

Kinase Vulnerabilities in Small Cell Lung Cancer

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Kinase Vulnerability in Lung Cancer

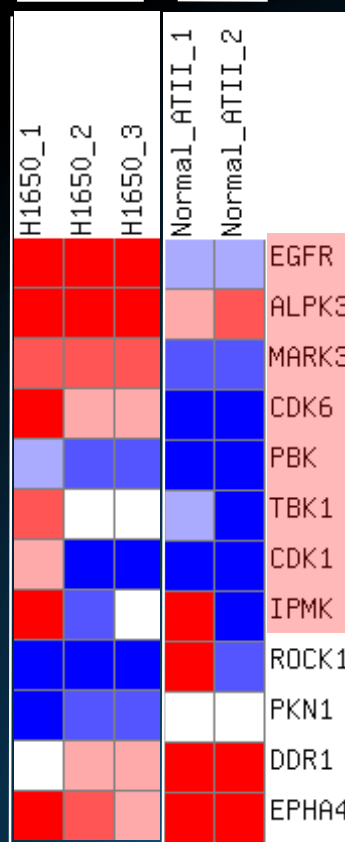
➤ NSCLC Platform

- Identify kinases that are essential for cell survival, and differentially expressed between transformed and non-transformed cells
 - Define expressed kinome in transformed cells (pulmonary adenocarcinoma and squamous cell carcinoma)
 - Define kinases essential for NSCLC cell survival
 - Define expressed kinome in non-transformed progenitor cells
 - Primary human Airway cells
 - Primary human ATII cells
 - Primary human Basal cells

Merging RNA Seq Kinase Expression with Functional Genomics Essential Kinase Screen

