UNIVERSITY OF MIAMI

NIH LINCS PROGRAM

A novel platform to identify synergistic drug combination to combat cancer recurrence and prolong clinical efficacy

ChemAxon User Meeting, Cambridge MA, March 25-26 2019

Stephan Schürer

Department of Molecular and Cellular Pharmacology, Department of Psychiatry, Sylvester Comprehensive Cancer Center, Center for Molecular Therapeutics, Center for Computational Science, BD2K LINCS Data Coordination and Integration Center, University of Miami, Miami, FL, USA

BD2K-LINCS DATA COORDINATION AND INTEGRATION CENTER

ChemAxon

Acknowledgements

BD2K-LINCS
DATA COORDINATION AND
INTEGRATION CENTER

- **Amar Koleti**
- Dušica Vidović
- John Turner
- Tanya Kelley
- Afoma Umeano
- Derek Essegian
- **Vasileios Stathias**
- Caty Chung
- Daniel Cooper
- Rimpi Khurana
- Avi Ma'ayan
- Mario Medvedovic
- Stephan Schürer
- **Nagi Ayad**

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BD2K-LINCS DCIC U54 HL127624

NIH LINCS
PROGRAM

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UNIVERSITY
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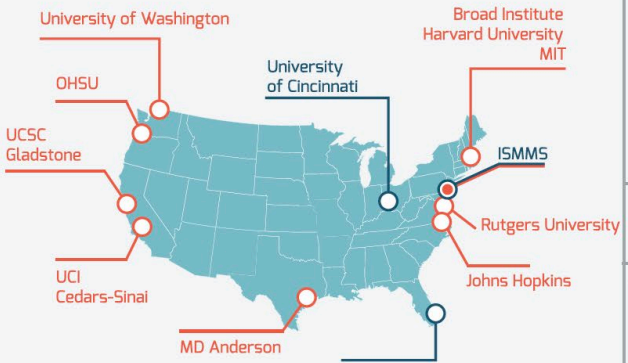
LINCS
BY THE NUMBERS

15 INSTITUTIONS



~100 scientists, technicians, and developers

Data Coordination and Integration Center

BD2K-LINCS | ISMMS | University of Miami | University of Cincinnati

Data and Signature Generation Centers

NeuroLINCS	MEP LINCS	DToxS	PCCSE
UCI Cedars-Sinai Glastone Johns Hopkins MIT	OHSU MD Anderson	ISMMS Rutgers University	Broad Institute University of Washington MIT

