugs and Sorafenib. Blue medicine is an effective example of several combinations. Red medicine is an poor example of several combinations.

In the figure below, each column is a drug. The color of the column indicates the CDI interval of this drug in combination with Sorafenib on the cell line. The more blue, the more effective the combination is in the cell line, the more red, the more invalid the combination.



Establishment of Liver Cancer Model Repository (LIMORE)

1, Establishment of cell line is of low efficiency

2, Cell lines gain additional mutations

3, Represent genetic heterogeneity and drug response

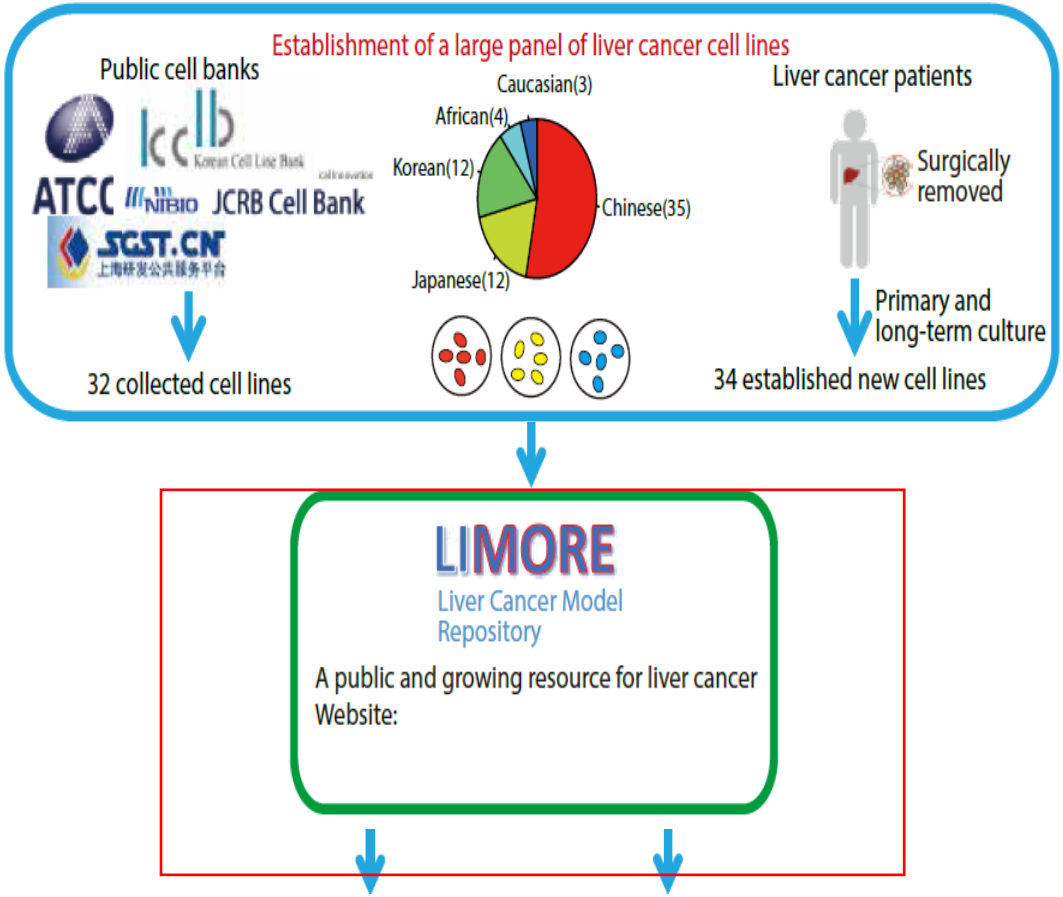
4, Database of LIMORE cell bank

LIMORE: Liver Cancer Model Repository

The world's largest liver cancer cell line, and an integrated database of "omics" and "drug action" data

Workflow

LIMORE: a preclinical platform for liver cancer by collecting available liver cancer cell lines and establishing new cell lines from primary liver cancers



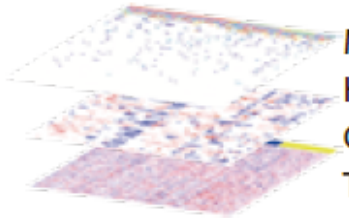
- 32 collected cell lines including the widely used Huh7, Hep3B and PLC/PRF/5.
- 34 established new cell lines from HCCs.

