CTD2: Functional Cancer Genomics

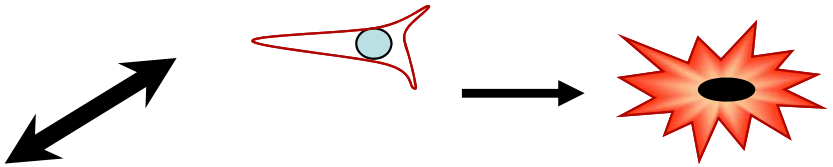
Characterization of cancer genomes is essential but not sufficient

- Hundreds to thousands of candidates in each tumor
- Distinguishing Driver vs. Passenger mutations
- Drivers: Tumor initiation or maintenance
- Context-specific actions of particular genetic elements

Prioritization must be based on <u>both</u> genomic <u>and</u> biological weight of evidence

Functional interrogation of cancer genomes

Gain-of-function: ORFs

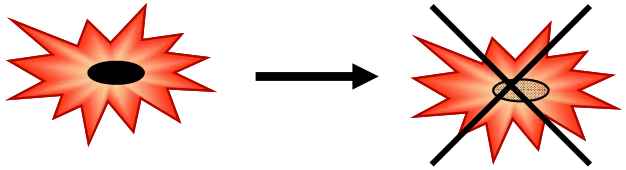


Connect genotype to function

Experimental cancer models

Cancer Genome Annotation

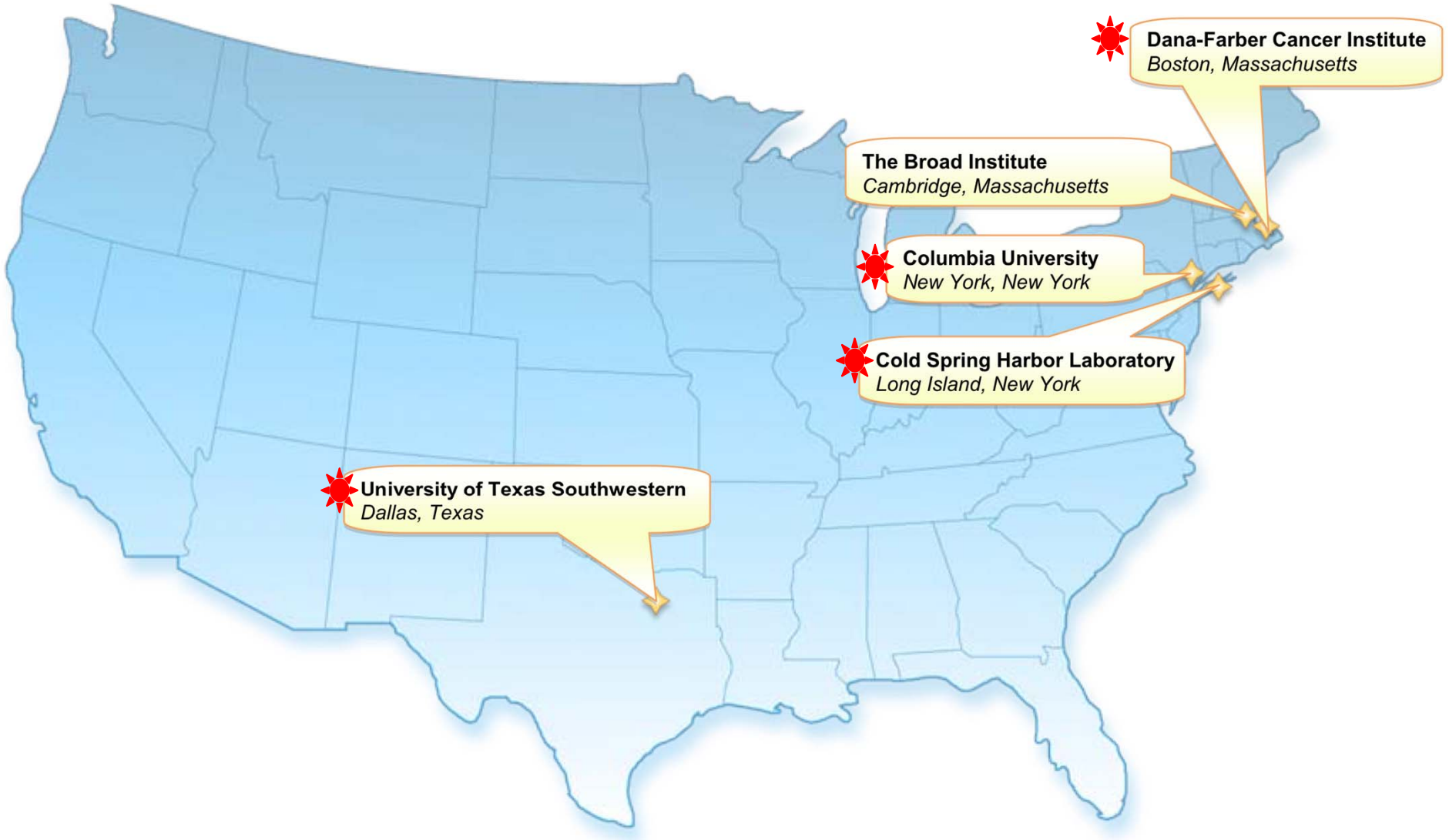
Loss-of-function: RNAi



Identify potential Achilles' Heels

Cancer Target Discovery and Development (CTD²) Network

OFFICE of CANCER GENOMICS



Integrated functional cancer genomics

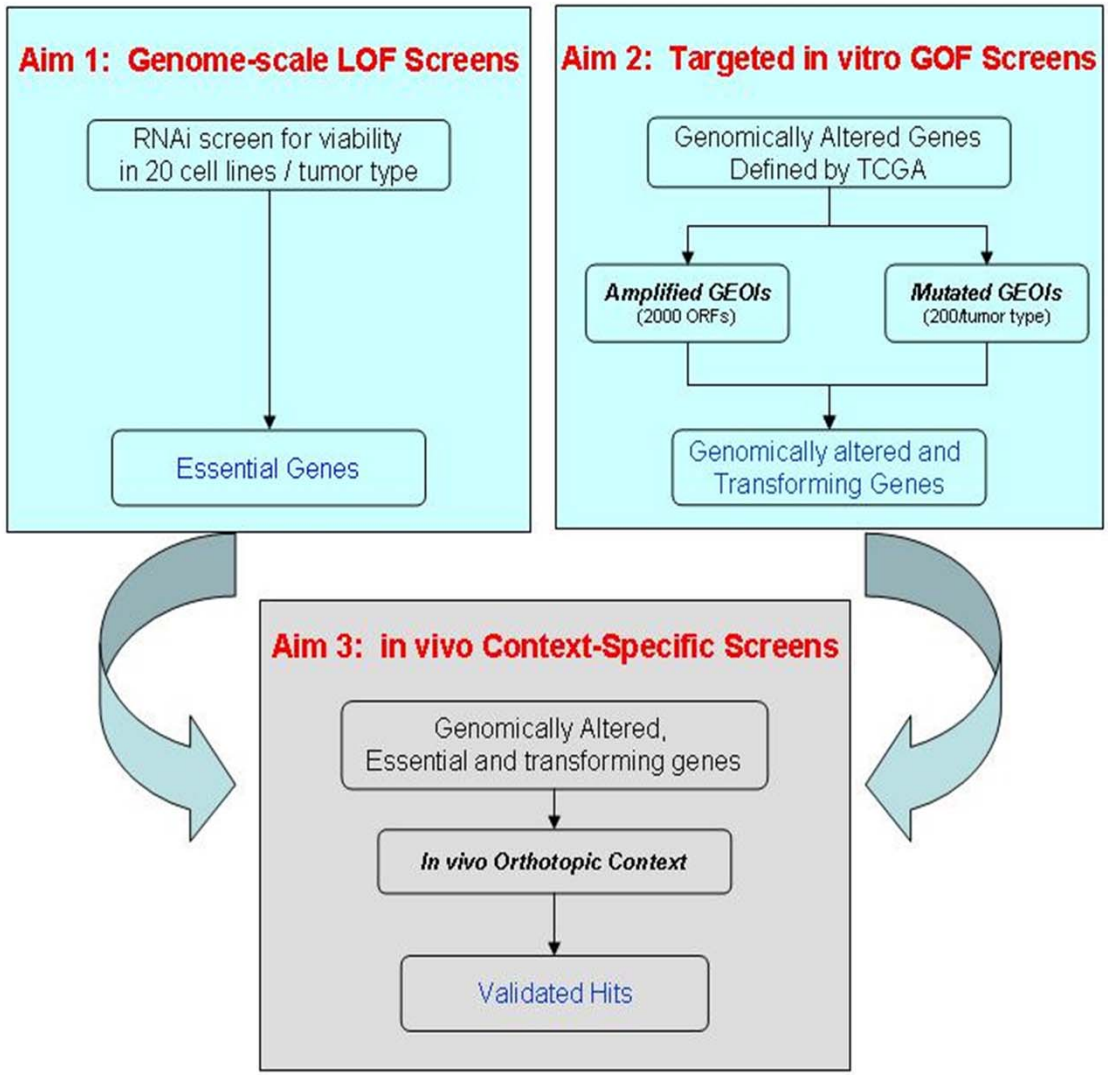
DANA-FARBER CANCER INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