HMS LINCS	Broad Transcriptomics
Harvard University UCSC	Broad Institute

4 PERTURBATION TYPES

41,847 Small Molecules

108 Antibodies

7,547 Genetic Perturbations

2,736 Microenvironment Perturbagens

5 CELL TYPES

1,131 Cell Lines

45 Primary Cells

18 IPSCs

11 Differentiated Cells

2 Embryonic Stem Cells

5 SIGNATURE TYPES

Transcriptomics
2 Assays
11 Datasets

Proteomics
4 Assays
8 Datasets

Binding
2 Assays
201 Datasets

Epigenomics
2 Assays
4 Datasets

Imaging
11 Assays
85 Datasets

FEATURED LINCS TOOLS

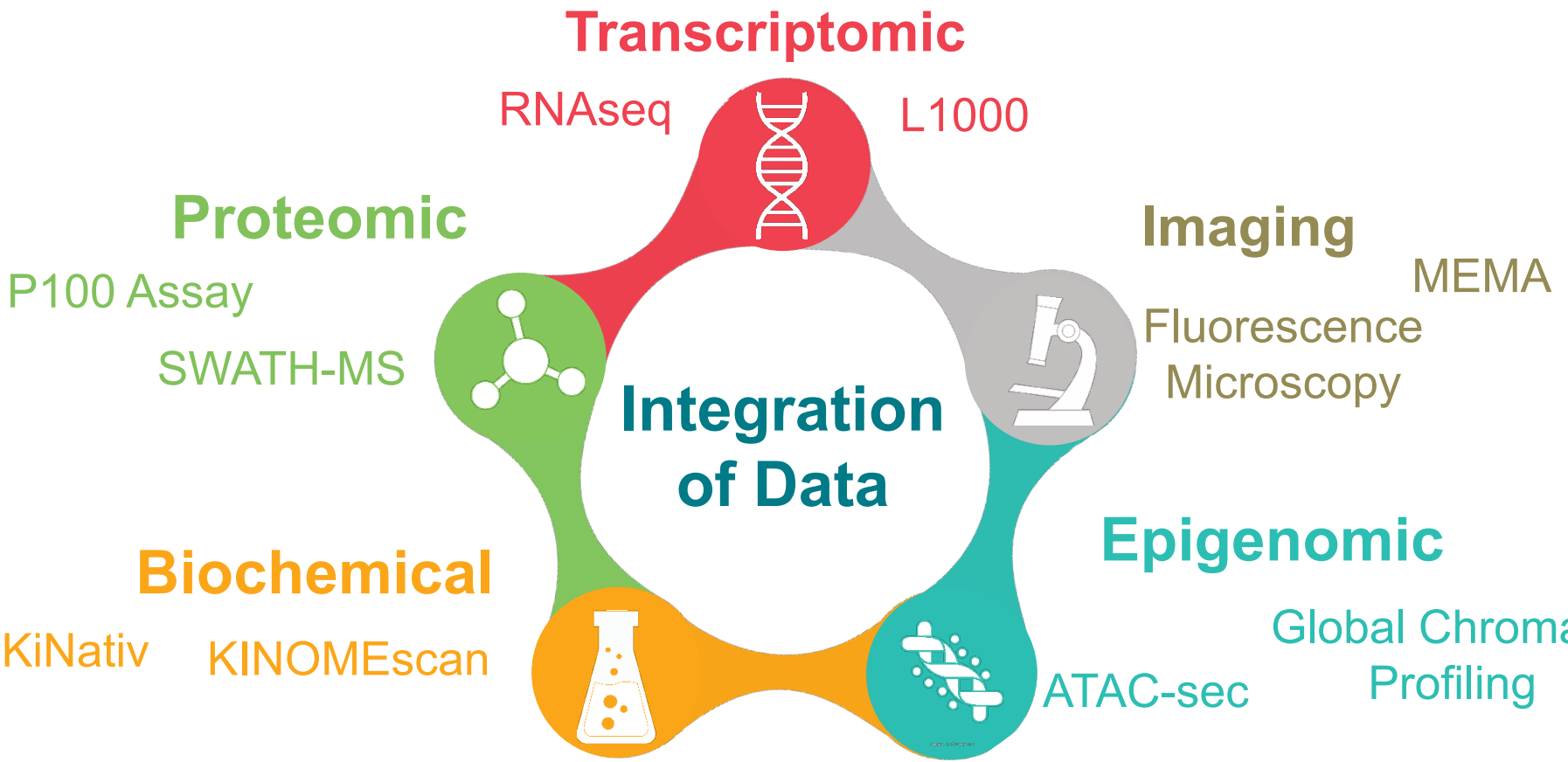
Download	Analyze
LINCS Data Portal	OmicsIntegrator
Slicr	L1000CDS
HMS LINCS Database	Enrichr
	SEP - L1000
	Breast Cancer Browser
iLINCS	
piLINCS	
Harmonizome	

