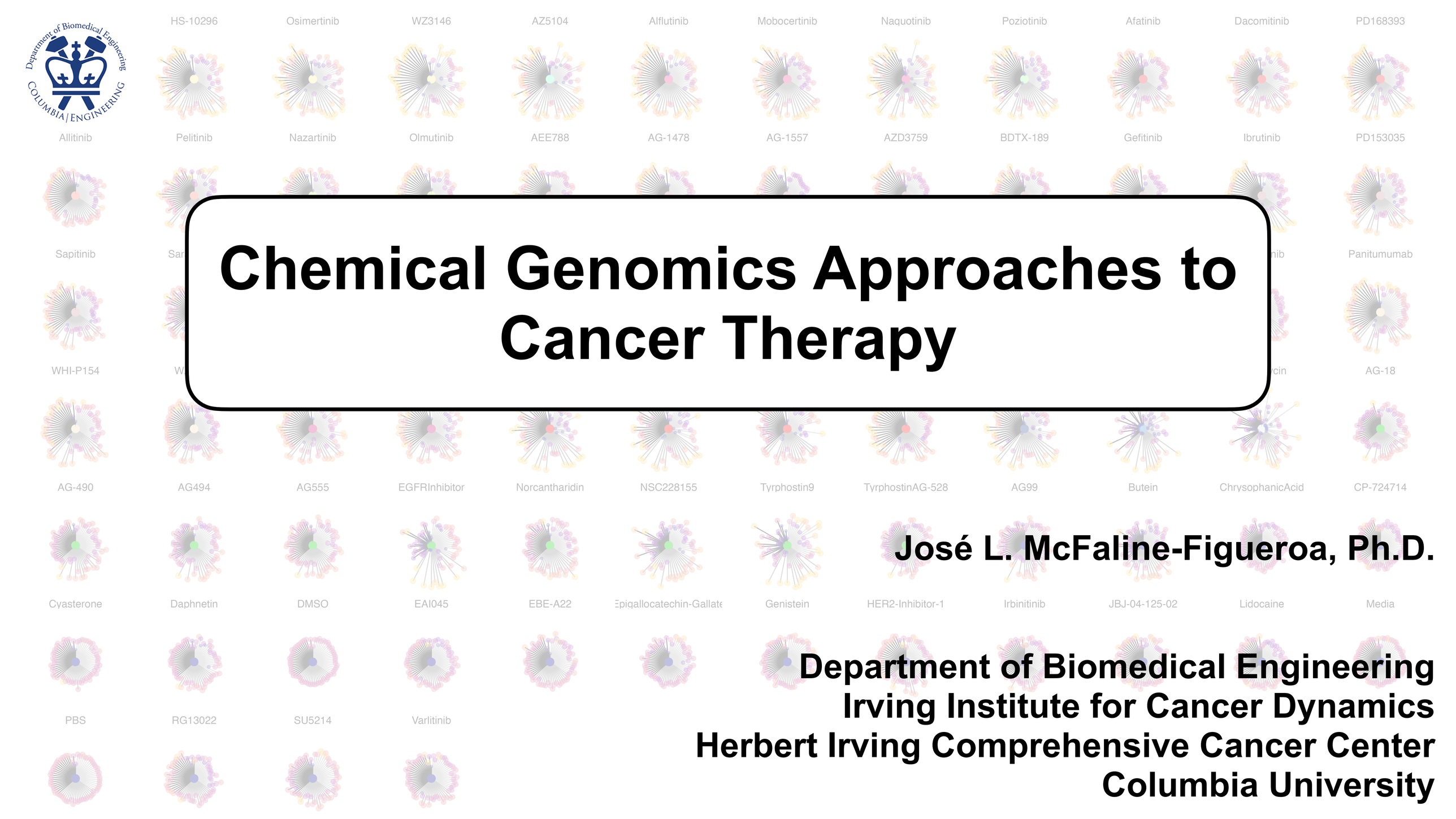


Chemical Genomics Approaches to Cancer Therapy

José L. McFaline-Figueroa, Ph.D.

Department of Biomedical Engineering
Irving Institute for Cancer Dynamics
Herbert Irving Comprehensive Cancer Center
Columbia University

Learning objectives

- Define Chemical Genetics and Chemical Genomics
- Identify advantages of single-cell resolution when examining therapeutic response
- Describe scalable and multiplex platforms for Chemical Genomics
- Familiarize yourself with approaches for the analysis of large-scale perturbation data

CHEMICAL GENETICS: LIGAND-BASED DISCOVERY OF GENE FUNCTION

Brent R. Stockwell

Chemical genetics is the study of gene-product function in a cellular or organismal context using exogenous ligands. In this approach, small molecules that bind directly to proteins are used to alter protein function, enabling a kinetic analysis of the *in vivo* consequences of these changes. Recent advances have strongly enhanced the power of exogenous ligands such that they can resemble genetic mutations in terms of their general applicability and target specificity. The growing sophistication of this approach raises the possibility of its application to any biological process.

(**2000**) *Nature Reviews Genetics*

THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

Joseph G. Lombardino and John A. Lowe III‡*

Abstract | The role of the medicinal chemist in drug discovery has undergone major changes in the past 25 years, mainly because of the introduction of technologies such as combinatorial chemistry and structure-based drug design. As medicinal chemists with more than 50 years of combined experience spanning the past four decades, we discuss this changing role using examples from our own and others' experience. This historical perspective could provide insights in to how to improve the current model for drug discovery by helping the medicinal chemist regain the creative role that contributed to past successes.

(**2004**) *Nature Reviews Drug Discovery*

Opinion

Chemical genomics: what will it take and who gets to play?

Gavin MacBeath

Address: Center for Genomics Research, Harvard University, 16 Divinity Avenue, Cambridge, MA 02138, USA.
E-mail: gavin_macbeath@harvard.edu

Published: 6 June 2001

Genome ***Biology*** 2001, **2(6)**:comment2005.1–2005.6

The electronic version of this article is the complete one and can be found online at http://genomebiology.com/2001/2/6/comment/2005

(**2001**) *Genome Biology*

Review article

Check for updates

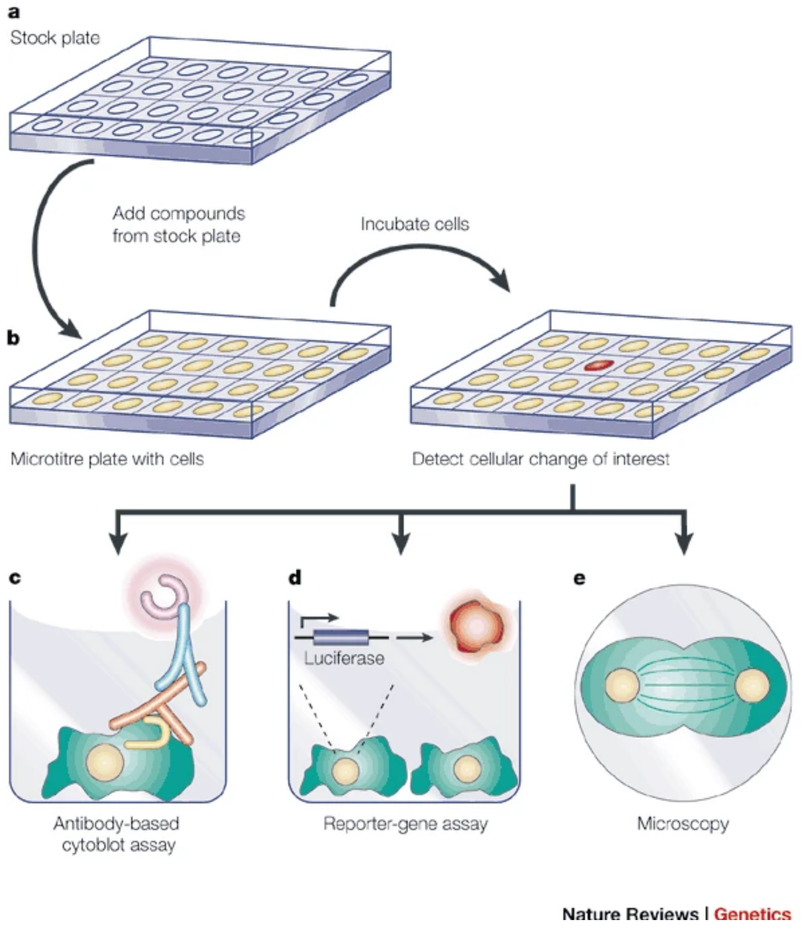
Applications of single-cell RNA sequencing in drug discovery and development

Bram Van de Sande[1,15], Joon Sang Lee[2,15], Euphemia Mutasa-Gottgens[3,15] ✉, Bart Naughton[4], Wendi Bacon[3,5], Jonathan Manning[3], Yong Wang[6], Jack Pollard[7], Melissa Mendez[8], Jon Hill[9], Namit Kumar[10], Xiaohong Cao[11], Xiao Chen[12], Mugdha Khaladkar[13], Ji Wen[14], Andrew Leach[3] & Edgardo Ferran[3]

(**2023**) *Nature Reviews Drug Discovery*

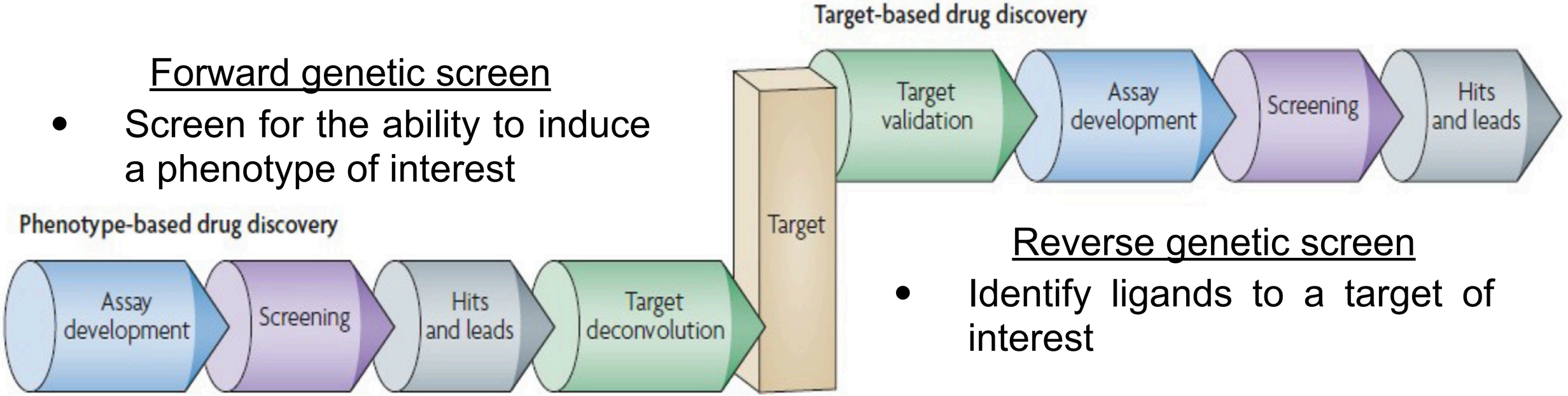
The Chemical Genetics Approach

- Approaches that use collections of small molecules or other treatment modalities to study gene product function
- Leverage large chemical or biomolecule libraries
- Function is studied in whole cells or organisms
- Coupled to a variety of readouts that allow parallelization (e.g., viability, reporter expression)
- Analogous to genetics, approaches can be divided into forward- and reverse-chemical genetics screens



Stockwell, B. (**2000**) *Nature Reviews Genetics*

Phenotype-based vs. Target-based Screens



Forward genetic screen

- Screen for the ability to induce a phenotype of interest

Reverse genetic screen

- Identify ligands to a target of interest

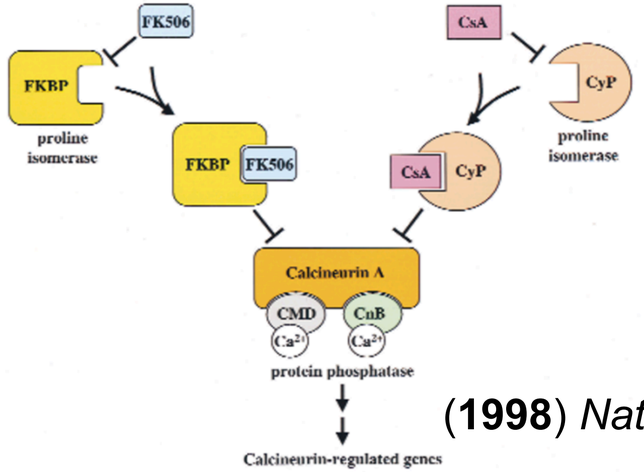
Image: Payghan, P.V. *et. al.* (**2018**) *Frontiers in Physics*
Stockwell, B. (**2000**) *Nature Reviews Genetics*

From Chemical Genetics to Chemical Genomics

Microarray

Drug target validation and identification of secondary drug target effects using DNA microarrays

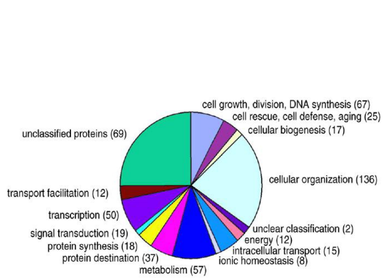
MATTHEW J. MARTON[1], JOSEPH L. DERISI[2], HOLLY A. BENNETT[1], VISHWANATH R. IYER[2], MICHAEL R. MEYER[1], CHRISTOPHER J. ROBERTS[1], ROLAND STOUGHTON[1], JULJA BURCHARD[1], DAVID SLADE[1], HONGYUE DAI[1], DOUGLAS E. BASSETT, JR[1]., LELAND H. HARTWELL[3], PATRICK O. BROWN[2] & STEPHEN H. FRIEND[1]

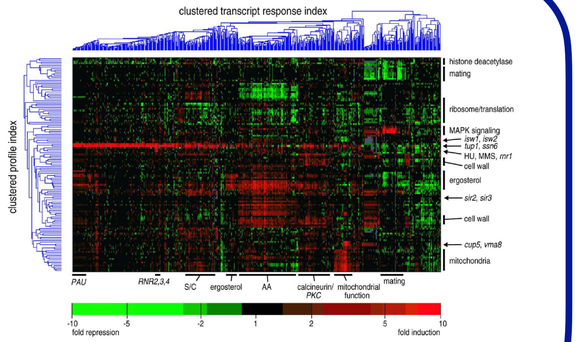


(**1998**) *Nature Medicine*

Microarray

Compendium of Signatures





Hughes, T.R. (**2000**) *Cell*

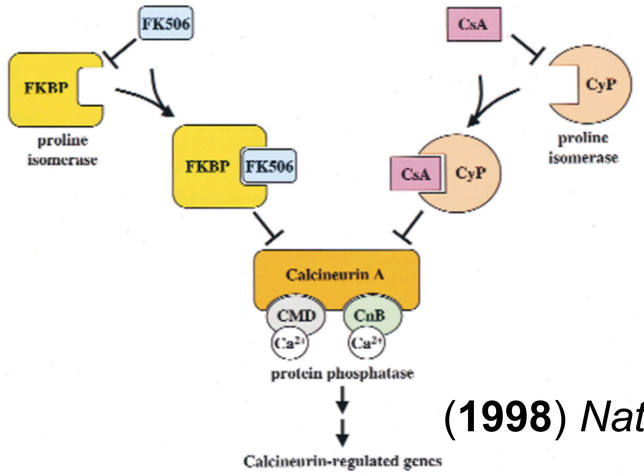
- Early approaches coupled perturbations to gene expression readouts using DNA microarrays

From Chemical Genetics to Chemical Genomics

Microarray

Drug target validation and identification of secondary drug target effects using DNA microarrays

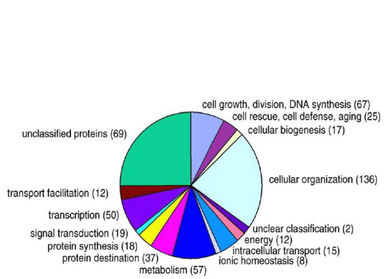
MATTHEW J. MARTON[1], JOSEPH L. DERISI[2], HOLLY A. BENNETT[1], VISHWANATH R. IYER[2], MICHAEL R. MEYER[1], CHRISTOPHER J. ROBERTS[1], ROLAND STOUGHTON[1], JULJA BURCHARD[1], DAVID SLADE[1], HONGYUE DAI[1], DOUGLAS E. BASSETT, JR[1]., LELAND H. HARTWELL[3], PATRICK O. BROWN[2] & STEPHEN H. FRIEND[1]

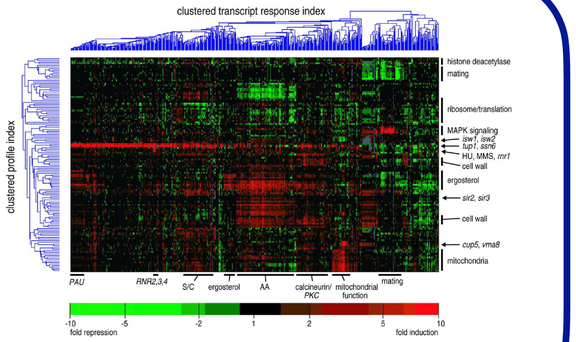


(**1998**) *Nature Medicine*

Microarray

Compendium of Signatures





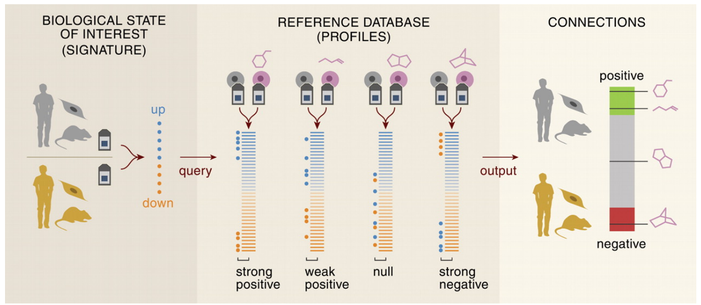
Hughes, T.R. (**2000**) *Cell*

- Marton *et al.* established the idea of a chemical signature to classify on/off target effects of inhibition of calcineurin signaling
- Hughes *et al.* proposed a compendium of signatures for gene loss-of-function in yeast

From Chemical Genetics to Chemical Genomics

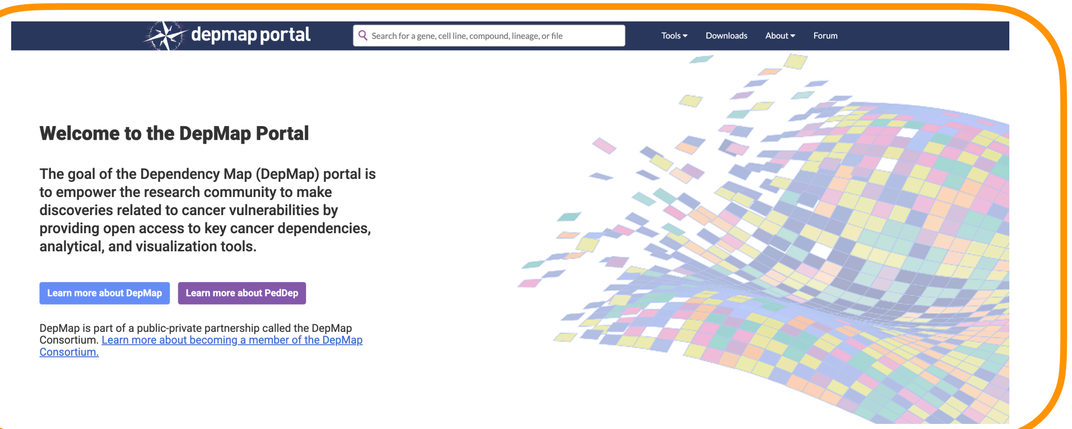
Connectivity Map

Microarray



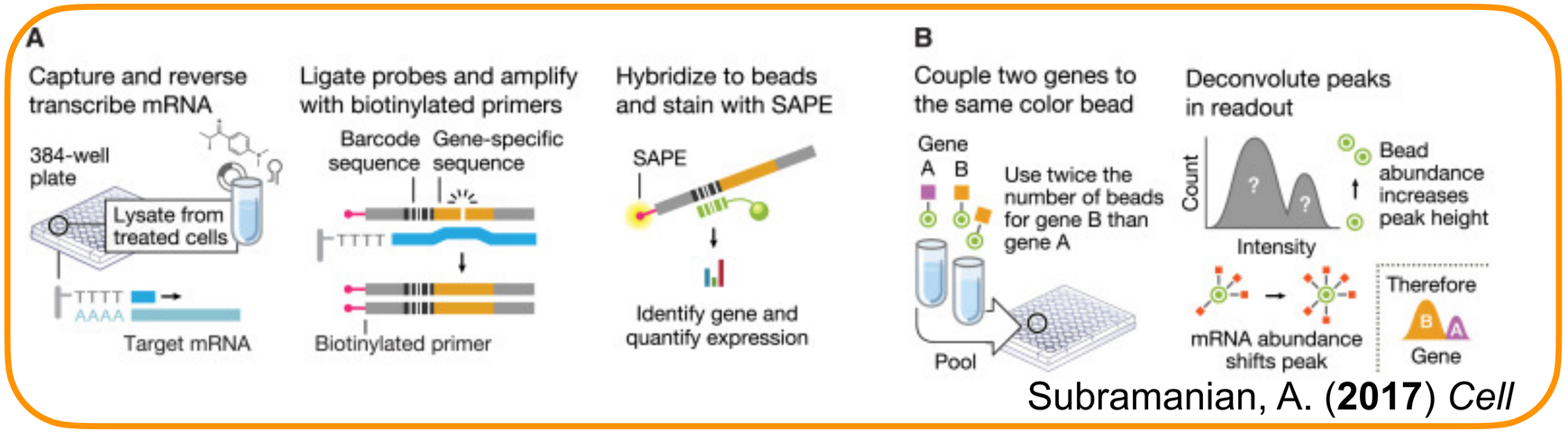
Lamb, J. (**2006**) *Science*

Dependency Map



Library of Integrated Network-based Cellular Signatures (LINCS)

L1000 assay

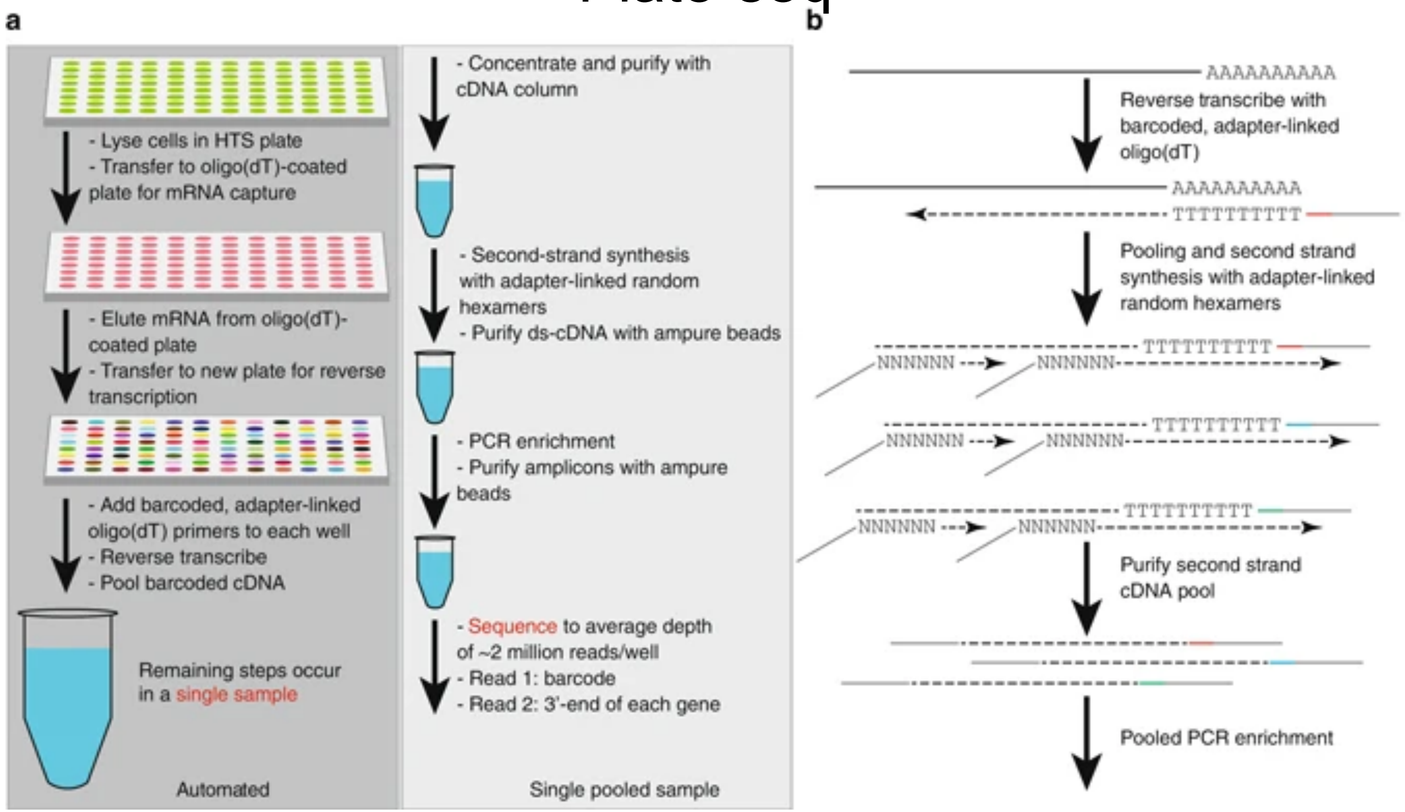


Subramanian, A. (**2017**) *Cell*

- Advances have focused on coupling chemical genetics screen to scalable molecular readouts

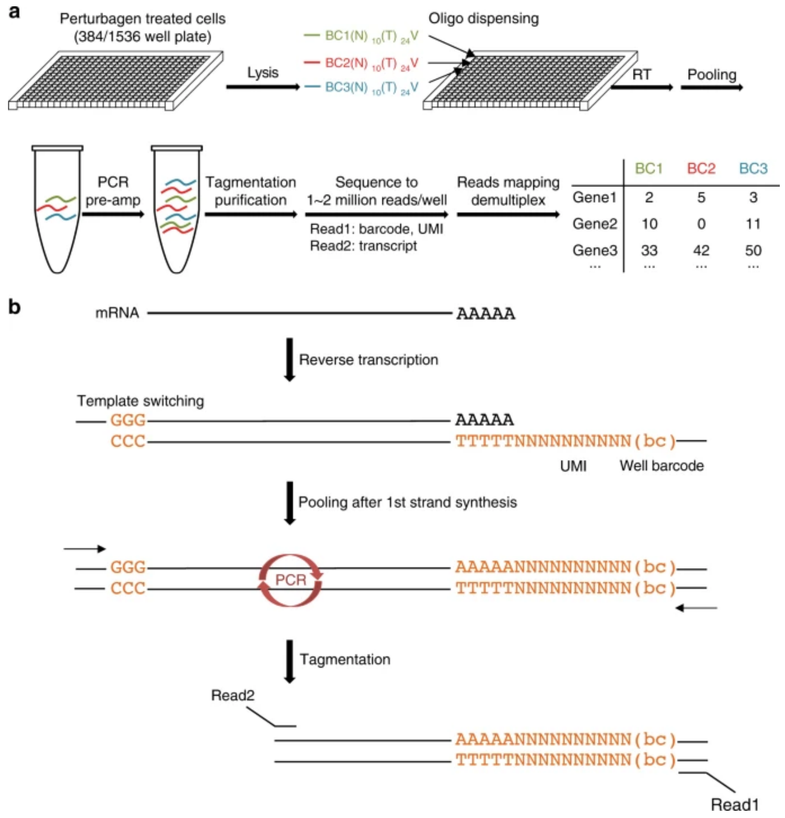
From Chemical Genetics to Chemical Genomics

Plate-seq



Bush, E.C. (**2017**) *Nature Communications*

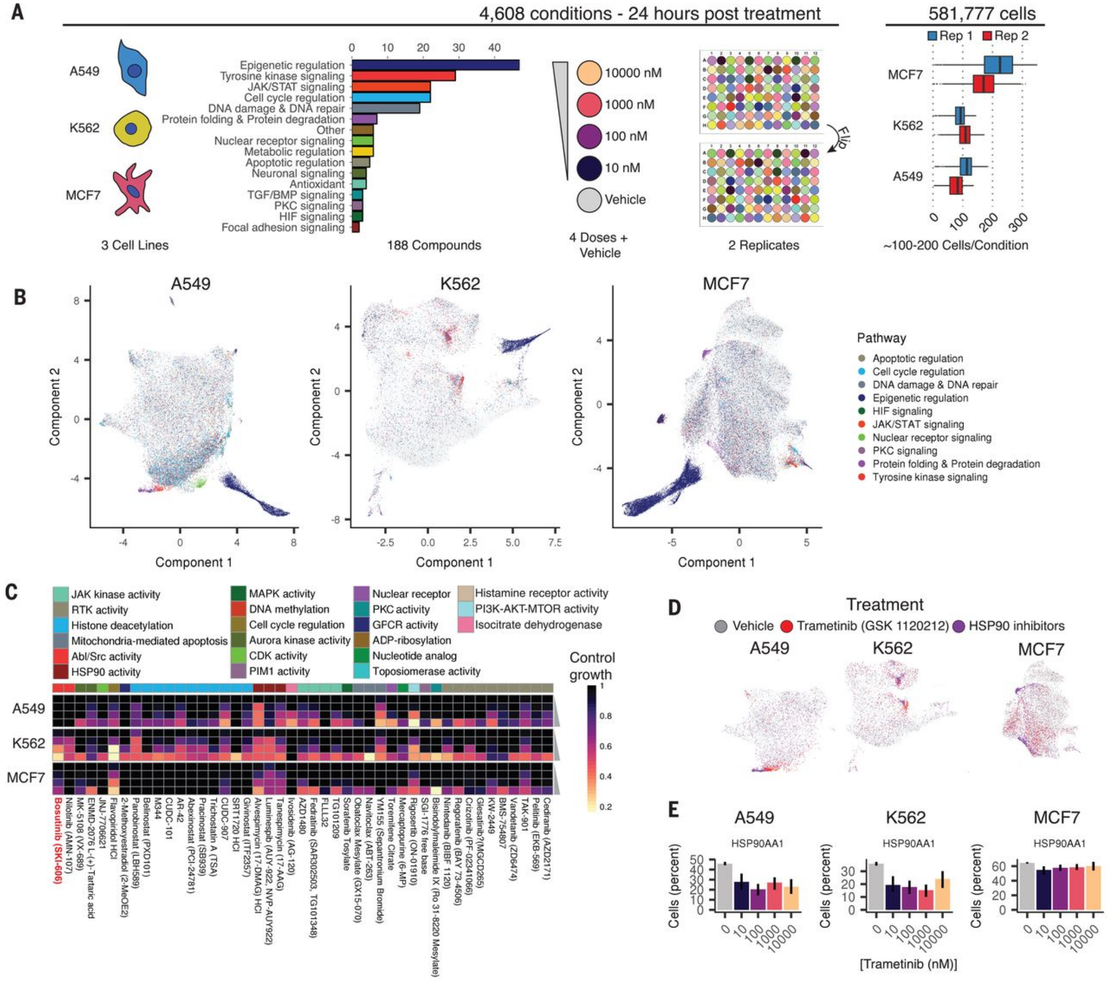
Drug-seq

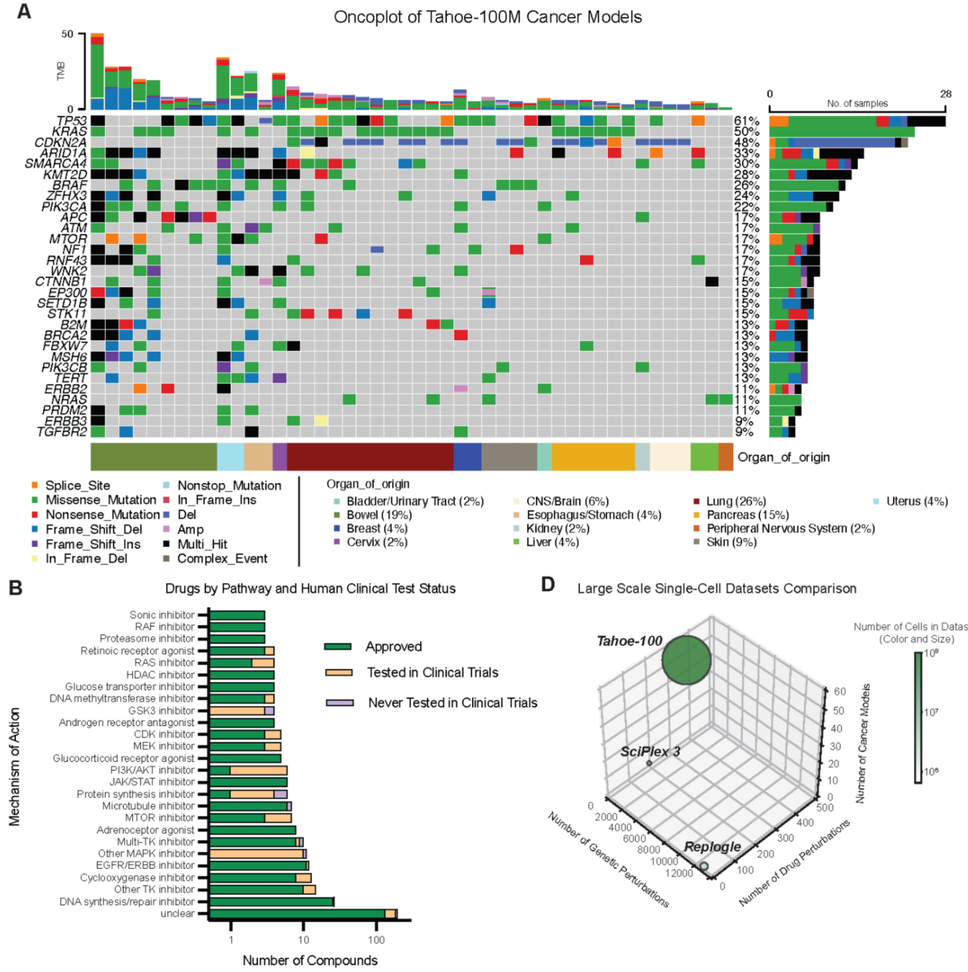


Ye, C. (**2018**) *Nature Communications*

✦ Unbiased gene expression profiling of drug-induced molecular effects by sample multiplexing of unique conditions during reverse transcription

Chemical genomics at single-cell resolution

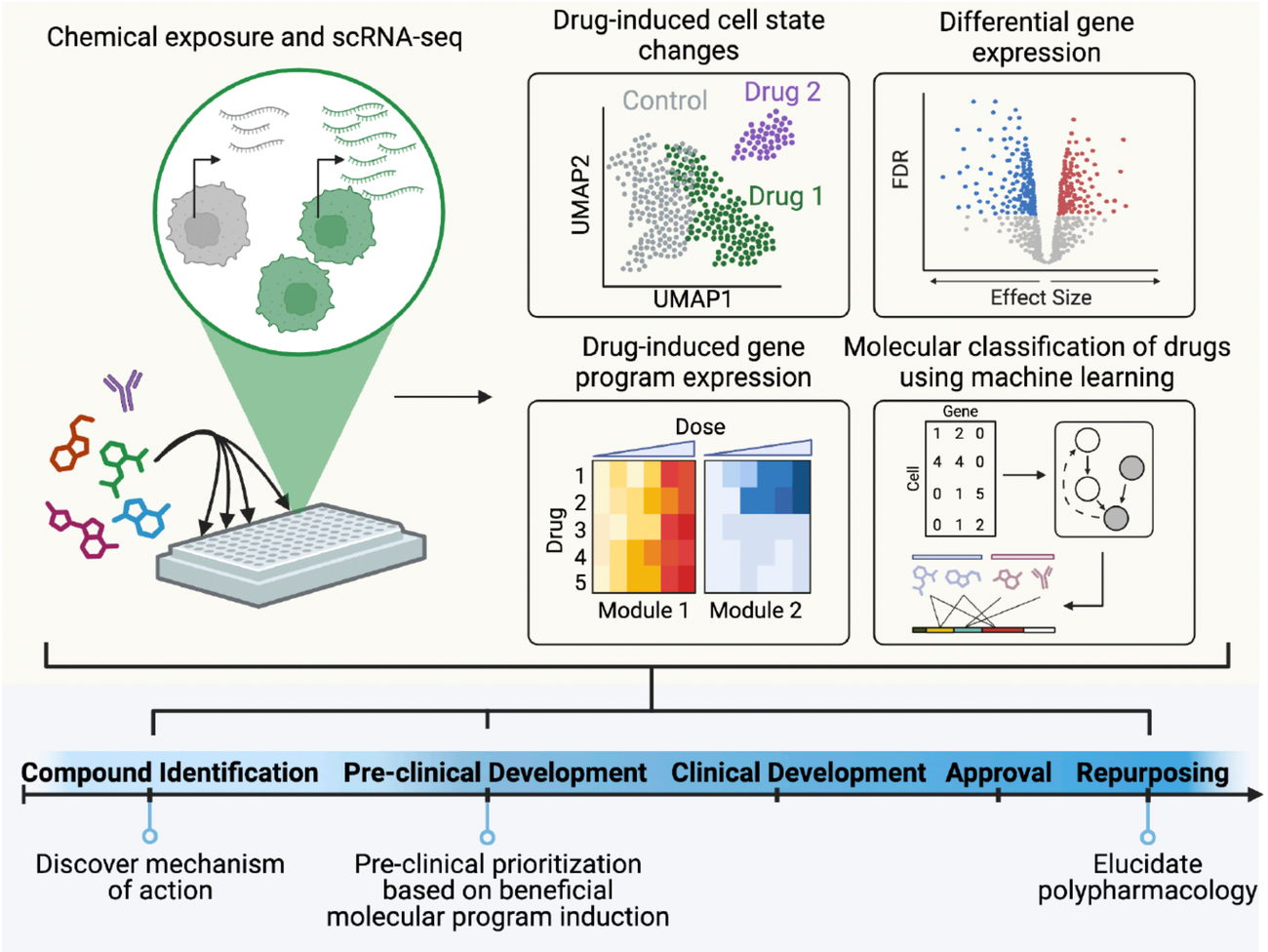


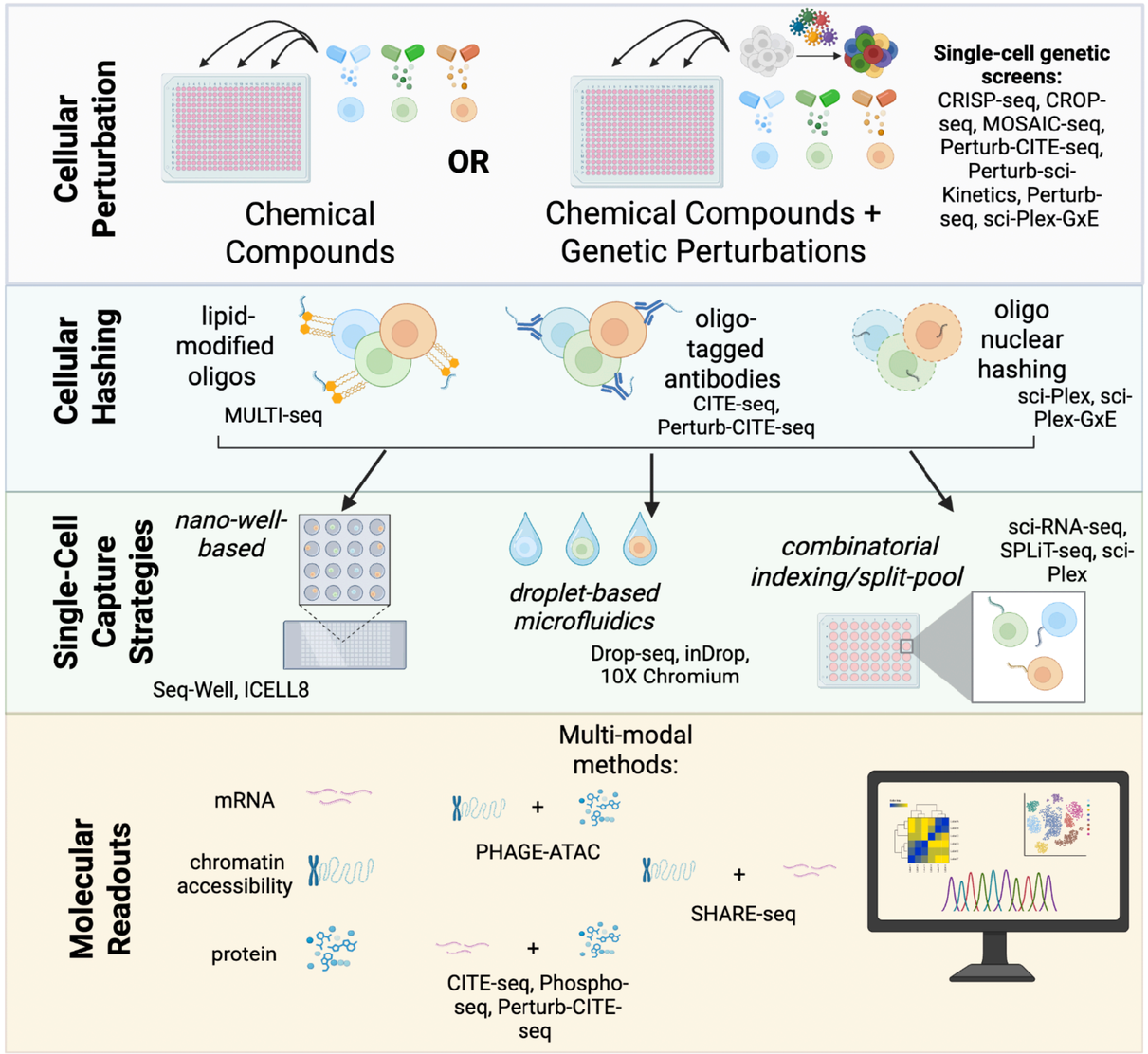


*Srivatsan, S., *McFaline-Figueroa, J.L., *Ramani, V. *et al.* (**2020**). Science.