BROAD INSTITUTE

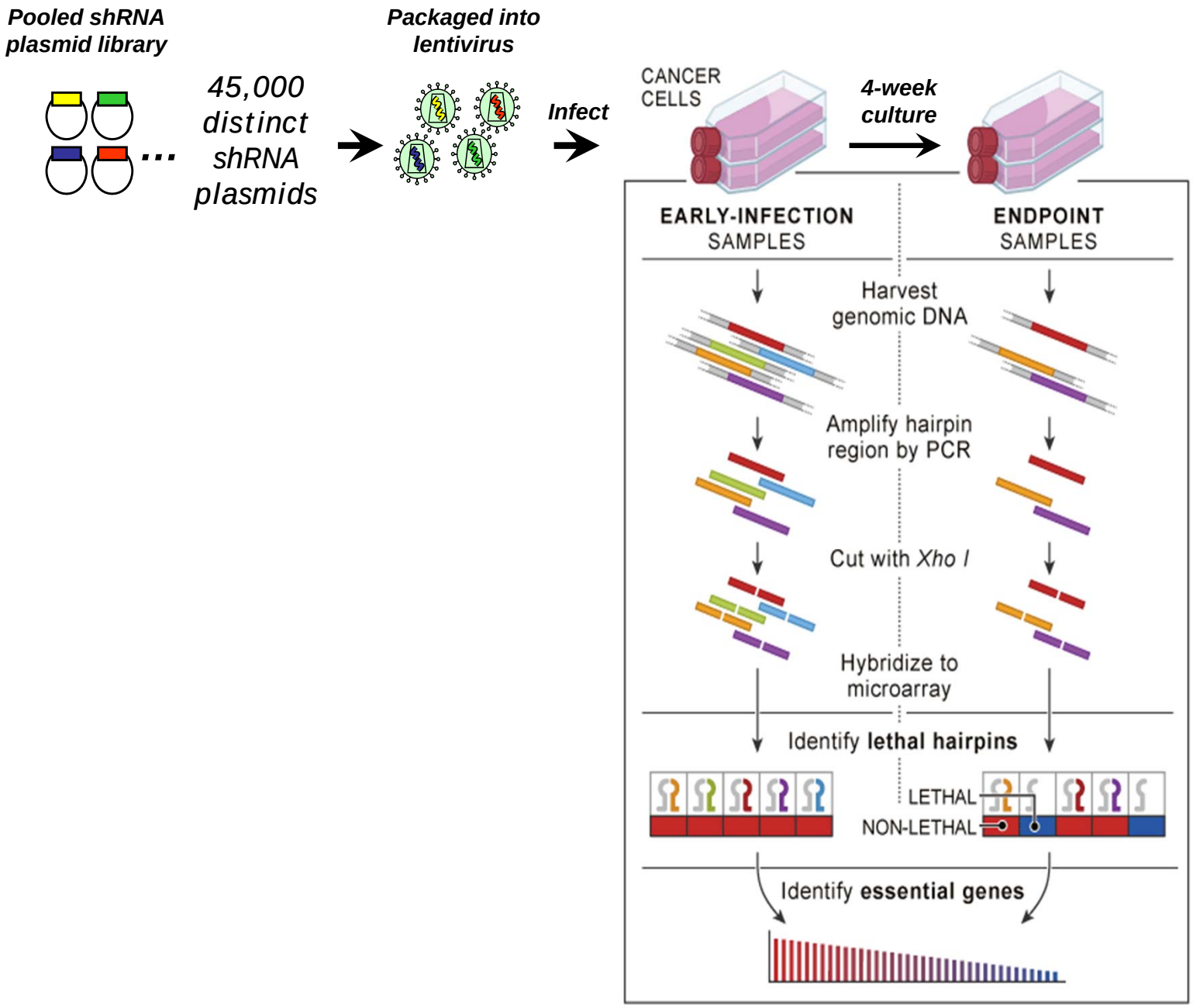
HARVARD MEDICAL SCHOOL

DFCI Cancer Target Discovery & Development Center



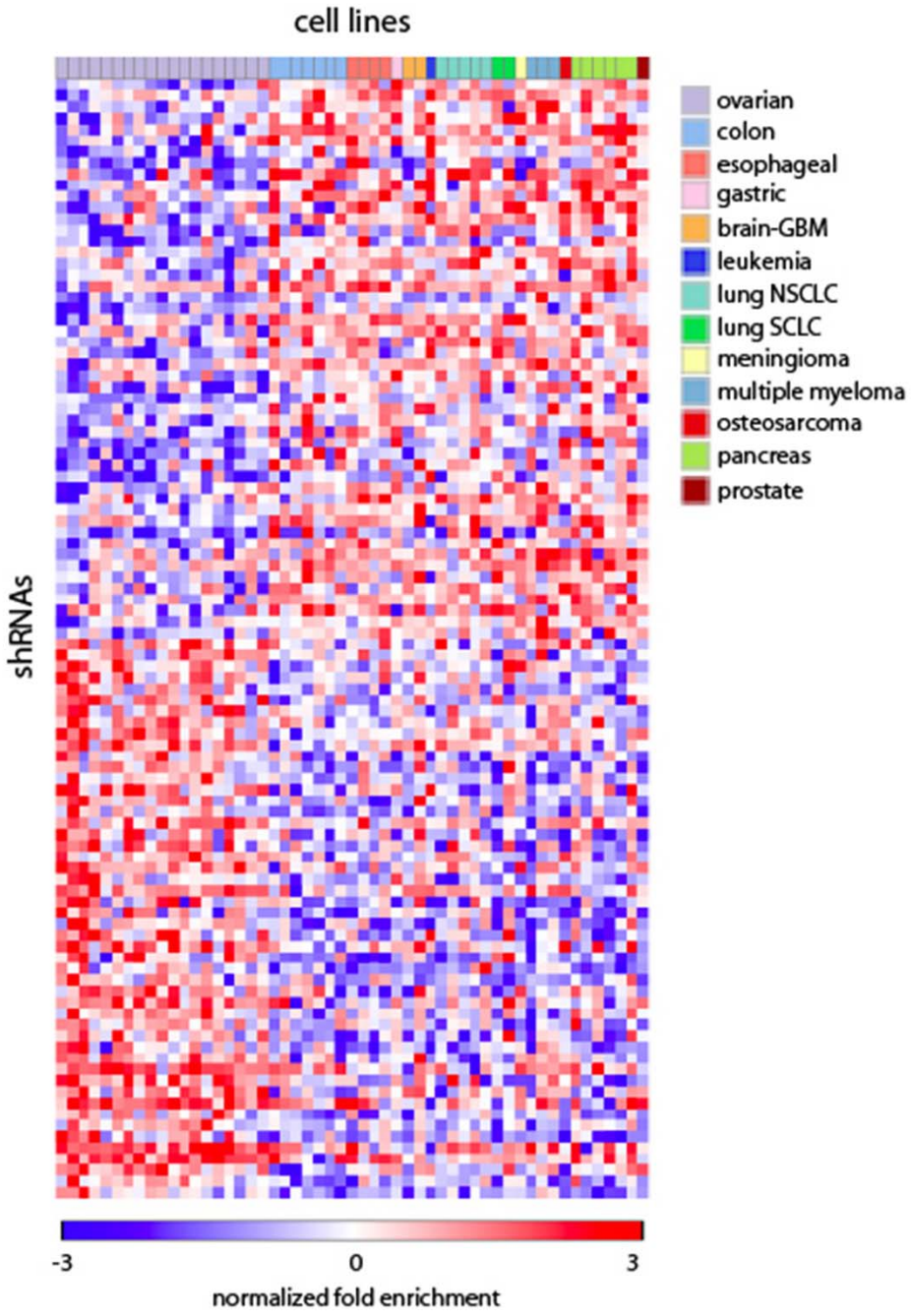
William Hahn
Lynda Chin
Ron DePinho

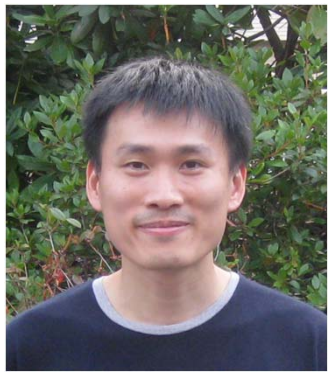
Genome scale barcoded shRNA screens



Biao Luo
Tony Cheung
Aravind Subramanian
David Root

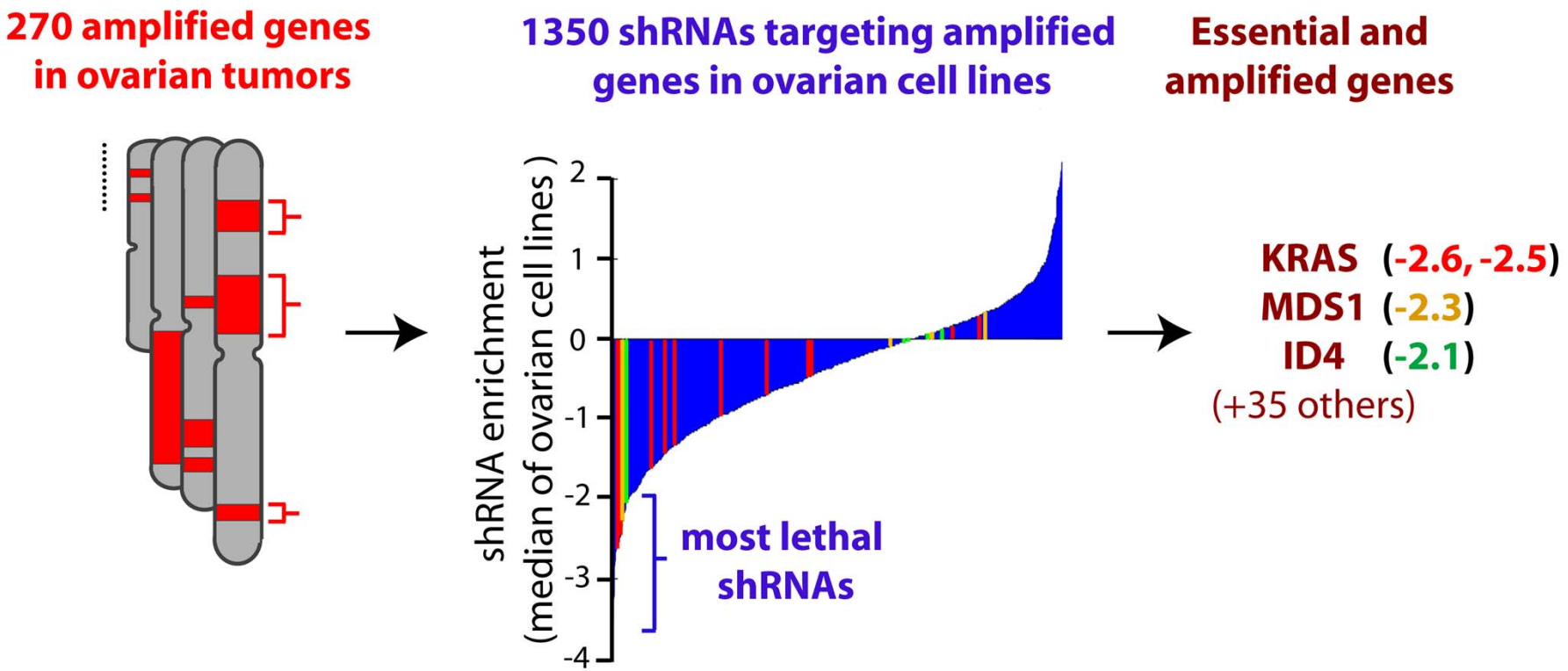