Kinome RNA-seq
Kinases Differentially Expressed
in H1650 compared to A711

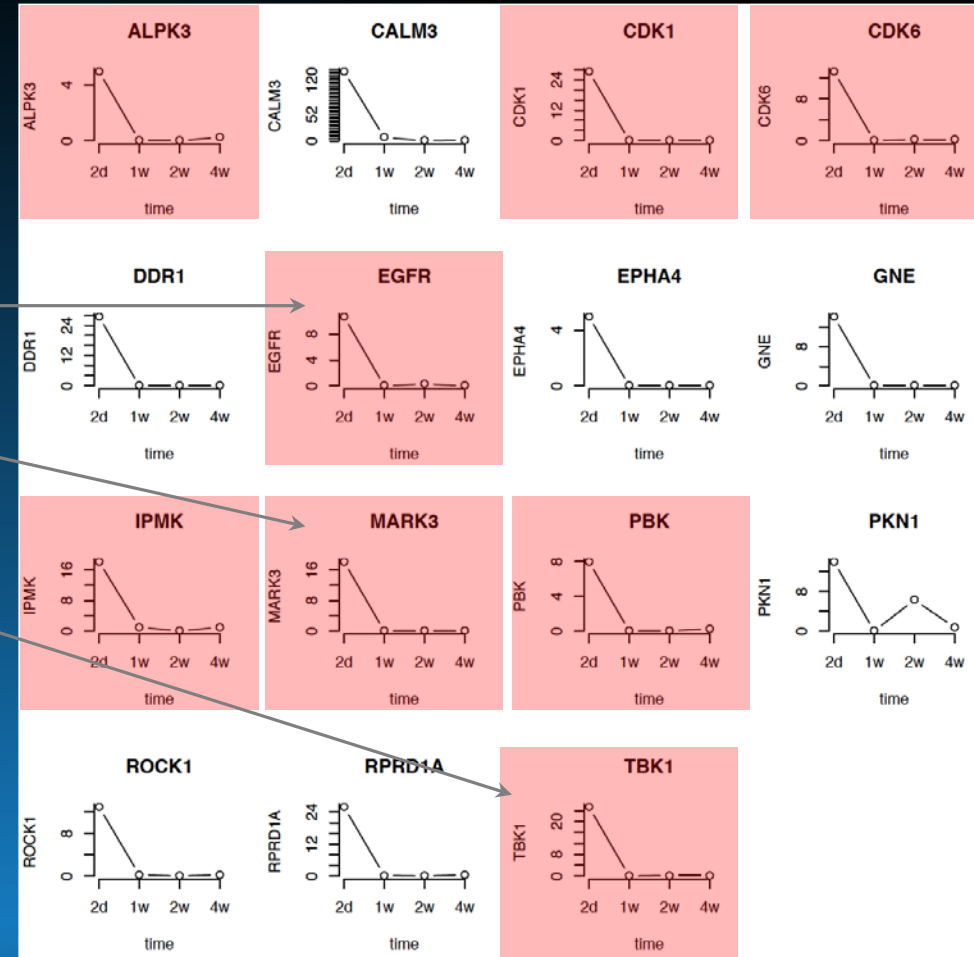
H1650 Alveolar Type II



Relative Gene Expression



Essential Kinase Screen
Fast Dropout



Kinase Vulnerabilities in SCLC

► Questions

- *Do essential kinases exist in SCLC?*
- *Does chemotherapy alter the essential kinase profile of chemoresistant SCLC vs chemosensitive/naïve SCLC?*
- *Will essential kinase profiling identify therapeutic targets for resistant and primary SCLC?*

► Goals

- In chemosensitive and chemoresistant SCLC
 - Identify kinases essential for cell survival