Zhang. *et. al.* (**2025**) *bioRxiv*

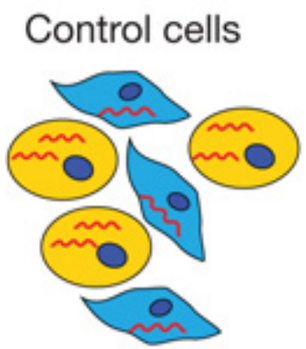
The expanding single-cell chemical genomics toolkit





Wyatt, A. *et. al.* (**2025**) *Biochemical Journal (accepted in principle)*

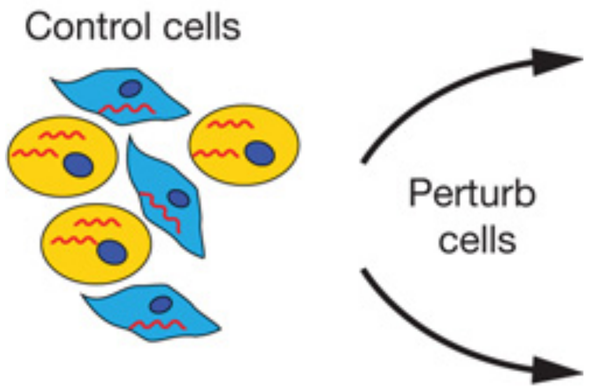
Defining the nature of molecular changes



Trapnell, C. (**2015**), *Genome Research.*

Adapted from: Liu, S., Trapnell, C. (**2016**) *F1000 Research.*

Defining the nature of molecular changes



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Trapnell, C. (**2015**), *Genome Research.*

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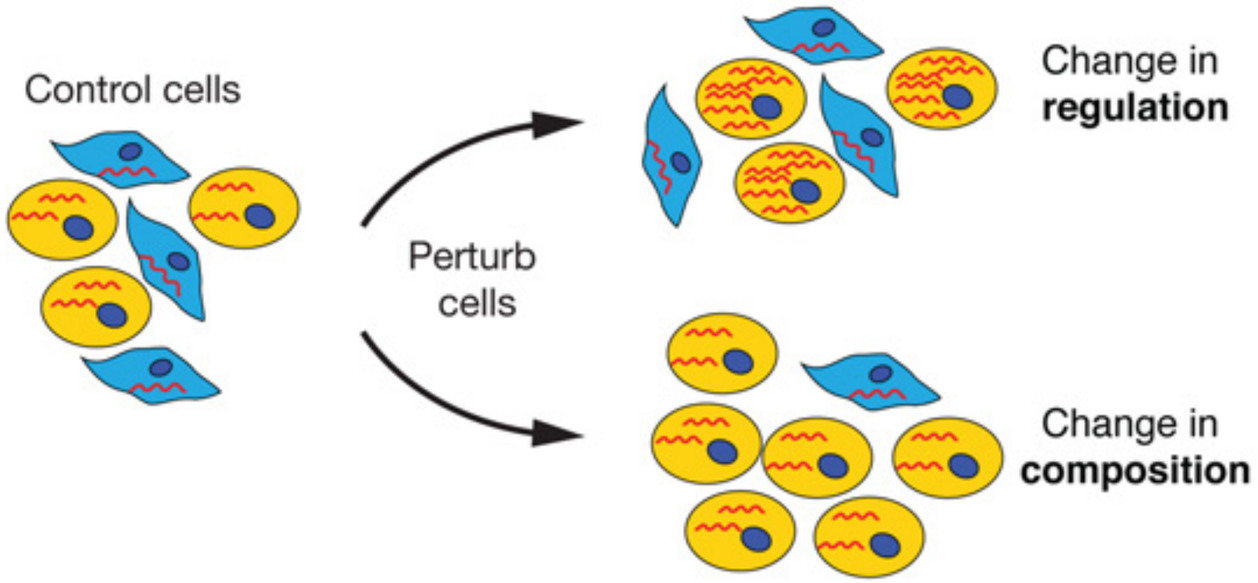
Defining the nature of molecular changes



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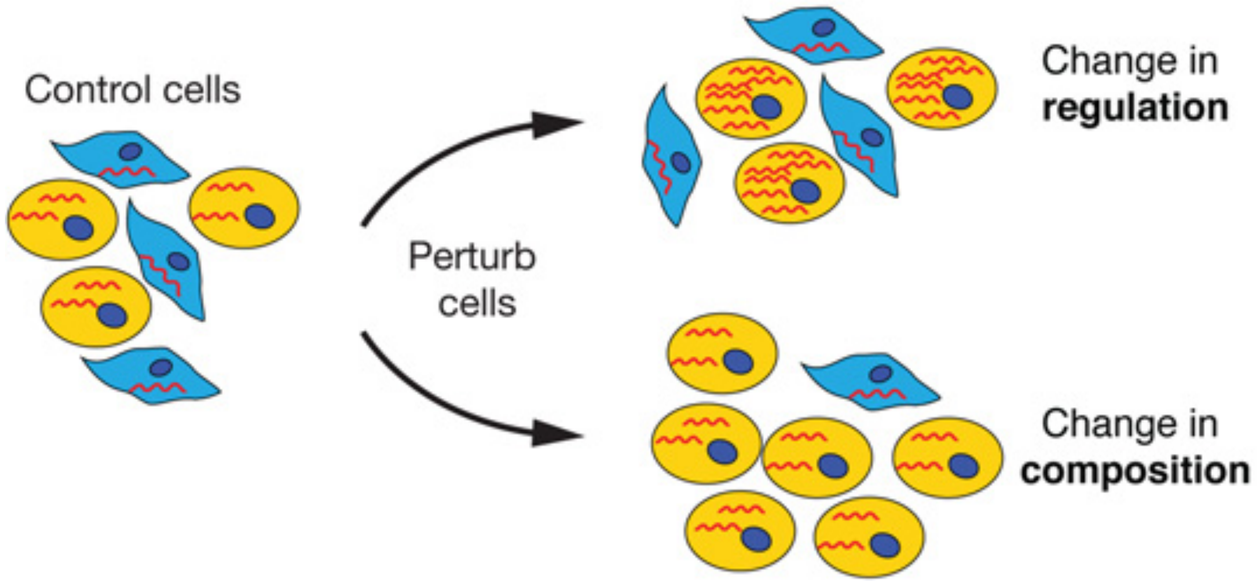
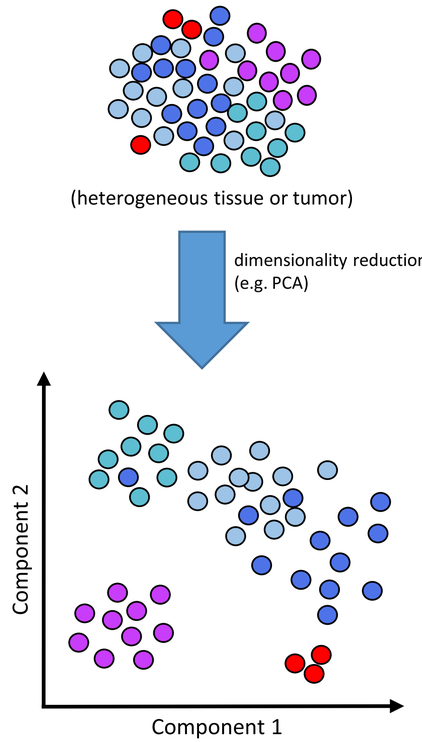
Defining the nature of molecular changes



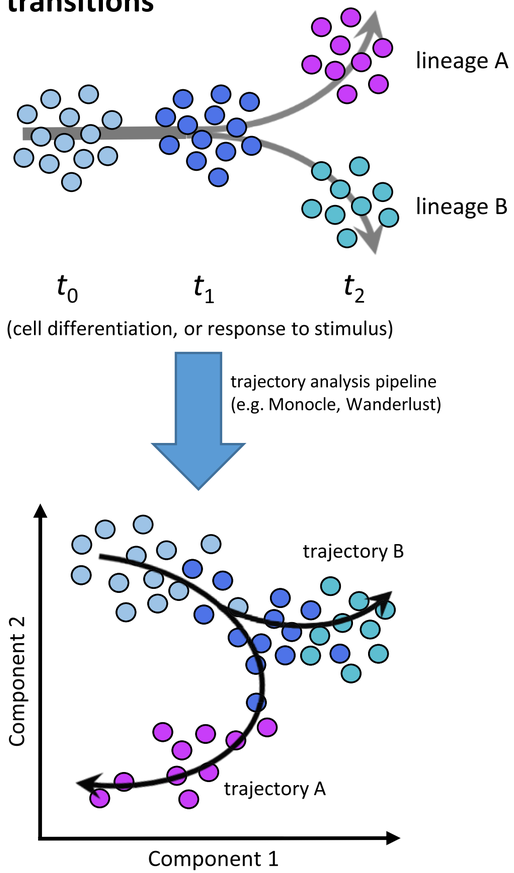
Trapnell, C. (**2015**), *Genome Research.*

Deconvolve populations

a) Deconvolving heterogeneous cell populations

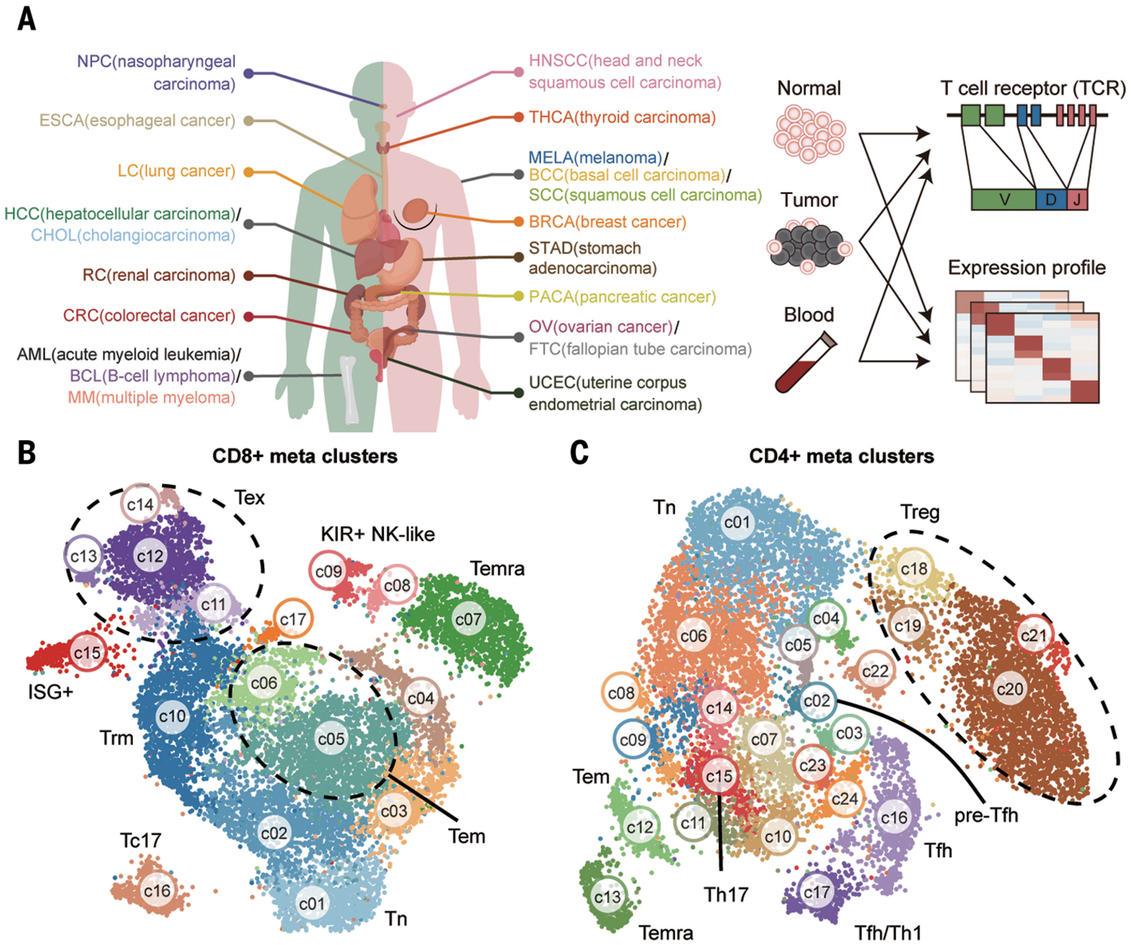


b) Trajectory analysis of cell state transitions

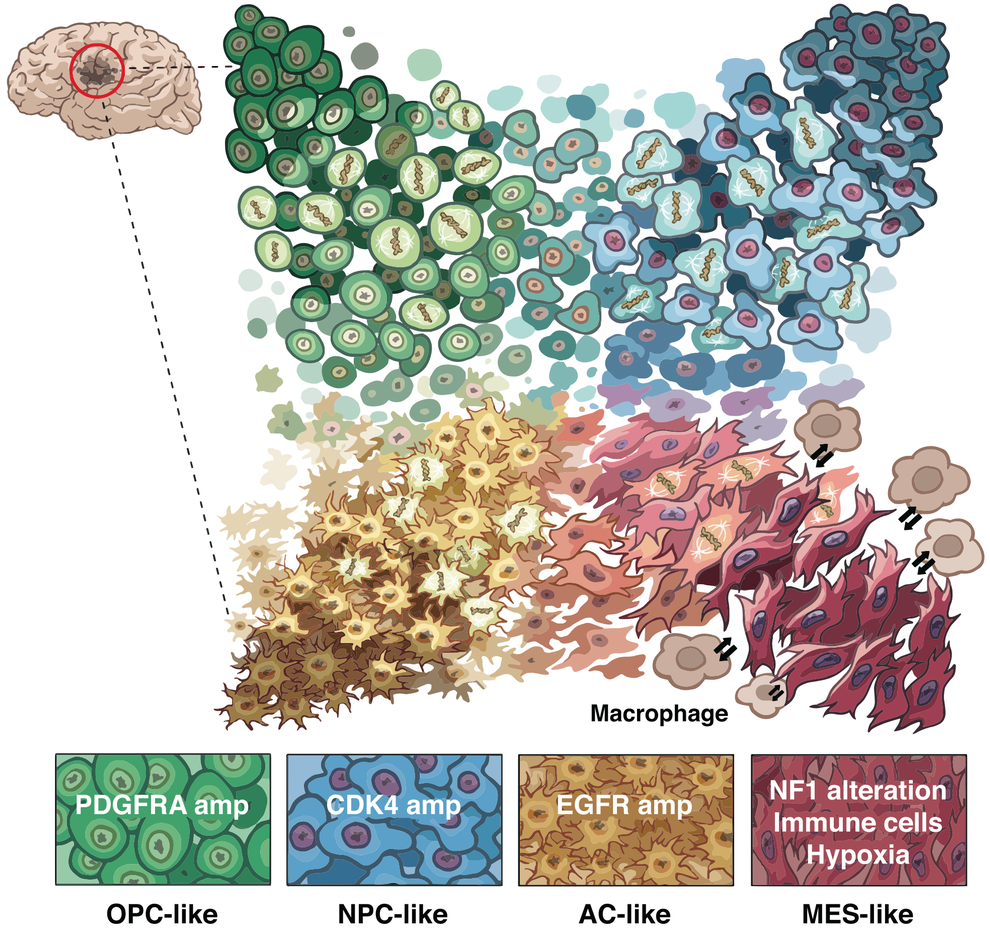


Adapted from: Liu, S., Trapnell, C. (**2016**) *F1000 Research.*

Single-cell approaches shed light on tumor heterogeneity



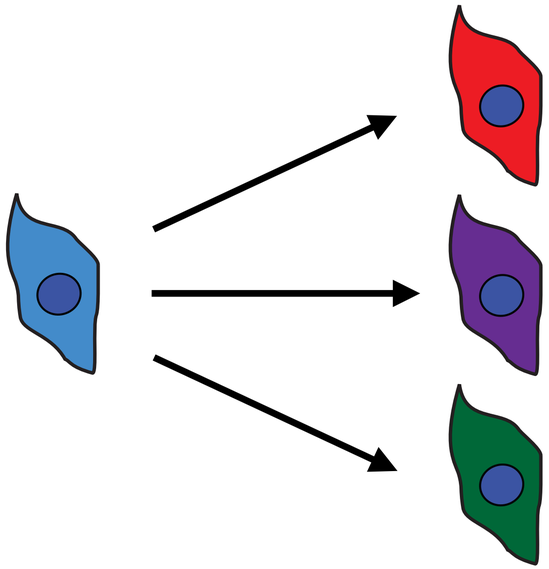
Lawson, D. (**2021**) *Science*



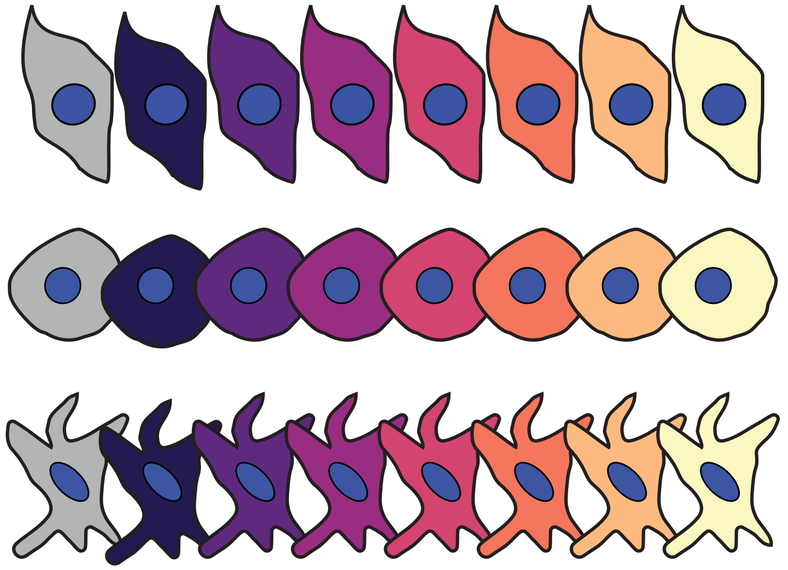
Neftel, C. *et. al.* (**2019**) *Cell*

Heterogeneity in drug response

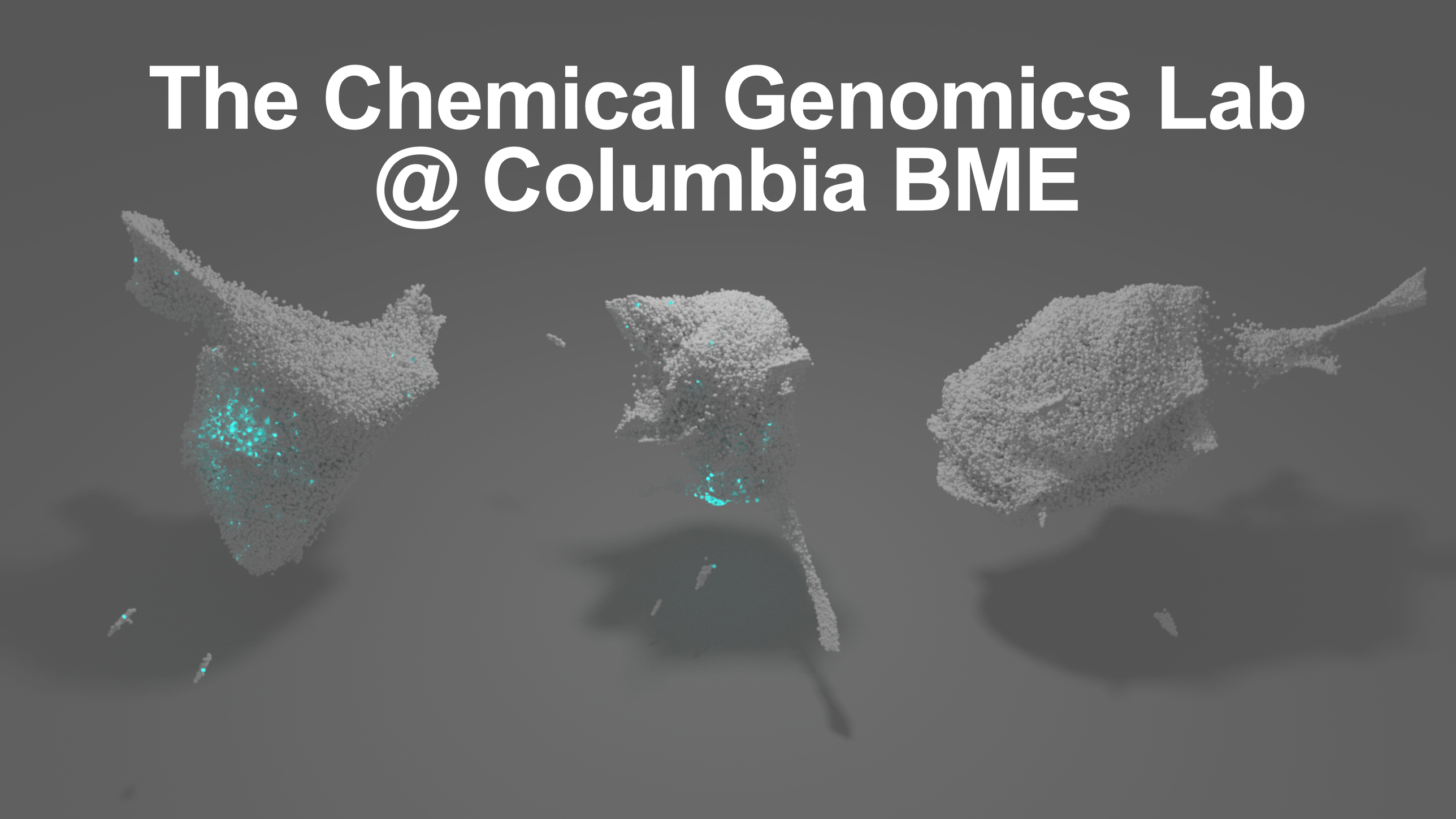
Induction of multiple cell states



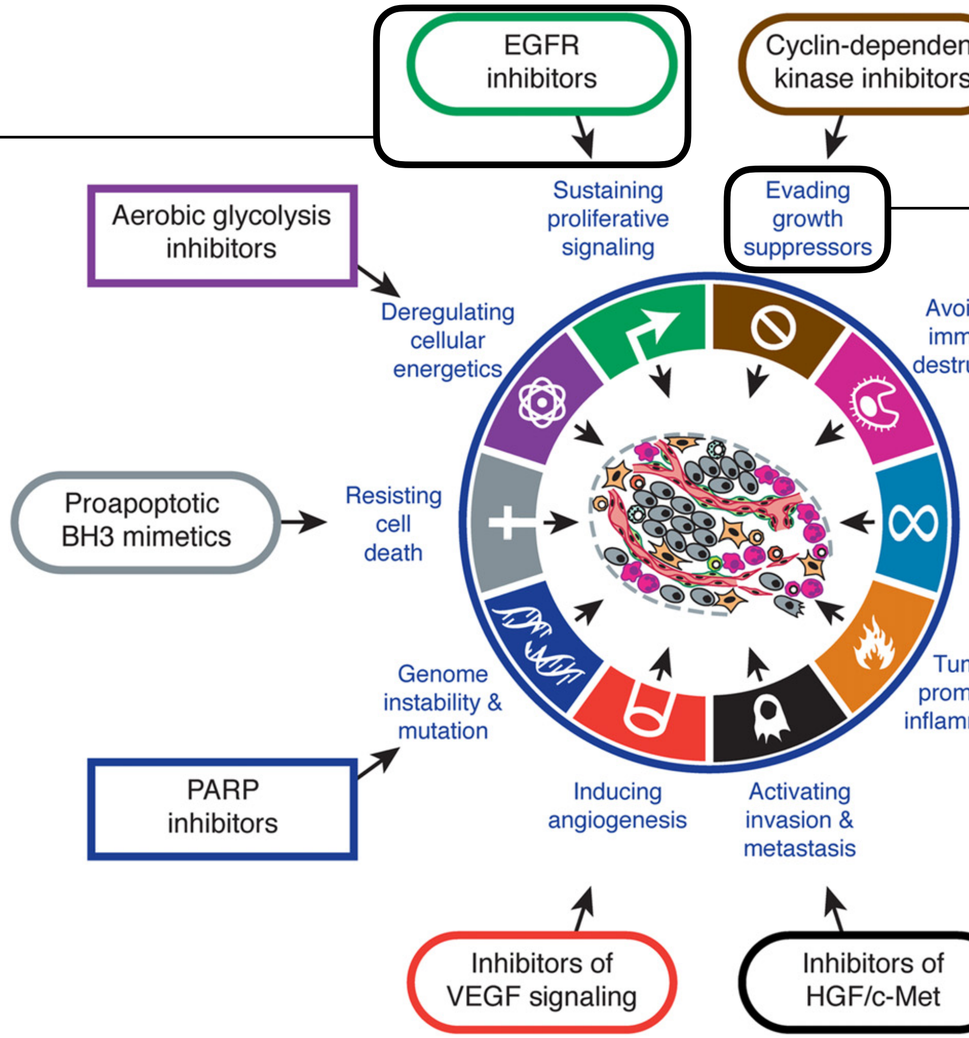
Continuum of cellular response



The Chemical Genomics Lab @ Columbia BME



Targeting cancer associated processes



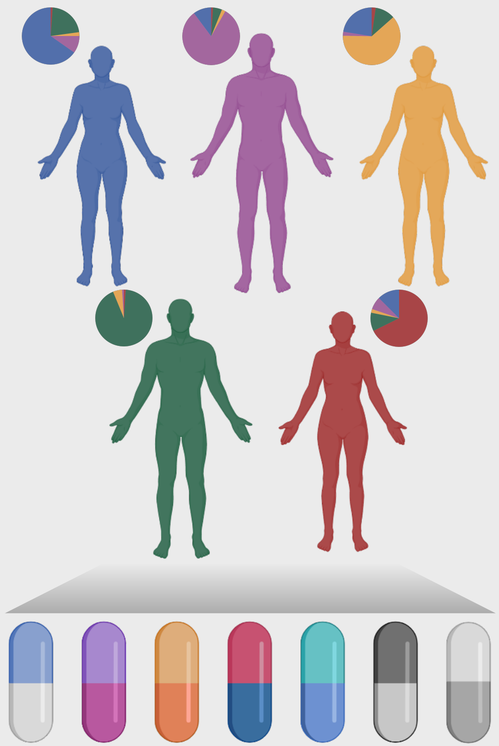
AEE788/Afatinib/
AG1478/Canertinib/
Cetuximab/
Dacomitinib/DIM/
Erlotinib/Genistein/
Gefitinib/GW583340/
HKI357/Lapatinib/
LavendustinA/
Osimertinib/
Panitumumab/Pelitinib

*APC/ARID1A/
ARID1B/ATM/BAP1/
BID/BRCA1/BRCA2/
CASP8/CDKN1B/
CDKN2A/CDH1/
CHEK1/CTCF/GATA3/
MLH1/MLL3/NCOR1/
NF1/PTEN/RAD51/
RB1/RUNX1/SETD2/
STK11/TP53/PTPN22/
PTPRD*

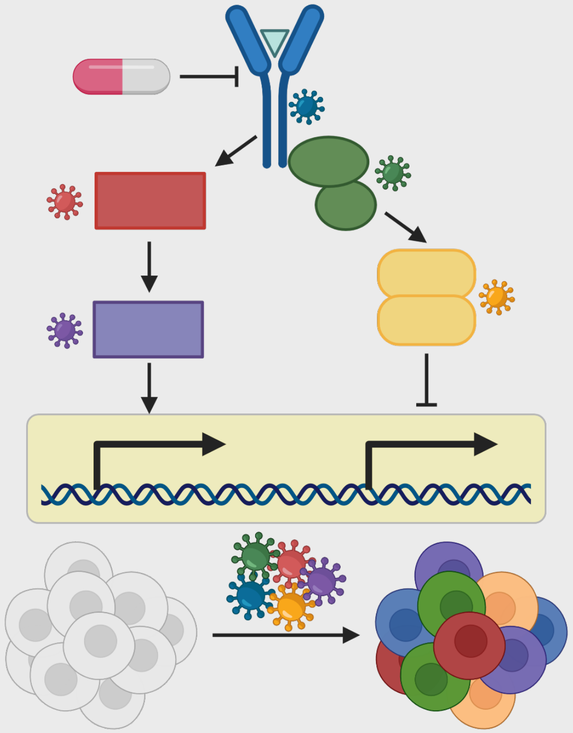
Hanahan, D. and Weinberg, R.A. (**2011**) *Cell.*

Multiplex single-cell perturbation genomics

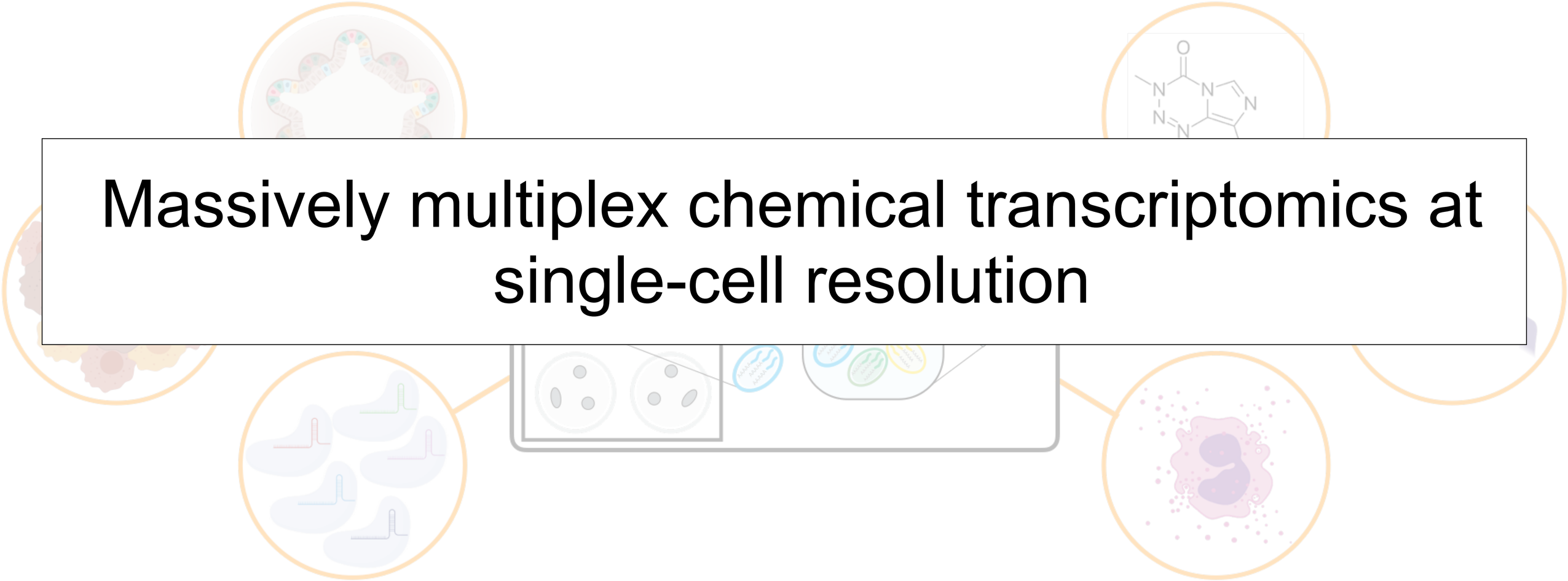
Map the transcriptional response to therapy



Regulation of treatment induced transcription

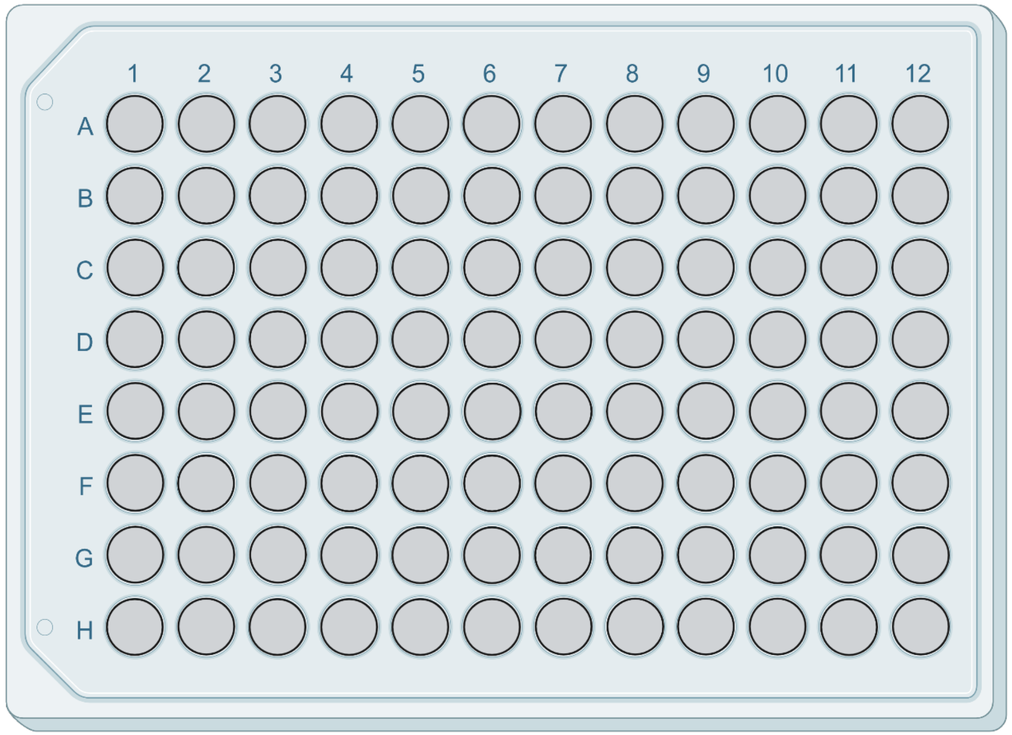


Massively multiplex chemical transcriptomics at single-cell resolution



*Srivatsan, S., *McFaline-Figueroa, J.L., *Ramani, V. *et al.* (**2020**). Science.