Identification of genes essential in ovarian cancer





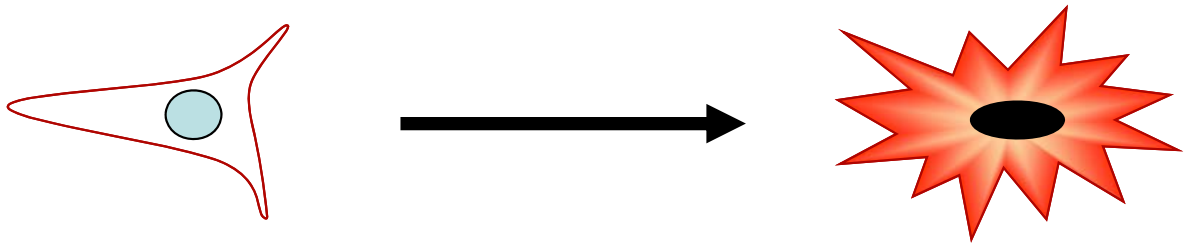
Tony Cheung, Glenn Cowley,
Barbara Weir, Biao Luo
Jesse Boehm, Dave Root

Integrating functional and structural genomics in ovarian cancer



Transformation of immortalized ovarian surface epithelial cells

Immortalized → *Transformed*



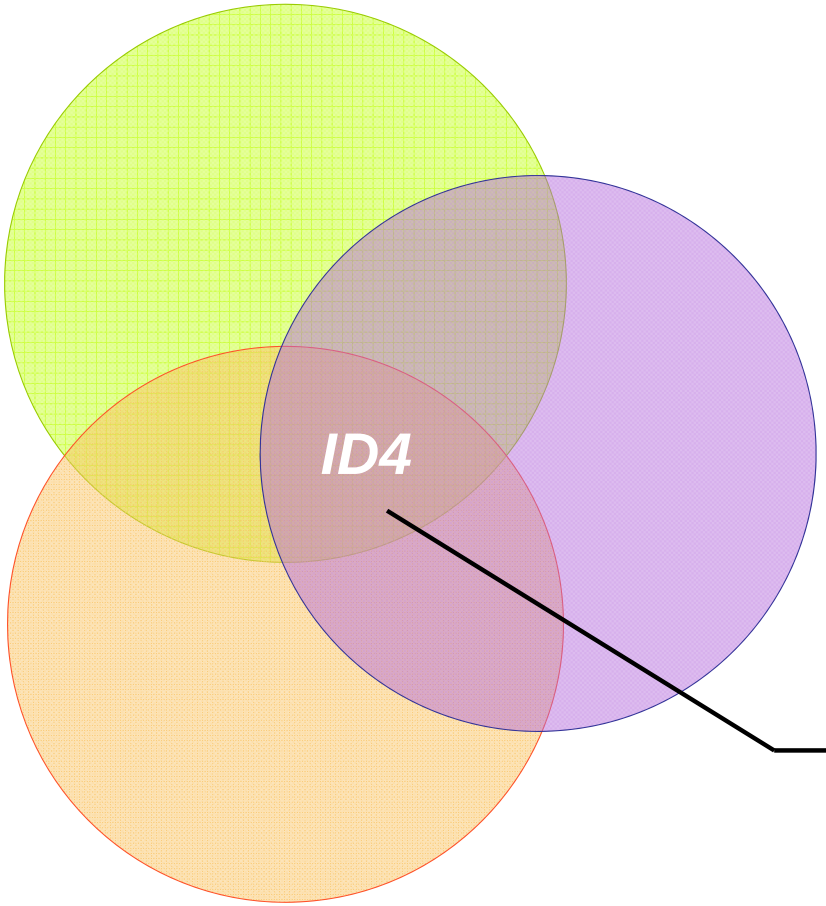