Workflow

Genetic characterization

LIMORE 66 cell lines Published patients: 500

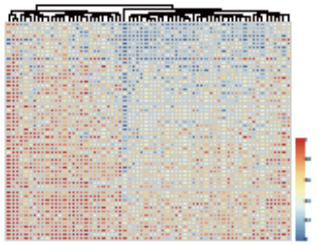
Comparison of heterogenetiy



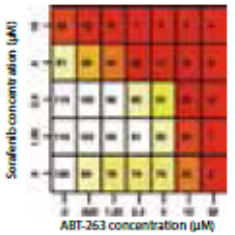
Mutations
HBV integratoin
CNA
Transcriptome

Highthroughput drug screen

100
single drug

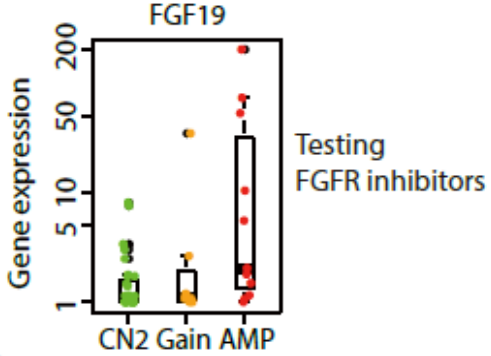


Sorafenib-based
drug combination



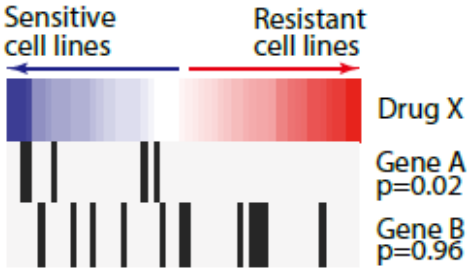
Pharmacogenomic analysis: 55 training, 11 validation

1. Target&drug validation

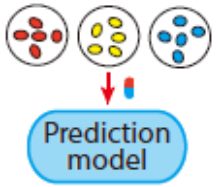


Testing
FGFR inhibitors

2. Biomarker identification



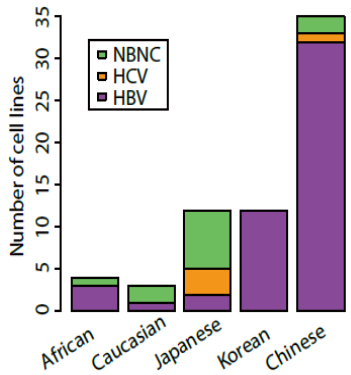
3. Patient stratification

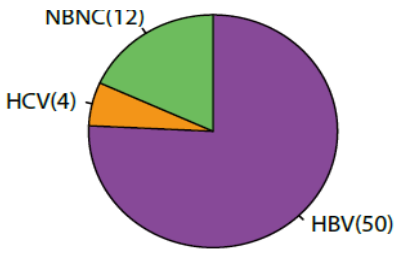


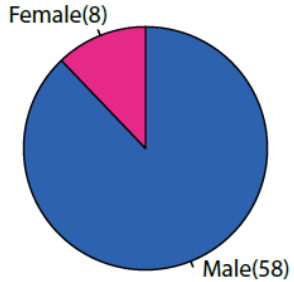
Data

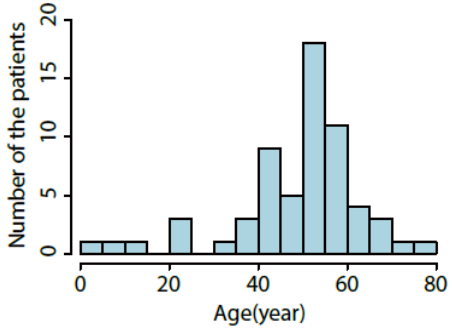
- number of cell lines: 66 (32 published and 34 established)
- data type: clinical data, whole genome sequencing (WGS), exome sequencing (WES) ,RNA sequencing (RNAseq) and drug response data

Pathological subtype	HCC	hepatoblastomas	hepatocellular adenoma
num of patients	63	2	1