High throughput screens (HTS) allow for multiplex perturbation screens



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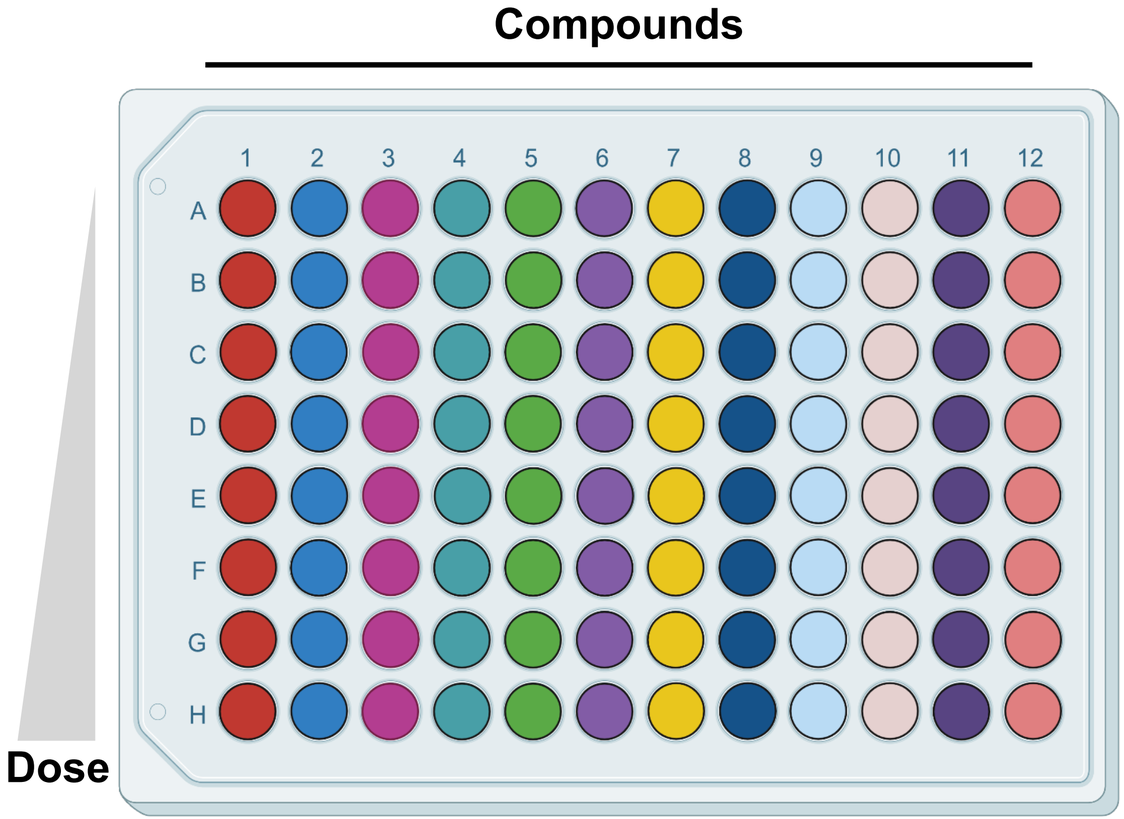
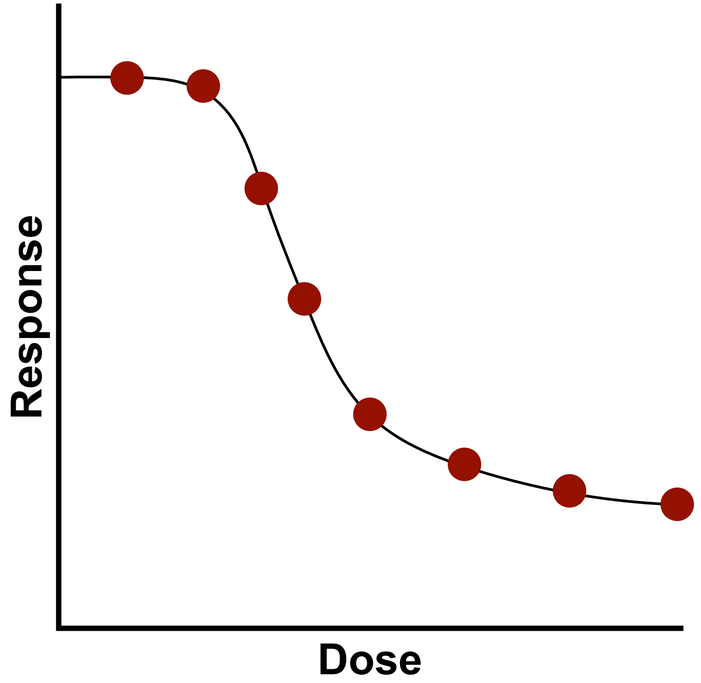
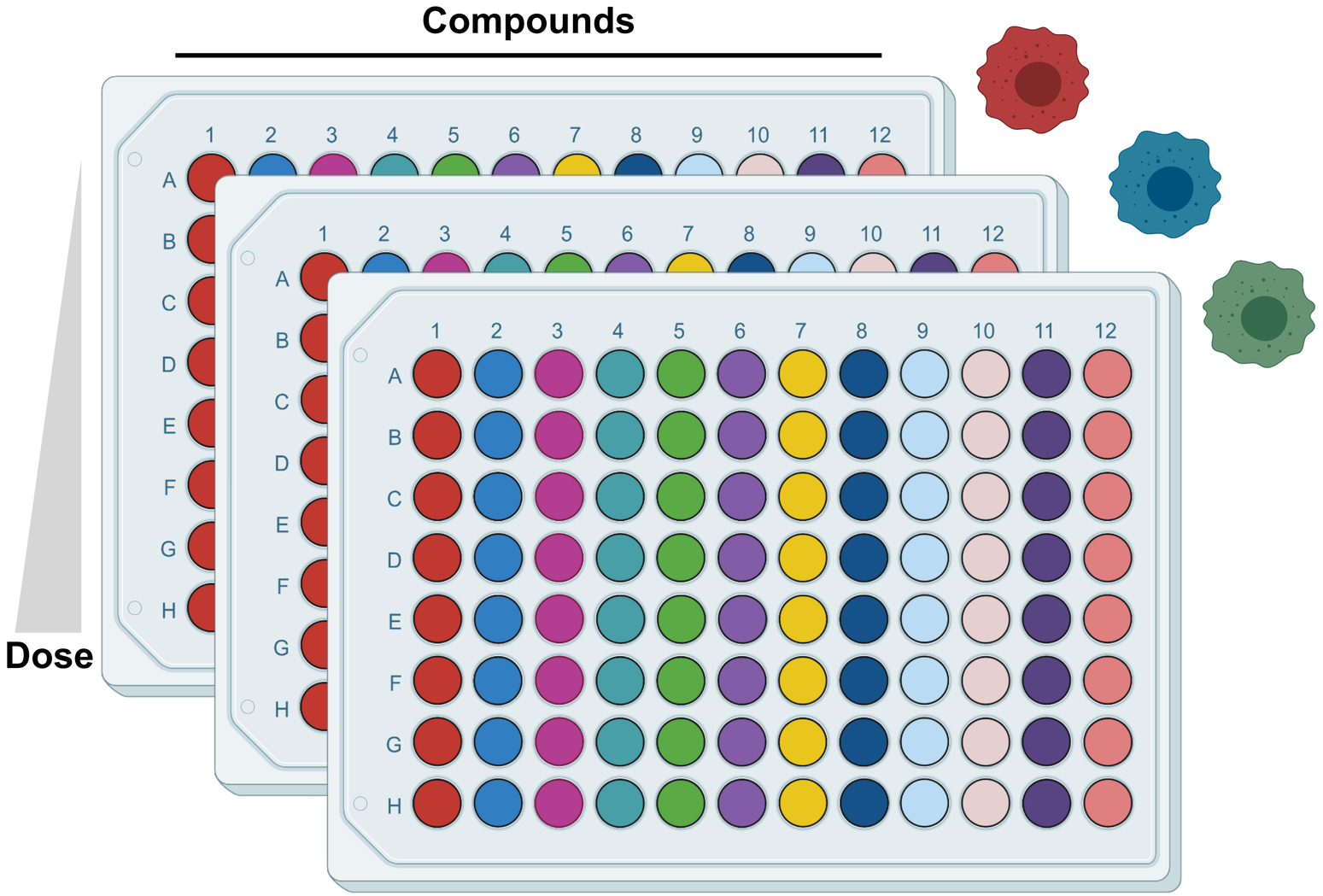
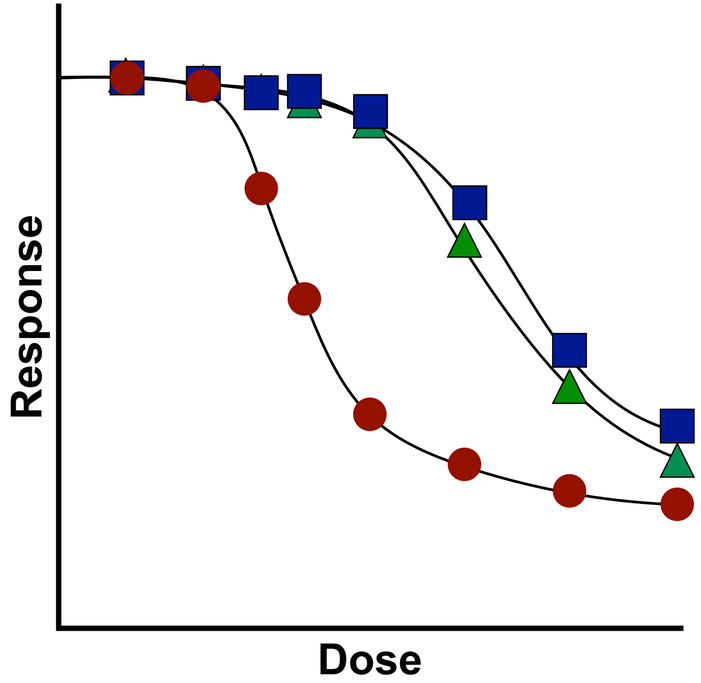




High throughput screens (HTS) allow for multiplex perturbation screens

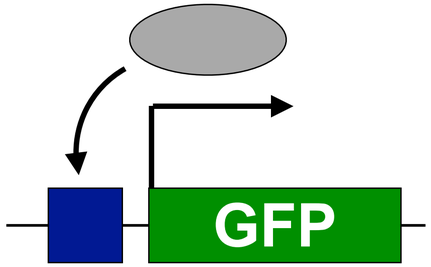


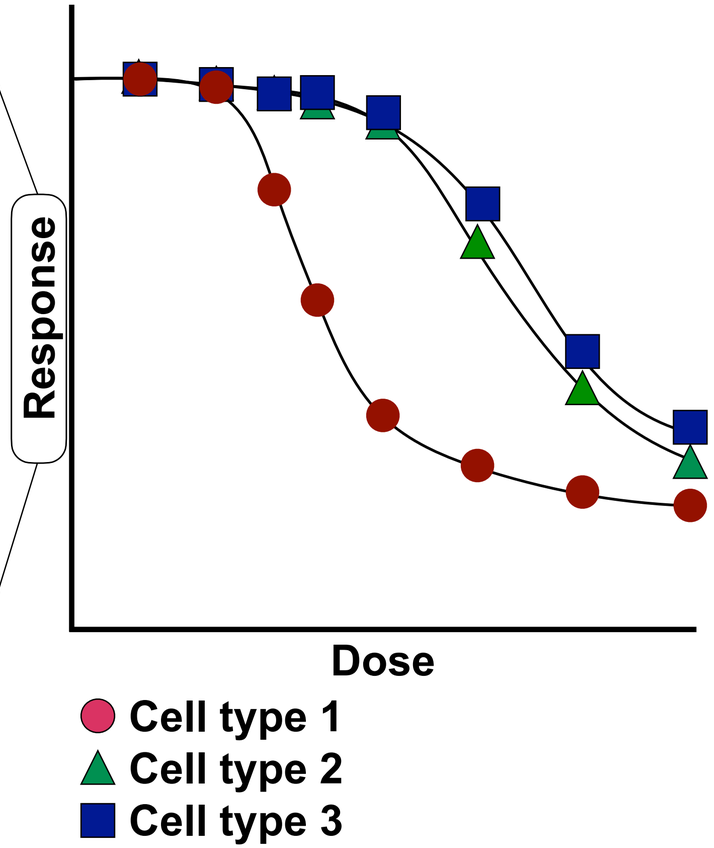


HTS is largely coupled to gross phenotypic or extremely specific molecular readouts

Viability

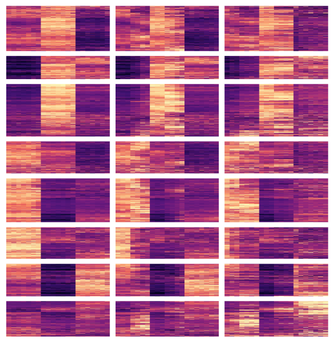
Reporter expression



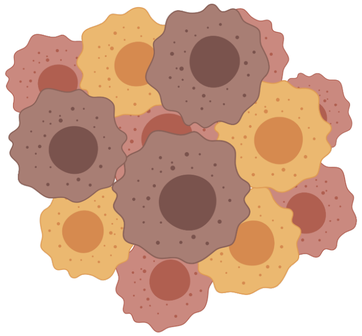


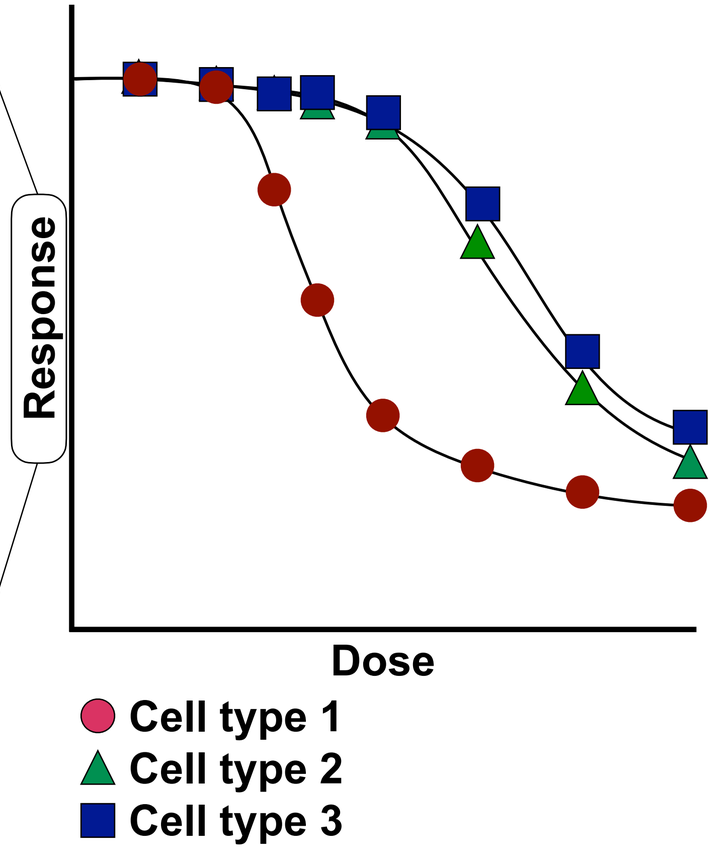
Transcriptomic readout of HTS screens

Global transcriptome



Complex populations

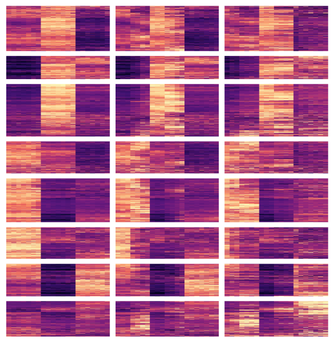




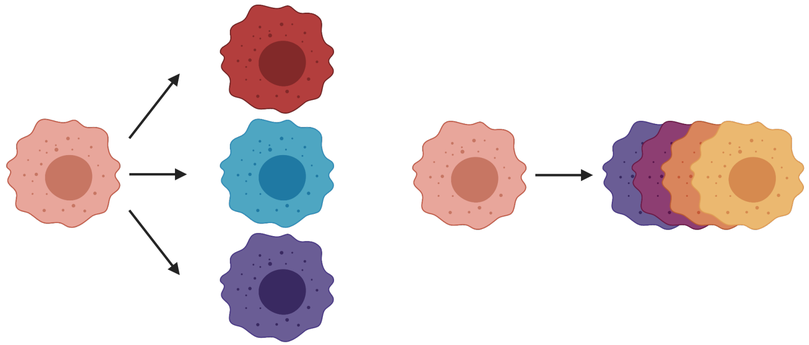
Ye, C. *et al*. (**2018**). *Nat Comm.* - Drug-Seq
Bush, E.C. et al. (**2017**). *Nat Comm.* - PLATE-Seq

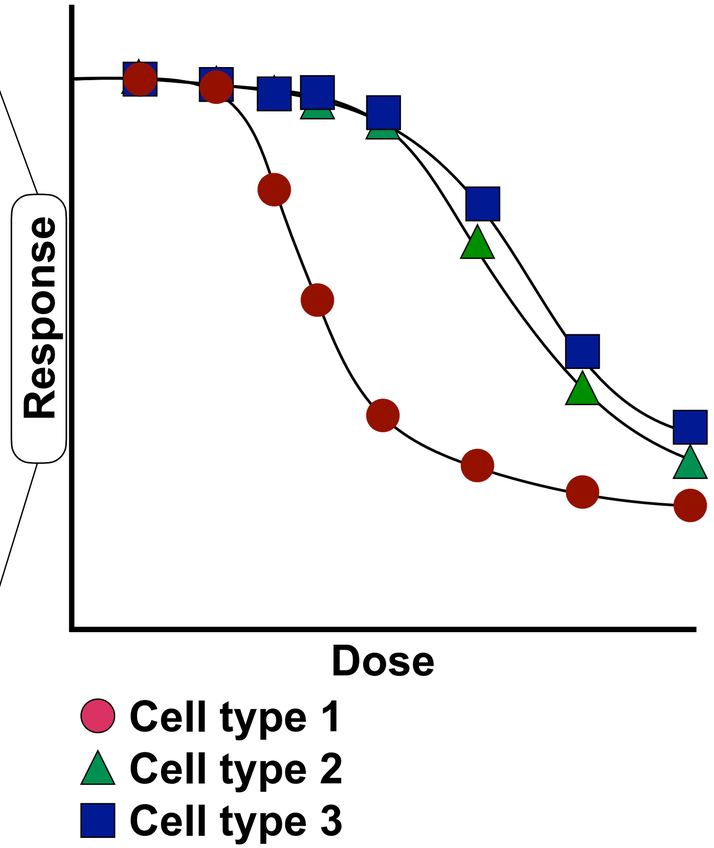
Transcriptomic readout of HTS screens

Global transcriptome



Heterogeneous response

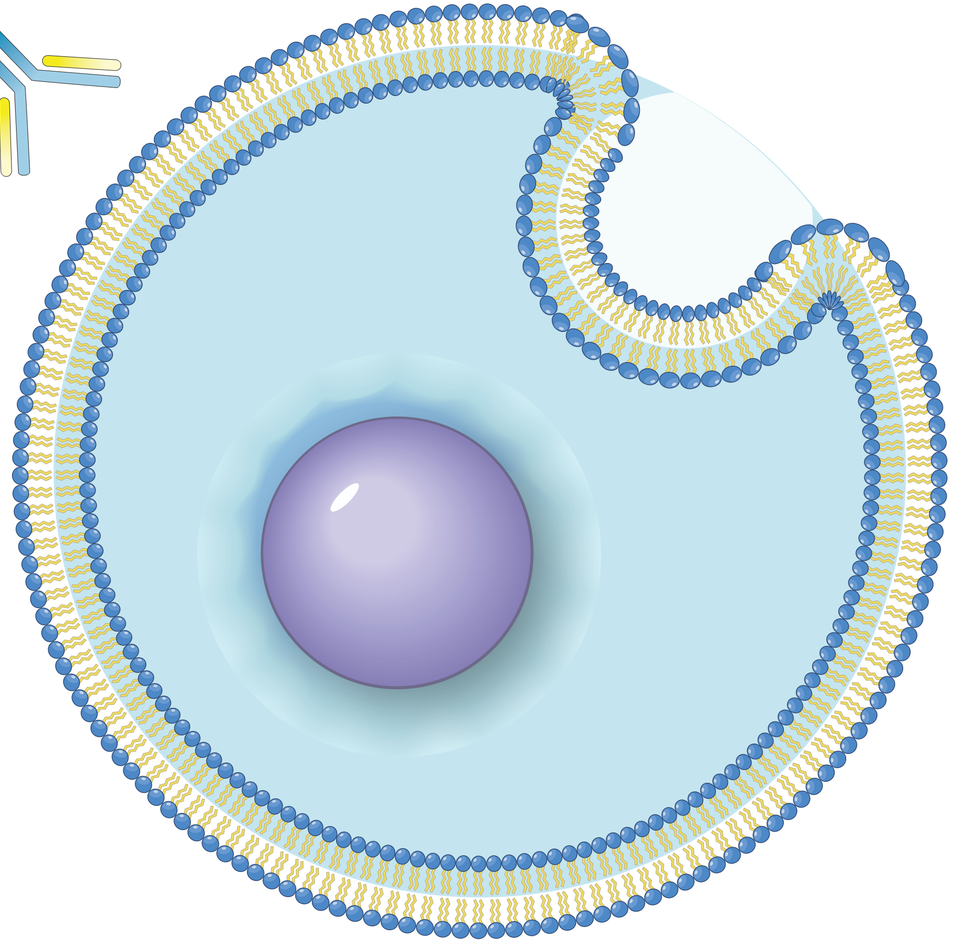


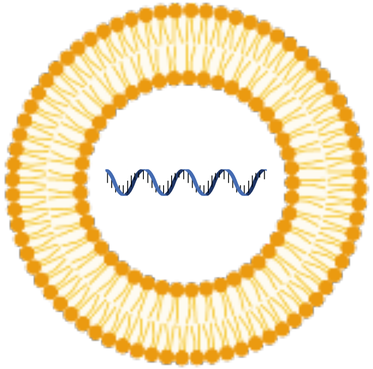


Ye, C. *et al*. (**2018**). *Nat Comm.* - Drug-Seq
Bush, E.C. et al. (**2017**). *Nat Comm.* - PLATE-Seq

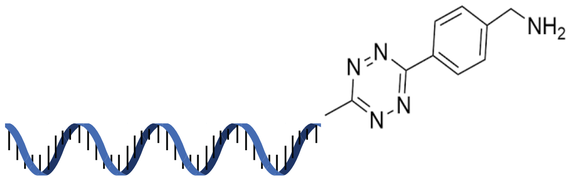
Single-cell “hashing” improves sample throughput

Stoeckius *et al*
Genome Biology 2018

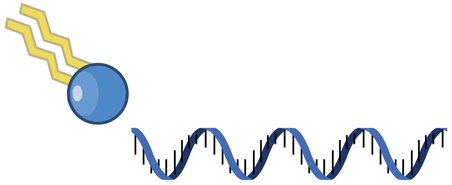




Shin *et al*
Science Advances 2019



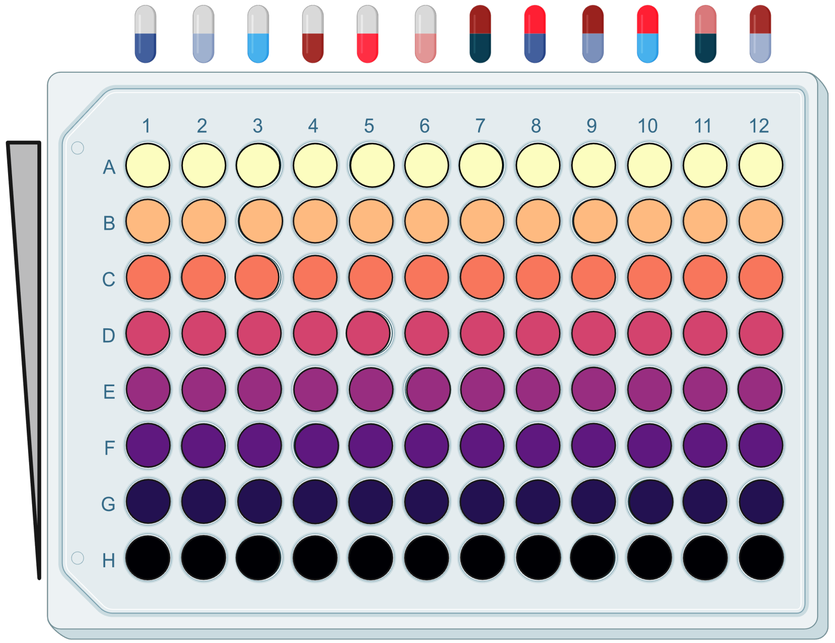
Gehring *et al*
biorXiv 2018



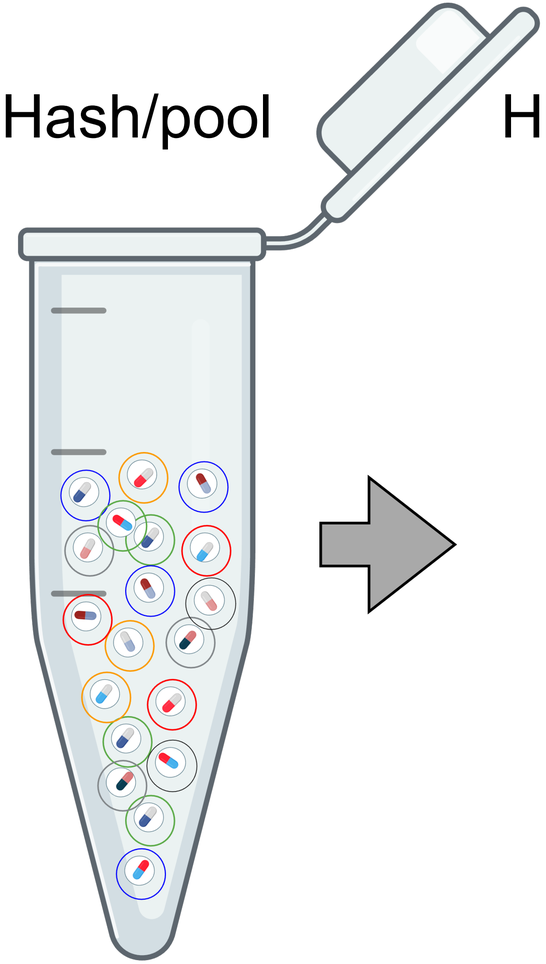
McGinnis *et al*
Nature Methods 2019

sci-Plex: Single-cell sample multiplexing

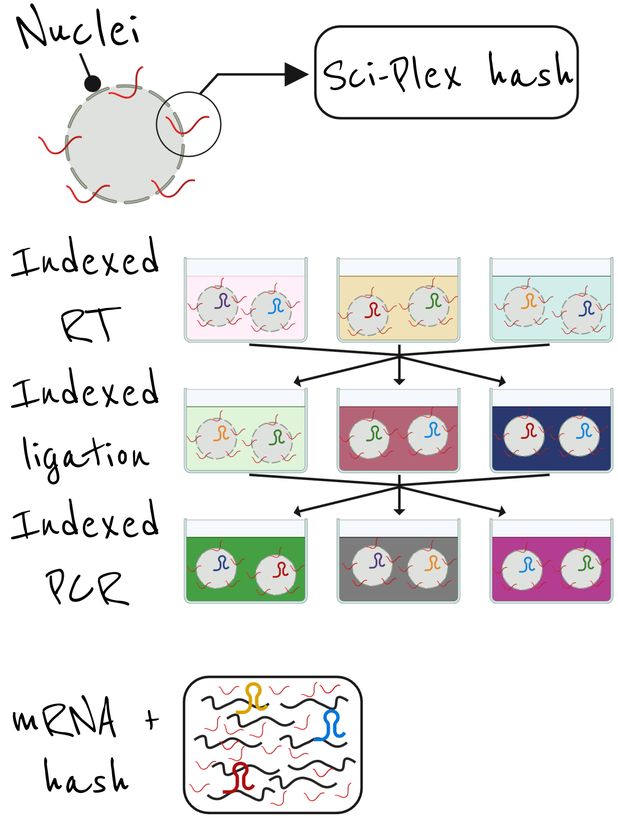
Chemically perturb



Hash/pool



Highly multiplex sci-RNA-seq



*Srivatsan, S., *McFaline-Figueroa, J.L., *Ramani, V. *et. al.* (**2020**), *Science*.

sci-RNA-seq:
*Cao, *Spielmann, *et. al.* (**2019**), *Nature*.

HTS single-cell profiling of chemical perturbations

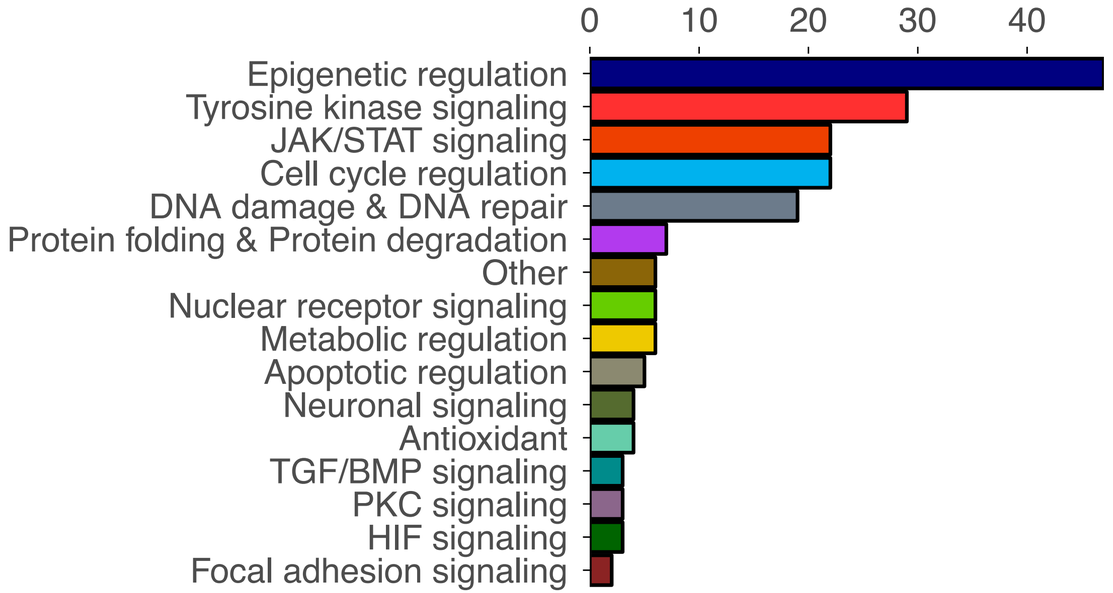
574,457 single-cell transcriptomes

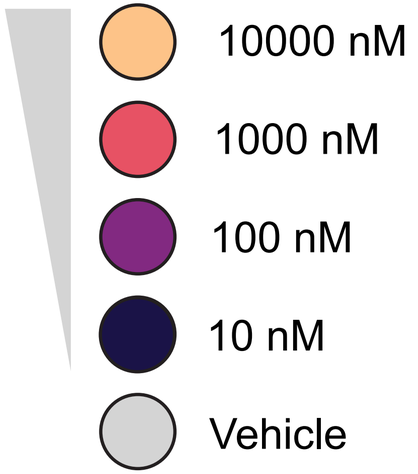
4,608 conditions (wells)

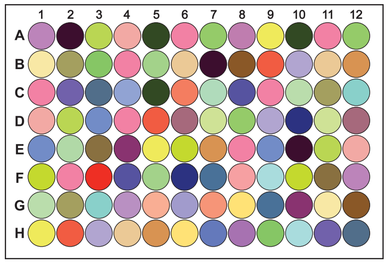
A549

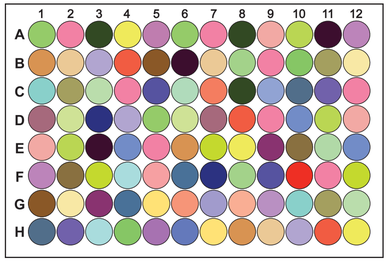
K562

MCF7





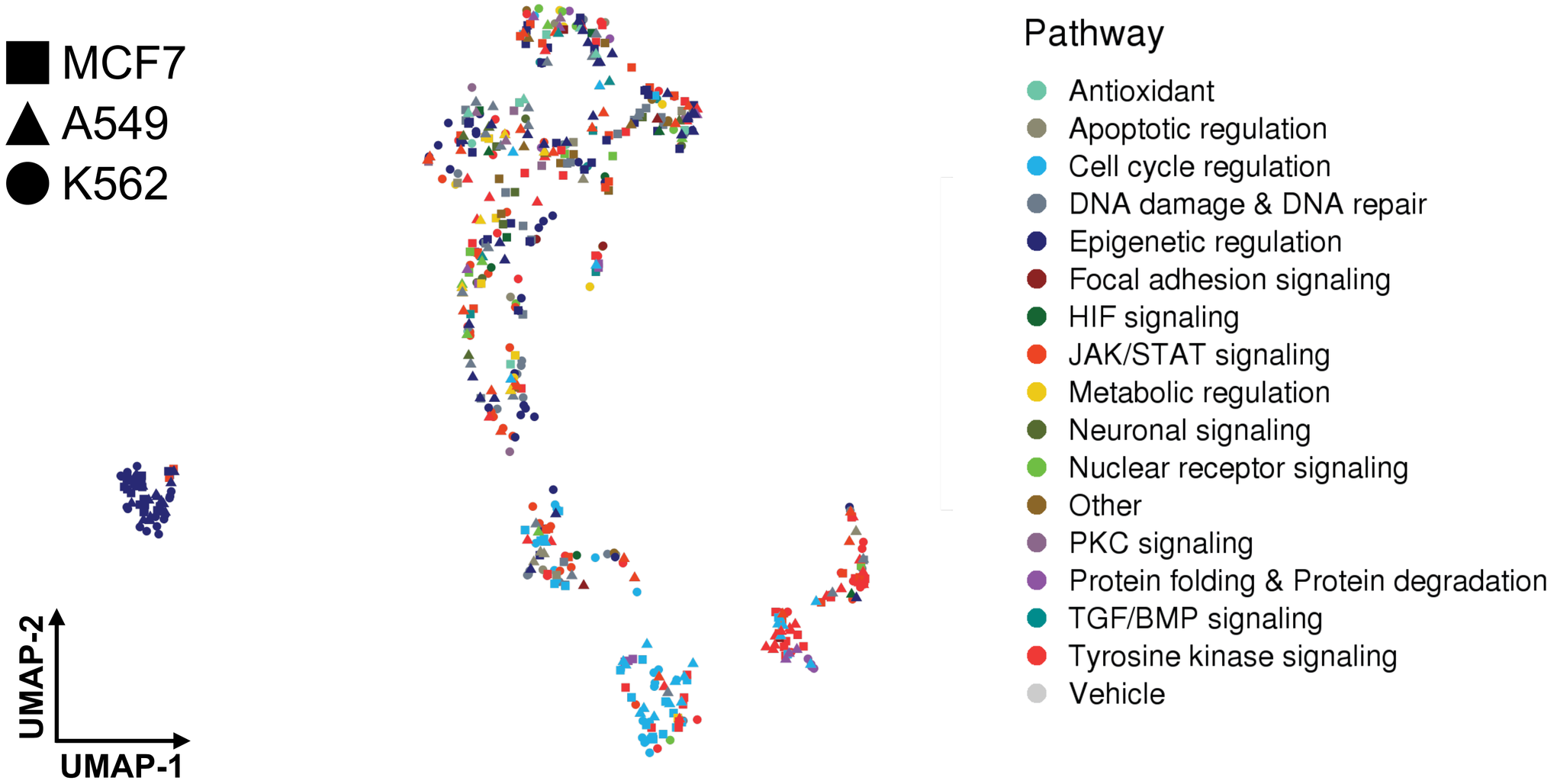




3 cell lines X 188 compounds X 4 doses X 2 replicates

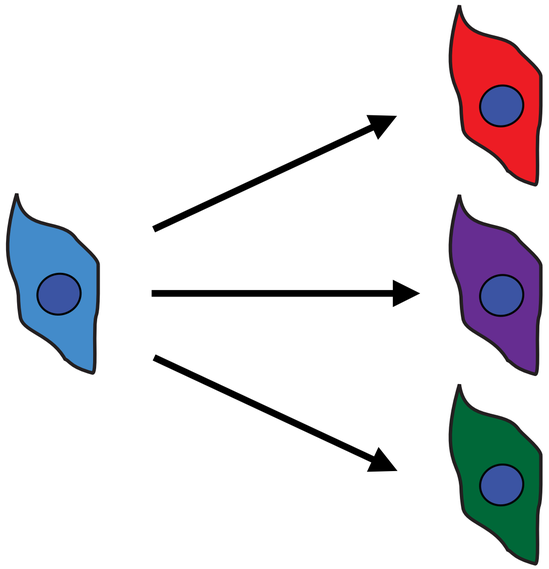
*Srivatsan, S., *McFaline-Figueroa, J.L., *Ramani, V. *et al.* (**2020**). Science.

sci-Plex recovers commonalities of compounds with similar mechanisms of action



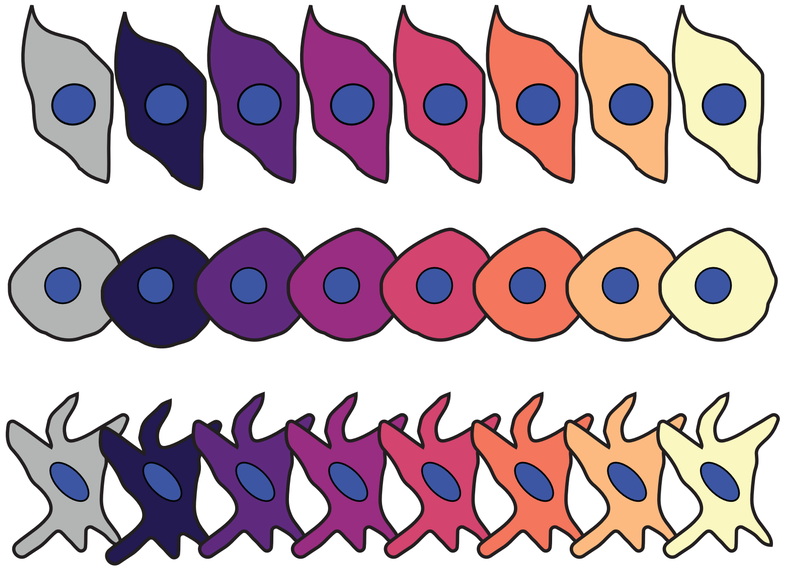
sci-Plex reveals heterogeneity in drug response