SV40 LT/ST, hTERT

Cell line	*# tumors/# injection sites*
Vector	***0/9***
ID4	***0/9***
MEK^{DD} + lacZ	***4/21***
MEK^{DD} + ID4	***21/27***
MEK^{DD} + ID4_DM	***2/18***

Identification of ID4 as an ovarian cancer oncogene

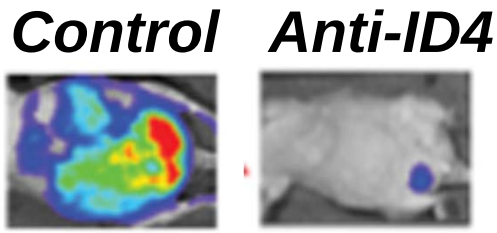
Loss-of-Function

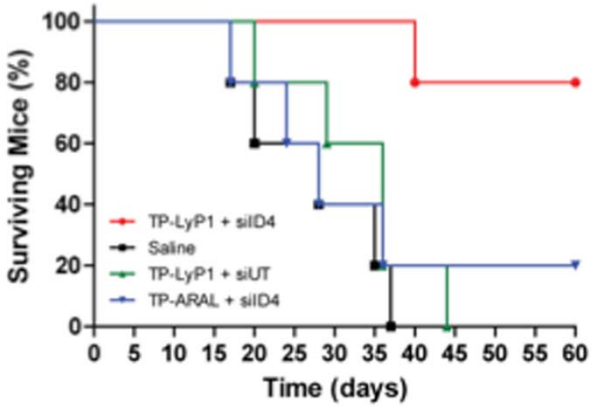
Genes essential for ovarian cancer proliferation