30 MORE TOOLS

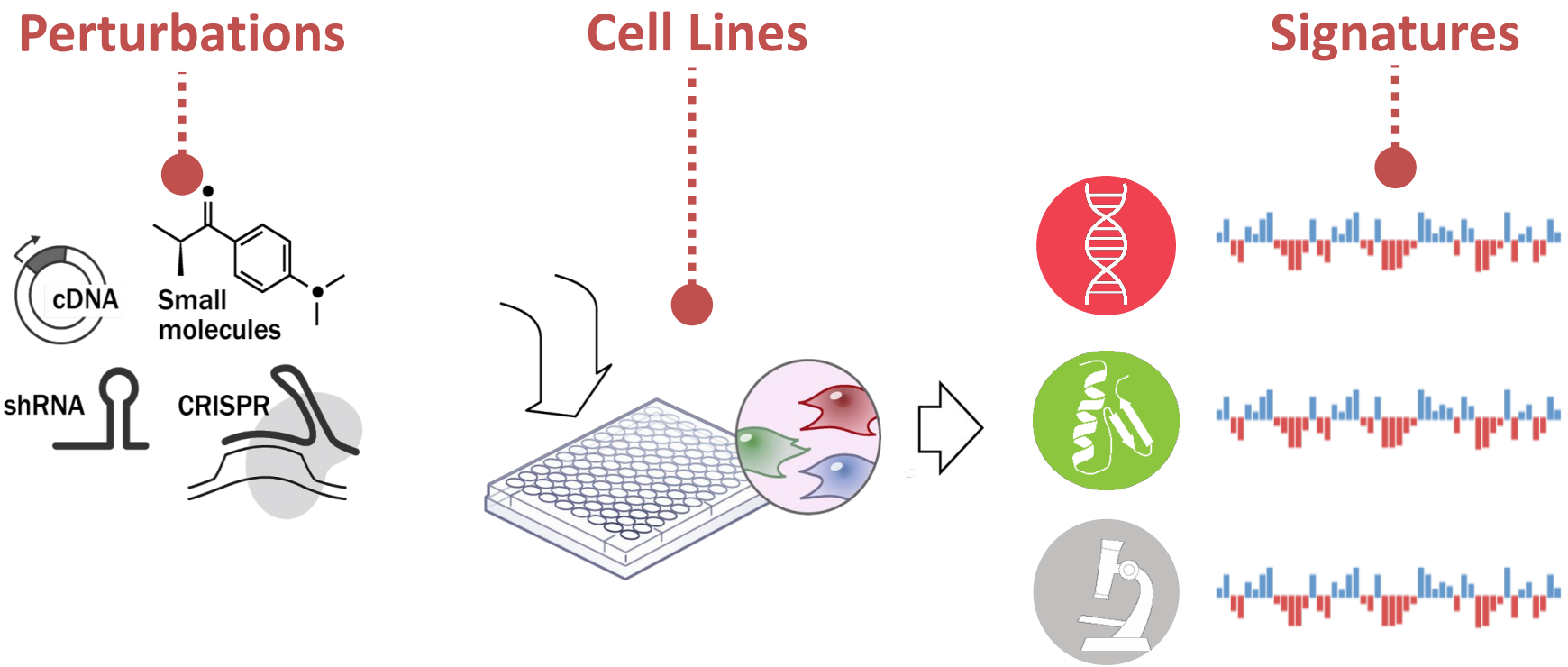
Download LINCS Datasets

Analyze LINCS Datasets

LINCS Project generates diverse multidimensional data

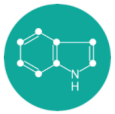


LINCS Signatures characterize diverse cellular responses upon perturbation



LINCS Data Portal - Home Page


381 Datasets


41847 Small Molecules


1127 Cells


978 Genes


1469 Proteins /155 Peptide Probes


8 Antibodies

14 Methods	**Binding**	**201 Datasets**	**KINOMEscan kinase-small molecule binding assay**
06 **Subject Areas**	Imaging	85 Datasets	**163 Datasets**
12 Centers	Transcriptomics	12 Datasets	KiNativ kinase-small molecule binding assay — 30 Datasets
06 Projects	Proteomics	9 Datasets	Bead-based immunoassay for protein state — 3 Datasets
11 Biological Processes	Epigenomics	4 Datasets	ELISA protein secretion profiling assay — 3 Datasets
	Metabolomics	1 Datasets	ELISA protein state assay — 2 Datasets

KINOMEscan kinase-small molecule binding assay

Assay Overview

Compounds that bind the kinase active site and directly (sterically) or indirectly (allosterically) prevent kinase binding to the immobilized ligand, will reduce the amount of kinase captured on the solid support (Panels A & B). Conversely, test molecules that do not bind the kinase have no effect on the amount of kinase captured on the solid support (Panel C). Screening hits are identified by

LINCS Data Portal - http://lincsportal.ccs.miami.edu/

Small Molecules

Accelerate the discovery of novel therapeutics for precision medicine by unravelling LINCS small molecules annotations for approved drugs, clinical phase and chemical probes.