Induction of multiple cell states

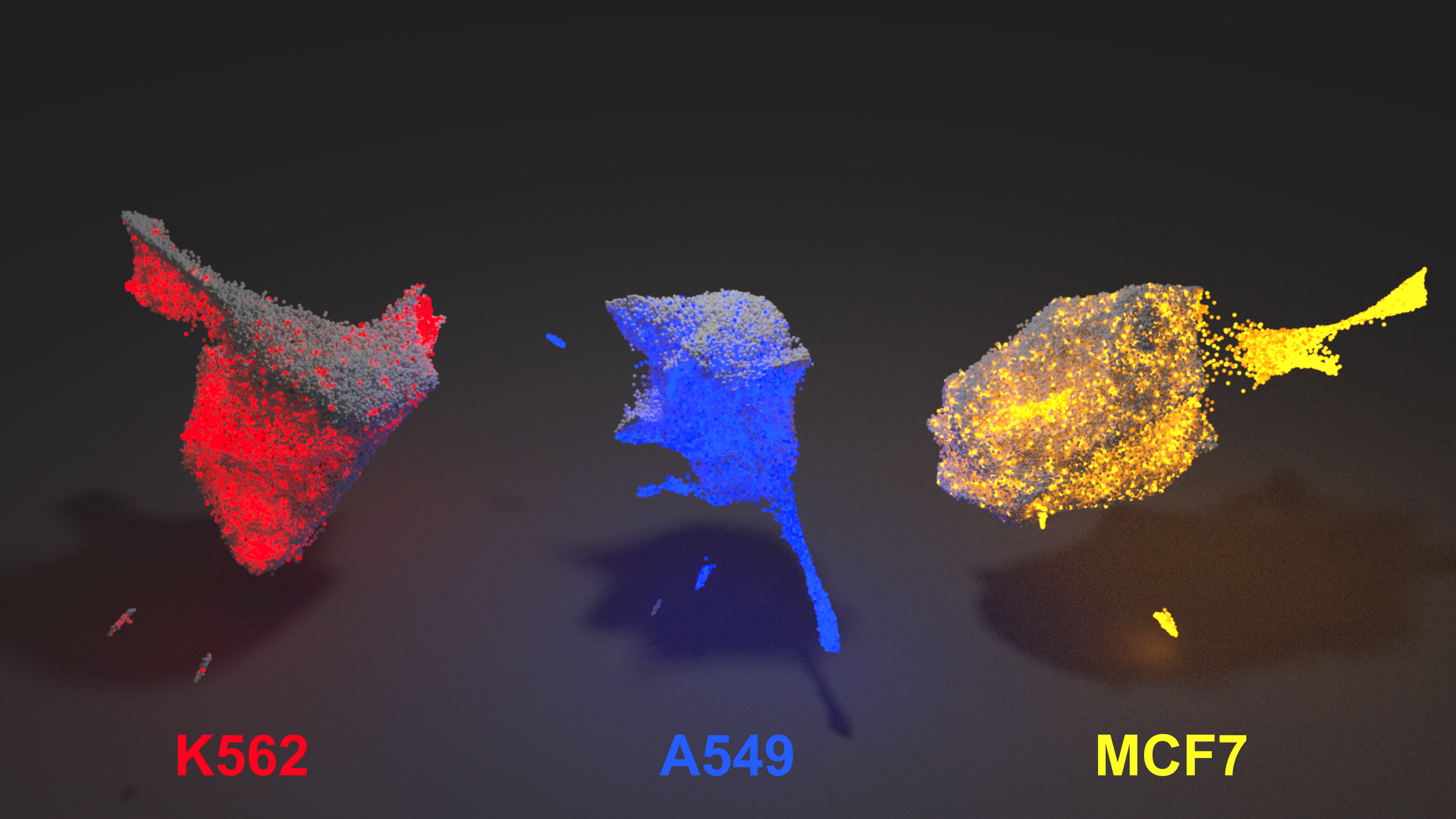


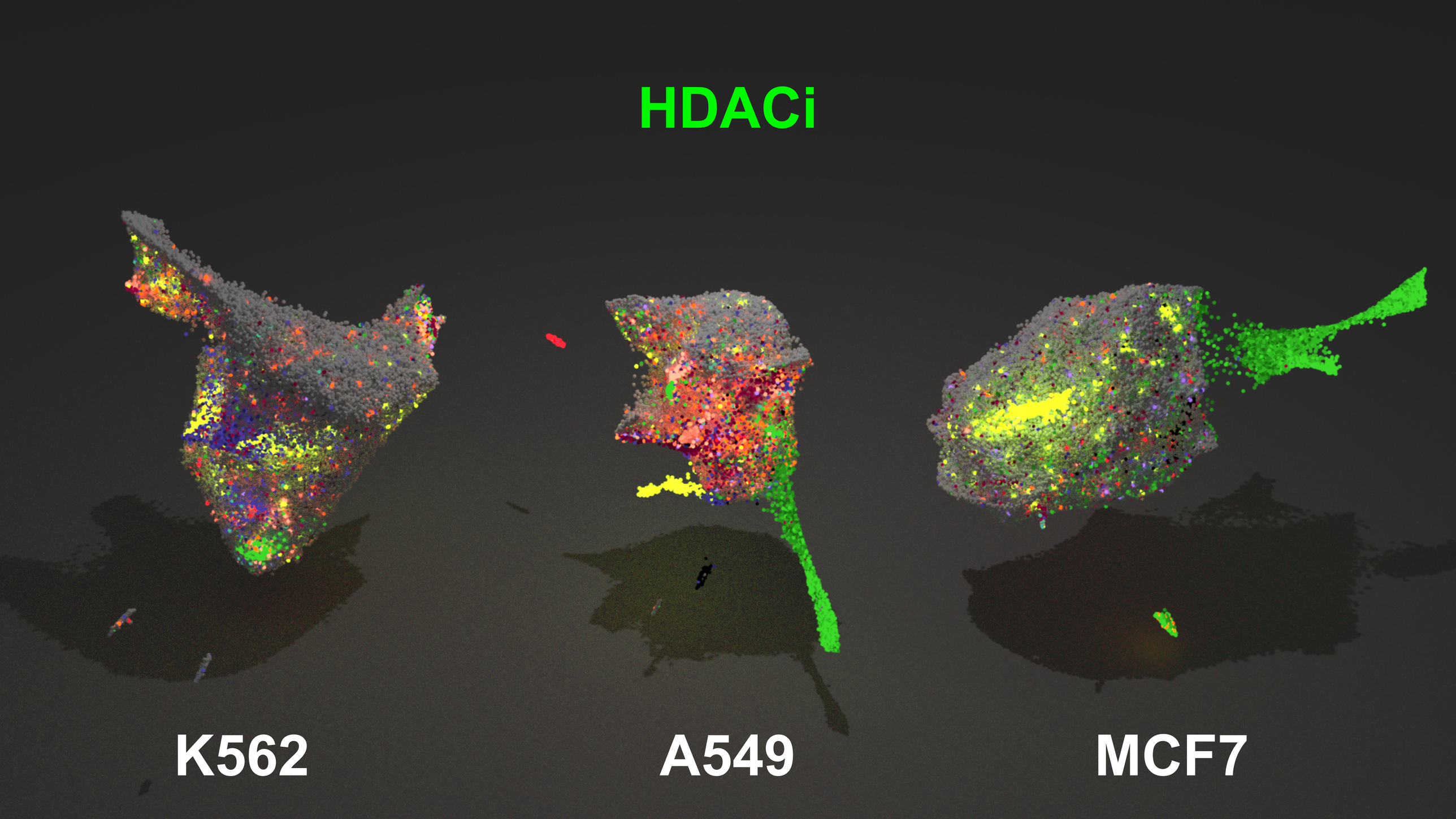
Microtubule targeting agents

Continuum of cellular response

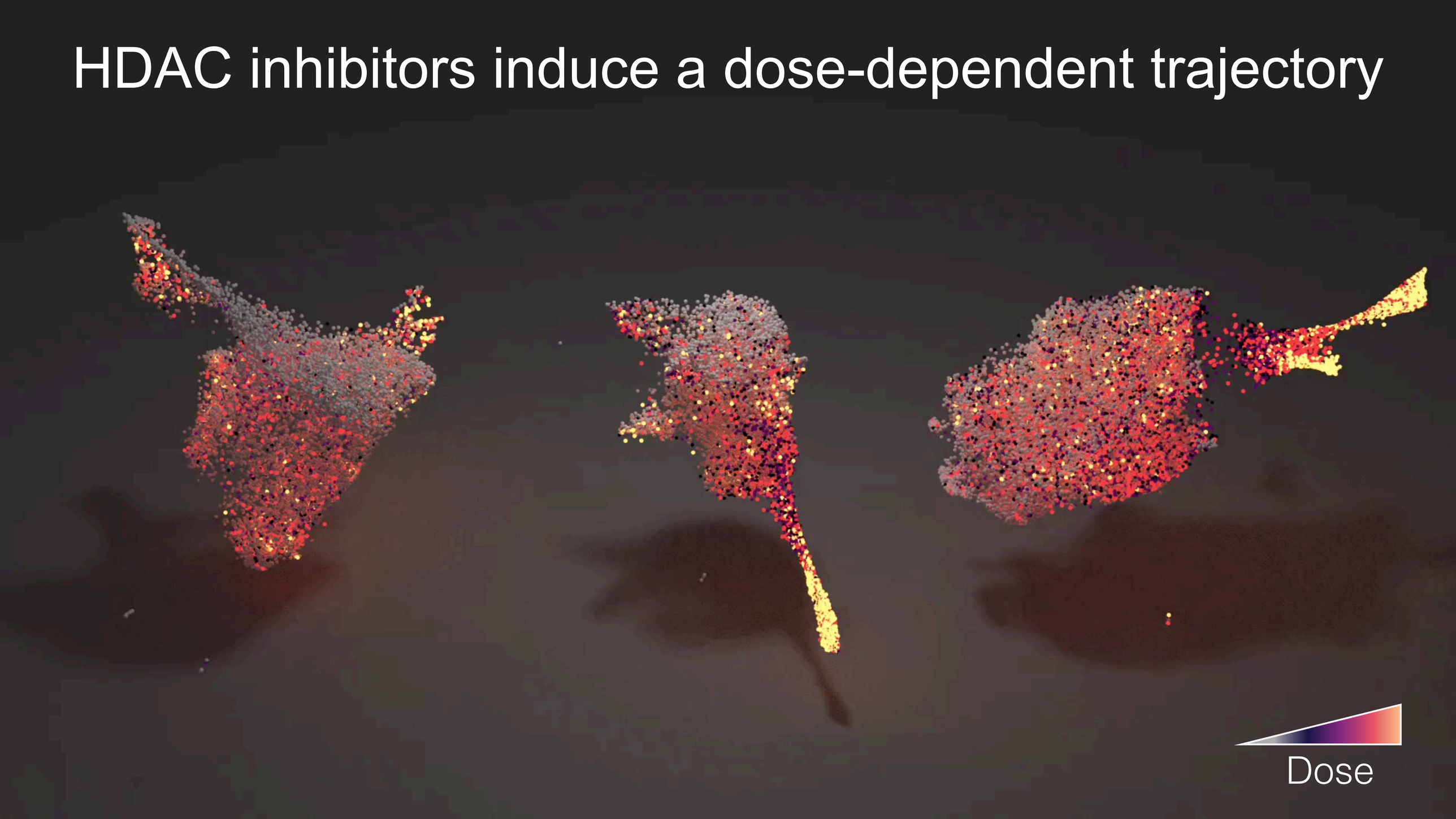


HDACi ⟞ Ac-CoA metabolism

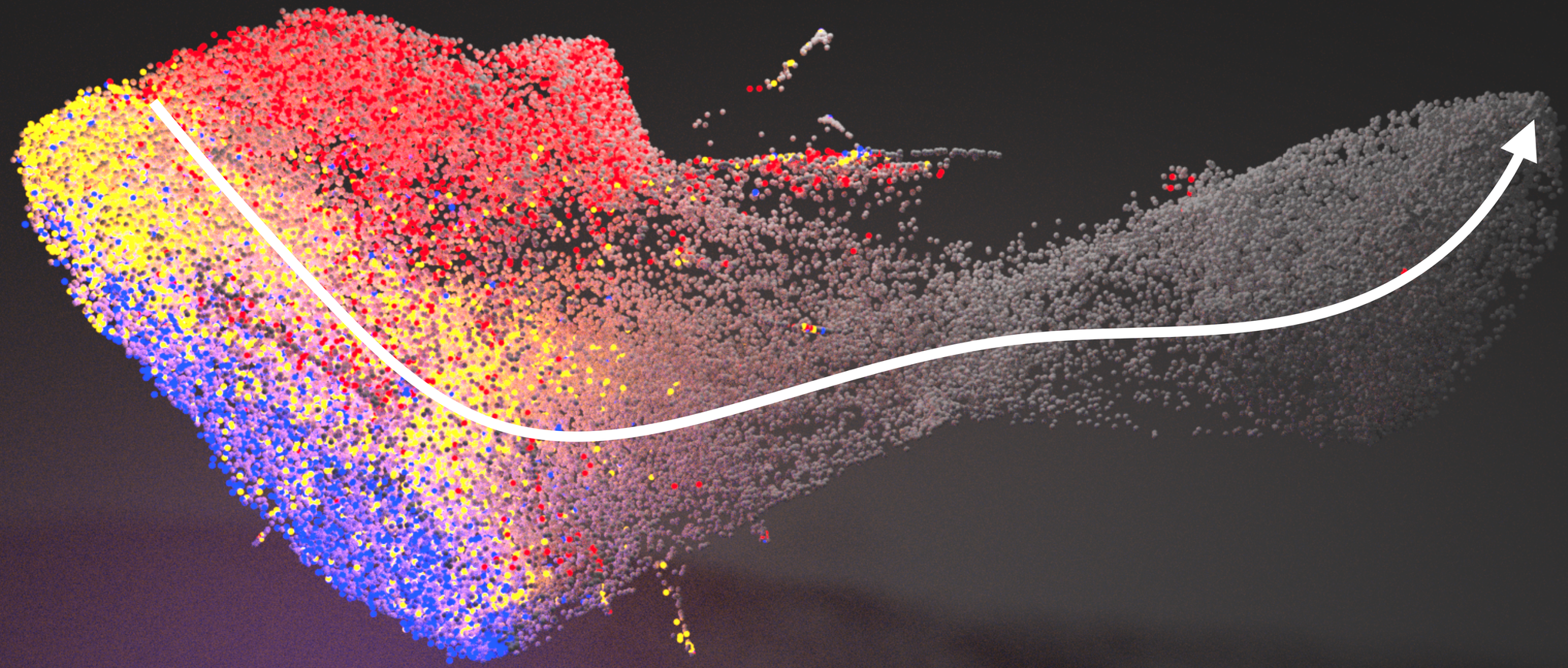

K562
A549
MCF7


HDACi
K562
A549
MCF7

HDAC inhibitors induce a dose-dependent trajectory



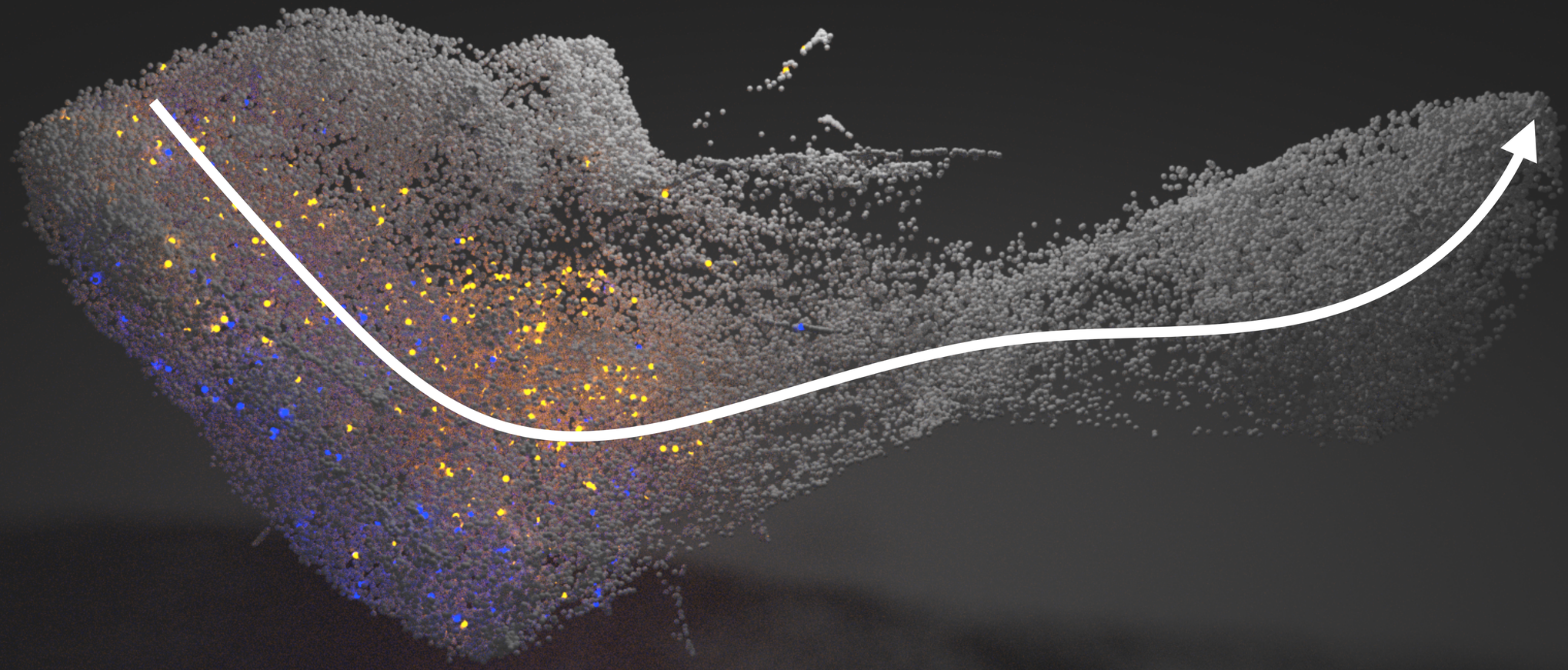
Vehicle



K562 A549 MCF7

Pracinostat

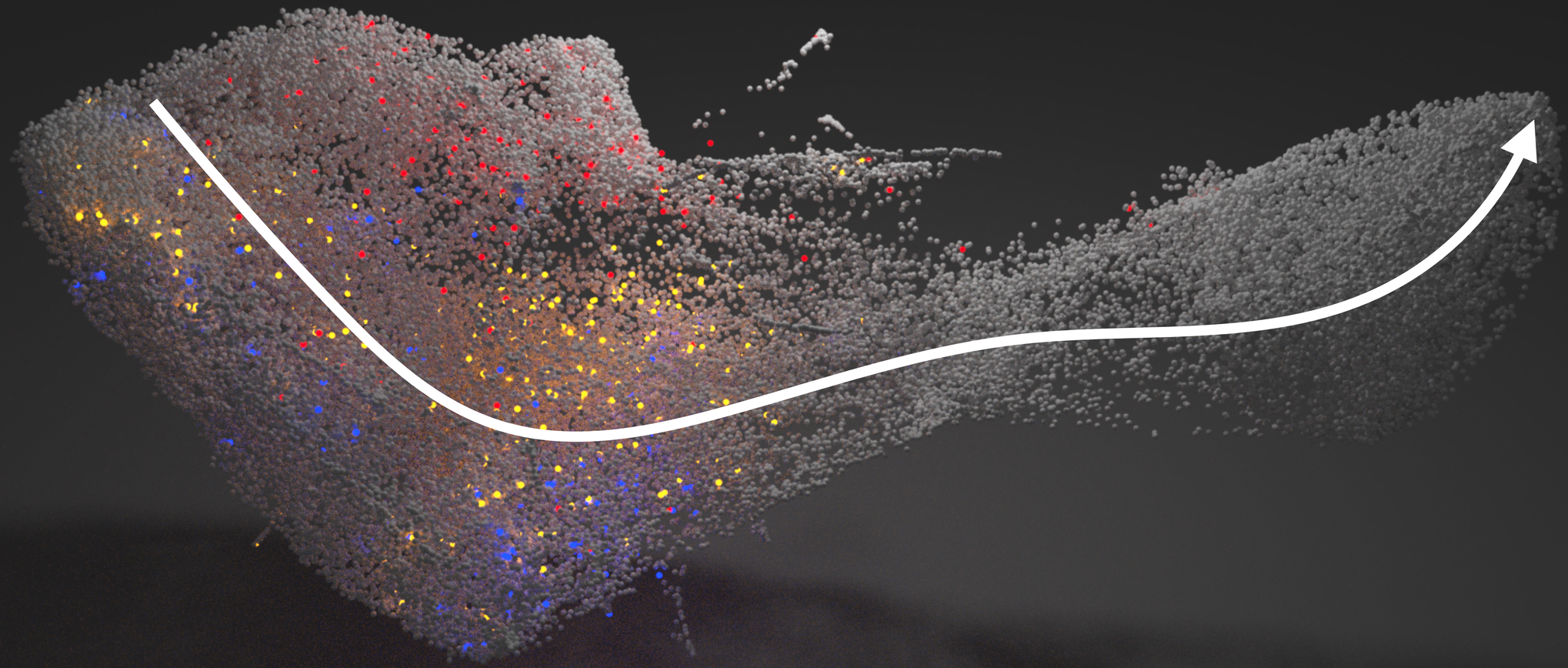
10 nM



K562 A549 MCF7

Pracinostat

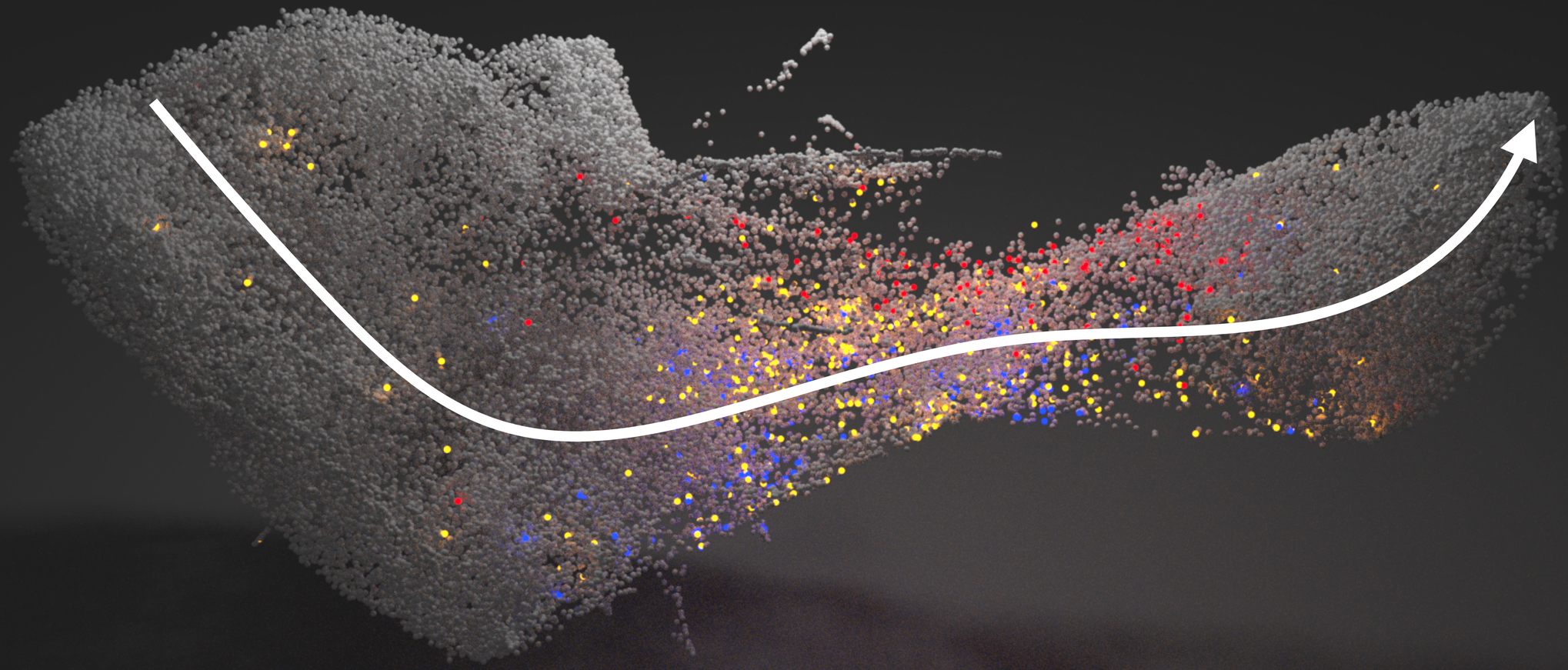
100 nM



K562 A549 MCF7

Pracinostat

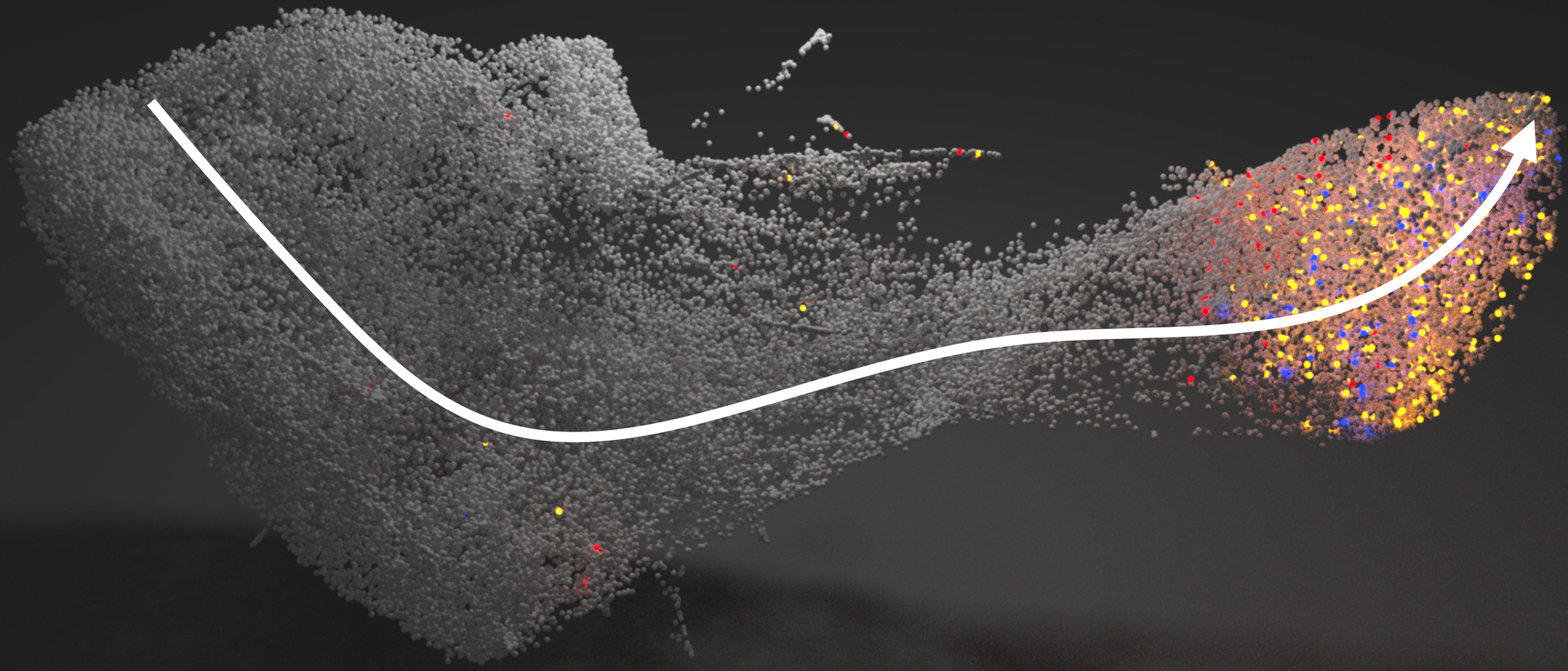
1,000 nM



K562 A549 MCF7

Pracinostat

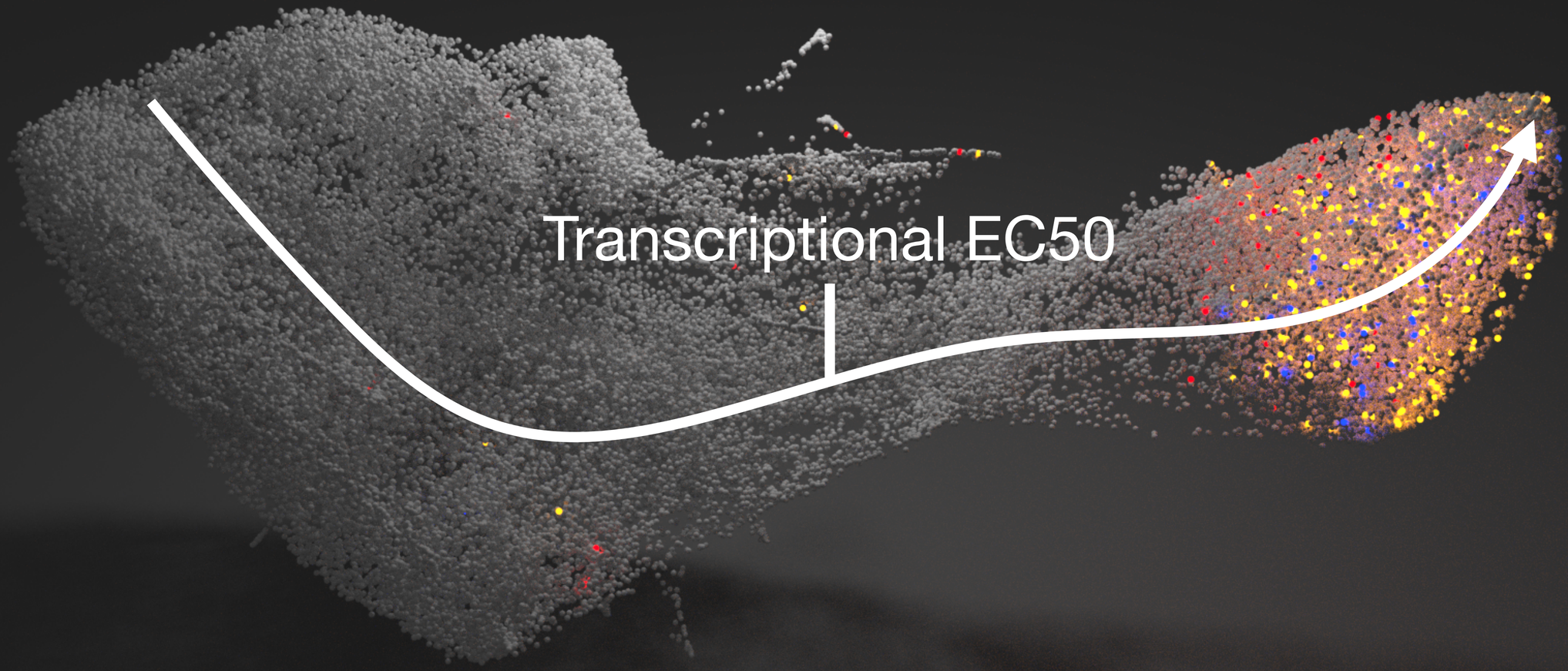
10,000 nM



K562 A549 MCF7

Pracinostat

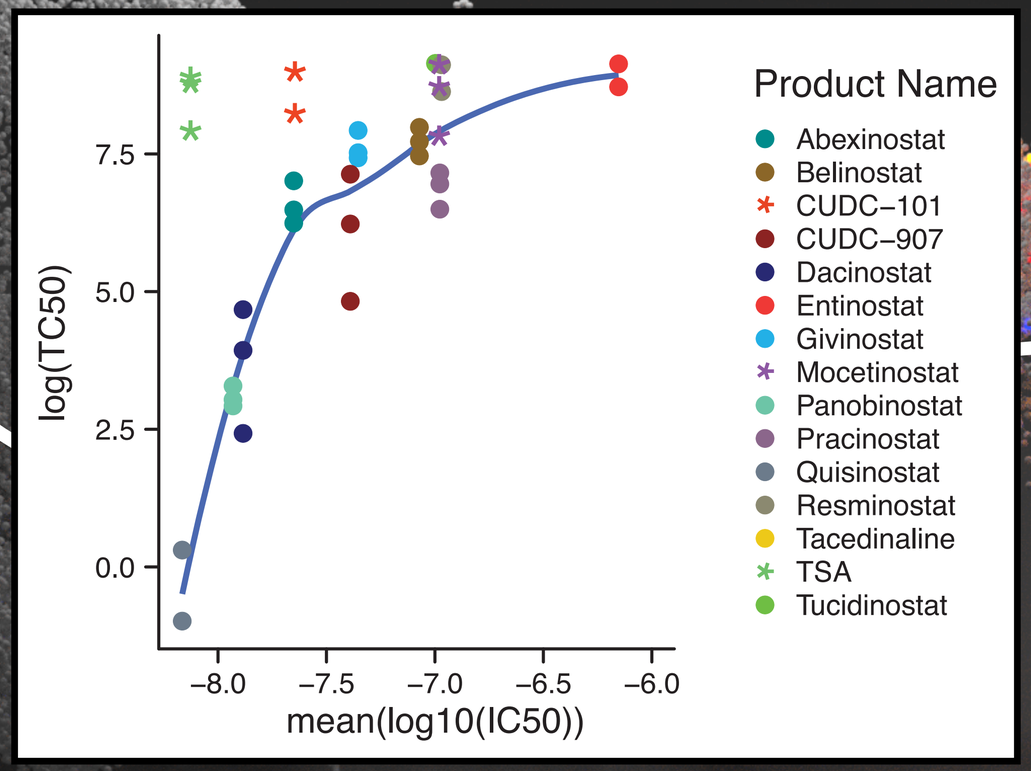
10,000 nM



K562 **A549** **MCF7**

Pracinostat

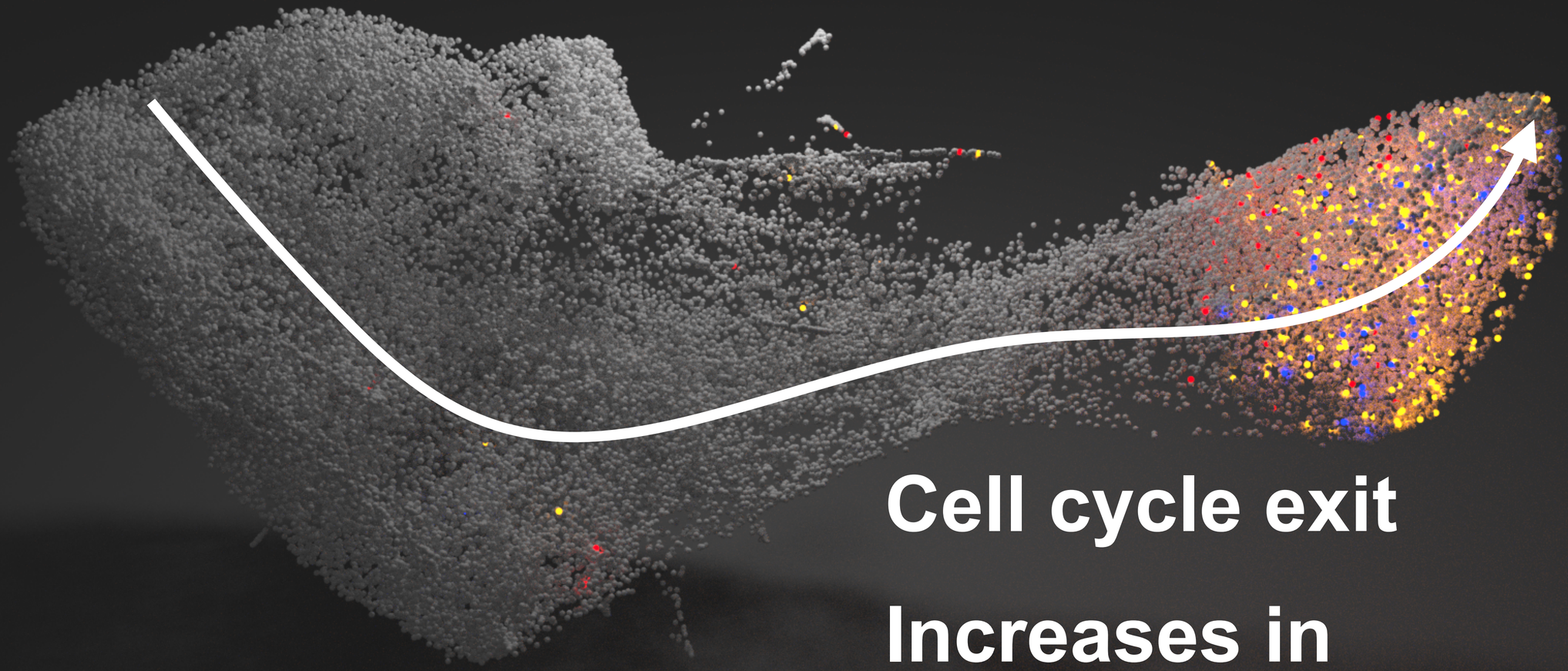
10,000 nM



K562 **A549** **MCF7**

Pracinostat

10,000 nM

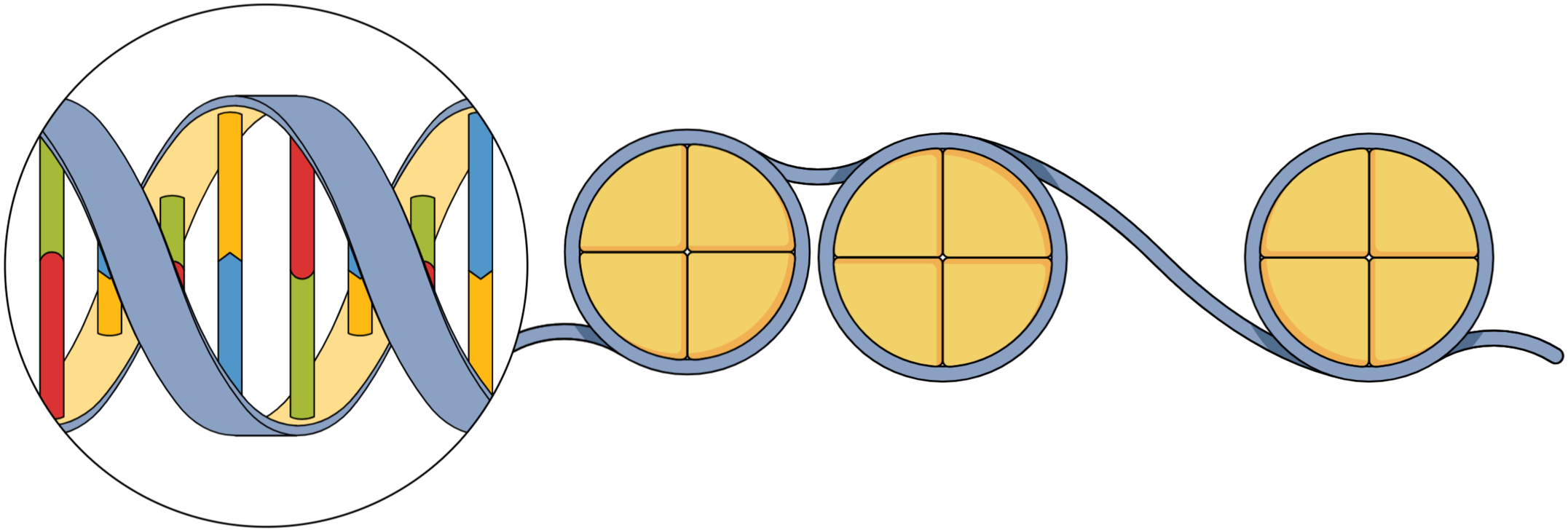


Cell cycle exit

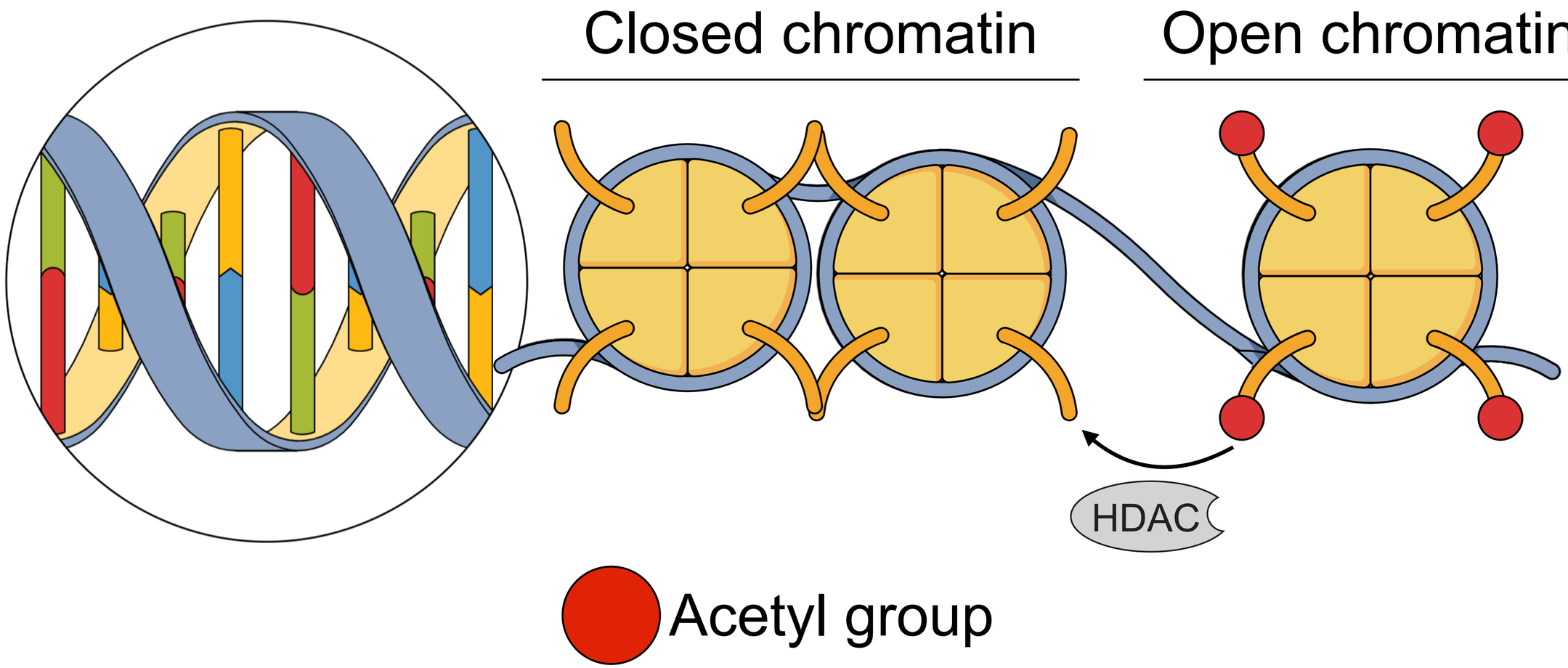
Increases in metabolism genes

K562 A549 MCF7

Histone acetylation regulates gene expression

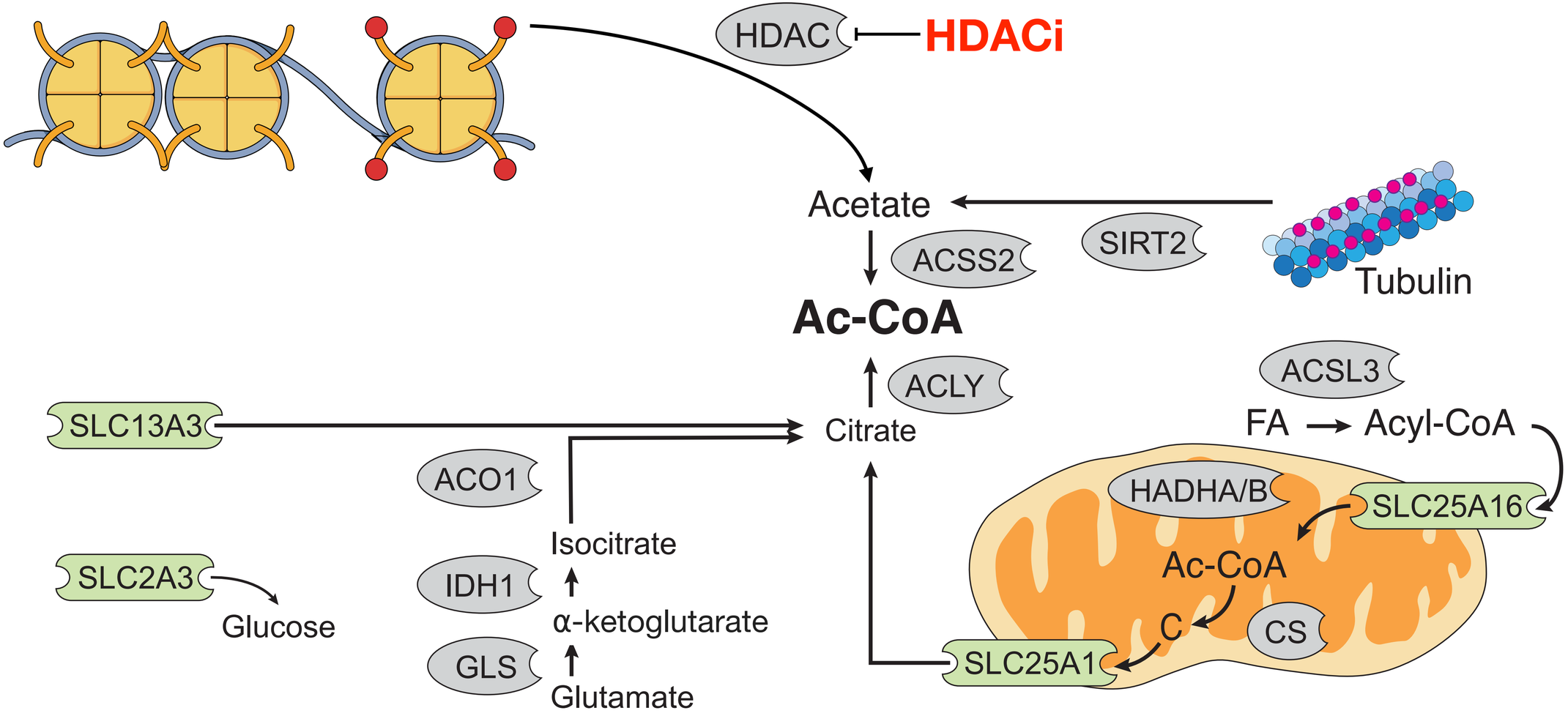


Histone acetylation regulates gene expression

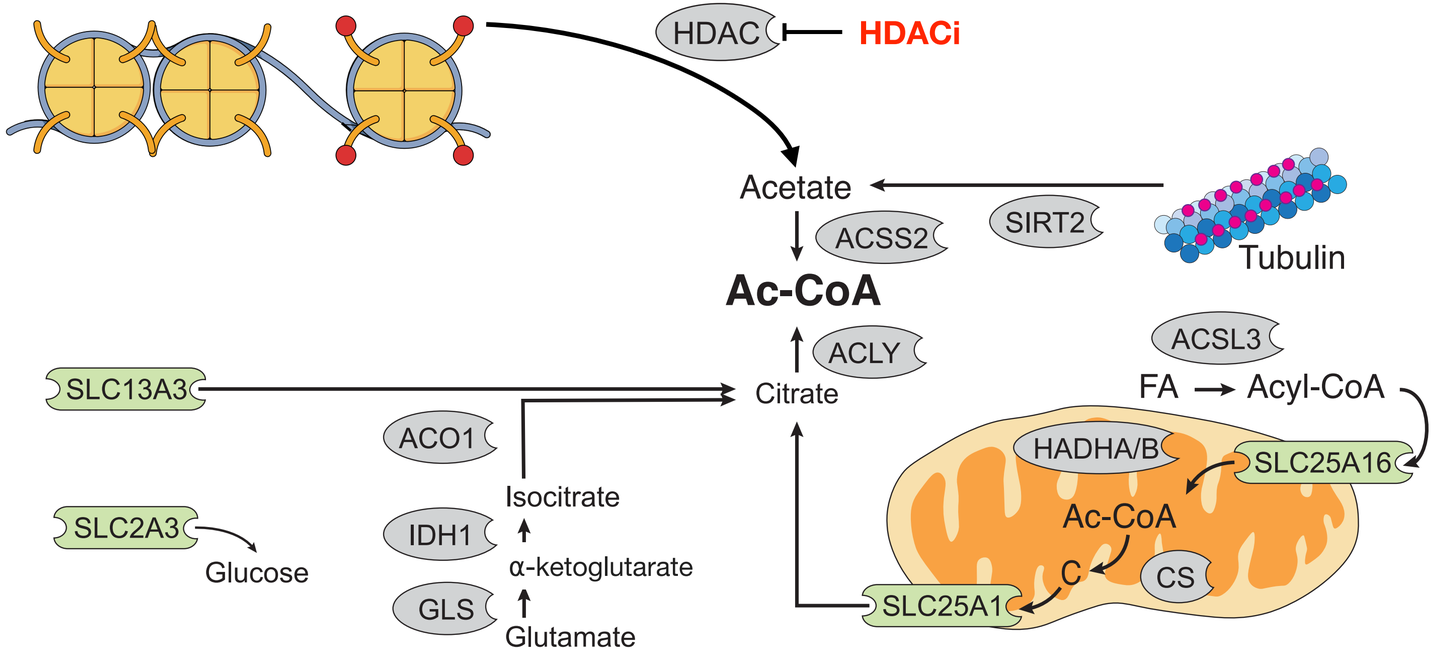


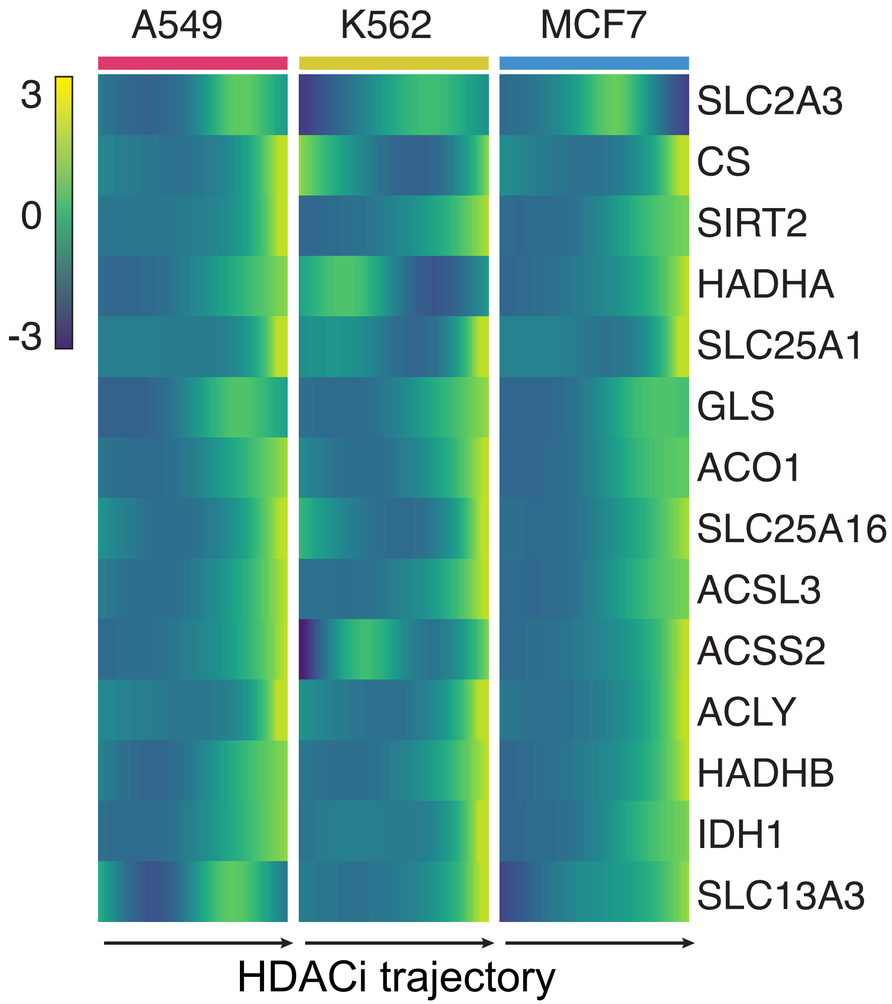
Kurdastani, S.K. (**2014**) Curr Opin Genet Dev.

Histone are a reservoirs for cellular acetate

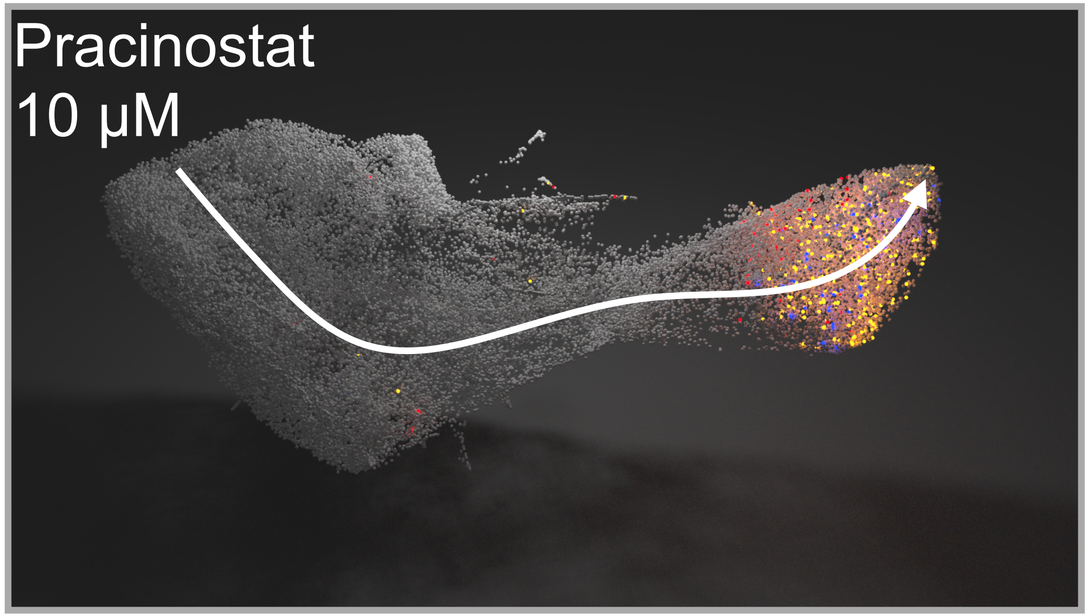


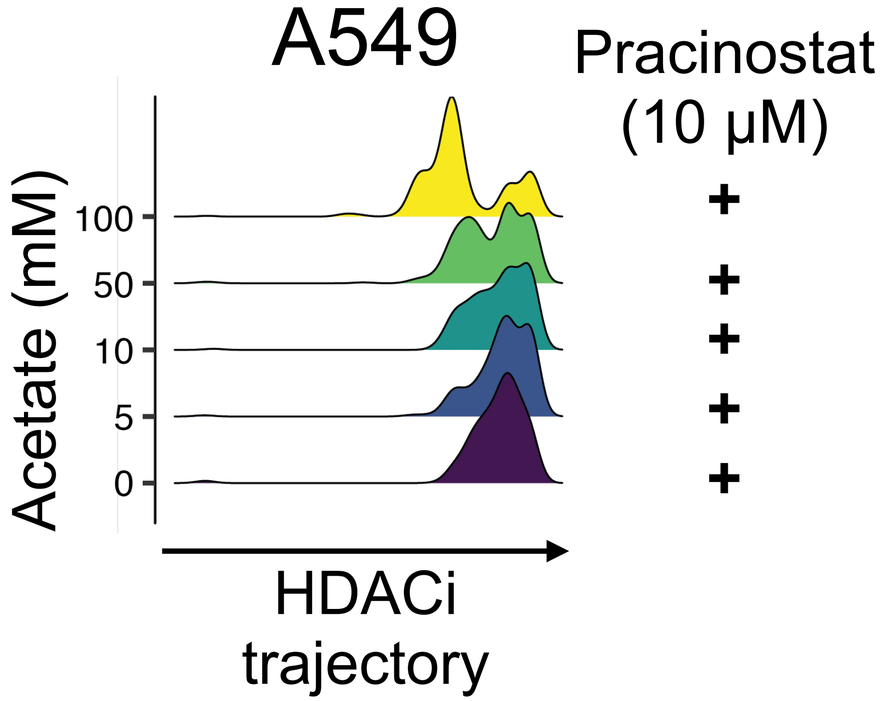
HDAC inhibition induces expression of acetate metabolism genes





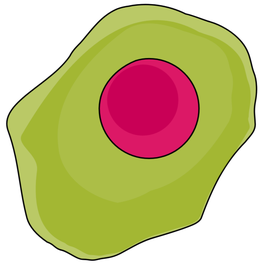
Ac-CoA precursors rescue the molecular phenotype induced by HDAC inhibition





A proportion of the sensitivity to HDAC inhibition is due to acetate deprivation

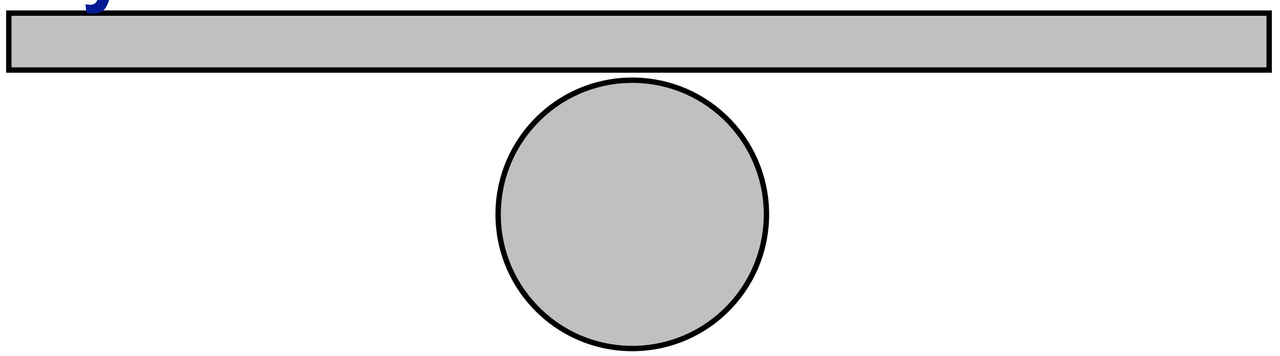
High Acetate



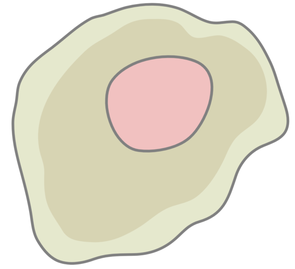
Cell survival

Acetate
Pyruvate

HDACi



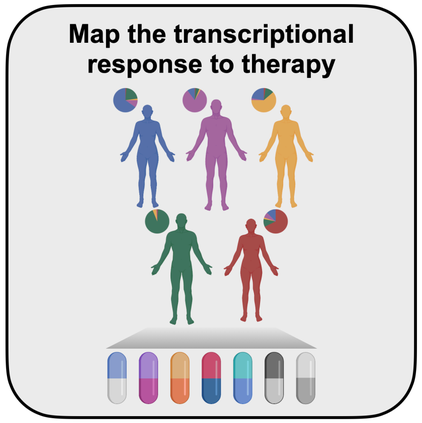
Acetate limited



Cell death

Vignette 1 summary

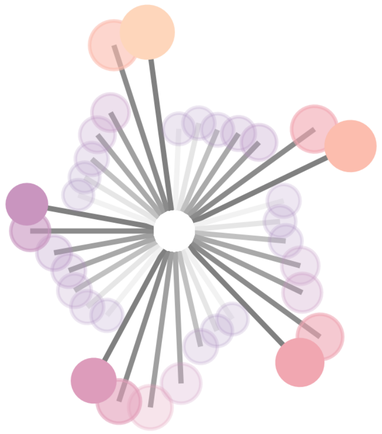
- Developed sci-Plex, an inexpensive sample multiplexing strategy compatible with single-cell RNA-seq
- Applied sci-Plex to perform high-throughput chemical transcriptomics at single-cell resolution