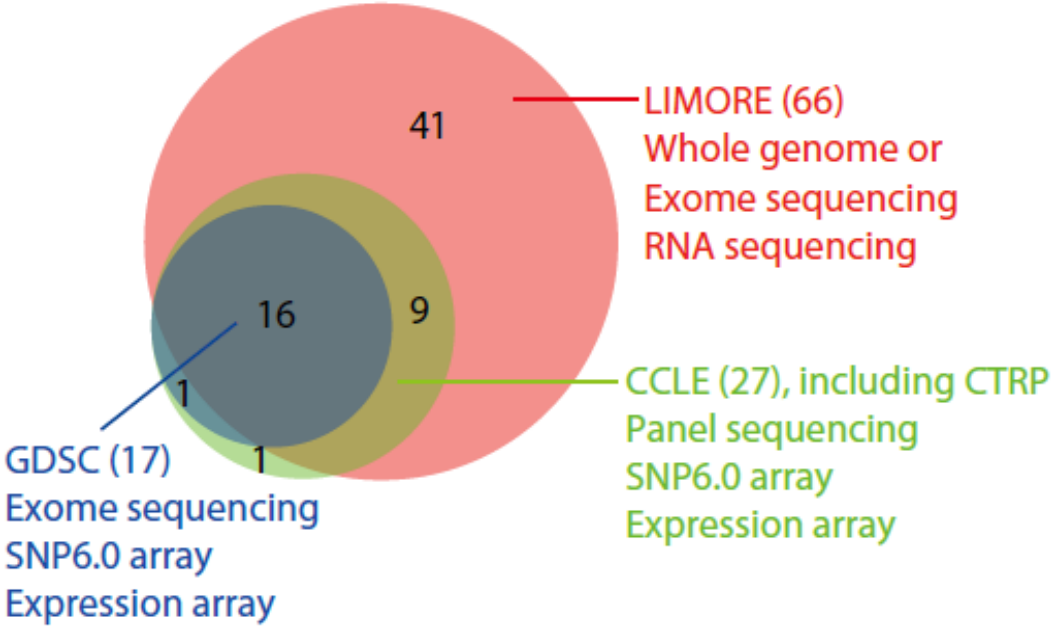






Data

- number of cell lines: 66 (32 published and 34 established)
- data type: clinical data, whole genome sequencing (WGS), exome sequencing (WES) ,RNA sequencing (RNAseq) and drug response data
- number of single drugs: 100



CCLE: "**Cancer Cell Line Encyclopedia**" maintained by Novartis

GDSC: "**The Genomics of Drug Sensitivity in Cancer**" Project is a collaboration between the Cancer Genome Project at the Wellcome anger Institute (UK) and the Center for Molecular Therapeutics, Massachusetts General Hospital Cancer Center (USA)