Search assays, cell lines, and perturbagens...

Browse | Structure Search | About | Help

Search for Small Molecule

Search LINCS small molecules by generic names, synonyms, trade names and explore across LINCS datasets, model systems and annotations.

Example search for Seliciclib can query using either "Roscovitine" or "CYC-202" .A comprehensive list of generic names and synonyms are also stored and can be used as search terms.

Explore Annotations

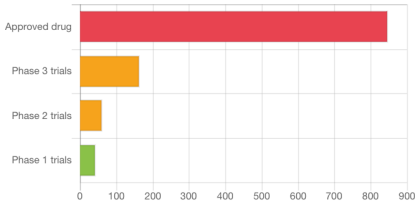
Search can be performed by a wide set of annotations such as mechanism of actions Cyclin-dependent kinase 2 inhibitor, MESH terms CARCINOMA, EFO terms CYSTIC FIBROSIS and cells MCF7.

Advanced Search

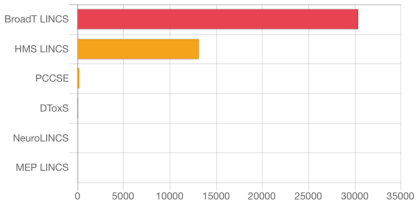
Search also facilitates AND , OR , NOT queries. Some examples 1) find Small Molecules that are used in KINOMEscan and L1000 assays. 2) Find Small Molecules that have annotated as Cyclin-dependent inhibitor or kinase inhibitor.

Statistics

Small Molecules by FDA PHASE



Small Molecules by Source



Cells

Accelerate the discovery of novel therapeutics for precision medicine by unravelling LINCS cells annotations.

Search assays, cell lines, and perturbagens...

Browse | About | Help

Search for Cells

Search LINCS cells by generic names, synonyms, diseases and explore across LINCS datasets, perturbagens and annotations.

Example search for MCF7 or explore more details through the Cell Landing Pages "MCF7". A comprehensive list of generic names and synonyms are also stored and can be used as search terms.

Explore Annotations

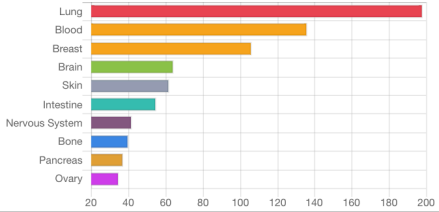
Search can be performed by a wide set of annotations such as organs Breast, Diseases Melanoma, Assays Fluorescence imaging cell growth inhibition assay and Small Molecules Enzastaurin.

Advanced Search

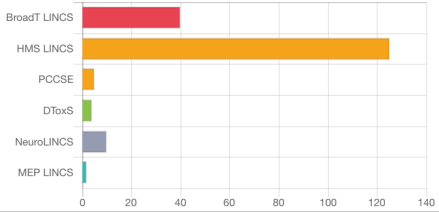
Search also facilitates AND , OR , NOT queries. Some examples 1) find cells that are used in P100 and L1000 assays. 2) Find cells that are derived from Lung.