- Identified heterogeneity in drug response of different cell types
- Single-cell resolution revealed heterogeneity in response to microtubule targeting compounds and HDAC inhibitors

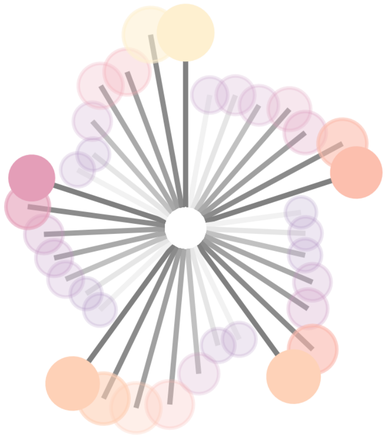


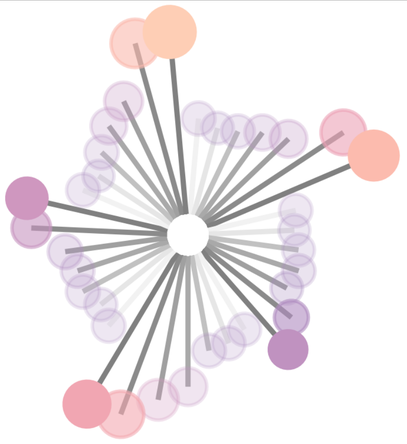
Defining the transcriptional landscape of EGFRi response in glioblastoma

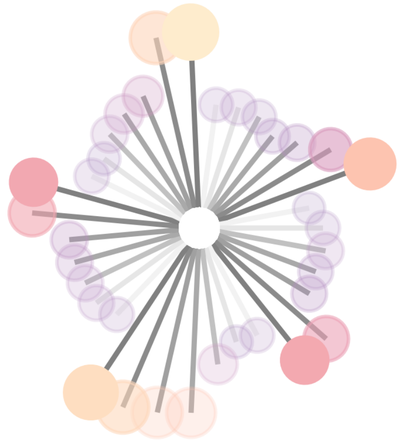
Giglio, R. *et. al.* (**2024**), *bioRxiv*

Ross Giglio

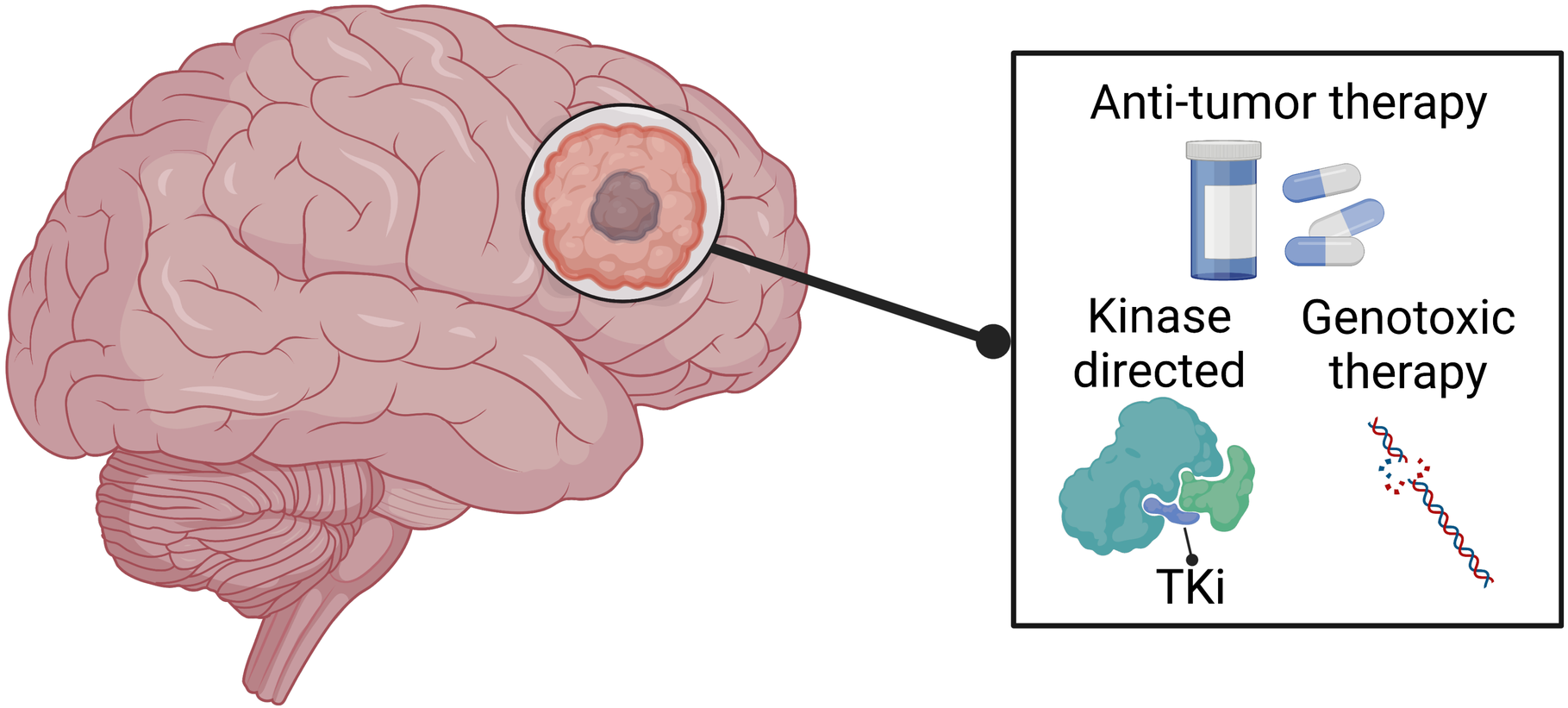








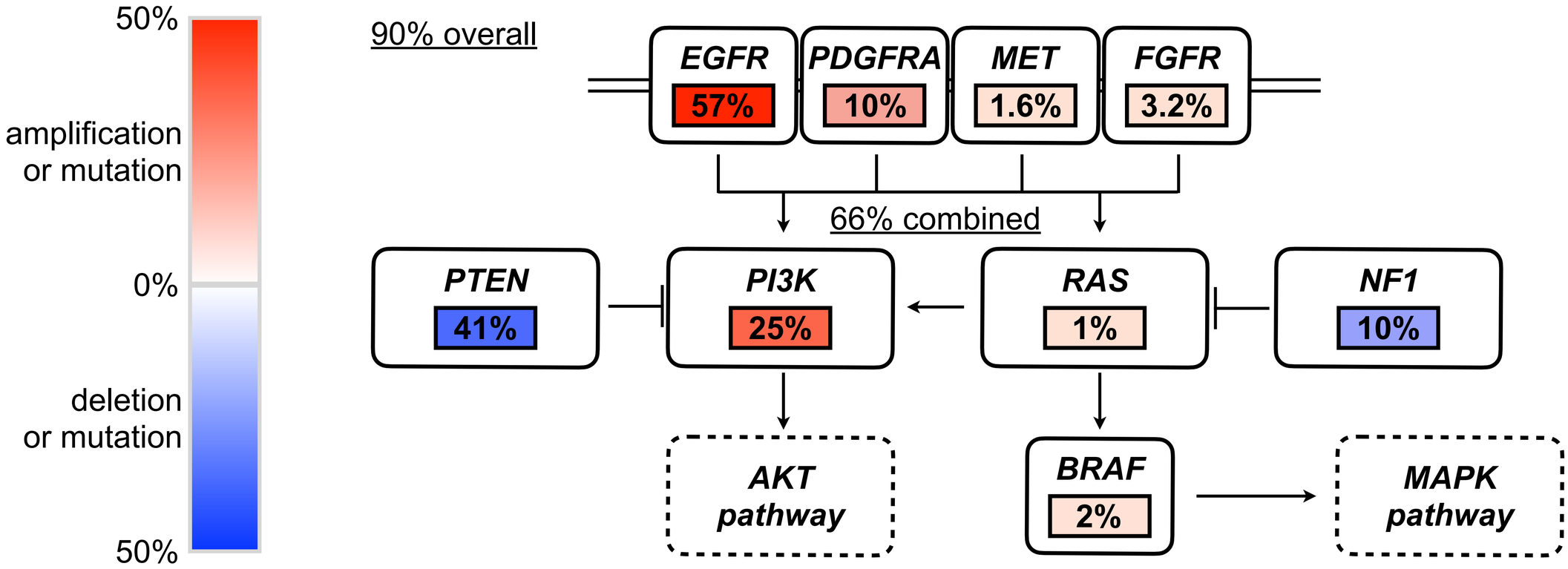
The current standard of care in GBM only marginally improves patient survival



- Most common and aggressive primary brain cancer
- Median survival of 12- 15 months

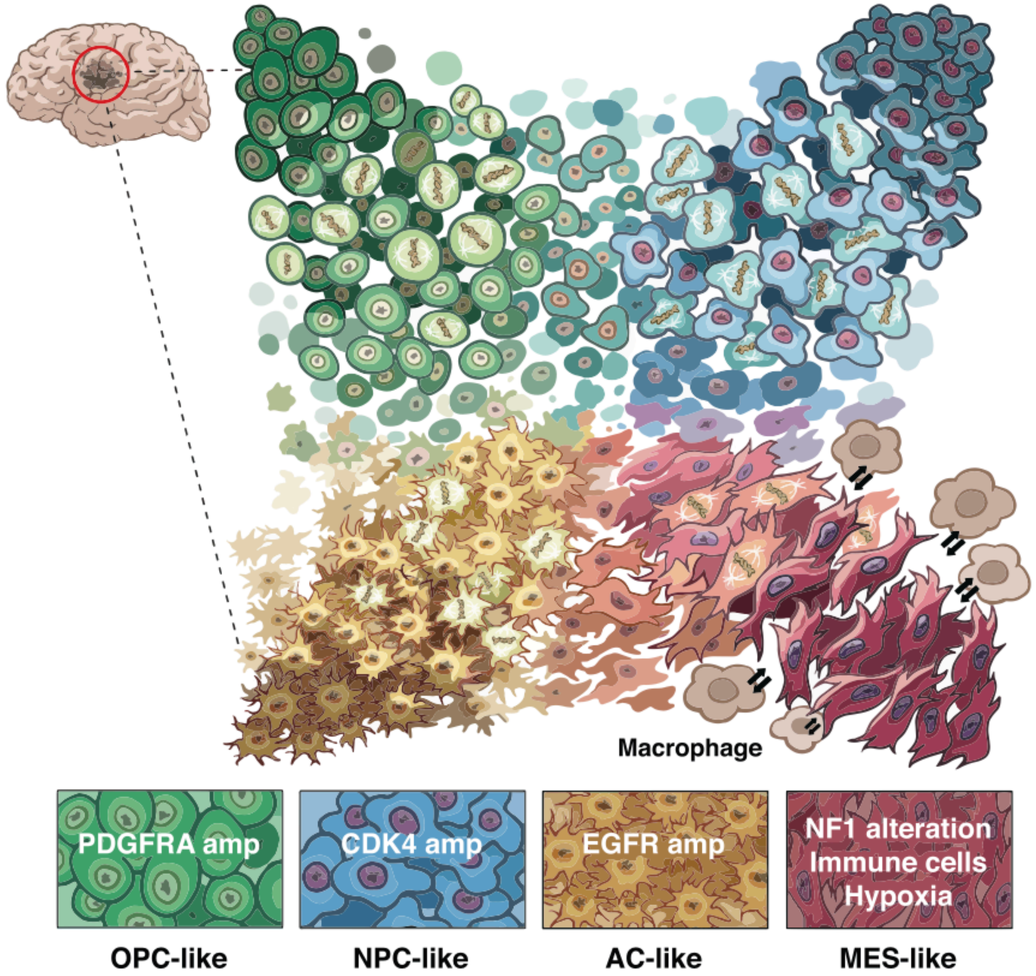
Stupp, R. *et al.* (**2005**). *NEJM.*

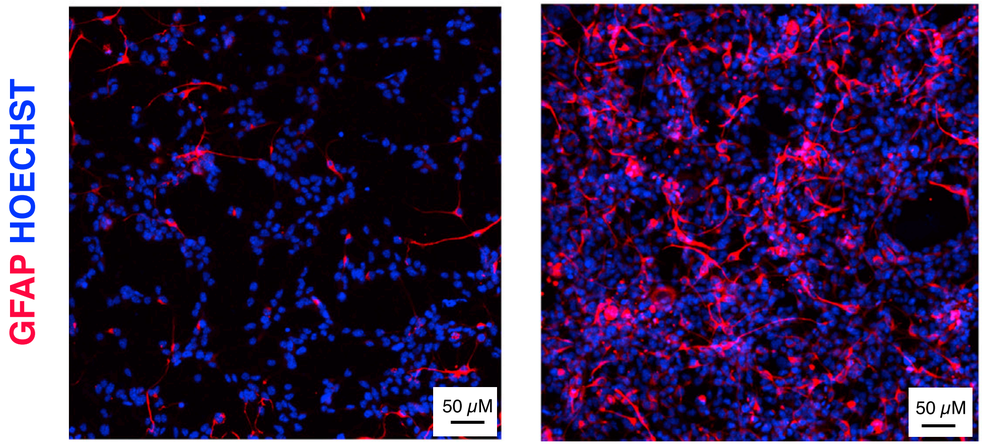
Receptor tyrosine kinases as an opportunity for the design of potent targeted therapies in glioblastoma

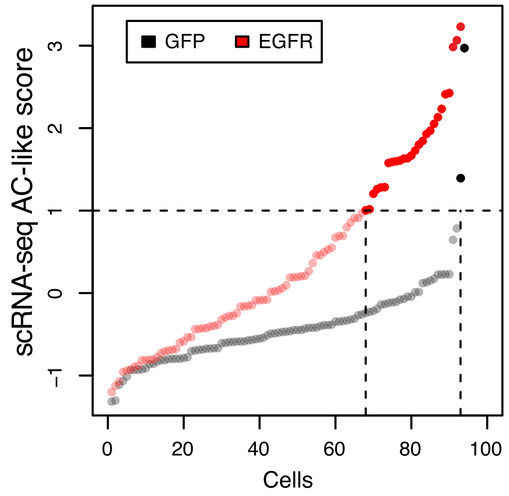


Adapted from: Brennan, C.W. *et al*. (**2013**), Cell. Cancer Genome Atlas network. **(2008)**, *Nature.*

EGFR defines a molecular subtype of IDHwt GBM

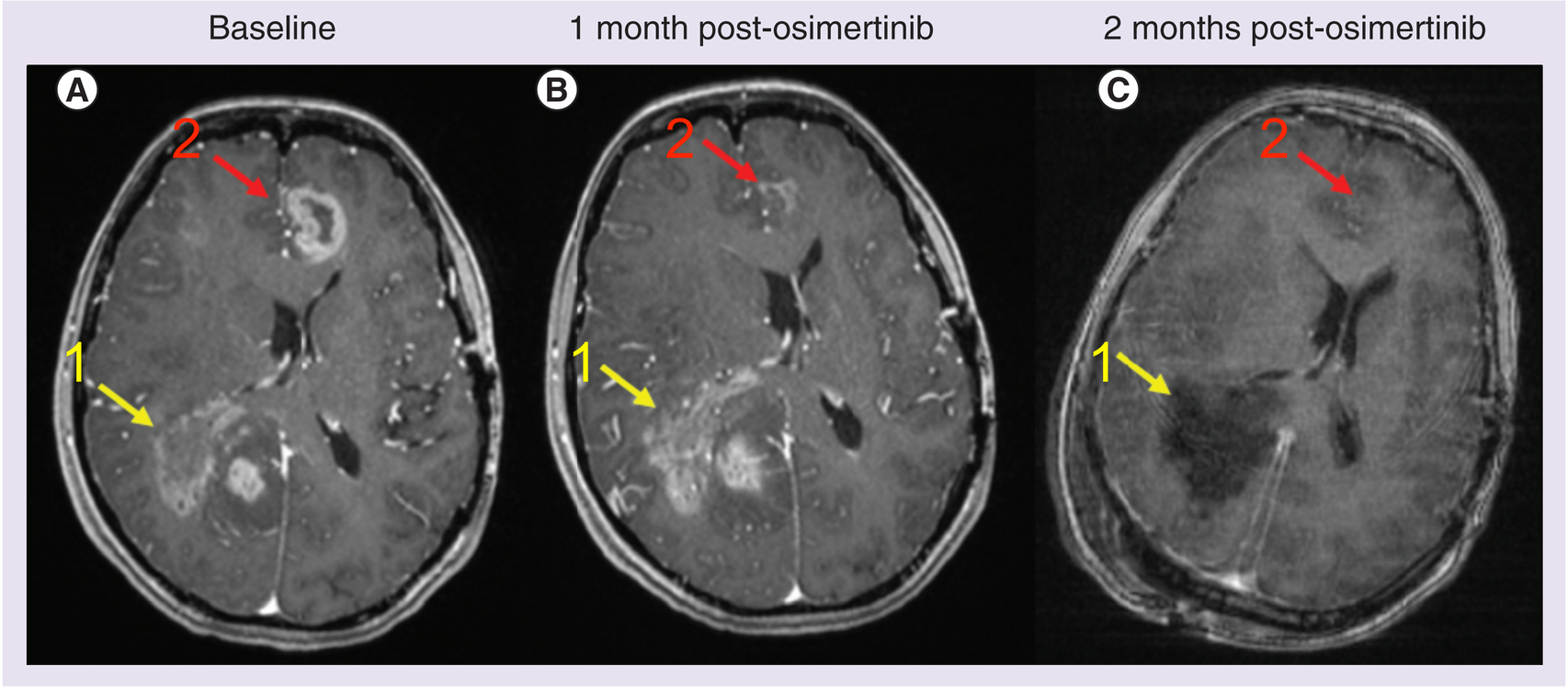






EGFR & AC-like GBM: Neftel, C. *et al.* (**2019**), *Cell*.

Clinical response to a brain penetrant EGFR inhibitor



EGFR status at resection per site

1

$EGFR^{Amp}/EGFR^{C628F}$

1^{R}

$EGFR^{A289V}/ EGFR^{C628F}$

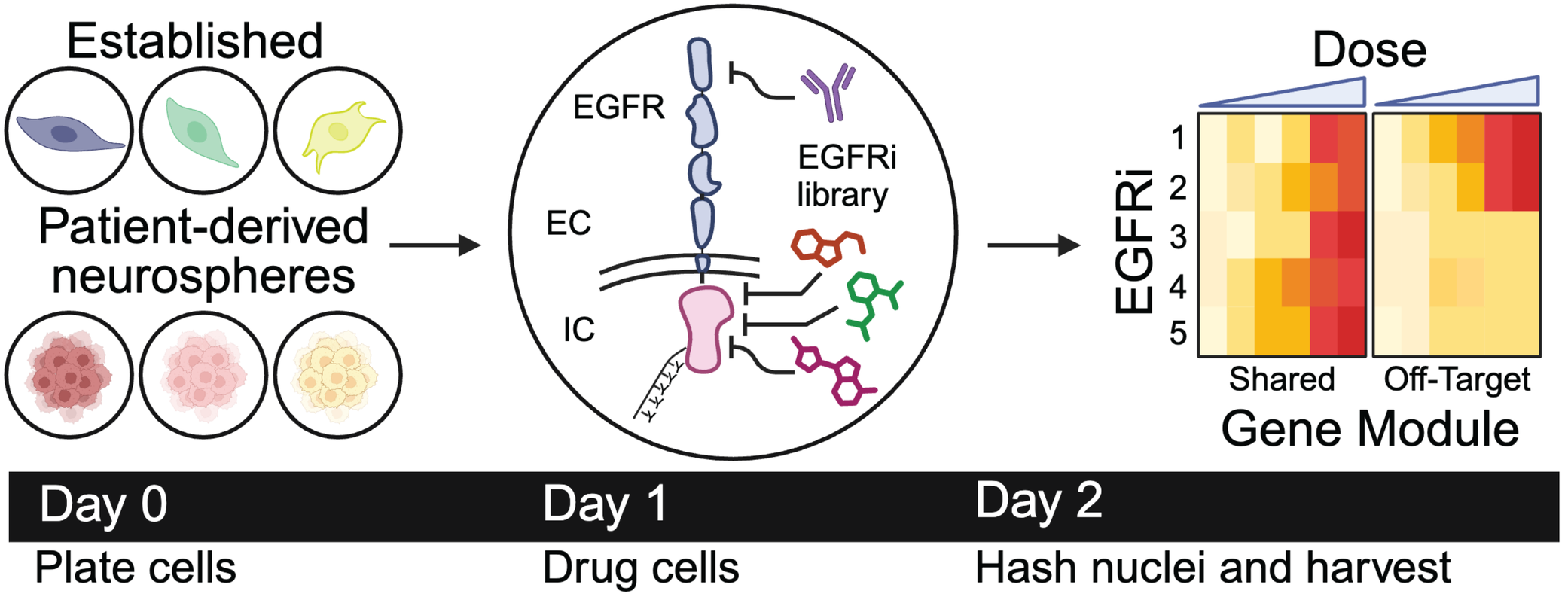
2^{R}

$EGFR^{Amp}/EGFR^{vIII}$

→ Osimertinib salvage therapy

Makhlin, I. et. al. (**2019**) *CNS Oncology*.

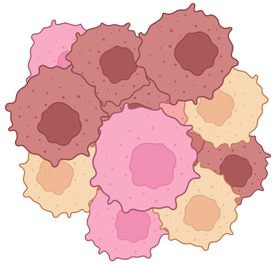
Mapping the molecular response to EGFR inhibitors



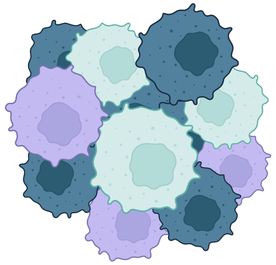
CMAP: Subramanian, A., Narayan, R., Corsello, S.M. *et al.* (2017) *Cell.*

Comprehensive sci-Plex profiling of EGFR inhibitors

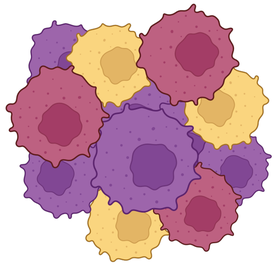
3 Patient-derived Neurosphere Cultures



BT112 (EGFRvIII/ Amp)



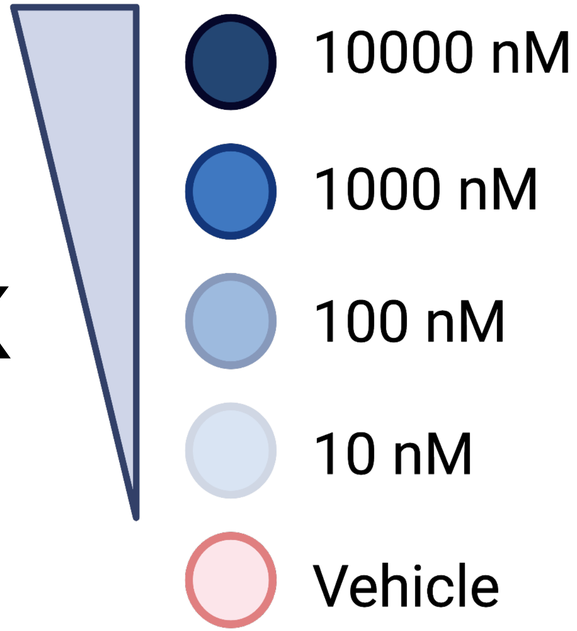
BT228 (EGFR wt/ Amp)



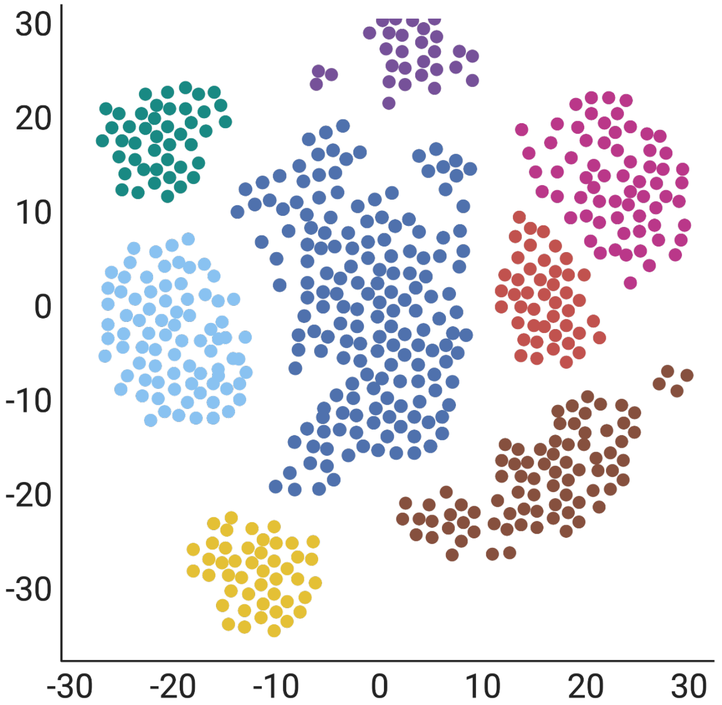
BT333 (EGFR F254I/ Amp)

74 EGFR Inhibitors 4 Doses

X



Chemical Transcriptomics Analysis



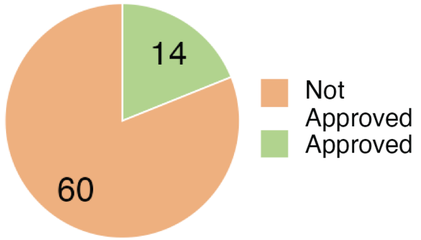
~3500 conditions (wells)
24 hr & 7 days post-exposure

Keith L. Ligon, M.D., Ph.D.