 - Identify alterations in the essential kinase profile induced by chemotherapy.
 - Inhibit essential kinases to determine role in SCLC survival



PDX Studied

➤ JHU-LX22

➤ JHU-LX33

➤ MSK-LX40

➤ JHU-LX48

➤ MSK-LX95

➤ JHU-LX108

➤ JHU-LX110

Charles Rudin, MD, PhD
Memorial Sloan Kettering Cancer Institute

Generation of Chemoresistant PDX

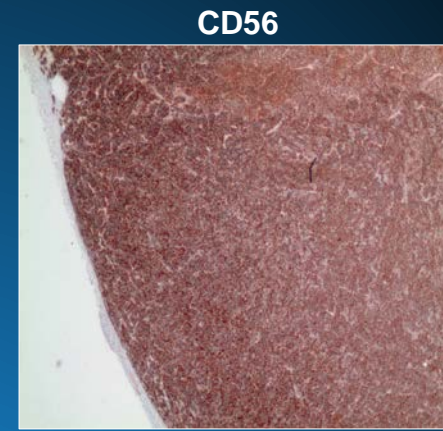
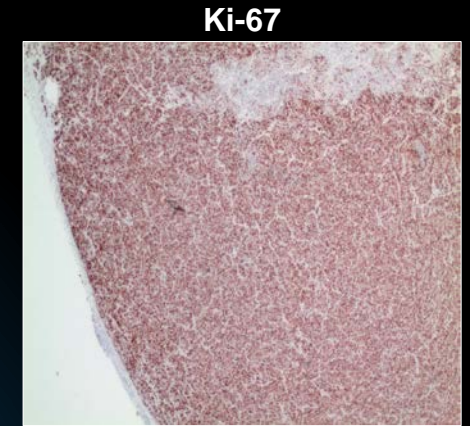
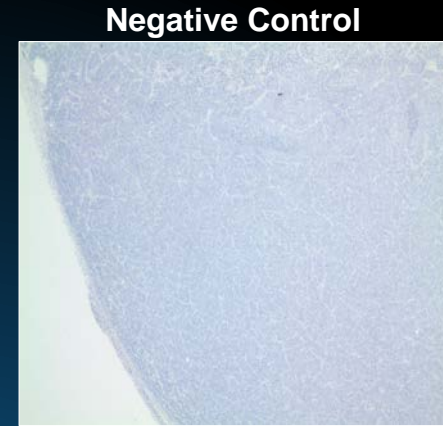
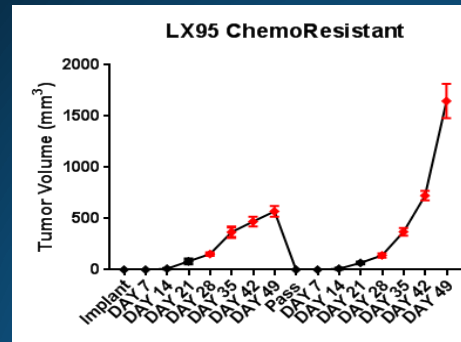
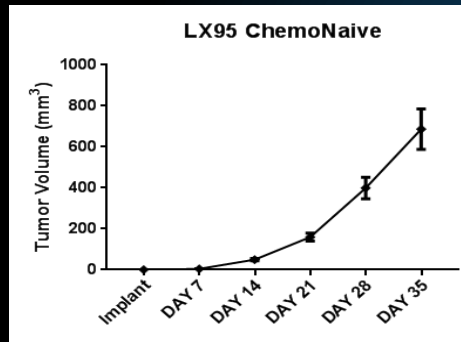
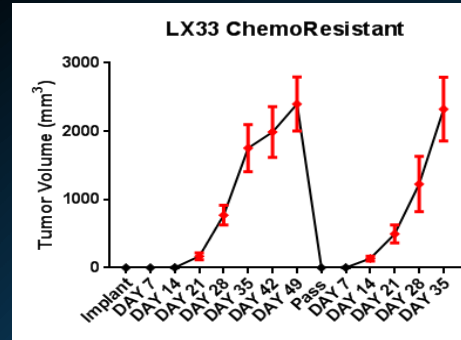
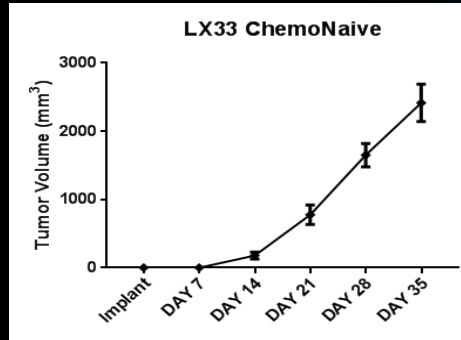