Statistics

Cells by Organ



Cells by Center



L1000 Dataset -small molecule perturbagens- LINCS Phase 2 (June 2015) (LDG-1227: LDS-1273, LDS-1274, LDS-1275, LDS-1233)

Transcriptomics Assay

Description | Metadata | Download | Analysis Tools | Visualize | Community

LINCS ID LDG-1227: LDS-1273, LDS-1274, LDS-1275, LDS-1233

Datas

Cente

Princ
Inves

Fund

Desc

for 978 representative genes in 15 cell lines treated with 241 small molecules

Data Source http://www.ncbi.nlm.nih.gov/g

Release Date Jun 30, 2015

Processing Pipeline https://github.com/cmap/l1kt

Citation Cite *To cite a specific datas*

Export: BibTeX (.bib) RIS (.ris

Assay Name L1000 mRNA profiling assay

Assay Description L1000 is a bead-based, high-th
chemical and genetic perturba
processed through a computa
expression signatures. The da
flow cytometry data from Lum
contains a fluorescence intens
per 1,000 genes after deconvo
directly measured landmark tr
quantile normalization. Level 4
scores for each profile relative

Assay Protocol

Keywords Transcriptomics L1000 Gene

Todd Golub, Aravind Subramanian: L1000 Dataset -small molecule perturbagens- LINCS Phase 2 (June 2015), 2015, LINCS (collection), http://identifiers.org/lincs.data/LDG-1227, retrieved: Oct 20, 2017.

L1000 Dataset -small molecule perturbagens- LINCS Phase 2 (June 2015) (LDG-1227: LDS-1273, LDS-1274, LDS-1275, LDS-1233)

Transcriptomics Assay

Description | Metadata | Download | Analysis Tools | Visualize | Community

277 Small molecules

5 Cell lines

Small molecules Search here...

Download

Name	LINCS ID	Center Sample ID	Provider	Provider Catalog ID
NU-7441	LSM-1061	BRD-K00337317-001-05-8	Shanghai Haoyuan Chemexpress Co., Ltd.	HY-11006
				XMD11-50; LRRK2-in-1
			xpress Co., Ltd.	HY-12041
			xpress Co., Ltd.	HY-10162
			xpress Co., Ltd.	HY-10162

Showing 1 to 5 of 277 small molecules

Download

er	Provider Catalog ID
ATCC_Own,Mario Niepel (Harvard Medical)	null,æHTB-22,HTB-22
	CCL-185
	CRL-4010
nstitute	contact provider
),The Broad Institute,æThe Broad Institute	contact provider,N/A

Showing 1 to of 5 cells

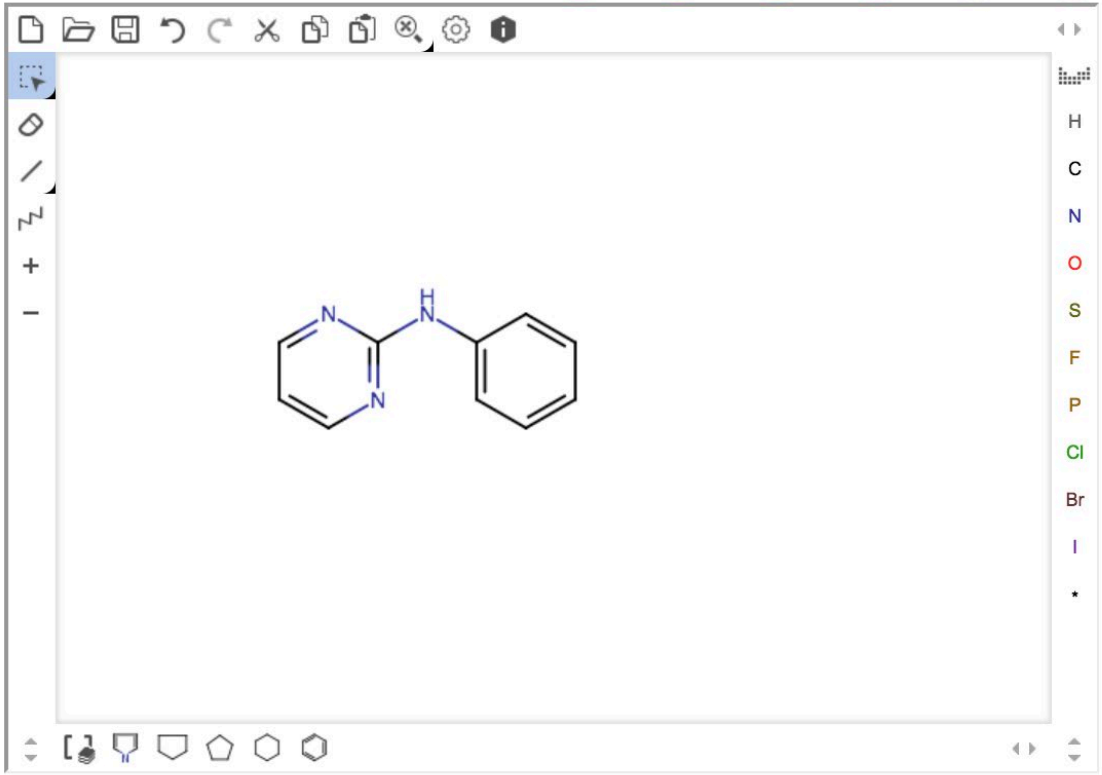
L1000 Dataset -small molecule perturbagens- LINCS Phase 2 (June 2015) (LDG-1227: LDS-1273, LDS-1274, LDS-1275, LDS-1233)