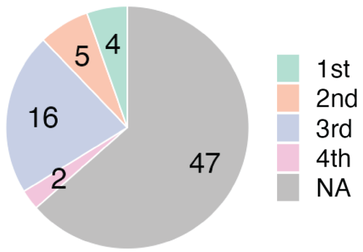
DFCI-CPDM

Comprehensive sci-Plex profiling of EGFR inhibitors

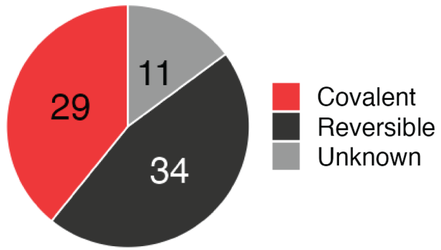
FDA Approval



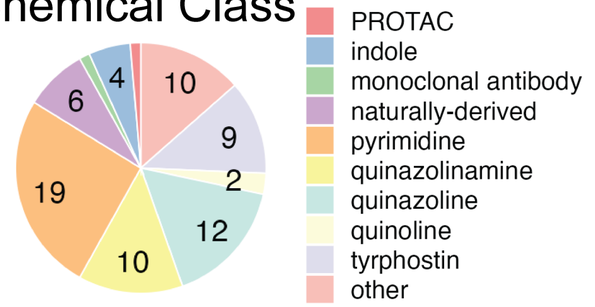
Generation



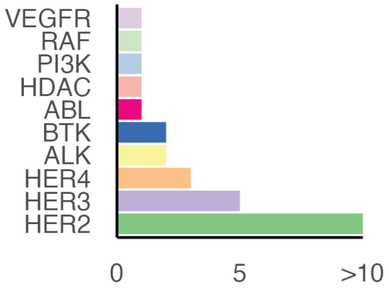
Reversibility



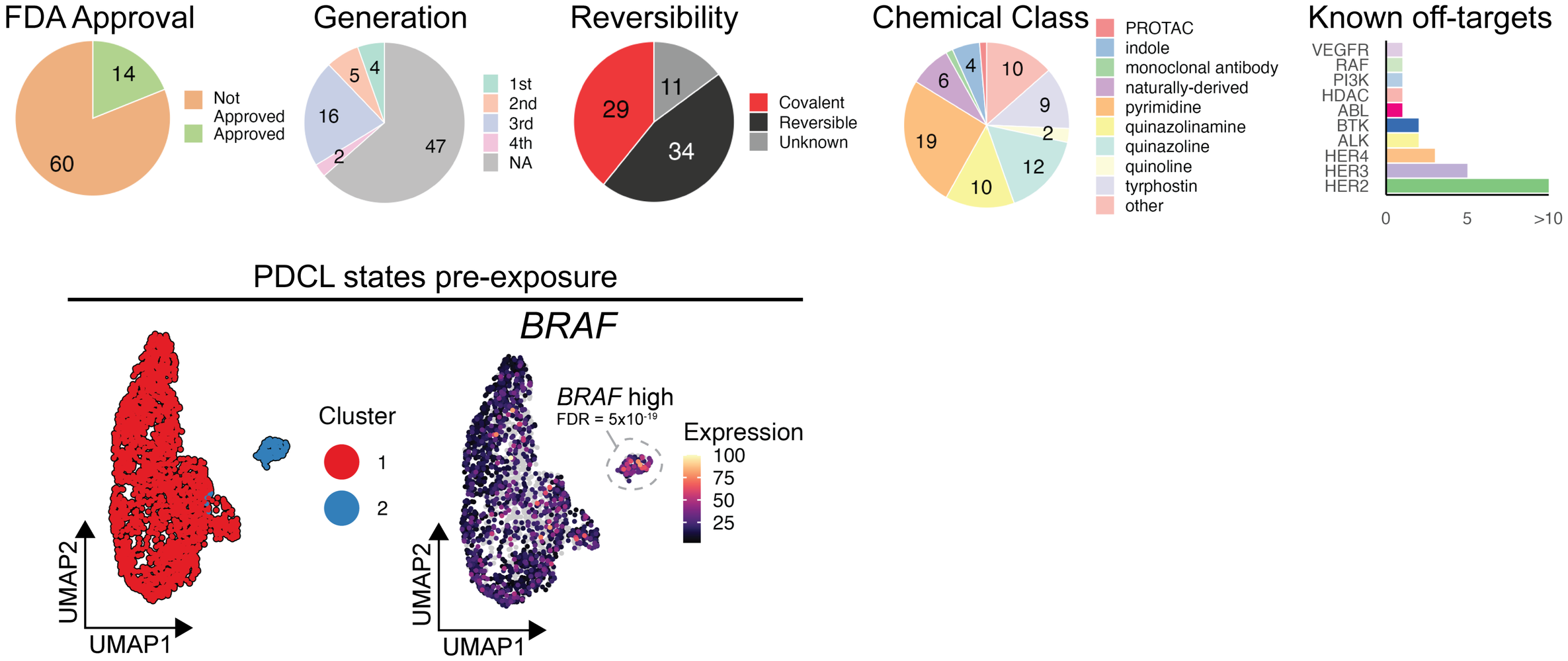
Chemical Class



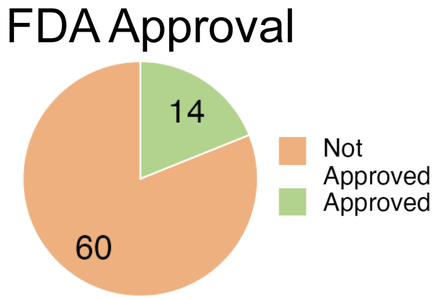
Known off-targets

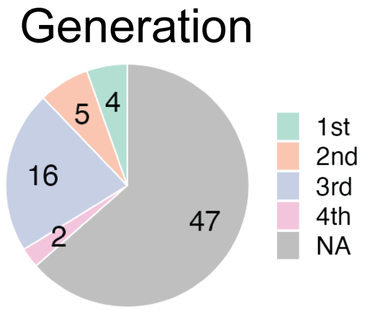


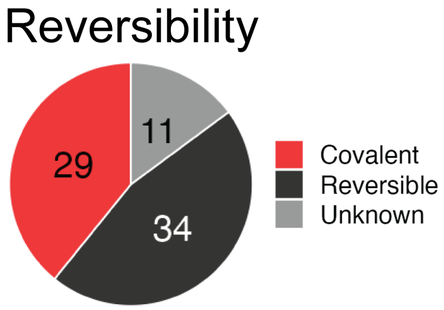
Tumor cell state heterogeneity and selection upon EGFRi

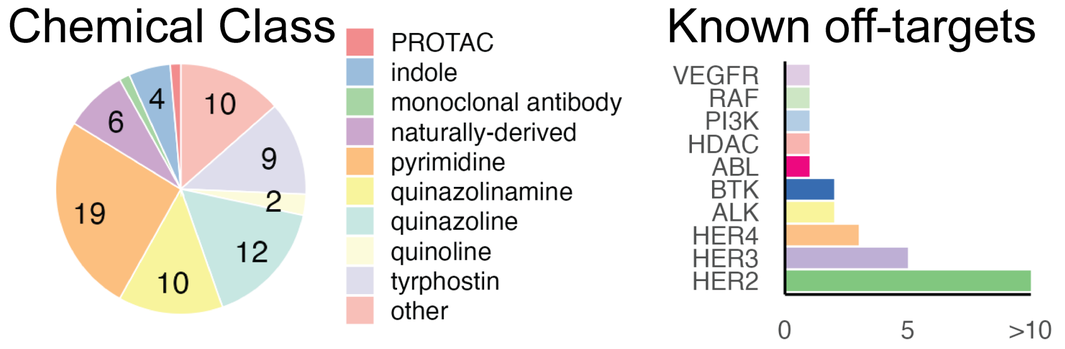


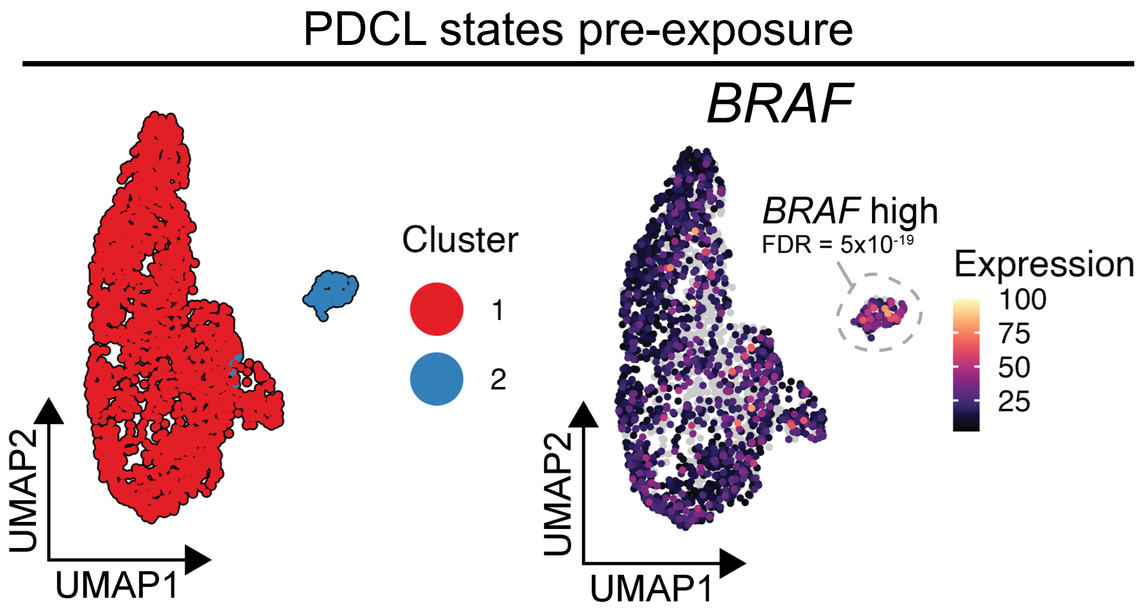
Tumor cell state heterogeneity and selection upon EGFRi

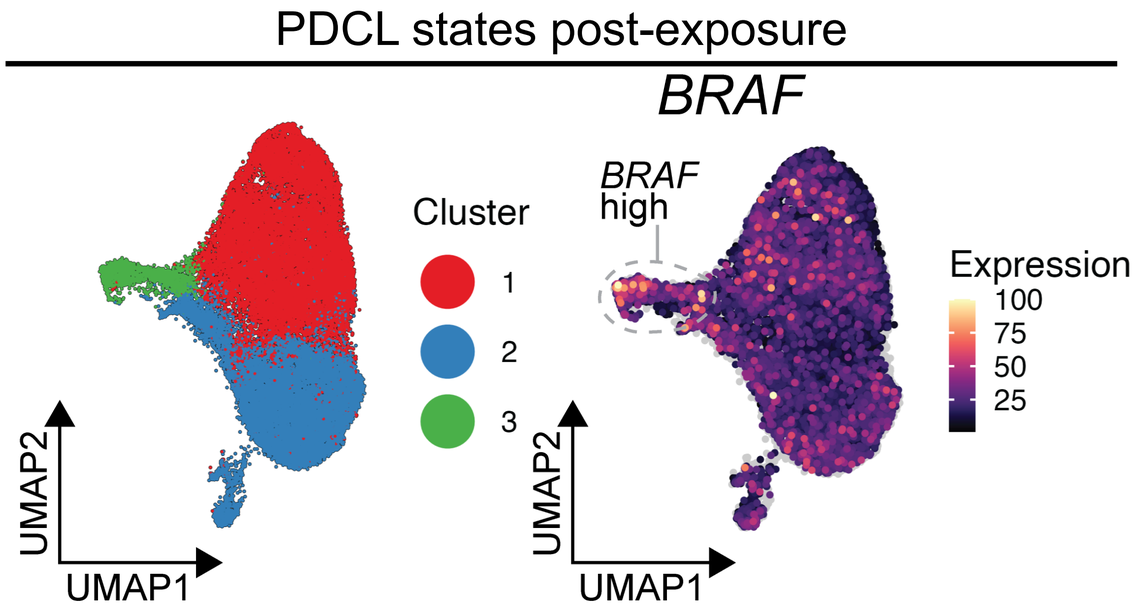




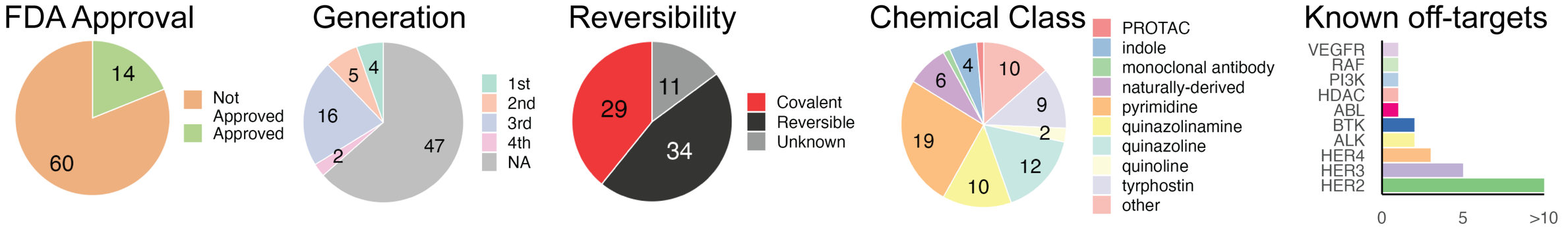




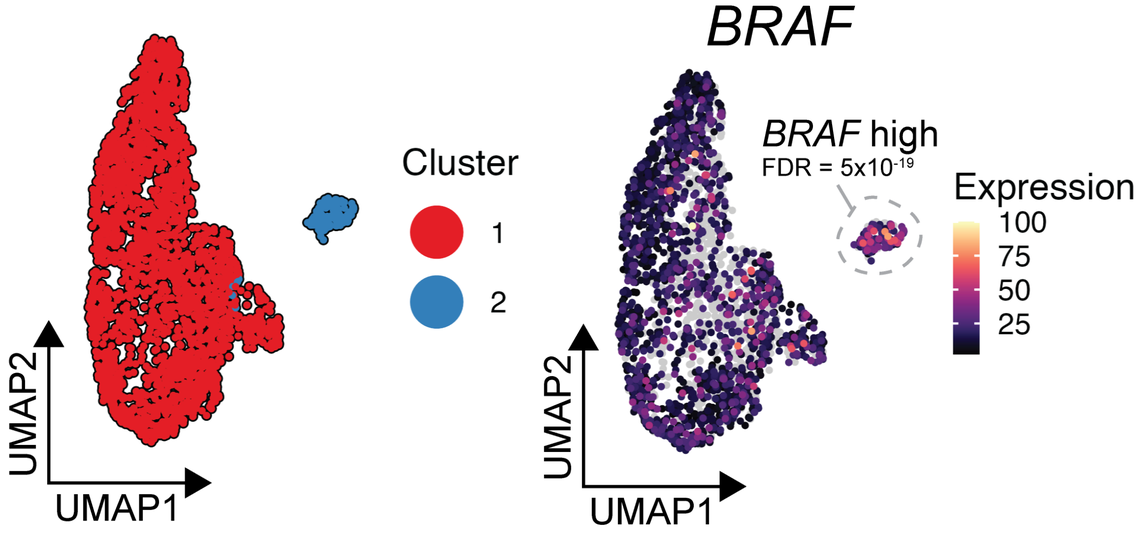




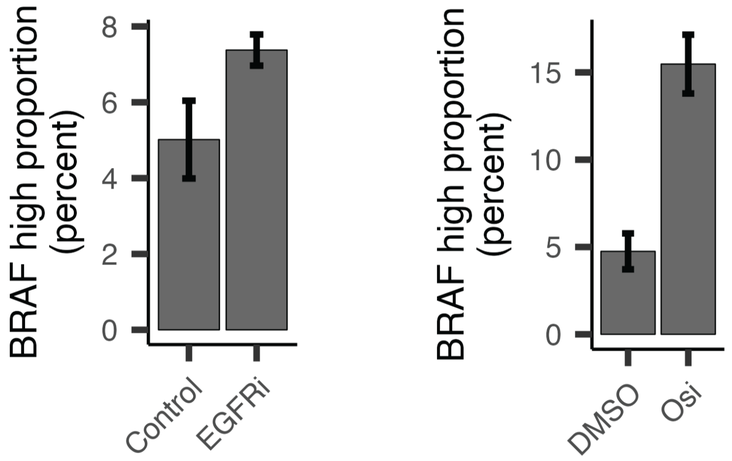
Tumor cell state heterogeneity and selection upon EGFRi



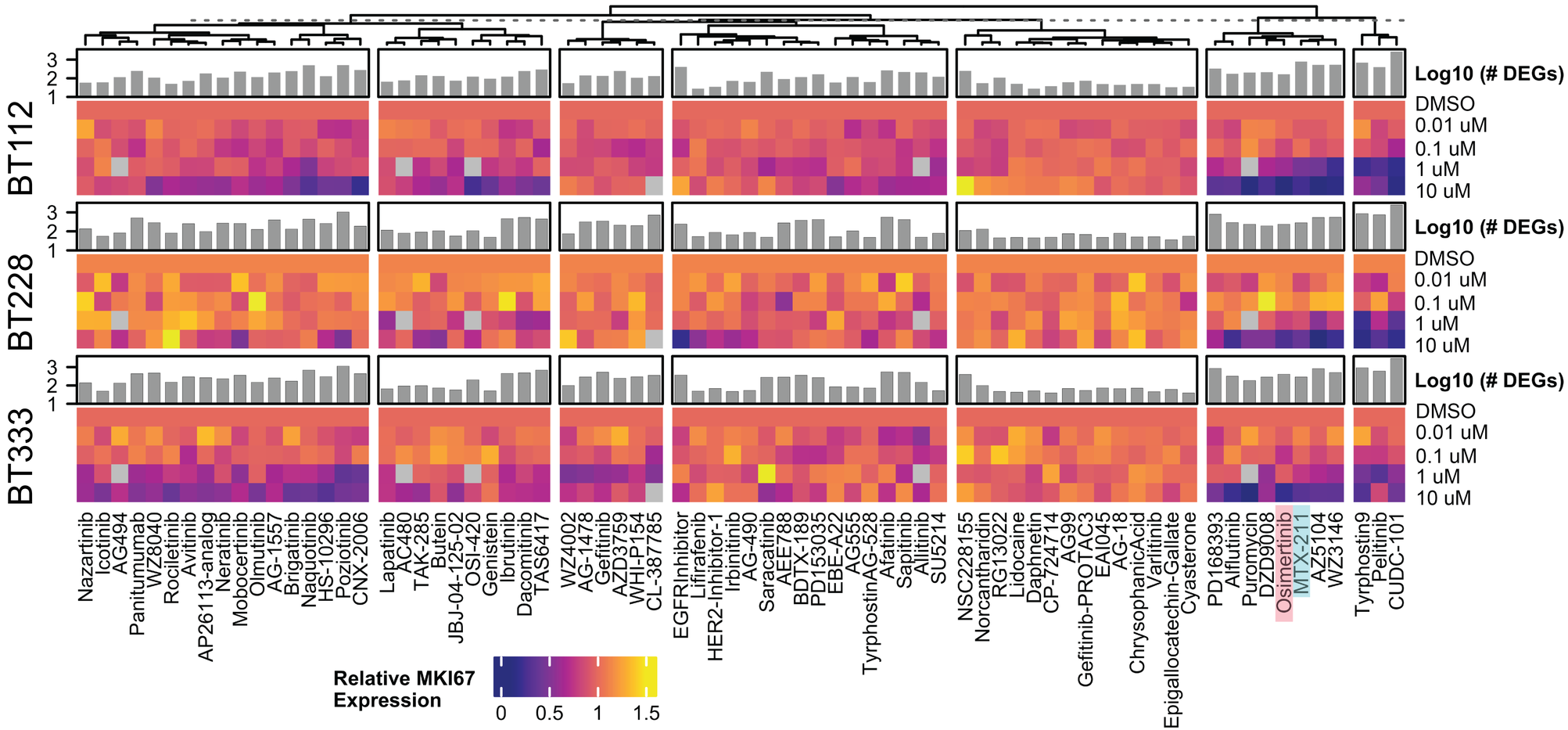
PDCL states pre-exposure



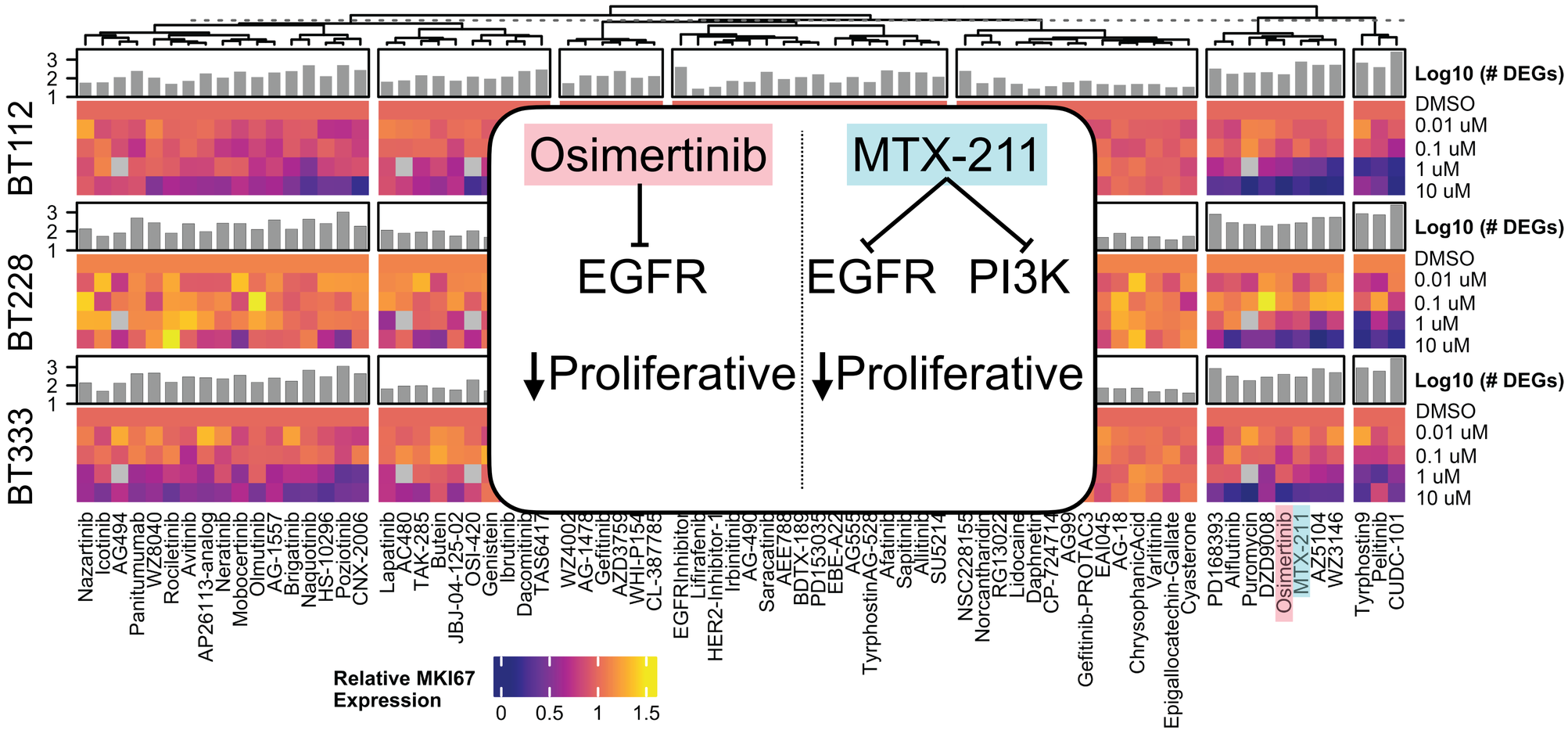
PDCL states post-exposure



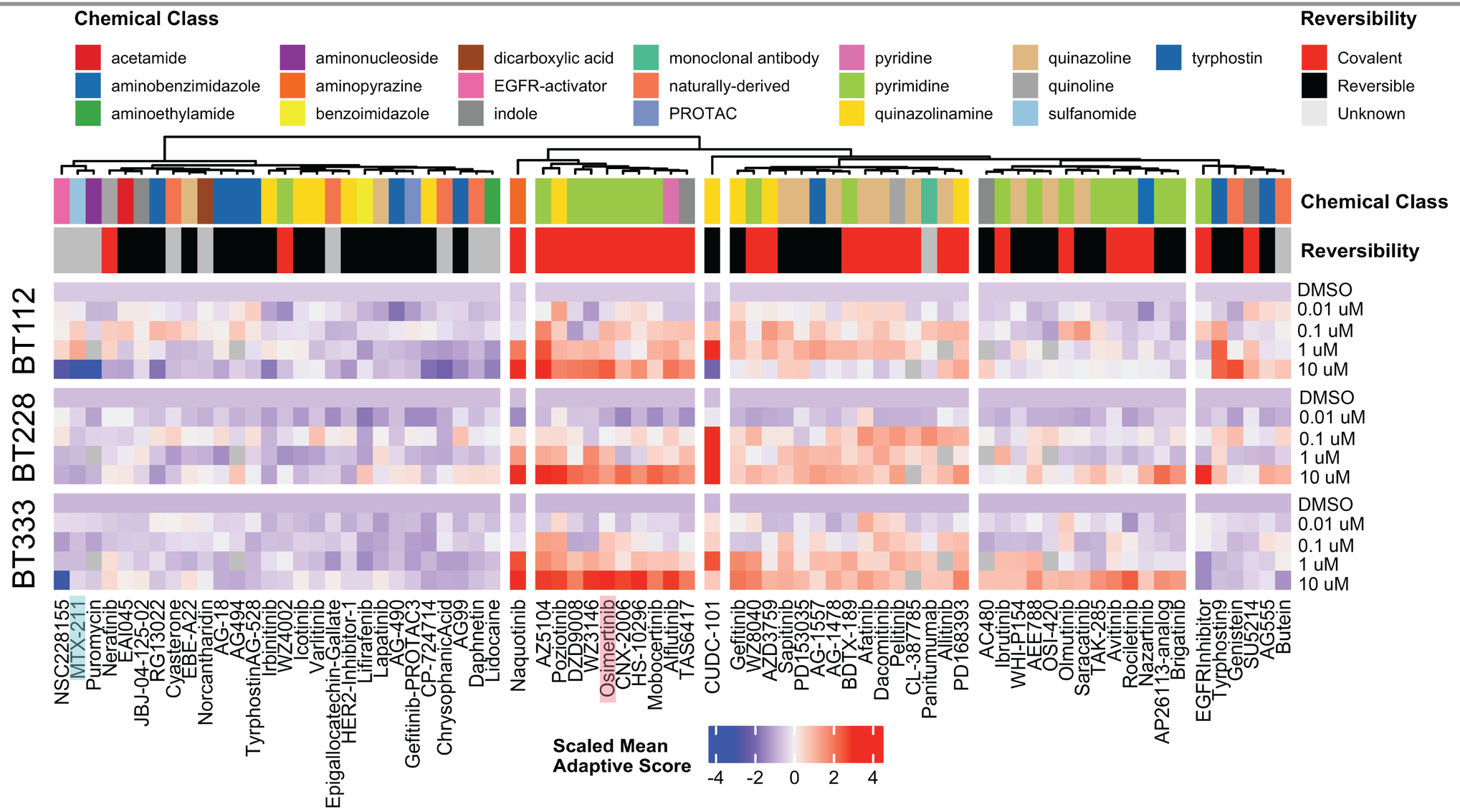
EGFRi’s differentially alter proliferative gene expression



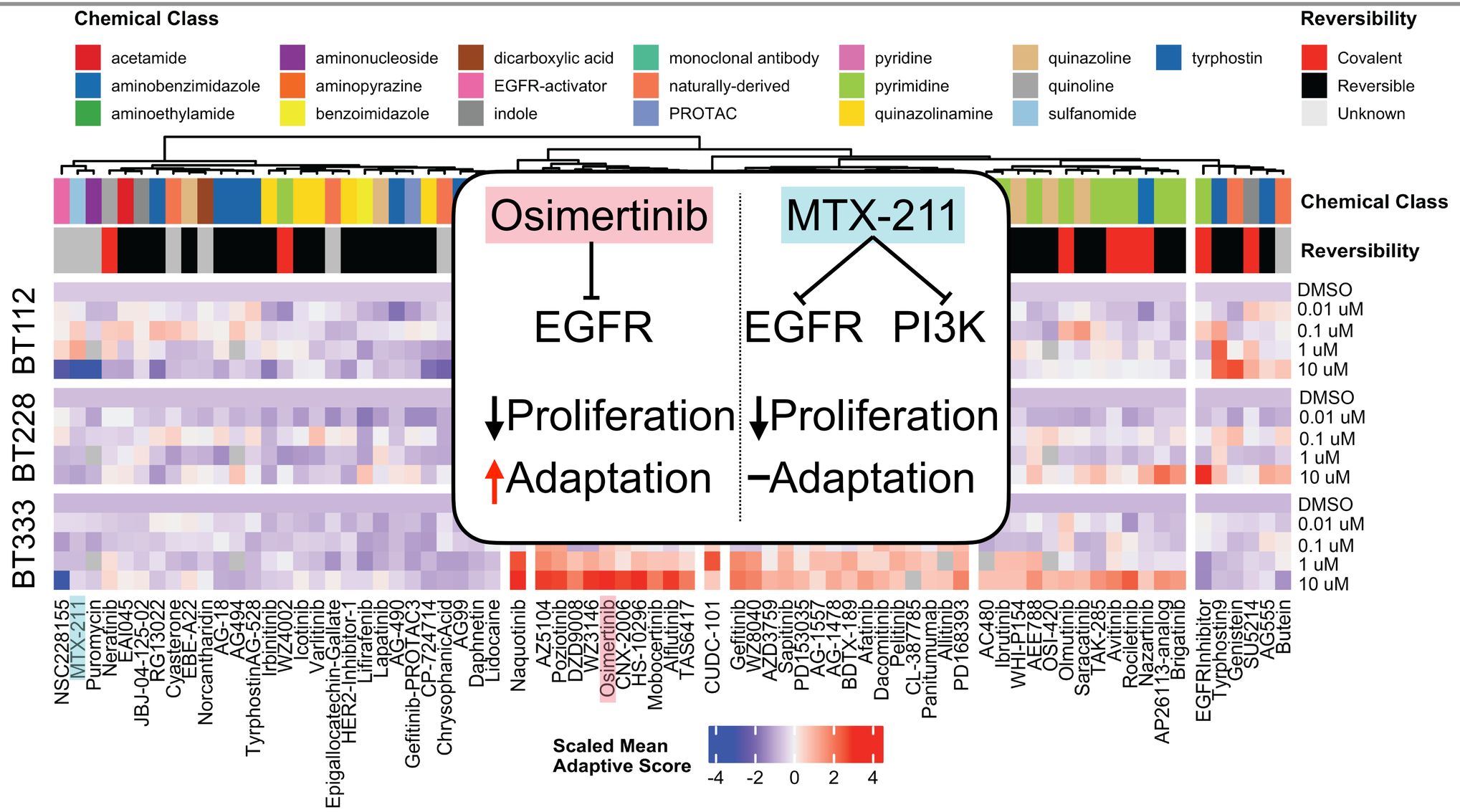
EGFRi's differentially alter proliferative gene expression



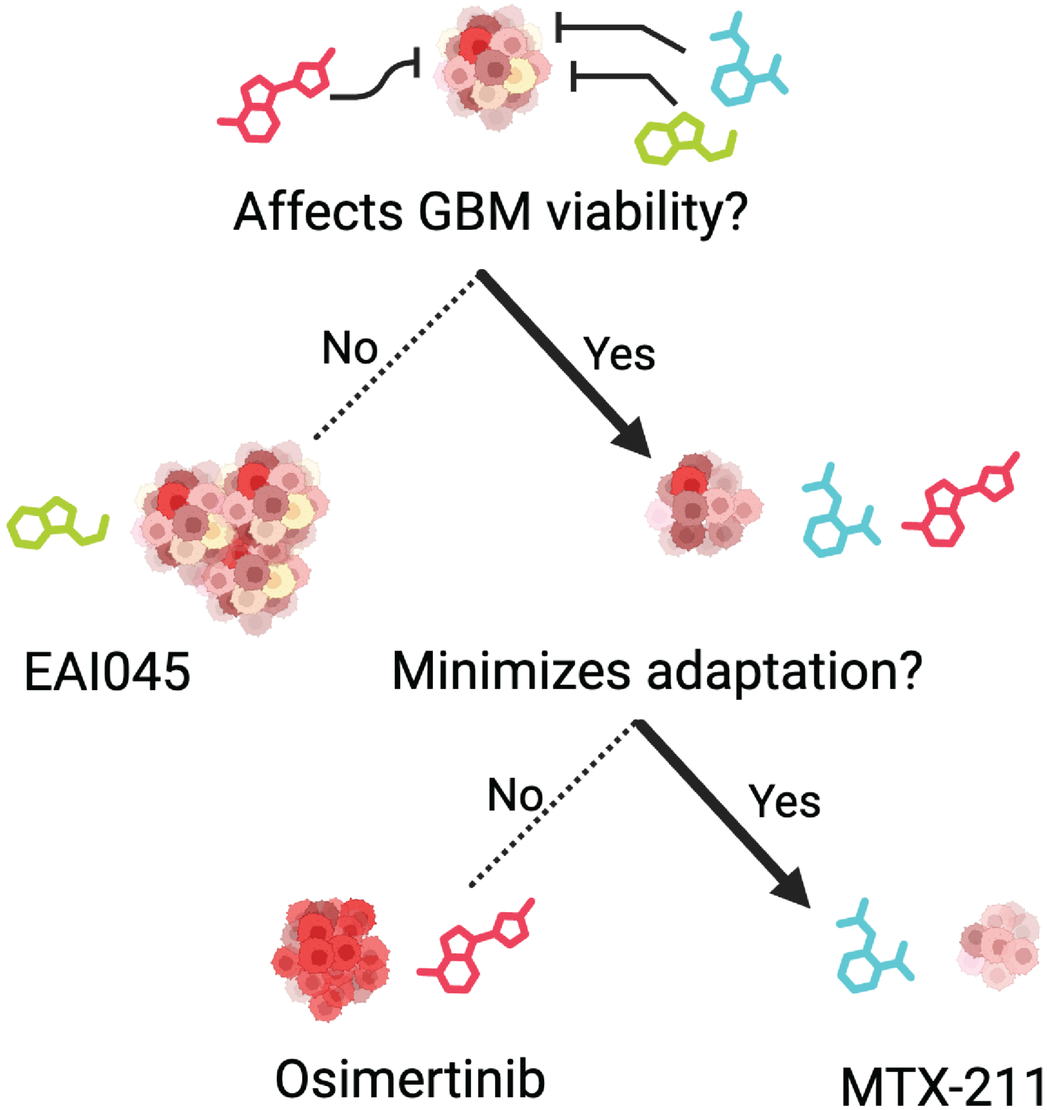
Some EGFRi's induce an adaptive resistance program



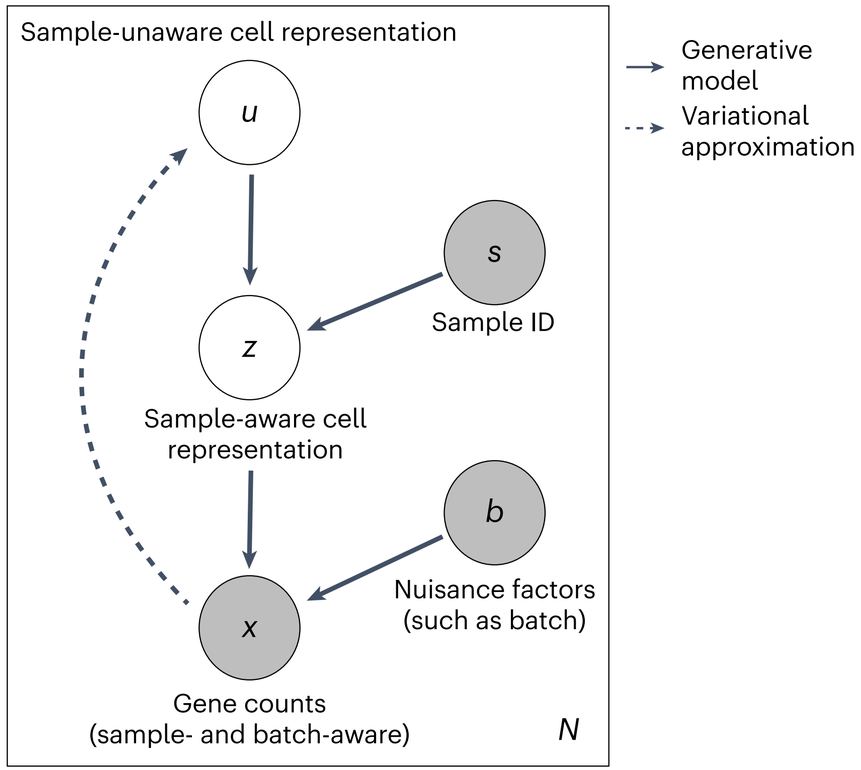
Differential activation of programs by EGFRi's

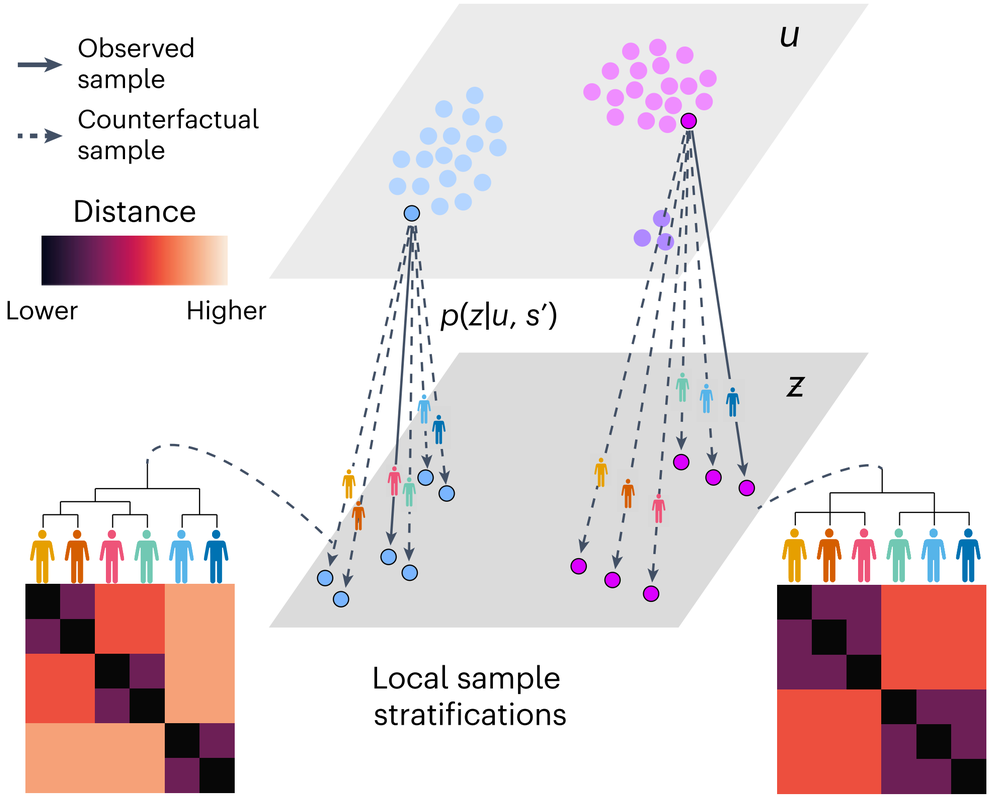


Maximizing GBM sensitivity to inhibition



Multi-**r**esolution **v**ariational **i**nference (MrVI)





MrVI: *Boyeau, P., *Hong, J. *et al.* (**2025**). *Nature Methods*.