Chemo-naïve PDX

Weekly
Cisplatin (d1)
Etoposide (d1-3)

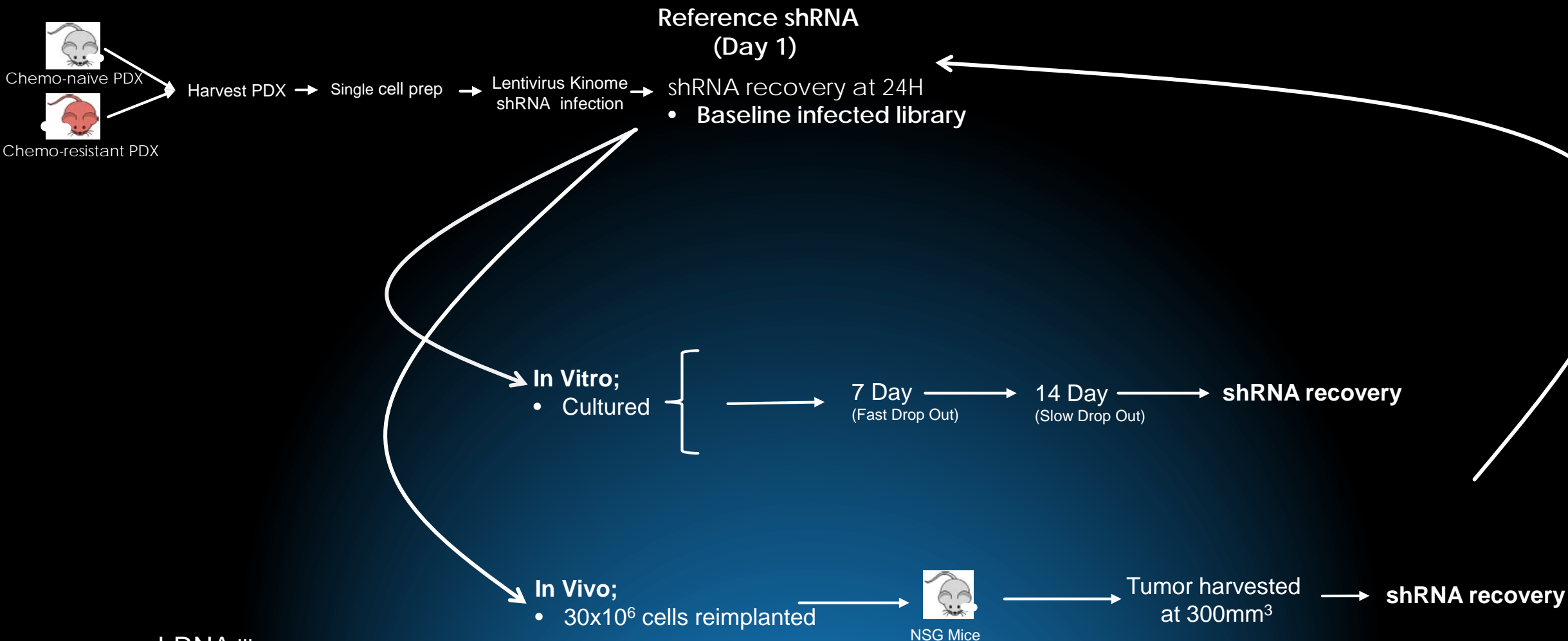


Chemo-resistant PDX



Red=Chemotherapy Given

Experimental Design

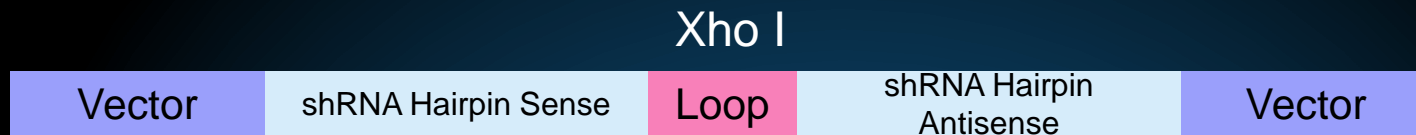
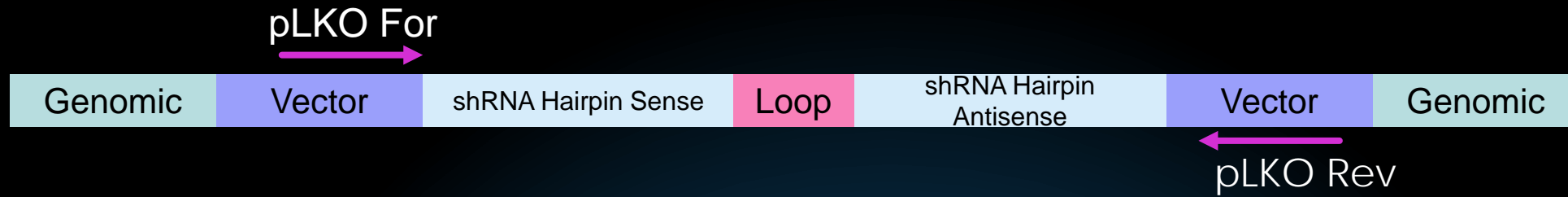


shRNA library:

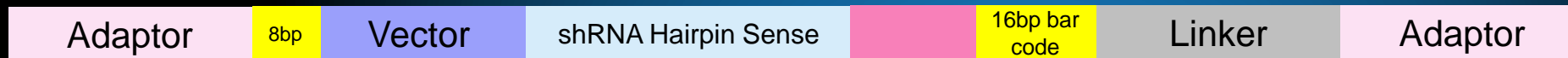
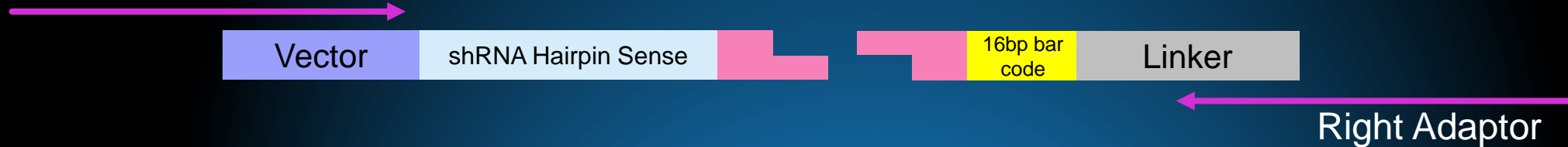
- 3,113 shRNAs targeting 670 kinases
(TRC1.5 lentivirus-based shRNA library, The RNAi Consortium, Broad Institute)
- 74 shRNAs targeting 30 murine genes (controls) STR Analysis

STR analysis at each step for comparison to original tumor

shRNA Library Generation



Left Adaptor + 8 bp bar code



Analysis Workflow

Tasks

Quality Control

Exclude unmapped/unannotated shRNAs

Align tags to library / RefSeq

Defined parameters for loss

Default:

$medA - maxB > 0$

Depleted in Treatment group

E-value < 2

Validation

Tools/Packages

Sequencing tags

Preprocessing

Mapping

Statistical Analysis

Post Analysis

Functional Analysis

Ranked list

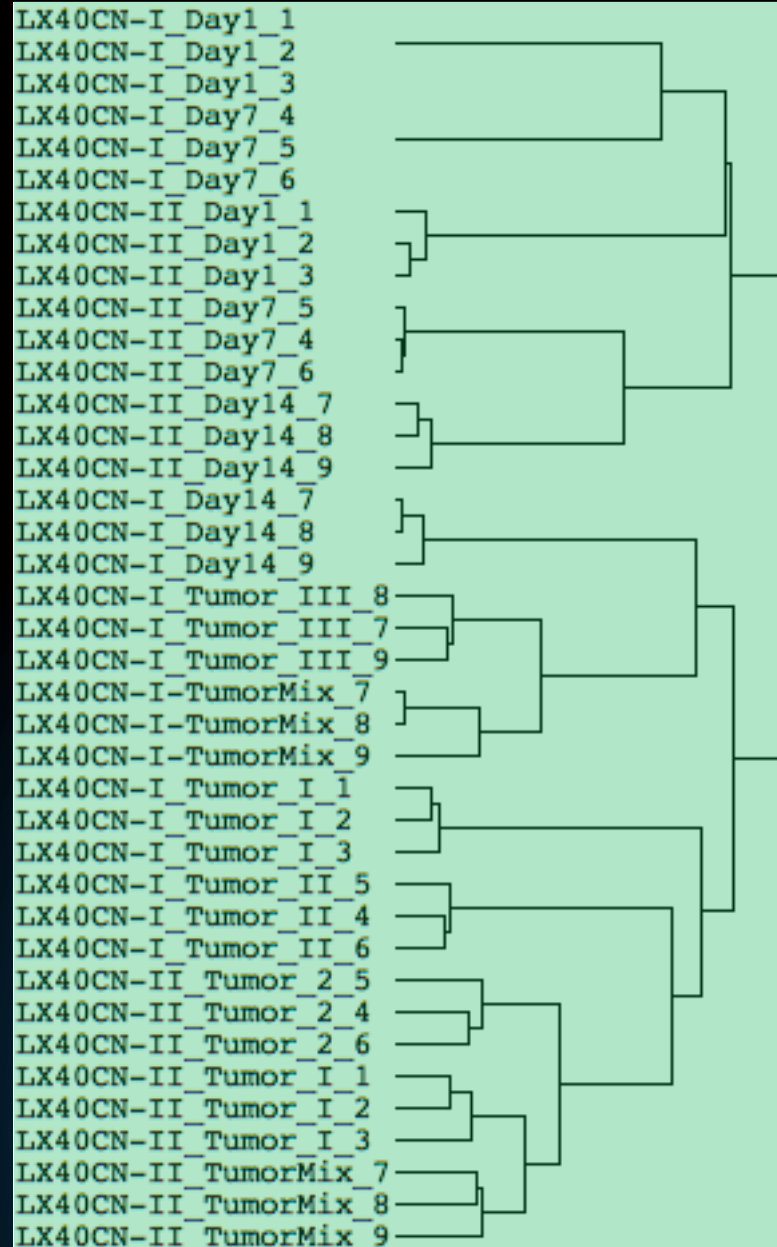
Bowtie (*Burrow-Wheeler Transform algorithm*)

edgeR (*Negative Binomial model*)