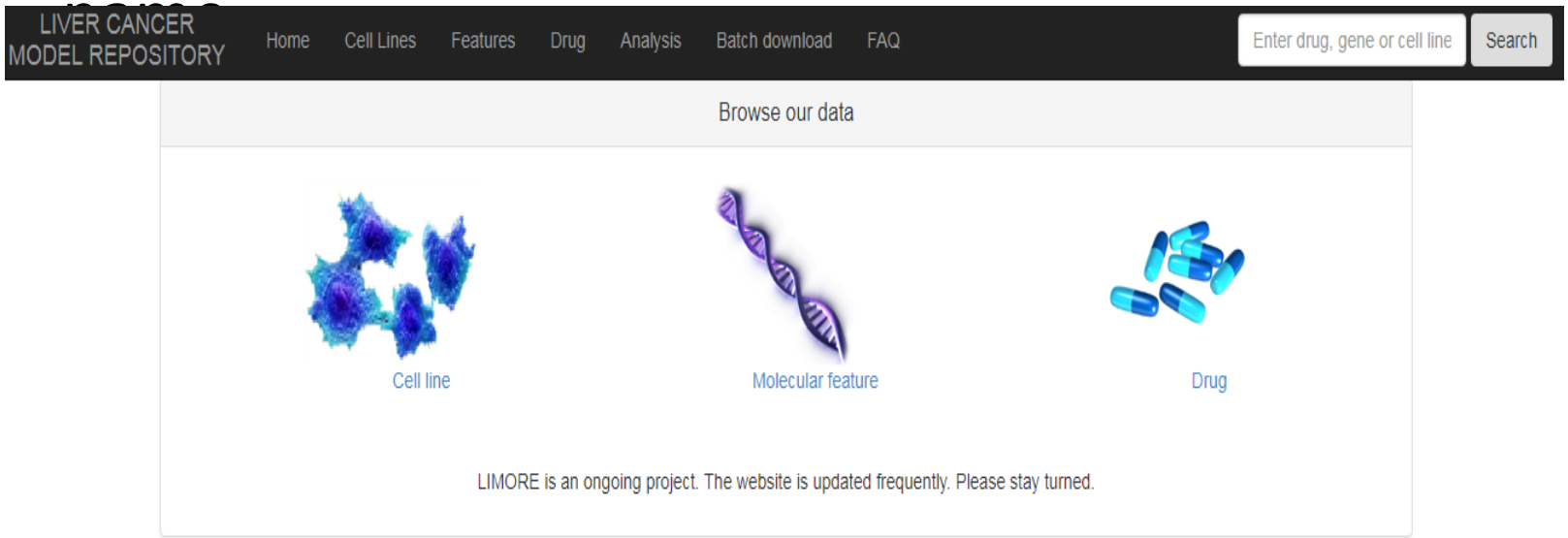
Implementation

- database: MySQL
- page: PHP+JQuery
- URL: www.picb.ac.cn/limore

Result

- Browse and result page

➢keyword: cell line, genomic features and drug



Result

- Browse and result page

➢keyword: cell line

Liver Cancer Cell Lines

Please query the registered cell line models and their related clinical, experimental and sequencing information.

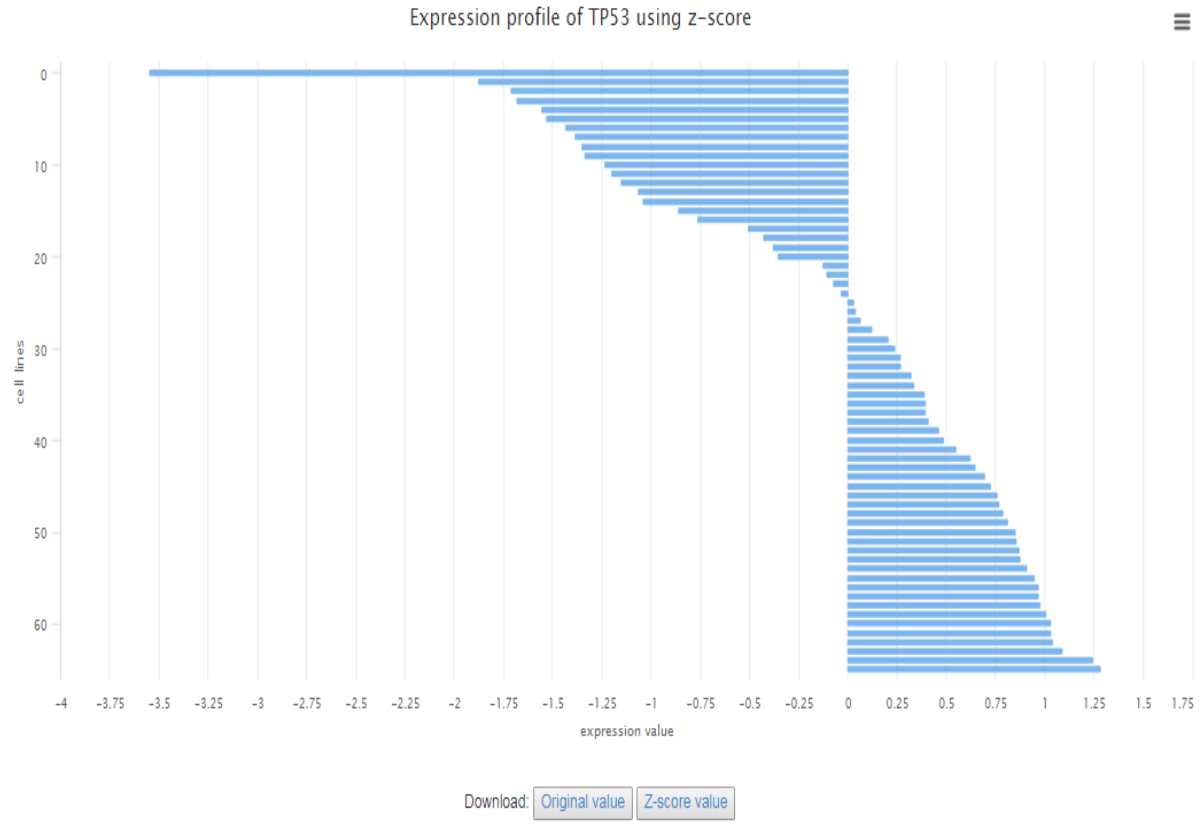
Show 10 entries Search:

Name	Ethnicity	Subtype	Virus	Mediums	DNA-Seq	RNA-Seq	Resource
CLC1	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New
CLC10	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New
CLC11	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New
CLC12	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New
CLC13	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New
CLC14	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New
CLC15	Chinese	HCC	HBV	ROCKi	WGS	RNA-Seq	New
CLC16	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New
CLC17	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New
CLC18	Chinese	HCC	HBV	primary medium	WGS	RNA-Seq	New

Result

- Browse and result page

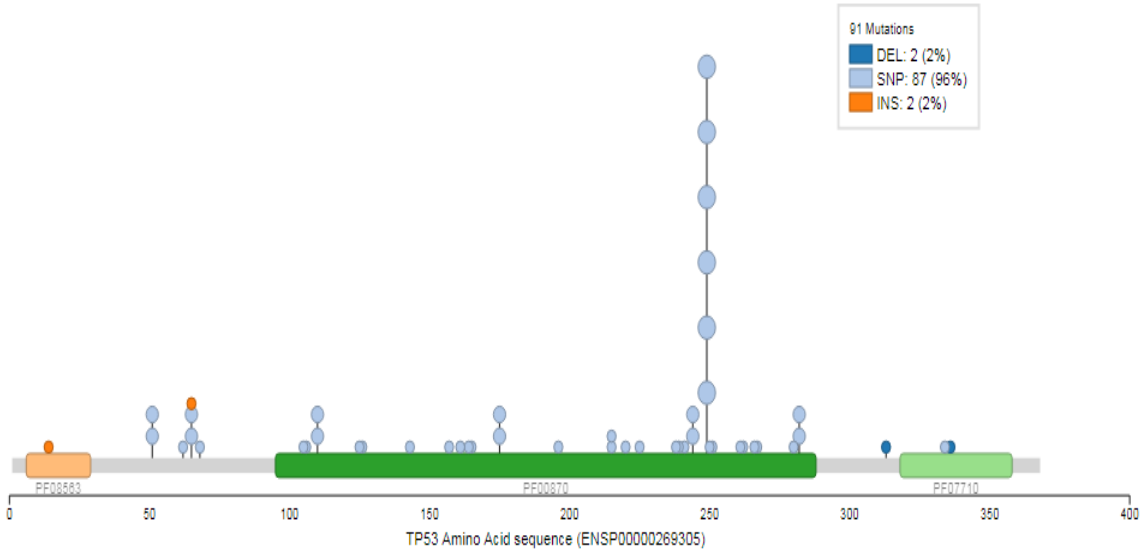
➢keyword: genomic features------expression



Result

- Browse and result page

➢keyword: genomic features------mutations



Result

- Browse and result page

➢keyword: genomic features------mutations

Show 10 entries Search:

Cell line ID	AA change	Classification	Type	Chr	Start pos	End pos	ref	Var	Strand
CLC1	p.V143M	Missense_Mutation	SNP	17	7578503	7578503	C	T	+	ENSP00000269305
CLC10	p.R196*	Nonsense_Mutation	SNP	17	7578263	7578263	G	A	+	ENSP00000269305
CLC11	p.C238F	Missense_Mutation	SNP	17	7577568	7577568	C	A	+	ENSP00000269305
CLC13	p.G105D	Missense_Mutation	SNP	17	7579373	7579373	C	T	+	ENSP00000269305
CLC14	p.R175H	Missense_Mutation	SNP	17	7578406	7578406	C	T	+	ENSP00000269305
CLC16	p.X261_splice	Splice_Site	SNP	17	7577157	7577157	T	A	+	ENSP00000269305
CLC17	p.E62*	Nonsense_Mutation	SNP	17	7579503	7579503	C	A	+	ENSP00000269305
CLC19	p.R282W	Missense_Mutation	SNP	17	7577094	7577094	G	A	+	ENSP00000269305
CLC2	p.G266E	Missense_Mutation	SNP	17	7577141	7577141	C	T	+	ENSP00000269305
CLC20	p.R282W	Missense_Mutation	SNP	17	7577094	7577094	G	A	+	ENSP00000269305

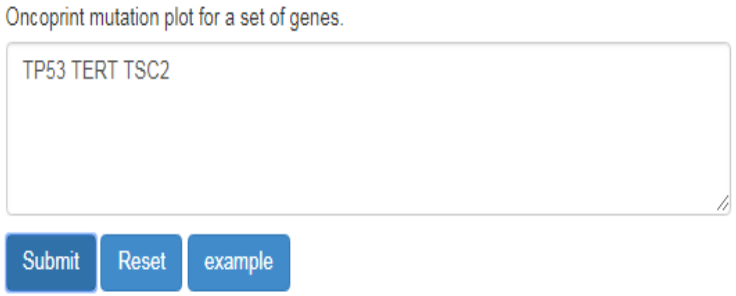
Download

Previous 1 2 3 4 5 Next

Result

- Browse and result page

➢keyword: genomic features------oncoprint



Result

- Browse and result page
  - ➢keyword: drug name

Show 10 entries Search:

Name	Alias	Targets	Category	Pathway	Clinical	Concentration	Company	Catalogue
17-AAG	Tanespimycin	HSP90	Protein Folding and Stability	Protein Folding	clinical development	10uM	Selleck	S1141
ABT-199	Venetoclax, GDC-0199	Bcl2	Apoptosis	Apoptosis	clinically used	10uM	Selleck	S8048
ABT-263	Navitoclax	Bcl2	Apoptosis	Apoptosis	clinical development	10uM	Selleck	S1001
Afatinib	BIBW2992	EGFR, HER2	Receptor/Upstream signal activation	EGFR signaling	clinically used	20uM	Selleck	S1011
Alisertib	MLN8237	Aurora A	Cell cycle	Mitosis	clinical development	10uM	Selleck	S1133
Apatinib	YN968D1	VEGFR	Receptor/Upstream signal activation	RTK signaling	clinically used	10uM	Selleck	S2221
AT-406	SM-406, ARRY-334543	IAP	Apoptosis	Apoptosis	clinical development	10uM	Selleck	S2754
AT-7519		CDK	Cell cycle	Cell cycle	clinical development	10uM	Selleck	S1524
Axitinib		VEGFR, PDGFR, c-Kit	Receptor/Upstream signal activation	RTK signaling	clinically used	10uM	Selleck	S1005
AZD6244	Selumetinib	MEK	Intracellular signaling pathway	MAPK signaling	clinical development	10uM	Selleck	S1008

Showing 1 to 10 of 99 entries Previous 1 2 3 4 5 ... 10 Next

Result

- Batch download page

Resource: this page allows access to all of LIMORE data for batch download.

Download link	Details
Clinical information of 66 liver cancer cell lines	The epidemiology information of patients from which LIMORE cell lines were derived from. Additional detailed information of our newly generated cell lines would be provided upon request.
Gene expression profiles of 66 cell lines	Gene expression profiles of 66 cell lines from RNA-Seq data.
Key somatic coding mutations of 66 cell lines	Somatic coding mutations in key cancer genes from 66 cell lines' WGS/WES data. All the somatic coding mutations can be obtained from the publication. All the somatic noncoding mutations would be added soon. All the germline mutations are under controlled access and would be available upon request.
HBV integration of 55 cell lines	HBV integration data of 55 cell lines from WGS data.
Copy number data of 55 cell lines	Copy number profiles of 55 cell lines from WGS data using GISTIC analysis.
Drug response data of 66 cell lines	This data contains all the screened drug responses in 66 cell lines. The value is the relative cell number after drug treatment (at the indicated dose) normalized to DMSO control.
More data	To be added: annotation of noncoding mutations.

Summary

- Over the past few years we have built the world's largest cell bank of liver cancer cell lines, ***Liver Cancer Model Repository (LIMORE)***
- **LIMORE *system is a completely new cell line system that comprehensively reflects the heterogeneity of liver cancer, and is a good and simple model system for studying liver cancer.***
- Established a corresponding "dry“ and "wet" combined database.
- Use LIMORE, we have screened out a number of potential disease biomarkers, which can be used as a biomarker for the evaluation of the efficacy and prognosis of anti-liver cancer drugs.
- We successfully used the LIMORE system to discover a disease biomarker that can be used as a companion diagnosis of Sorafenib's prognosis and efficacy.
- LIMORE Cell Bank is a very valuable and potential platform to help us conduct precision medicine research on liver cancer treatment.

Acknowledgement

SIBCB: Prof. Lijian Hui and lab members
CAS-MPG Partner Institute for Computational Biology, CAS
Hong Li
Chao Li
Keke Zou
Sheng He
Eastern Hepatobilliary Surgery Hospital
Haibin Zhang
Shanghai Medical College, Fudan Univ
Zhiqiang Meng
Liping Zhuang
Zhenfeng Zhu
Zhongshan Hospital, Fudan Univ
Yuan Ji
Xiaowu Huang
The First Affiliated Hospital, Nanjing Medical Univ
Jianjie Qin