Ross Giglio

Defining EGFRi programs with MrVI

Nicholas Hou

Justin Hong

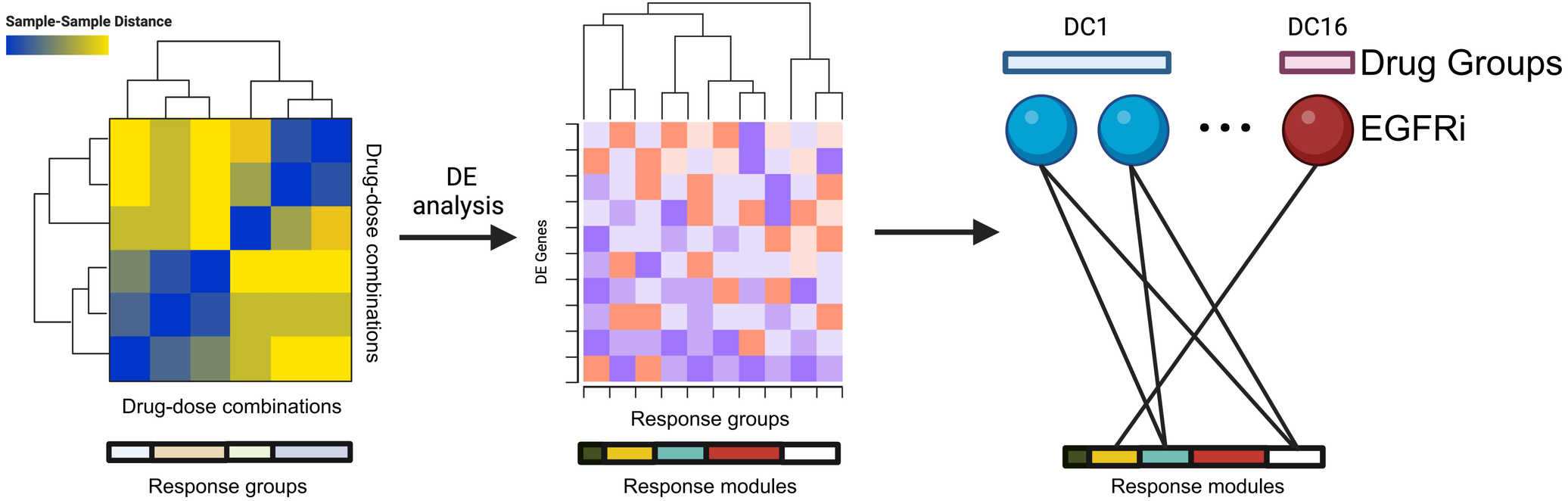
Elham Azizi, Ph.D.

Nir Yosef, Ph.D.

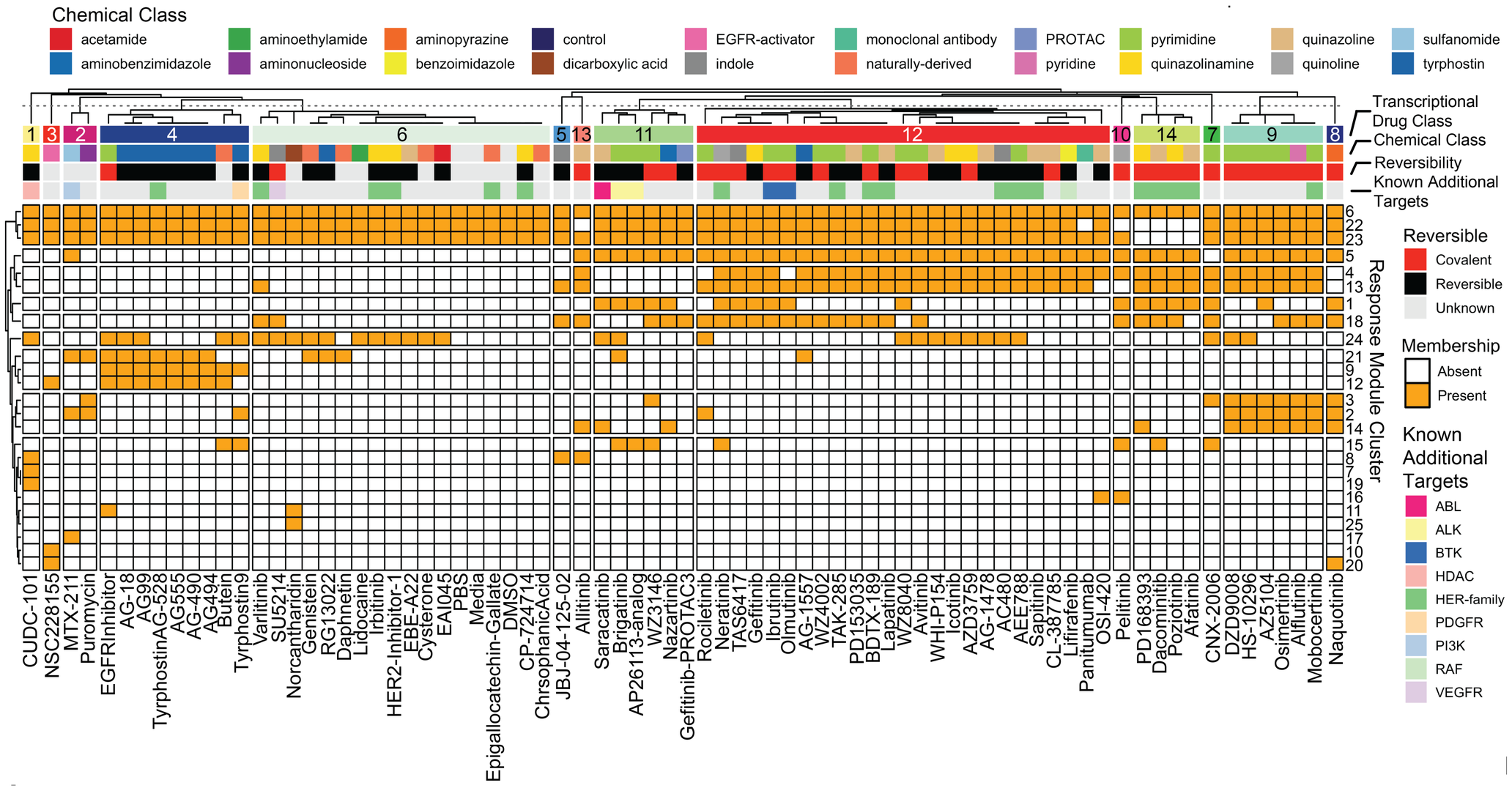
Identify drug-dose combinations with similar effects (per PDCL)

Identify broader response Modules (across PDCLs)

Collapse EGFRis by their induction of response modules

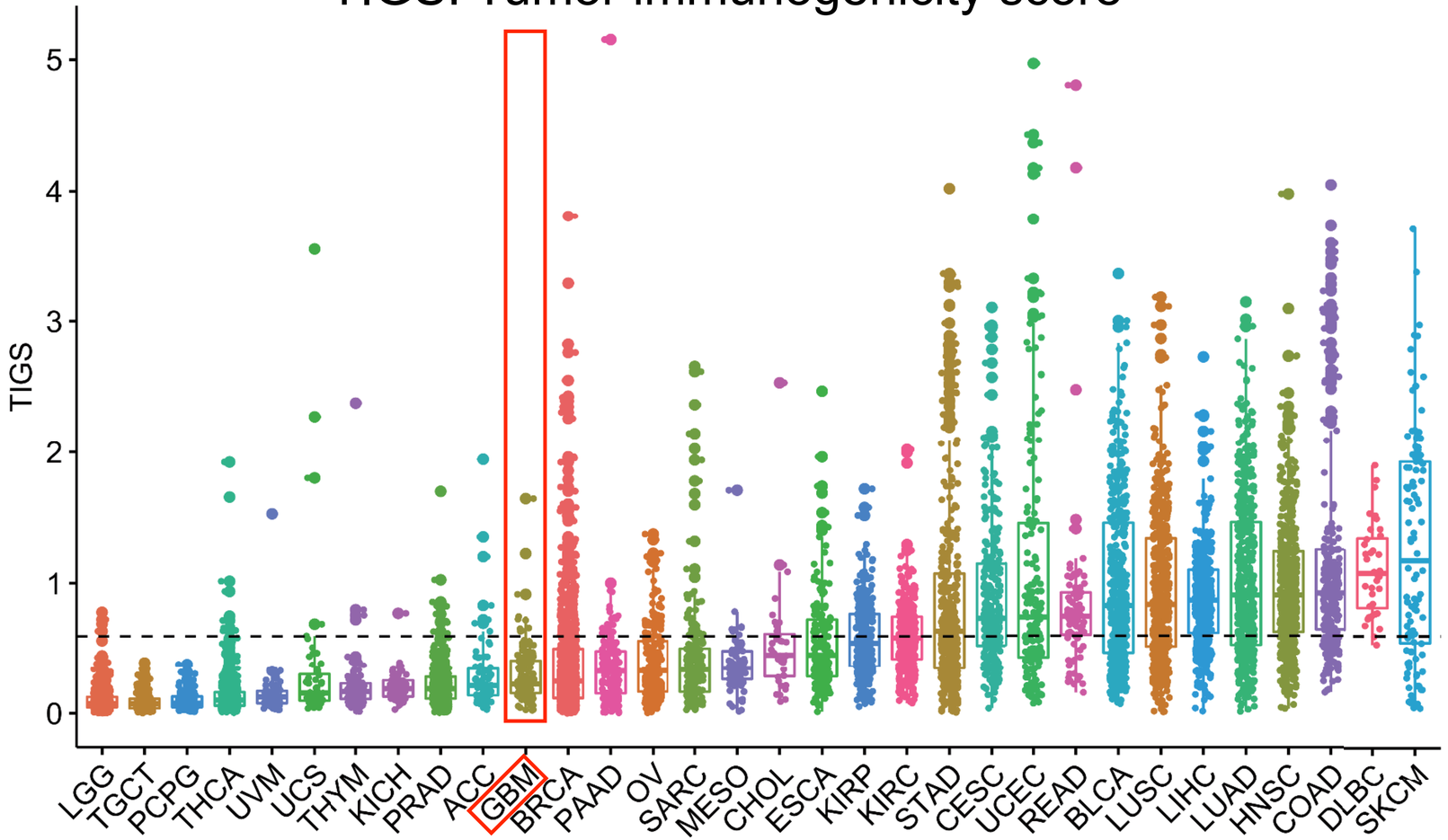


Grouping EGFRi's by their ability to modulate distinct molecular responses

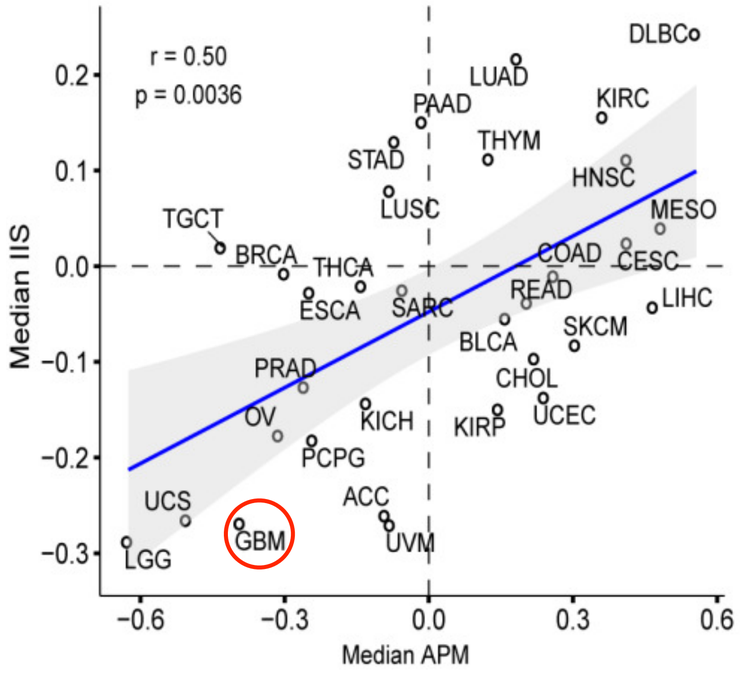


Glioblastoma tumors are immunologically “cold”

TIGS: Tumor immunogenicity score



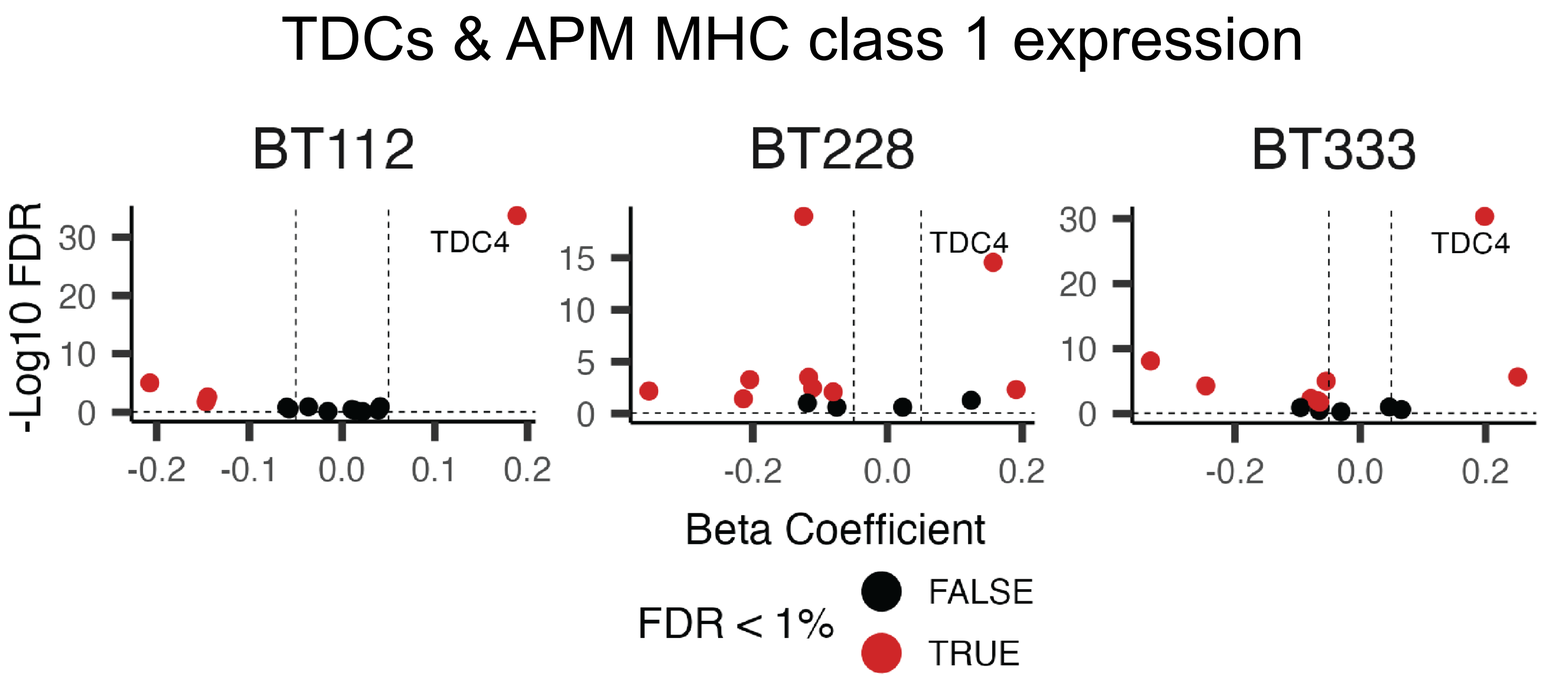
Immune infiltration vs APM expression

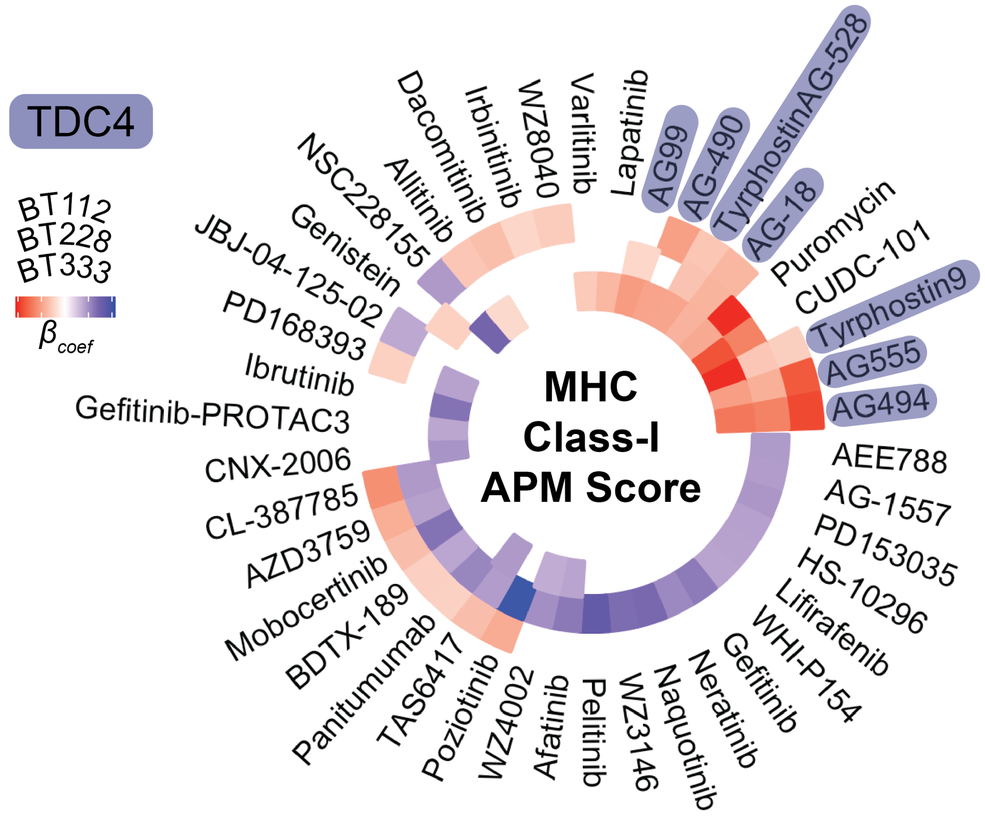


Wang et al. *Elife* **2019.**

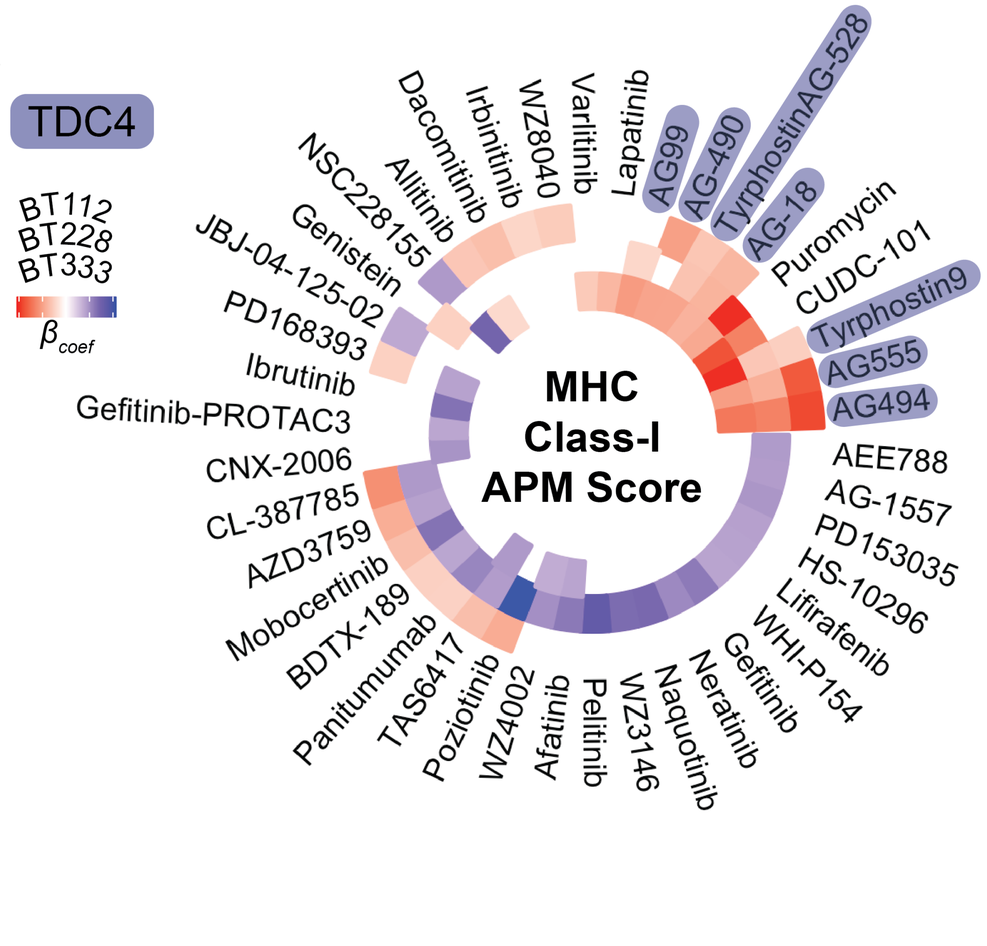
Association between RTK signaling and response to PD-1: Zhao et al. *Nat Medicine* **2019.**

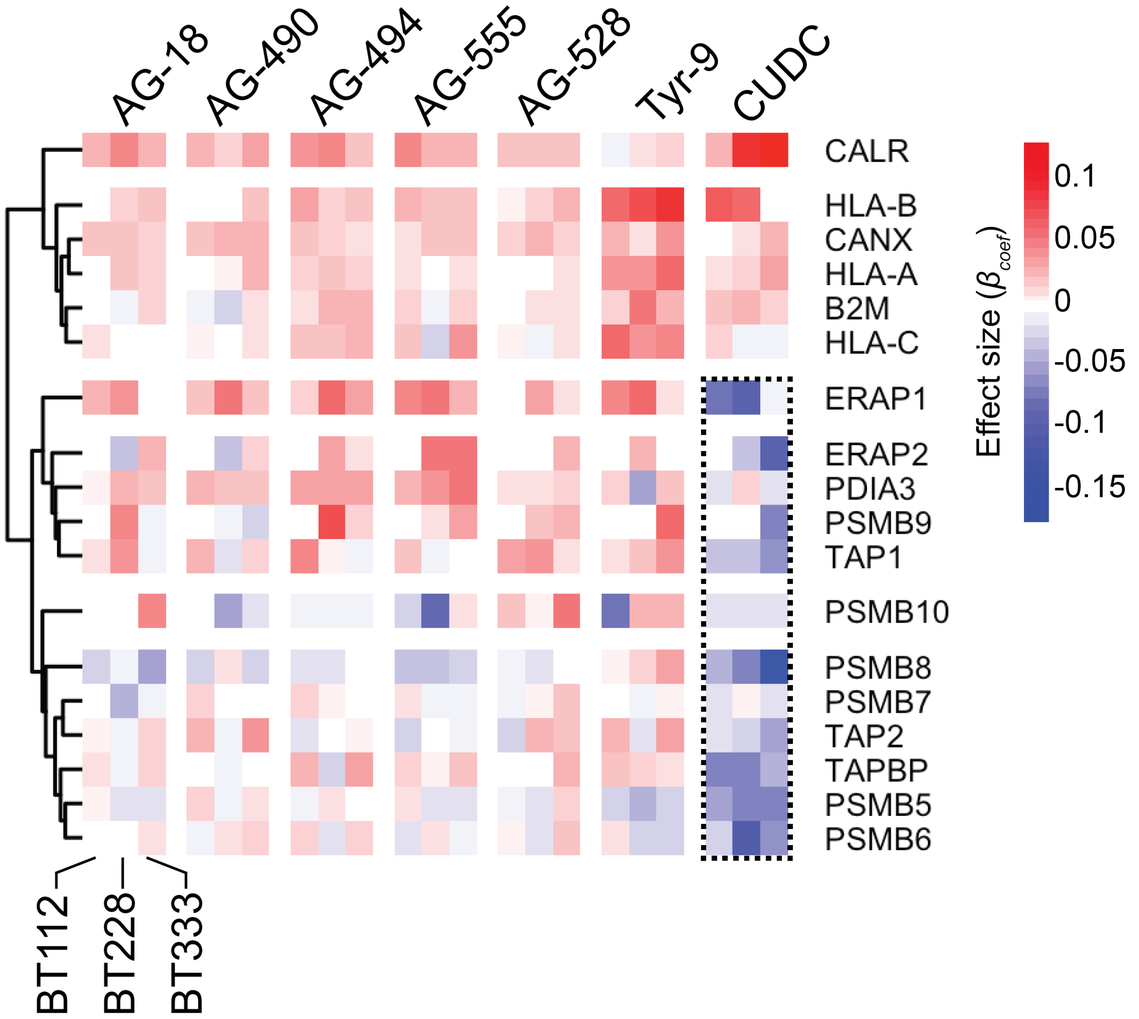
TDC4 is associated with increased APM expression



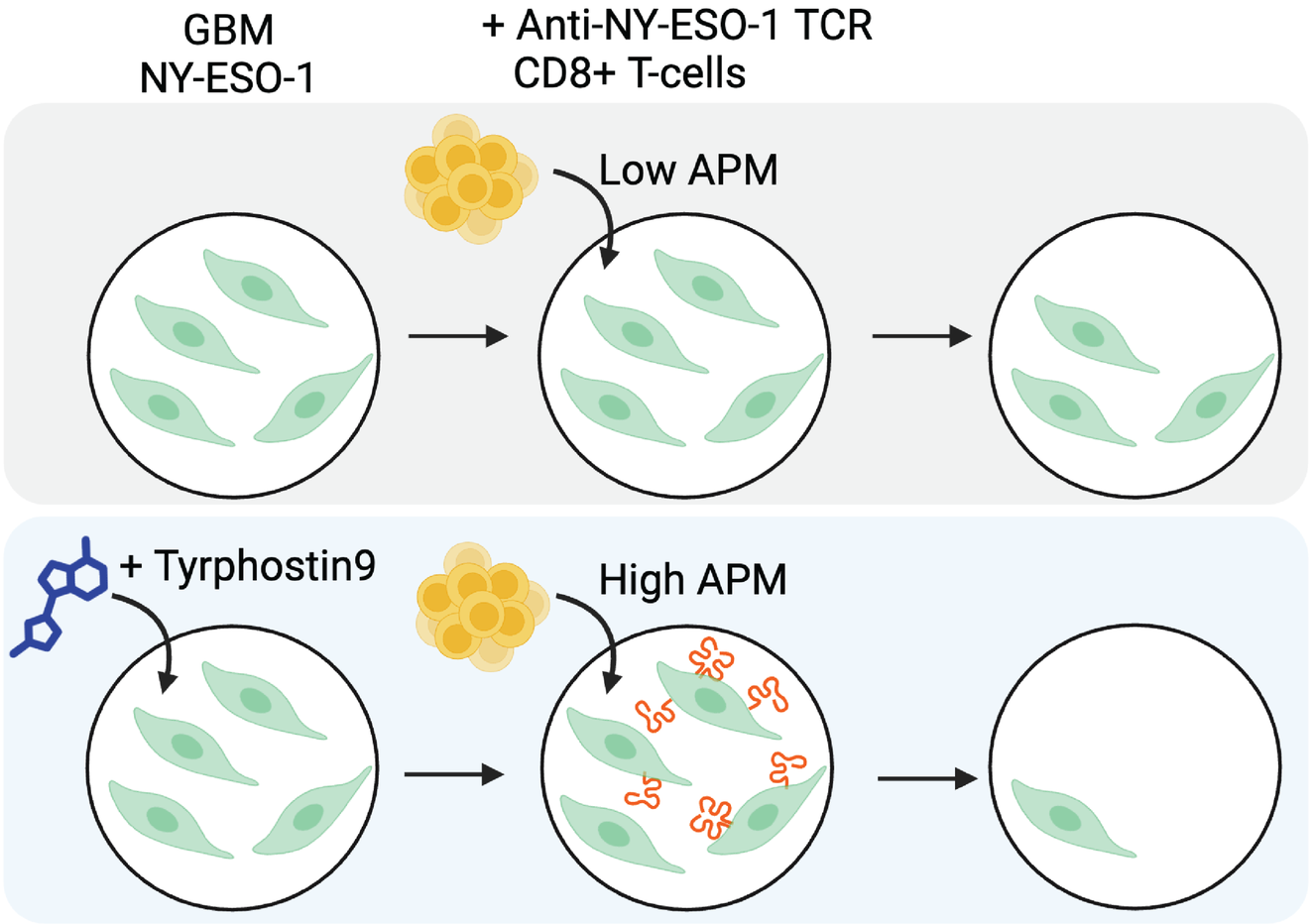


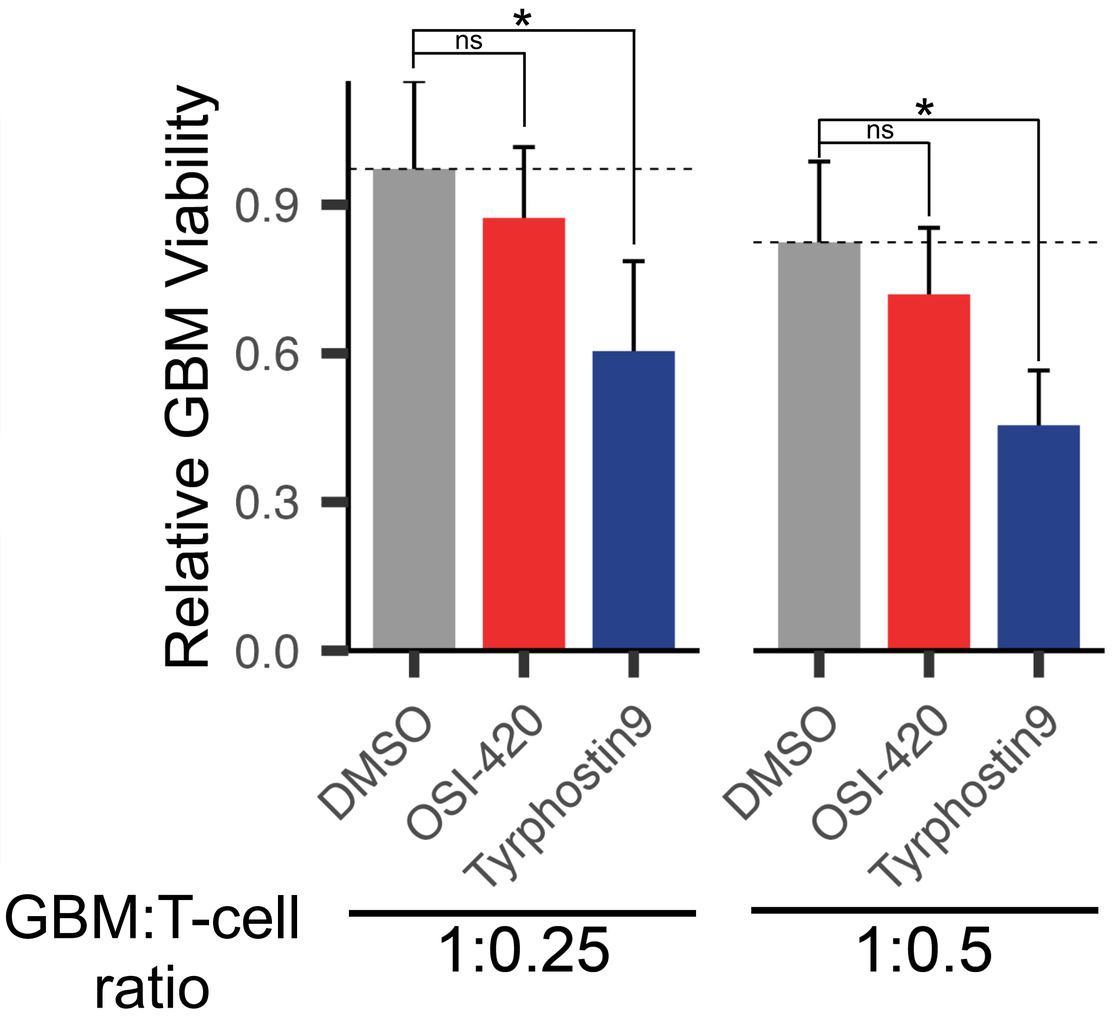
TDC4 is associated with increased APM expression





Tyrphostin-9 promotes T-cell mediated tumor cell killing



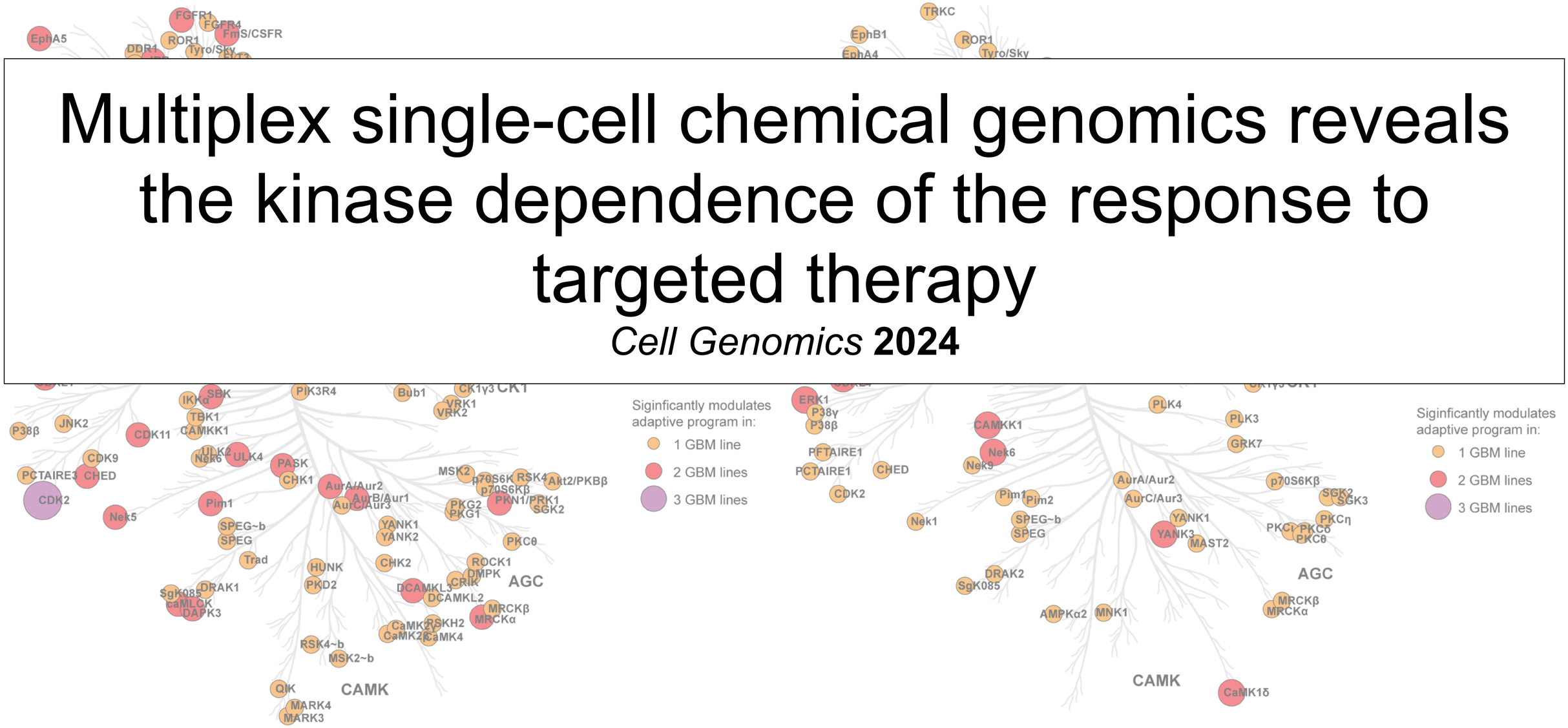


Vignette 2 summary

- Profiled EGFRi-induced transcription in patient-derived and natively-heterogenous GBM models.
- Identified heterogeneity in the induction of molecular programs upon EGFR inhibition.
- A subset of tyrphostin family EGFR inhibitors modulates the expression of APM and sensitizes GBM to T-cell mediated killing.