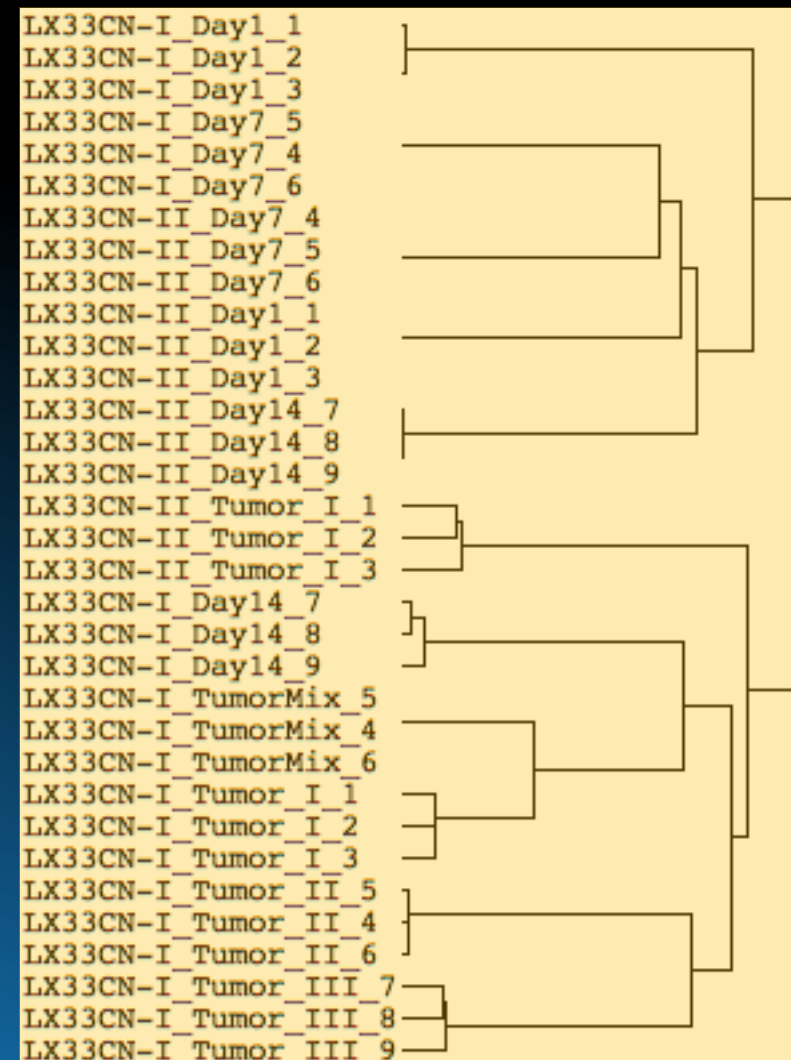
NIH DAVID (*hypergeometric test*)

dbs: [KEGG, BioCarta, GO]