Transcriptomics Assay

Description | Metadata | Download | Analysis Tools | Visualize | Community

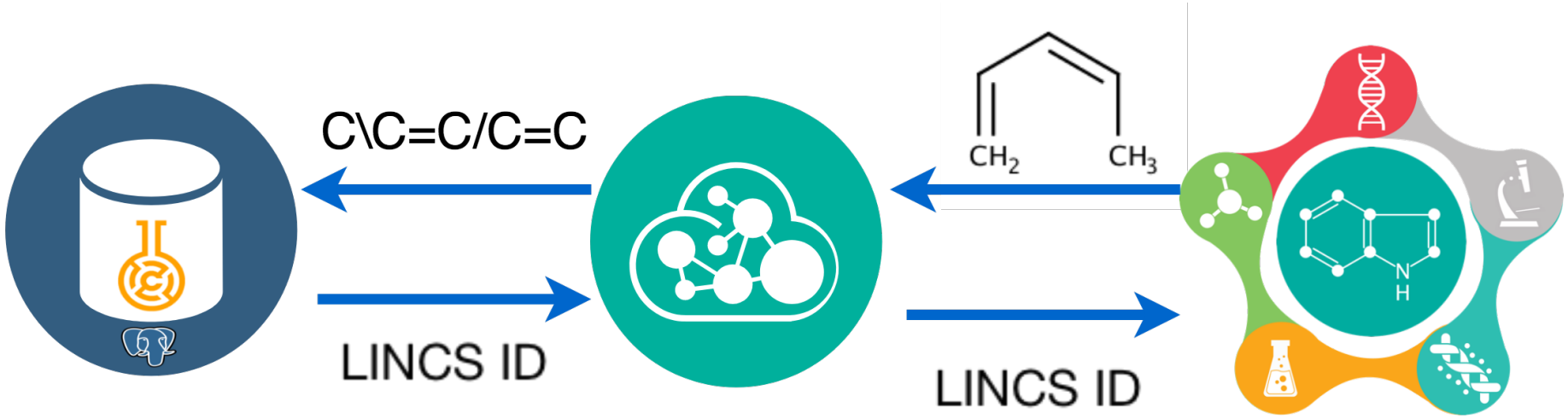
Download all levels

Data Level	Data Description	Dataset ID	Version	Size	Download	Cite
1	LDS-1273	Raw dataset	1.0	51736.33 MB		Cite Export
2	LDS-1274	Processed raw dataset	1.0	372.90 MB		Cite Export
3	LDS-1275	Normalized dataset	1.0	11294.75 MB		Cite Export
4	LDS-1233	Signature dataset	1.0	9769.81 MB		Cite Export



Substructure Search | Similarity Search

LDP Chemical Structure Search Engine



SMDB

JChem Postgres Cartridge

API Servlet

Structure Search

Marvin JS or direct

OR

LINCS Center

- BroadT LINCS 67
- HMS LINCS 48

More

Bioassay Type

- L1000 mRNA profiling assay 68
- KINOMEscan kinase-small molecule binding assay 39

More

Clinical Phase

- Approved drug 7
- Phase 2 trials 7

More

Pharmacological Classification

- Tyrosine kinase inhibitors 9
- Protein kinase inhibitors 6

More

Mechanism of Action

- Epidermal growth factor receptor erbB1 inhibitor 2
- Focal adhesion kinase 1 inhibitor 2

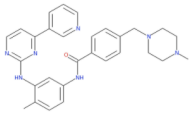
More

Search assays, cell lines, and perturbagens...