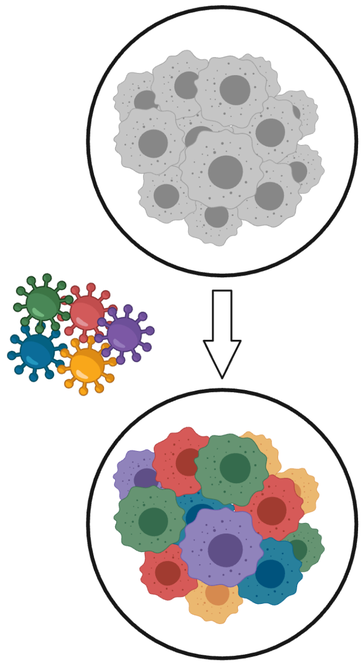
Multiplex single-cell chemical genomics reveals the kinase dependence of the response to targeted therapy

Cell Genomics **2024**

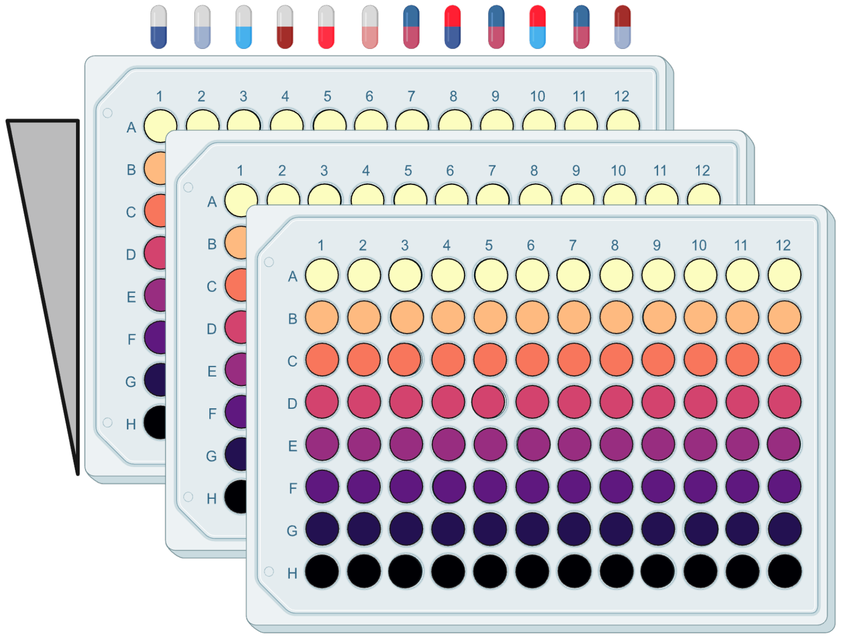


sci-Plex-GxE: A workflow for combined single-cell genetic and exposure screens

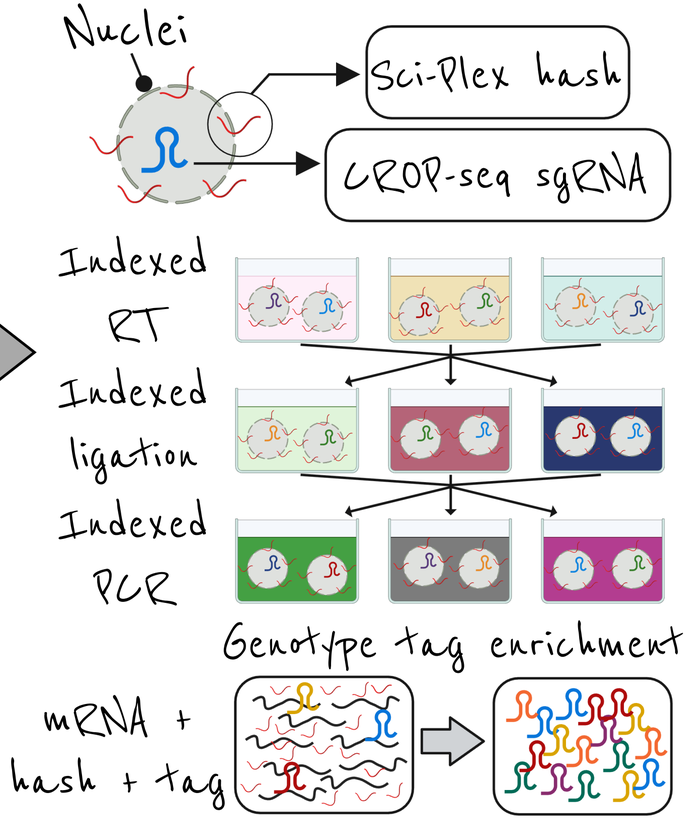
Genetically perturb



Chemically perturb



Highly multiplex sci-RNA-seq



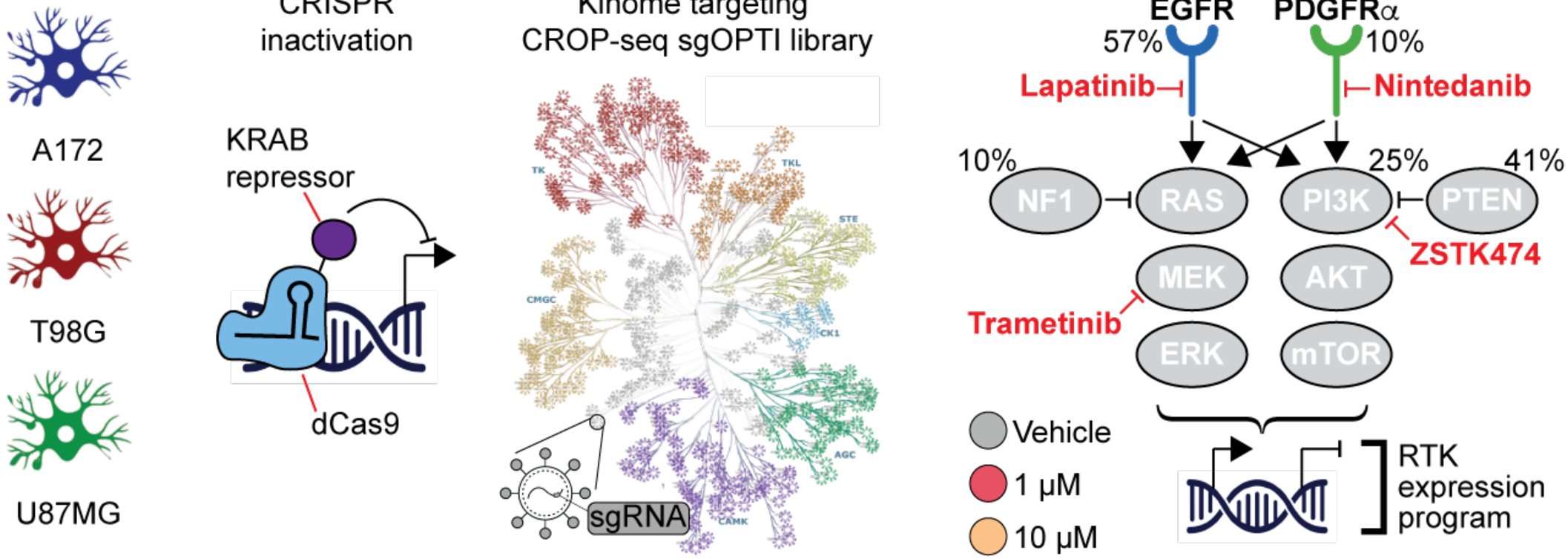
#McFaline-Figueroa, J.L. *et. al.* #Trapnell, C. (**2024**), *Cell Genomics*.

Perturb-seq:
Adamson *et. al.* (**2016**) Cell.
Dixit *et. al.* (**2016**) Cell.
Jaitin *et. al.* (**2016**) Cell.
Dattlinger *et. al.* (**2017**) Nat. Methods.

Contribution of the human protein kinome to therapy induced transcription

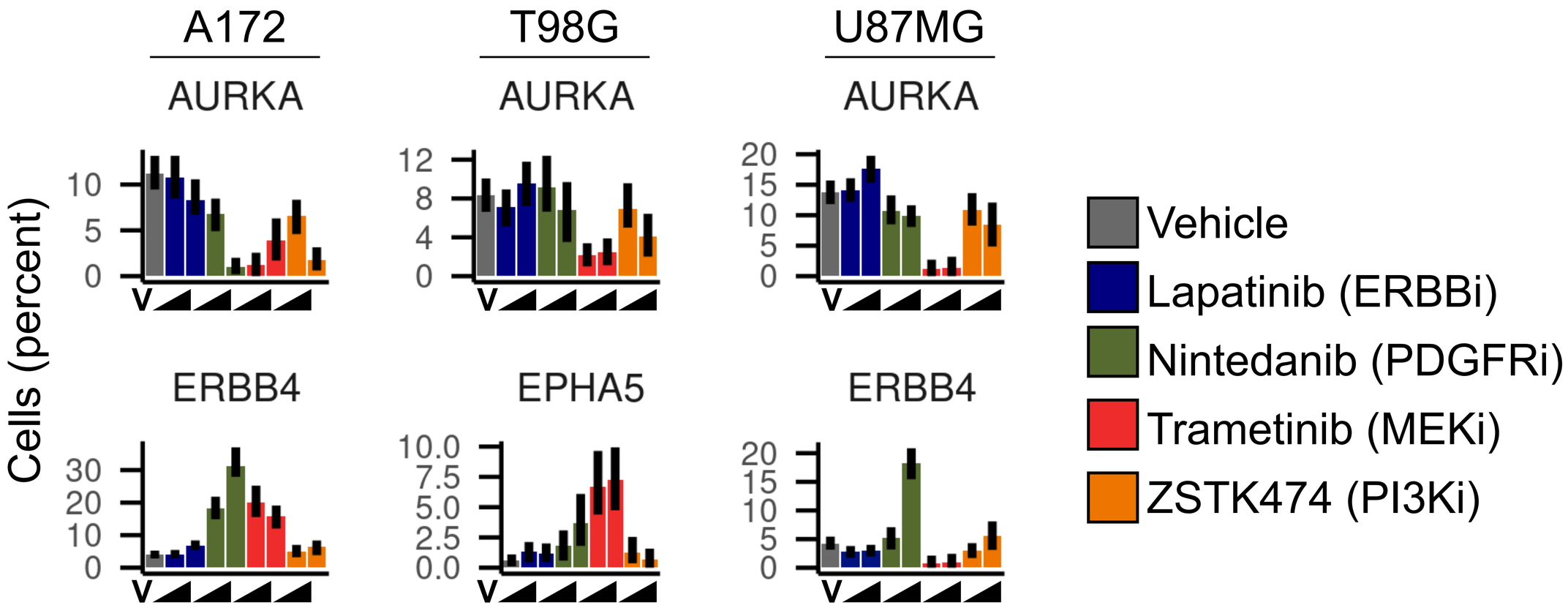
1,000,050 single-cell transcriptomes

14,121 gene-chemical combinations

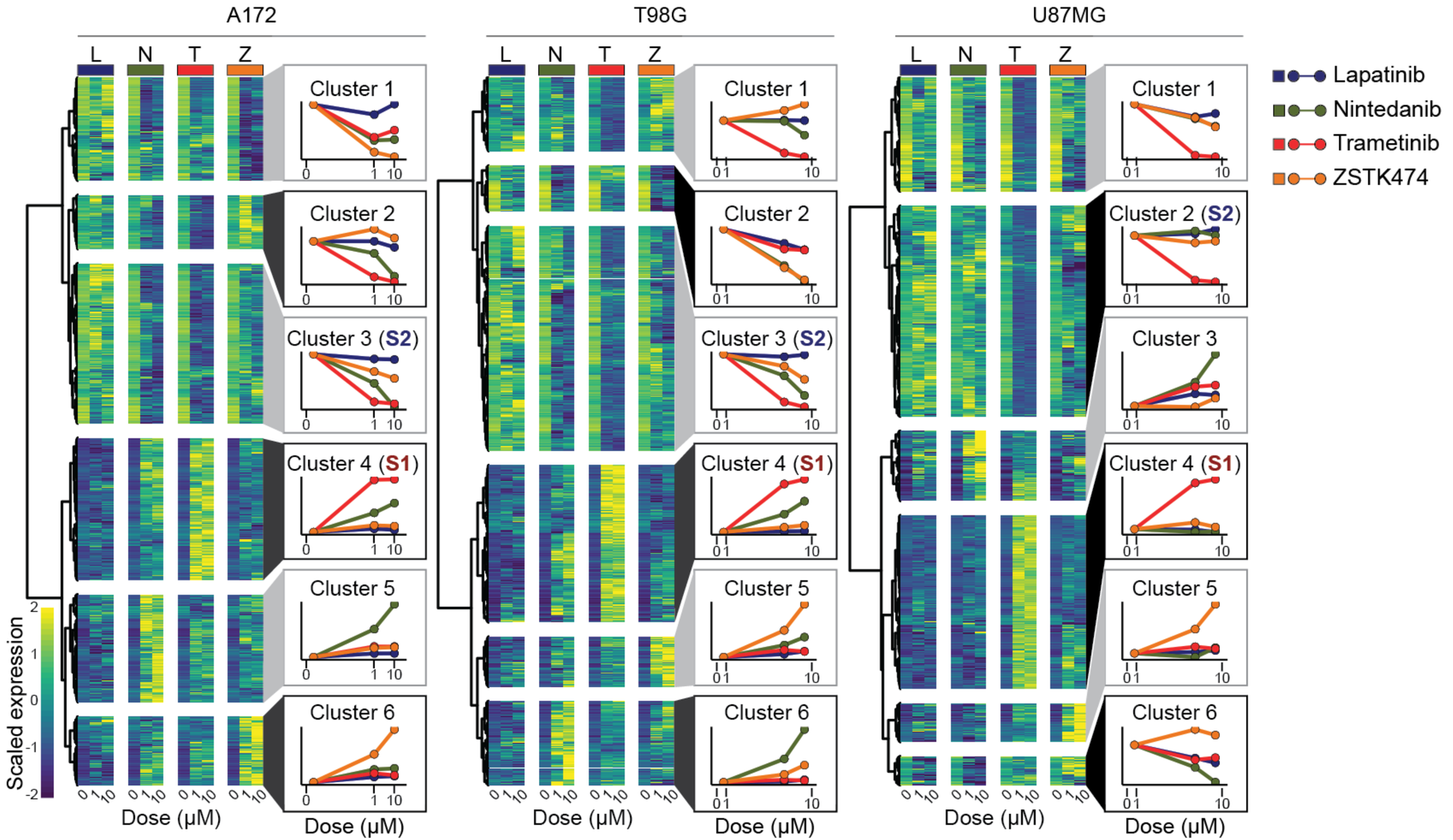


3 GBM lines x Genetic perturbation x 522 targets + controls x 4 RTK pathway targeting compounds at 2 doses + vehicle control

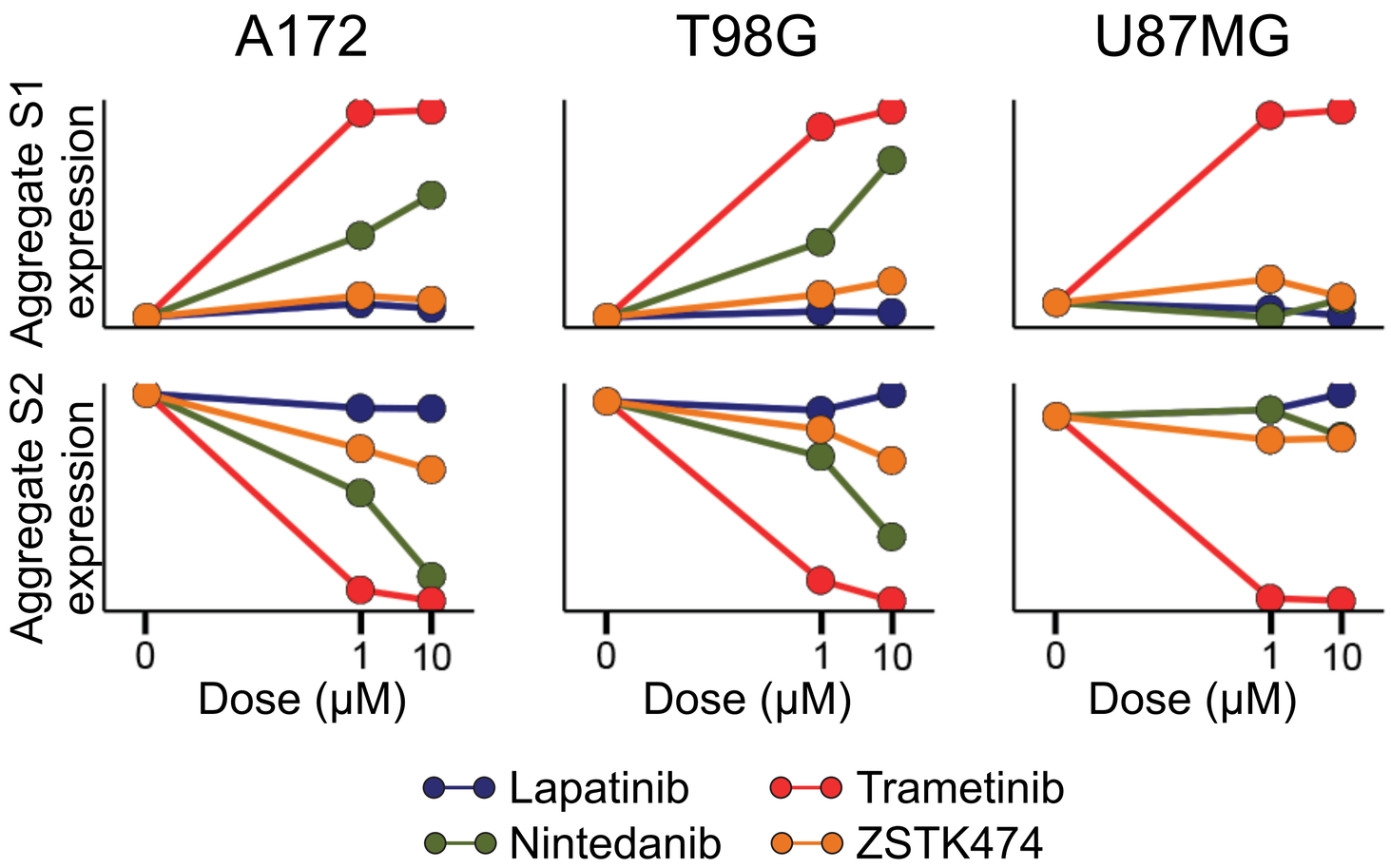
The kinome is dynamic in response to treatment



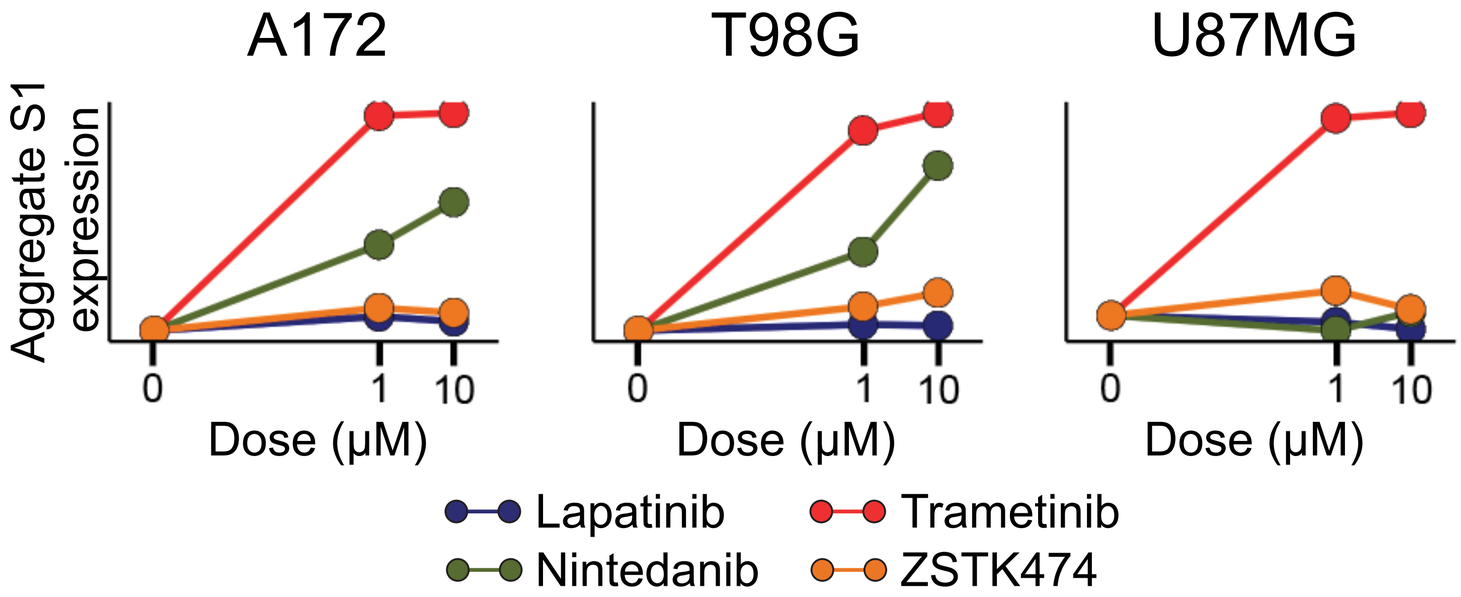
Transcriptome remodeling after kinase inhibition



Conservation of a putative adaptive resistance program



Conservation of a putative adaptive resistance program

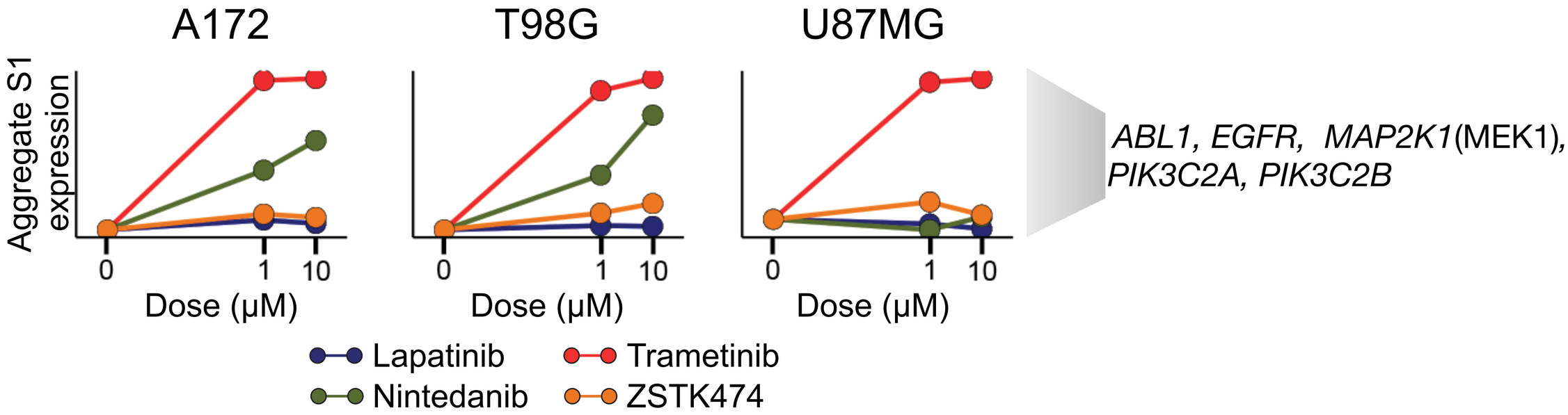


Oncogenic signatures

VEGF-A / ERBB2 / ATF2 /
RAF / KRAS / EGFR / PTEN /
MEK / JNK / AKT / MTOR

Gene set predicts increase, decrease or conflicting changes in activity

Conservation of a putative adaptive resistance program

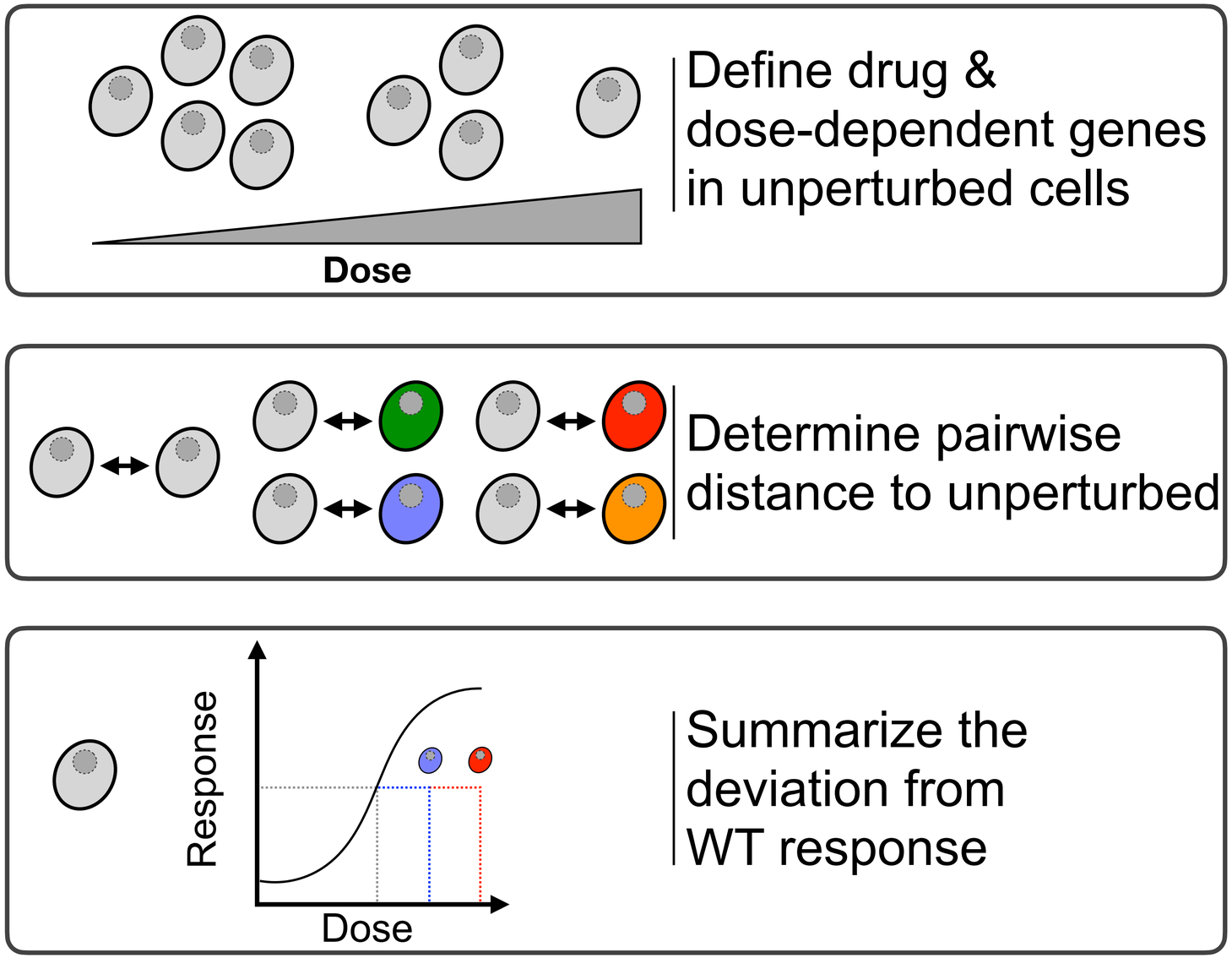


ABL1, EGFR, MAP2K1(MEK1), *PIK3C2A, PIK3C2B*

Oncogenic signatures

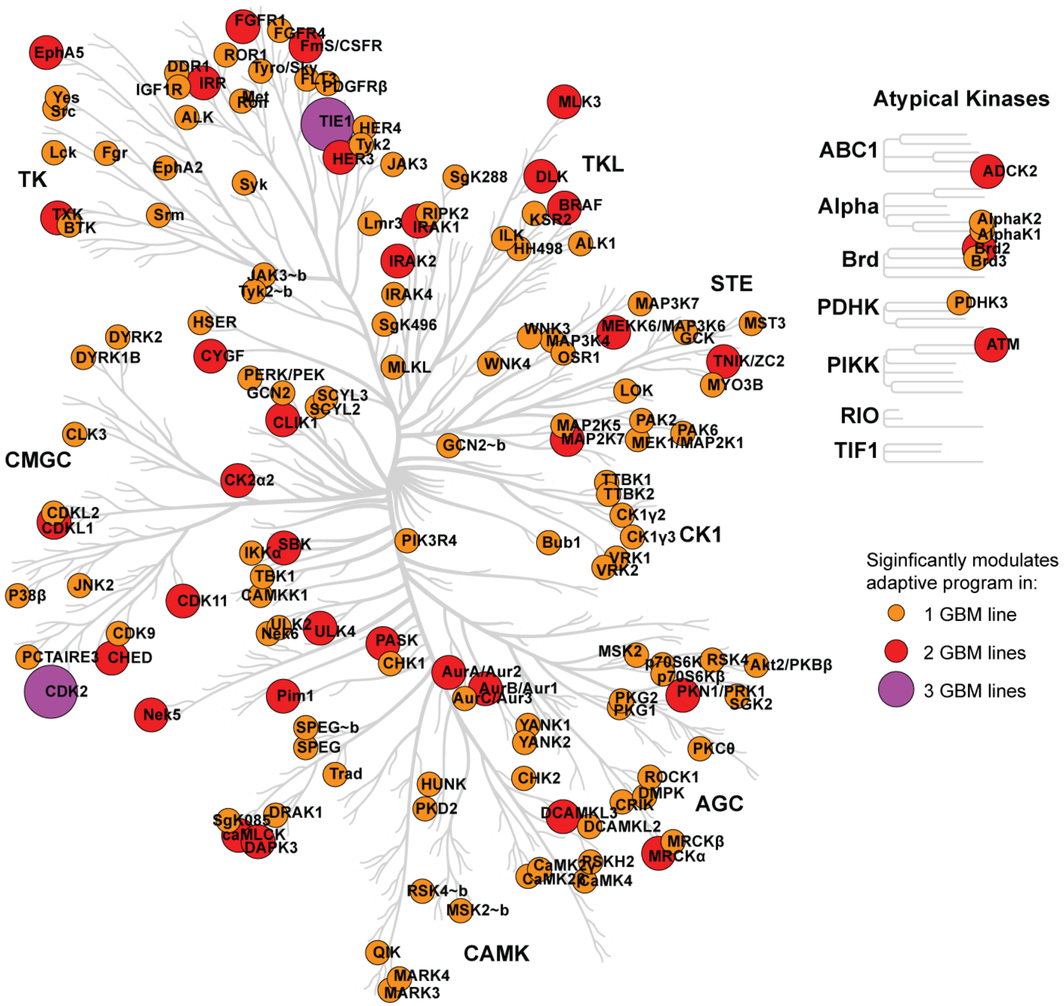
VEGF-A / ERBB2 / ATF2 /
RAF / KRAS / EGFR / PTEN /
MEK / JNK / AKT / MTOR

Gene set predicts increase, decrease or conflicting changes in activity

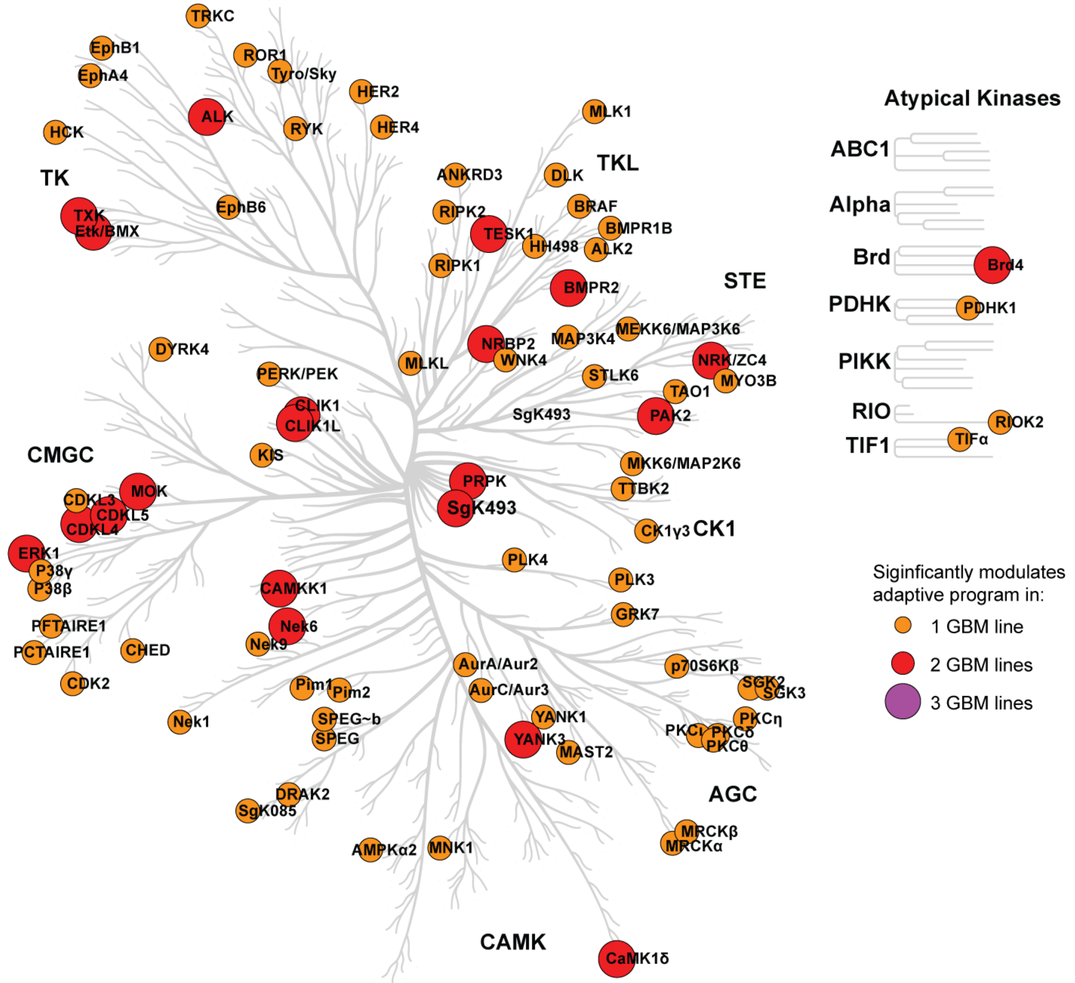

Dose
Define drug &
dose-dependent genes
in unperturbed cells
Determine pairwise
distance to unperturbed
Response
Dose
Summarize the
deviation from
WT response

Kinase regulation of conserved drug-induced programs

Gene effect

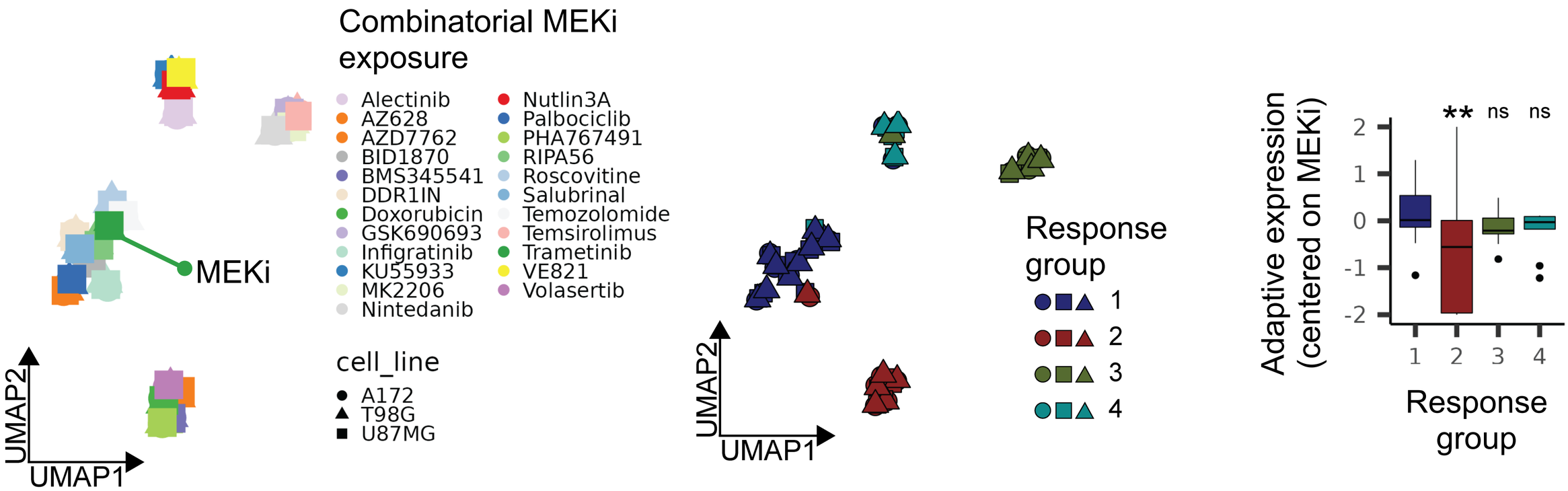


Gene x Environment effect



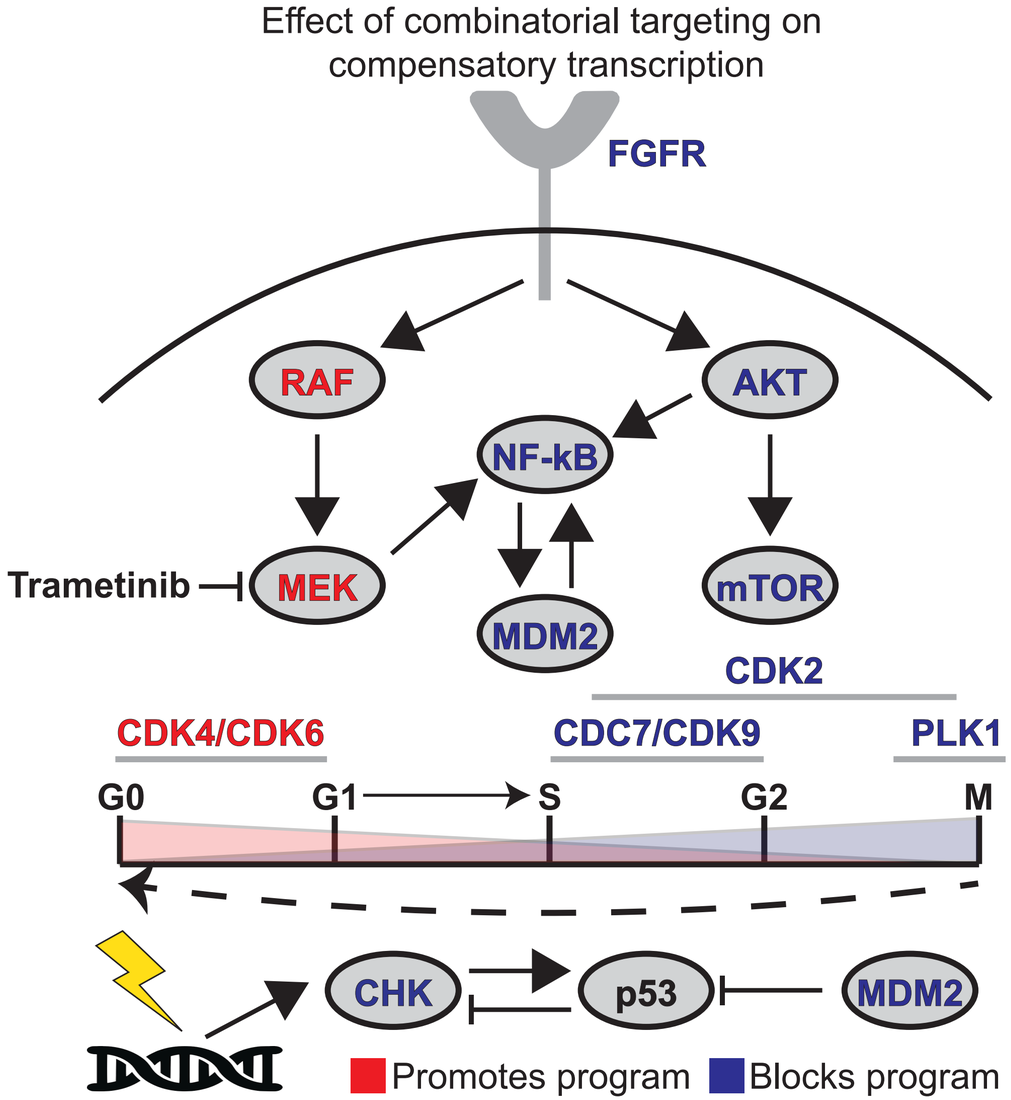
Created with Coral: http://phanstiel-lab.med.unc.edu/CORAL/

Effect of combinatorial kinase inhibition on the expression of the adaptive program



Combinatorial MEKi exposure	Effect on program
Response group 2: CHKi, NFkBi, CDC7i/CDK9i, PLKi, FGFRi	↓↓↓
Response group 3: AKTi, MTORi, PDGFRi	↓

Molecular regulation of putative adaptive program



Vignette 3 summary

- Introduced sci-Plex and sci-Plex-GxE, perturbation multiplexing strategies compatible with single-cell RNA-seq
- Performed high-throughput chemical genomic screens for the regulation of drug-induced transcription
- Multiplexed methods revealed kinases involved in regulating the response to RTK inhibition
- Prioritized combinatorial treatments towards fates of interest

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Thank you!

Department of Biomedical Engineering
COLUMBIA | ENGINEERING

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