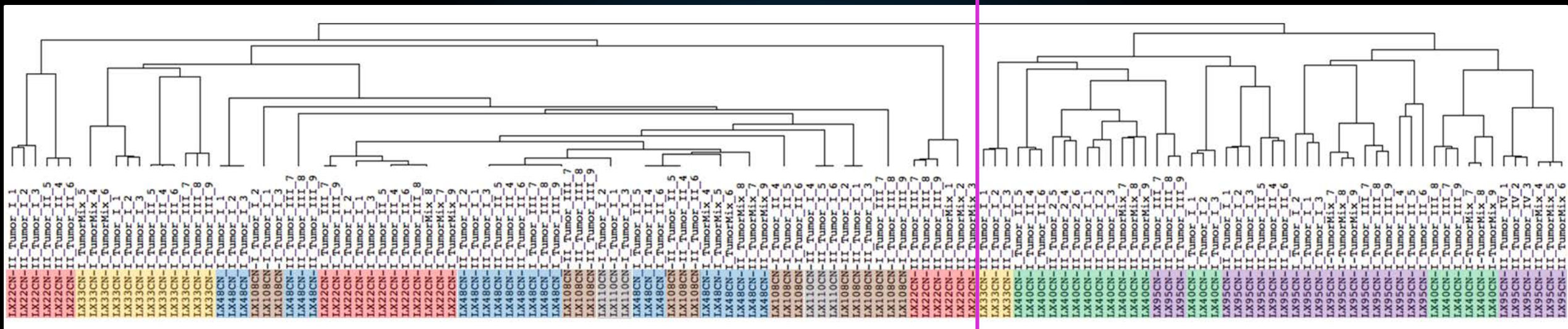
Clustering : MSK-LX40CN



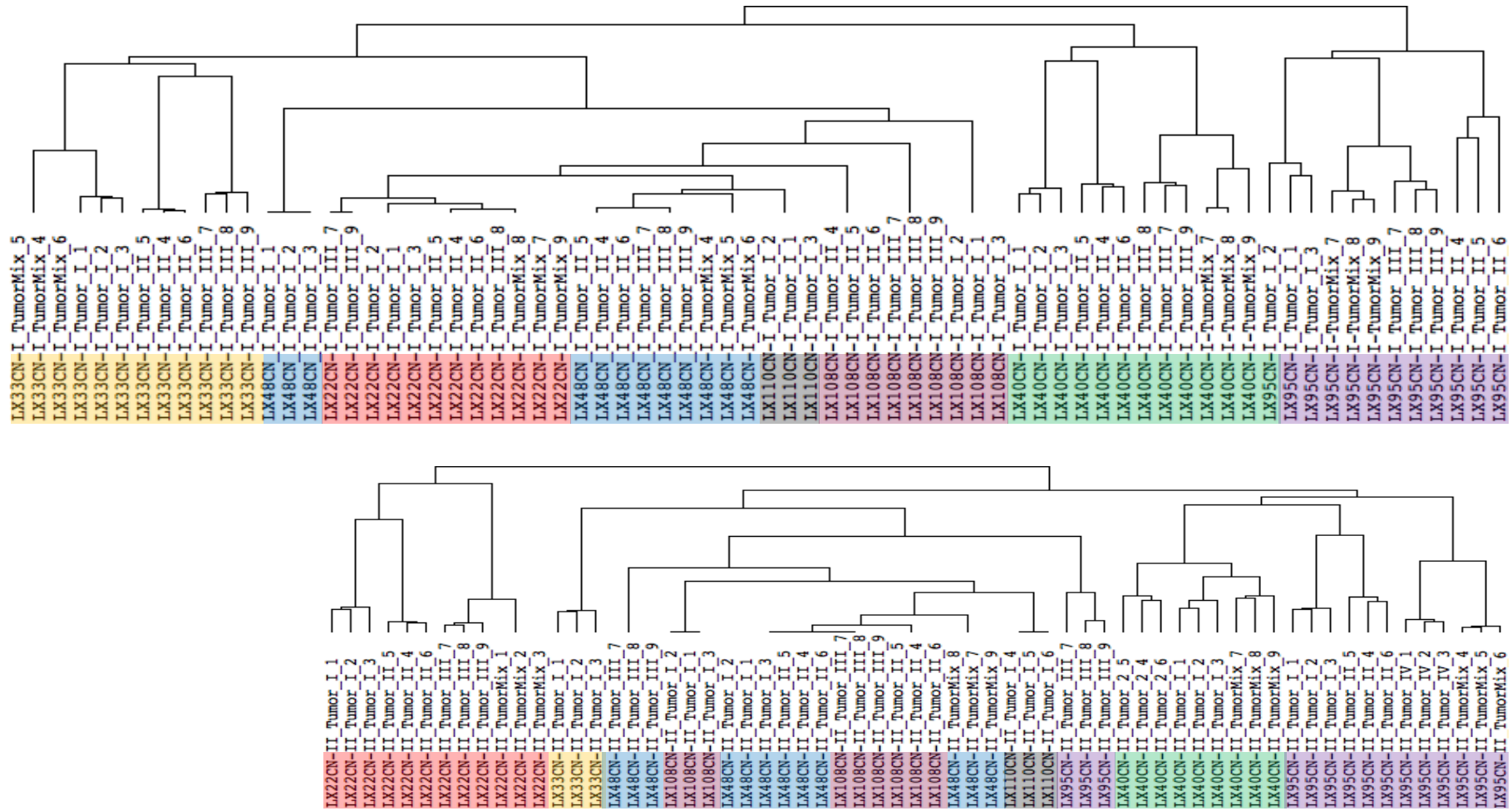
JHU-LX33CN



Clustering of Chemonaive SCLC PDX: *in Vivo*



Clustering of Chemonaive SCLC PDX: *in Vivo*



Next Steps

- ▶ Chemonaive PDX
 - ▶ Validate essential kinases – shRNA, chemical inhibition
 - ▶ Sequence for mutation
 - ▶ Filter data by *MYC* status

- ▶ Define normal kinome

- ▶ Chemoresistant PDX
 - ▶ Define essential kinases
 - ▶ Define changes in kinome in chemoresistant vs chemonaive SCLC
 - ▶ Validate and target essential kinases

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