Cancer Genome Annotation

Cross reference with genes in amplified regions in OvCa (TCGA)



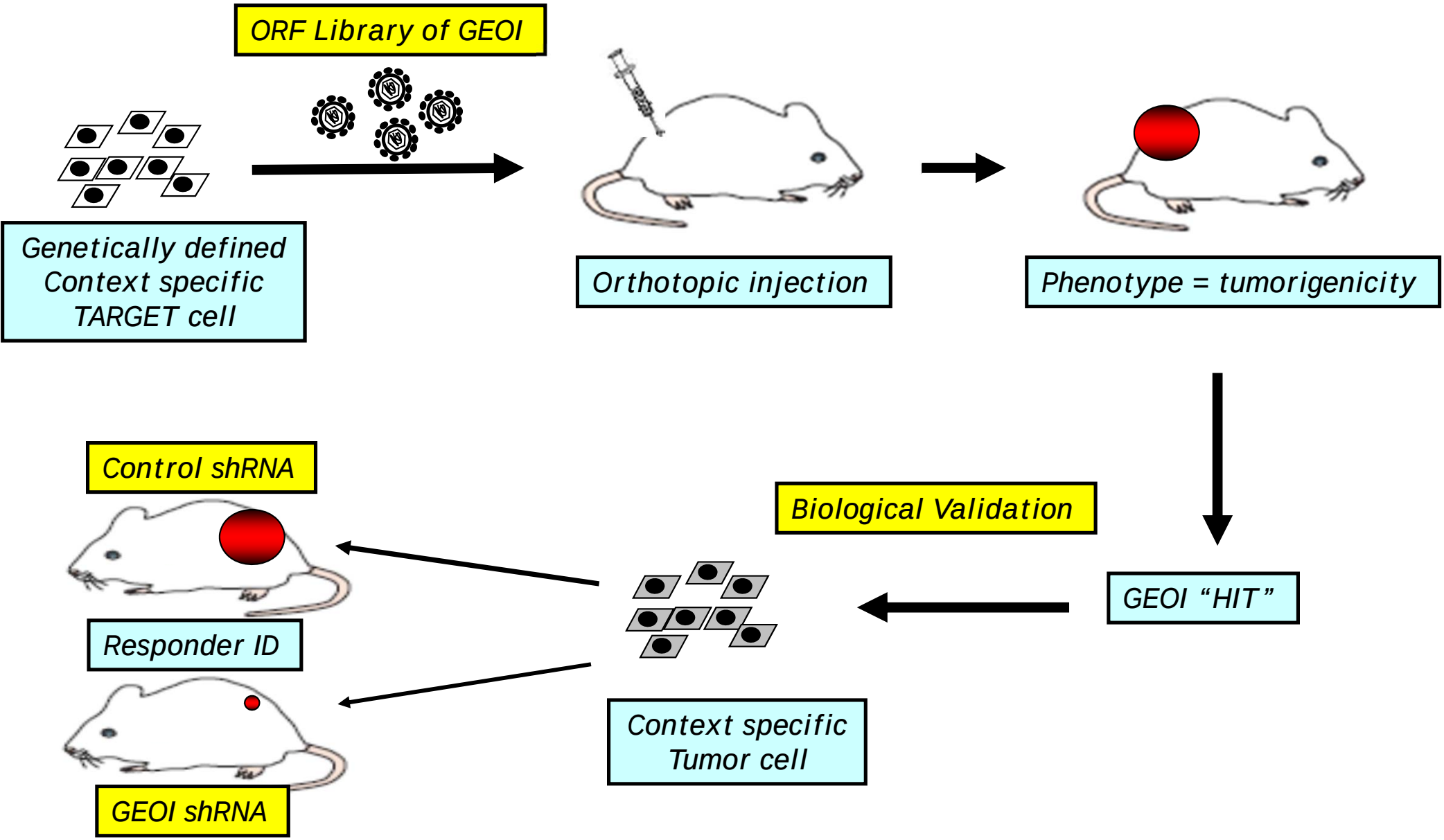


Gain-of-Function

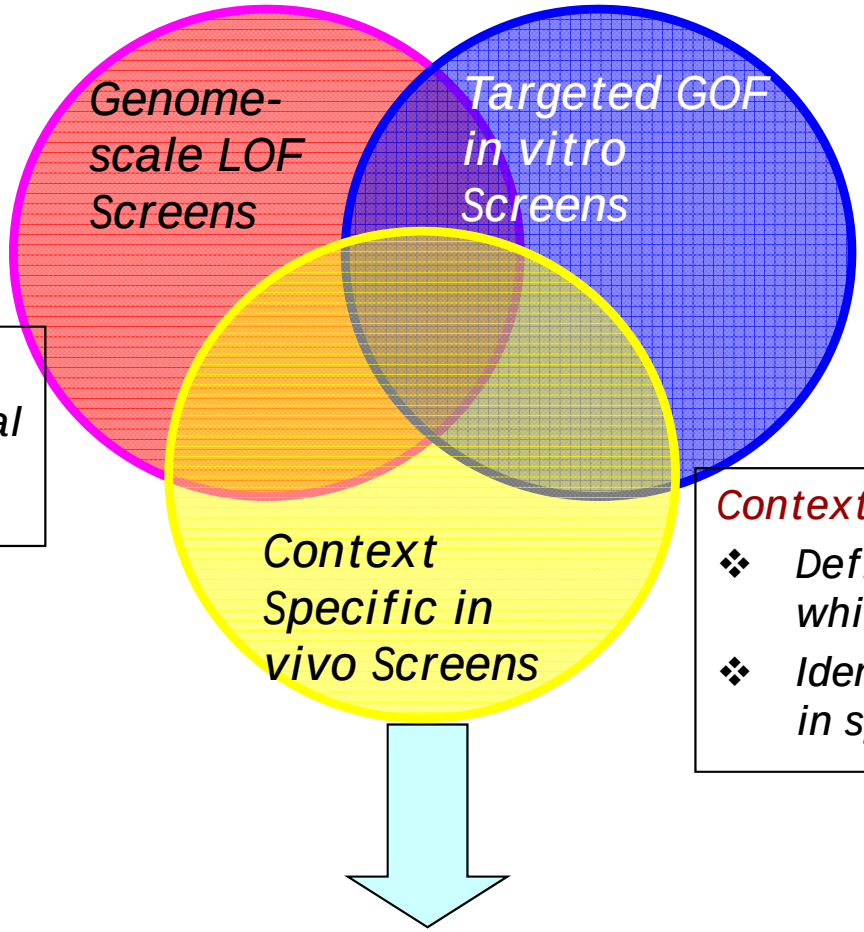
Genes that induce ovarian tumor formation