Filtered by: LSM-15449" OR "LSM-21027" OR "LSM-24505" OR "LSM-1459" OR "LSM-18669" OR "LSM-4750" OR "LSM-36387" O *(lincsidentifier)* clear all

Total Small Molecules: 93

List view | Table view | Download



Imatinib

Synonyms: CGP-57148B; Gleevec; Glivec; Imatinib; IMATINIB (3524741); Imatinib Mesilate; Imatinib Mesylate; IMATINIB (STI571); STI-571

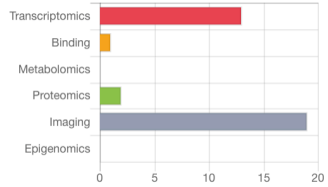
Max Phase: Approved drug

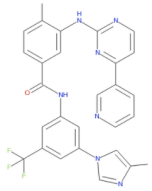
Mechanism of Action: Platelet-derived growth factor receptor beta inhibitor; Stem cell growth factor receptor inhibitor; Tyrosine-protein kinase ABL inhibitor Explore

Pharmacological Classification: Tyrosine kinase inhibitors; Protein kinase inhibitors Explore

Model Systems: 669 cell-lines used Show Explore

Datasets: Used in 32 Datasets Show Explore





Nilotinib

Synonyms: AMN-107; Nilotinib; NILOTINIB (AMN-107); Nilotinib Hydrochloride Monohydrate; Tasigna

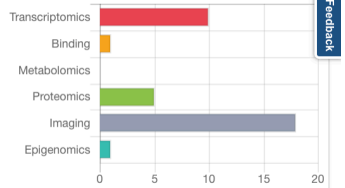
Max Phase: Approved drug

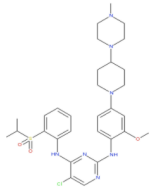
Mechanism of Action: Tyrosine-protein kinase ABL inhibitor Explore

Pharmacological Classification: Tyrosine kinase inhibitors; Protein kinase inhibitors Explore

Model Systems: 162 cell-lines used Show Explore

Datasets: Used in 31 Datasets Show Explore



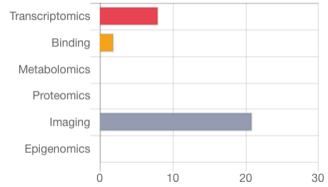


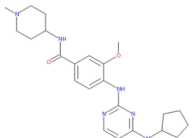
TAE-684

Synonyms: NVP-TAE684

Model Systems: 637 cell-lines used Show Explore

Datasets: Used in 28 Datasets Show Explore





BI-2536

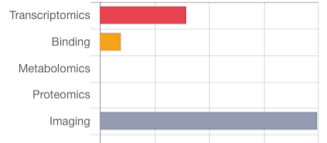
Synonyms: BI 2536; BI-2536; NPK33-1-98-1

Max Phase: Phase 2 trials

Mechanism of Action: Serine/threonine-protein kinase PLK1 inhibitor Explore

Model Systems: 644 cell-lines used Show Explore

Datasets: Used in 27 Datasets Show Explore



Provide Feedback

OR

LINCS Center

- BroadT LINCS 6
- HMS LINCS 5

+ More

Bioassay Type

- L1000 mRNA profiling assay 6
- KINOMEscan kinase-small molecule binding assay 5

+ More

Clinical Phase

- [x] Approved drug 7
- Phase 2 trials 7

+ More

Pharmacological Classification

- Protein kinase inhibitors 5
- Tyrosine kinase inhibitors 4

+ More

Mechanism of Action

- Human immunodeficiency virus type 1 reverse transcriptase inhibitor 2
- Stem cell growth factor receptor inhibitor 2

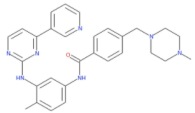
+ More

Search assays, cell lines, and perturbagens...