Yin Ren, Sangeeta Bhatia
Tony Cheung, Jesse Boehm, Glenn Cowley

Context Specific Functional Genomic Screening Platform



Integrated genomic pipeline



Genome-scale LOF screens

- *Identify genes essential to ovarian cancer and GBM viability.*

Context-specific GOF screens

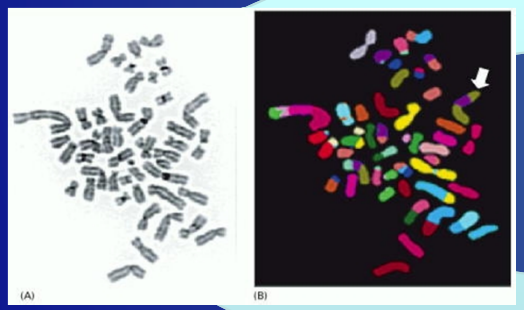
- *Define cell- and genetic contexts in which GEOI is functionally relevant*
- *Identify GEOIs with in vivo activity in specific context*

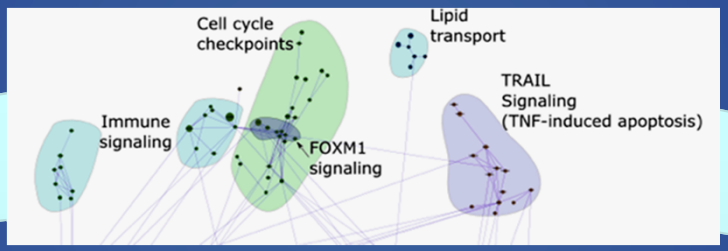
Novel validated cancer drivers that merit consideration for drug discovery efforts

Cold Spring Harbor Laboratory
Cancer Target Discovery & Development Center

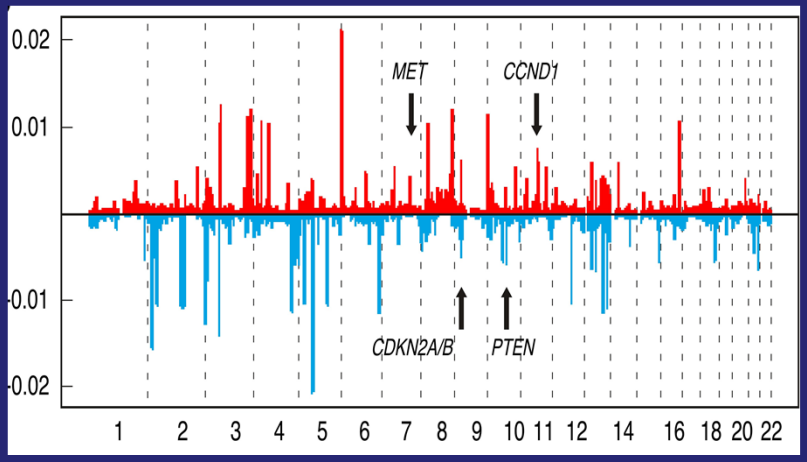
Scott Powers, Scott Lowe

Integrate cancer genome computational analysis, mouse models, and in vivo screening to identify and validate new cancer genes, pathways, and tumor dependencies / therapeutic targets

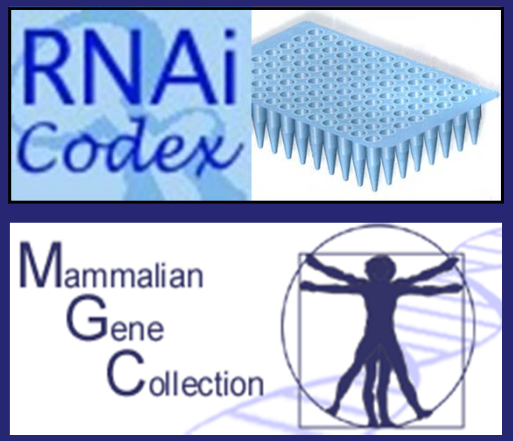




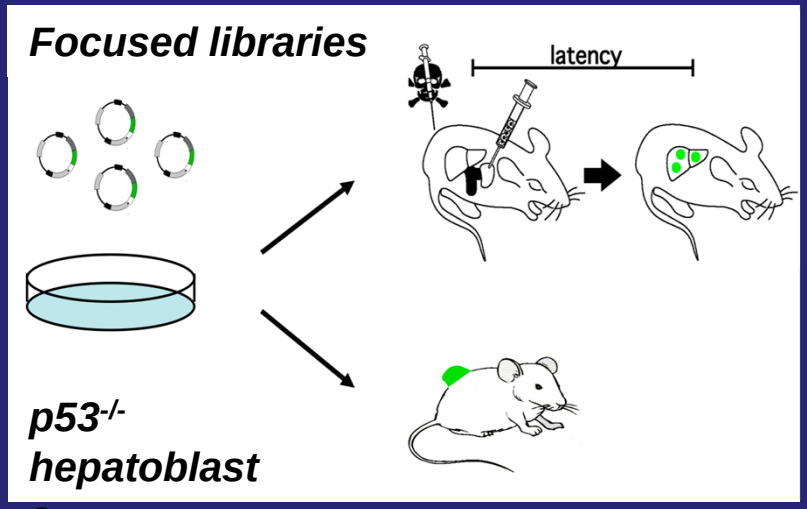
1. *Computational Analysis of Cancer Genomes*



2. *Construction of oncogenomically focused shRNA and cDNA libraries*



3. *Screen for oncogenicity with a transplantable mouse model*



4. *Test for tumor dependency with mouse models and human cancer cell lines*

Under construction

Cold Spring Harbor Laboratory
Cancer Target Discovery & Development Center

Summary of findings

- *Discovery and validation of 20 novel TSGs and oncogenes*
- *Unexpected number of identified tumor suppressors encode secreted proteins*
- *Discovered FGF19 oncogene dependency in human HCC cell lines containing the FGF19 amplicon*
- *This pinpoints for the first time a candidate cancer drug that selectively targets a genetic abnormality in HCC.*

UTSW Cancer Target Discovery & Development Center

A CONCERTED ATTACK ON PATIENT SPECIFIC ONCOGENIC VULNERABILITIES IN LUNG CANCER

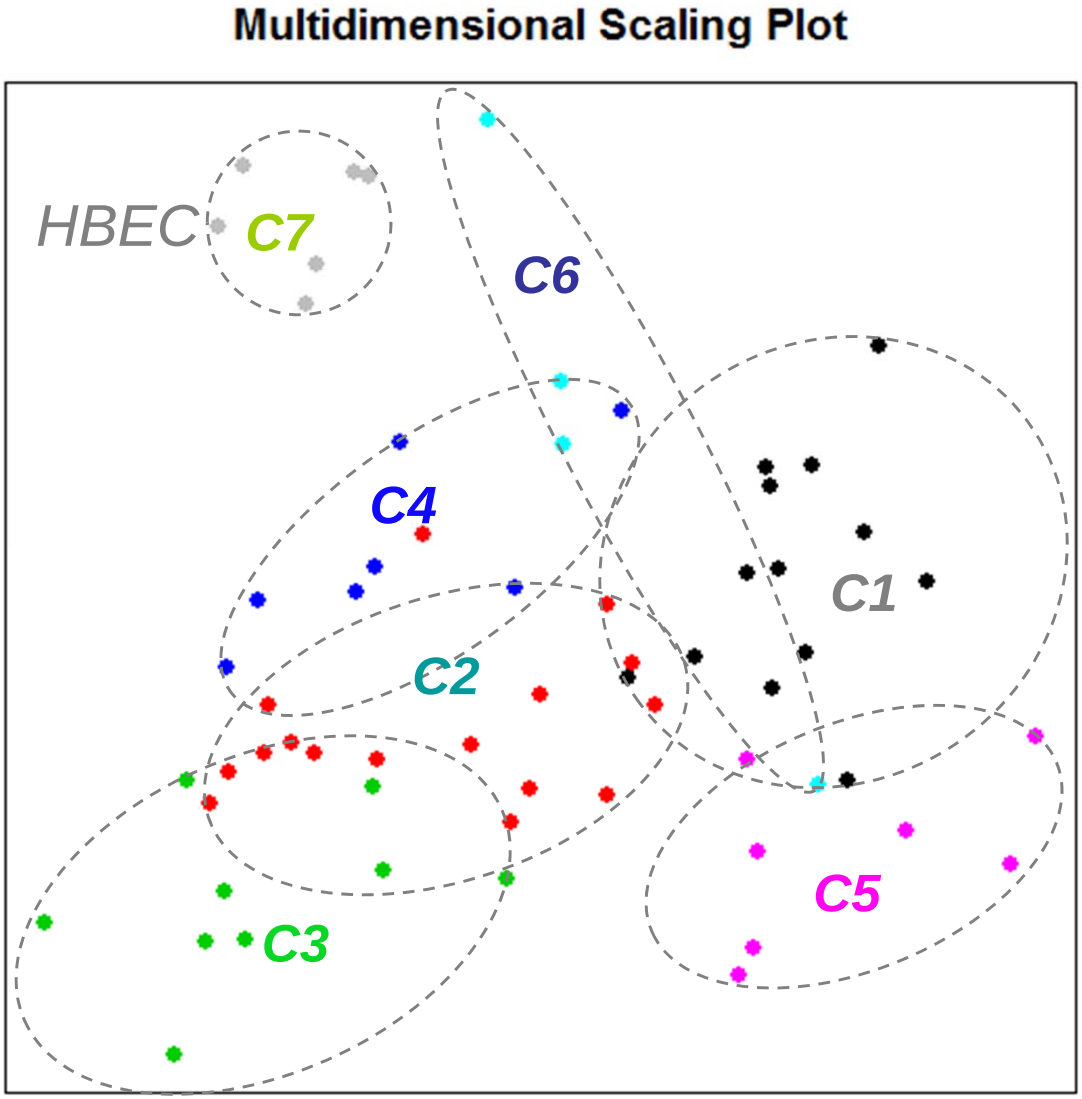
Objective : to employ parallel phenotypic screening of genome-wide siRNA libraries and a diverse chemical compound file to return authentic drug lead/target relationships

Mike Roth
Michael White
John Minna

UT SOUTHWESTERN MEDICAL CENTER

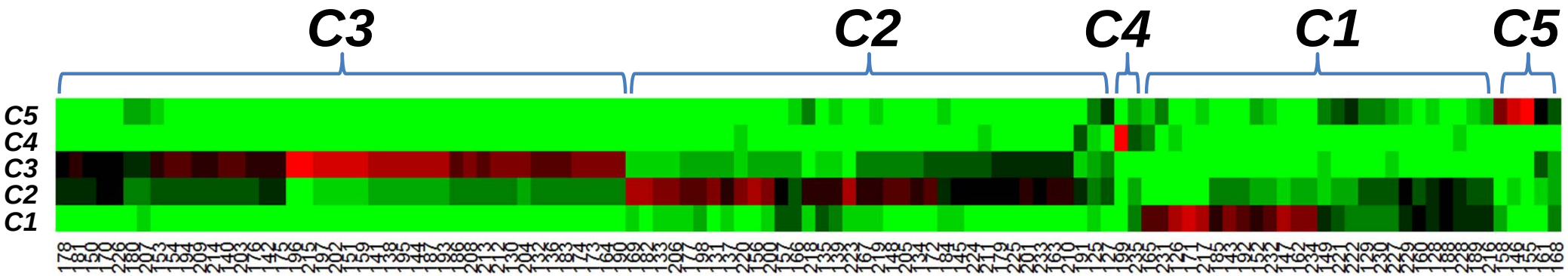
mRNA Expression Profiles Identify 6 Major Subtypes (Clades) of Non-Small Cell Lung Cancer

6 HBECs
56 NSCLCs



UT SOUTHWESTERN MEDICAL CENTER

mRNA Defined Clades from the NSCLC Lines Are also Found in Primary NSCLCs



(N = 111)

Probability (using PAM, prediction analysis of microarray method) of each primary tumor sample belonging to a particular NSCLC Line Defined Clade

Low probability of belonging to a Clade

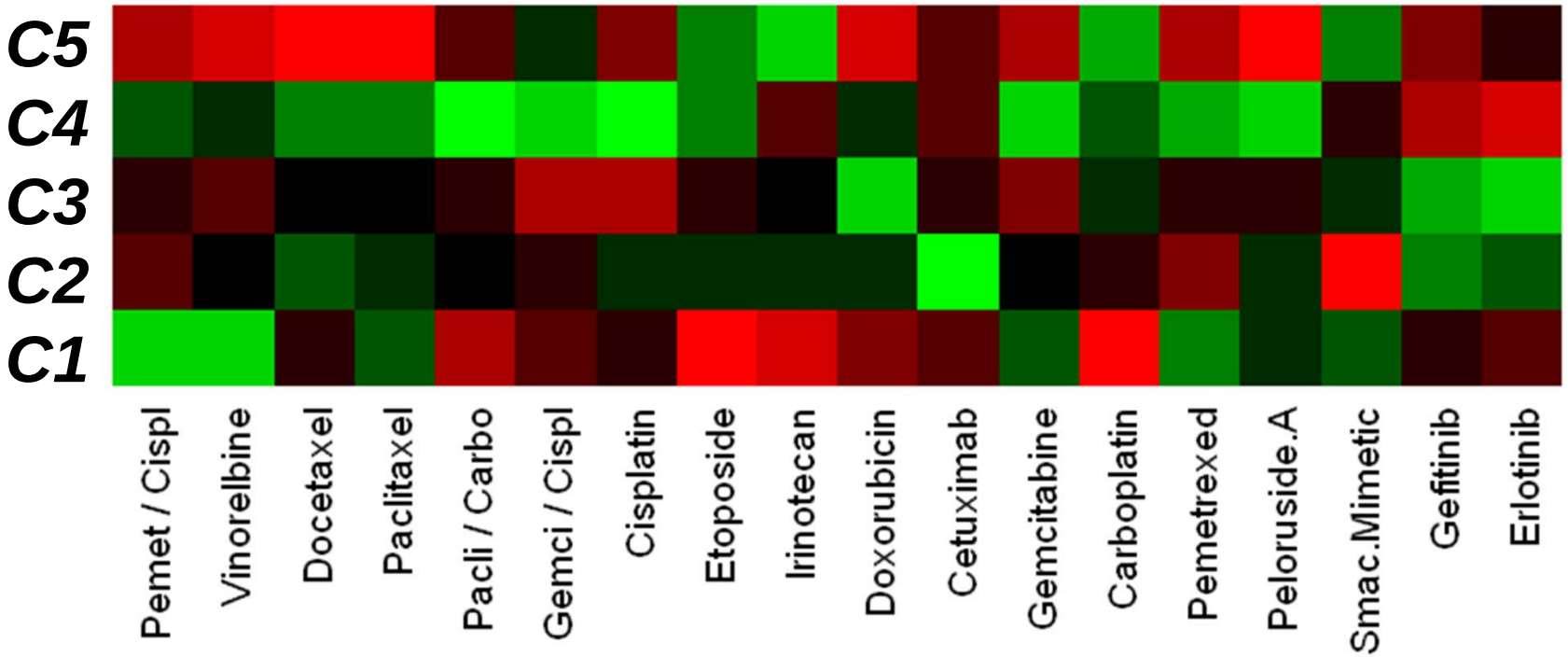
High probability of belonging to a Clade

UT SOUTHWESTERN MEDICAL CENTER

(NSCLC Data from Bild Nature 2006 (439), 353-357)

mRNA Defined Clades Identify Different NSCLC Drug Response Phenotypes

Drug Sensitivity Frequency in Clades

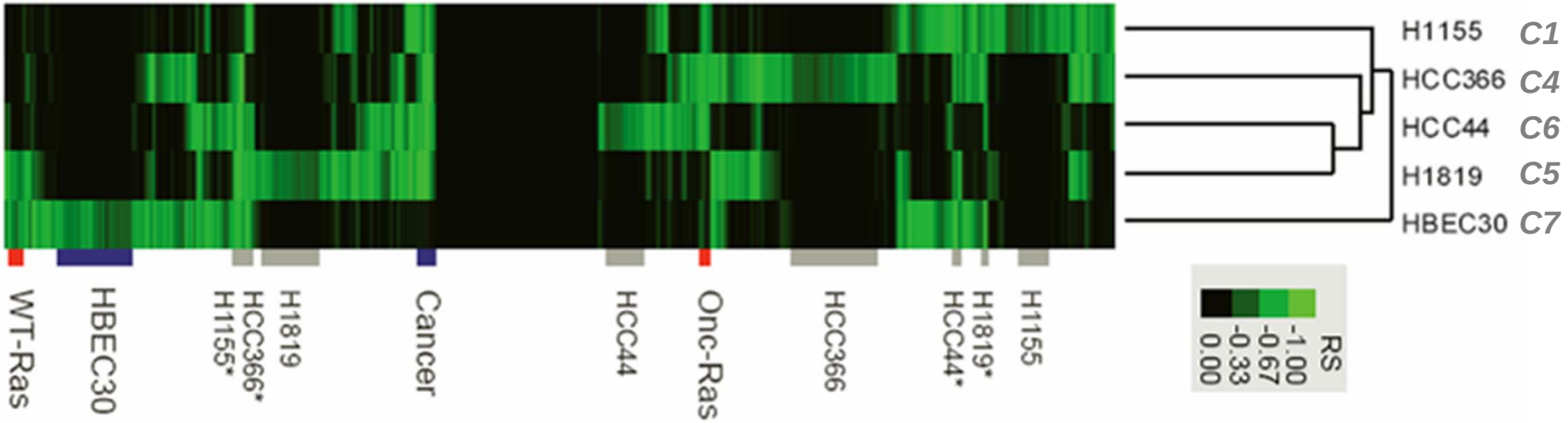


High probability of sensitivity

High probability of Resistance

UT SOUTHWESTERN MEDICAL CENTER

Genome Wide siRNA Library Screens Reveal Clade-Selective Vulnerabilities



UT SOUTHWESTERN MEDICAL CENTER

Cancer Target Discovery and Development (CTD^2) Network

OFFICE of CANCER GENOMICS

Network interactions and synergy

- *State of the art technological platforms*
- *Data sharing*
- *Model sharing*
- *Development of new informatics*

Deliverables to cancer research community

- *Reagents and Informatic tools*
- *Large scale functional datasets (in vitro and in vivo)*
- *Experimental models*
- *Integrative data to inform investigator initiated research*