Filtered by: LSM-15449" OR "LSM-21027" OR "LSM-24505" OR "LSM-1459" OR "LSM-18669" OR "LSM-4750" OR "LSM-36387" O *(lincsidentifier)* ✖ Approved drug *(FDA_PHASE)* ✖ clear all ✖

Total Small Molecules: 7

List view | Table view | Download



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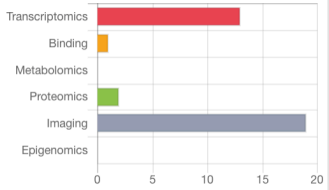
Max Phase: Approved drug

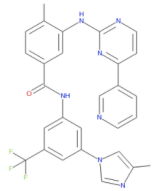
Mechanism of Action: Platelet-derived growth factor receptor beta inhibitor; Stem cell growth factor receptor inhibitor; Tyrosine-protein kinase ABL inhibitor Explore

Pharmacological Classification: Tyrosine kinase inhibitors; Protein kinase inhibitors Explore

Model Systems: 669 cell-lines used Show Explore

Datasets: Used in 32 Datasets Show Explore





Nilotinib

Synonyms: AMN-107; Nilotinib; NILOTINIB (AMN-107); Nilotinib Hydrochloride Monohydrate; Tasigna

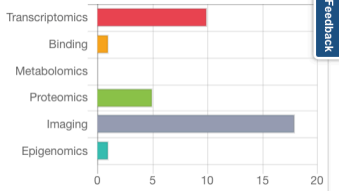
Max Phase: Approved drug

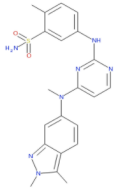
Mechanism of Action: Tyrosine-protein kinase ABL inhibitor Explore

Pharmacological Classification: Tyrosine kinase inhibitors; Protein kinase inhibitors Explore

Model Systems: 162 cell-lines used Show Explore

Datasets: Used in 31 Datasets Show Explore





Pazopanib

Synonyms: 635702-64-6; GW786034; GW786034B; Pazopanib; Pazopanib HCl; Pazopanib Hydrochloride; Votrient

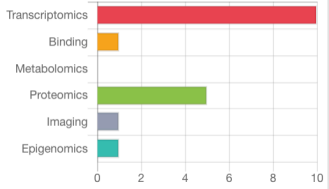
Max Phase: Approved drug

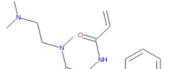
Mechanism of Action: Fibroblast growth factor receptor 3 inhibitor; Macrophage colony stimulating factor receptor inhibitor; Tyrosine-protein kinase LCK inhibitor; Tyrosine-protein kinase ITK/TSK inhibitor; Vascular endothelial growth factor receptor inhibitor; Stem cell growth factor receptor inhibitor; Platelet-derived growth factor receptor inhibitor; Fibroblast growth factor receptor 1 inhibitor Explore

Pharmacological Classification: Angiogenesis inhibitors; Protein kinase inhibitors Explore

Model Systems: 1115 cell-lines used Show Explore

Datasets: Used in 13 Datasets Show Explore

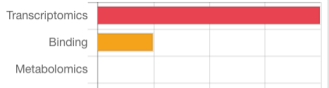




Osimertinib

Synonyms: AZD-9291; AZD-9291 MESYLATE; HG-14-8-02; Osimertinib; Osimertinib Mesylate; Tagrisso

Max Phase: Approved drug



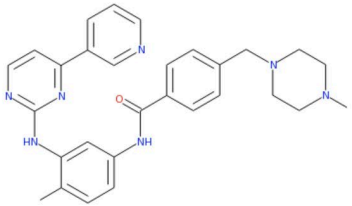
Provide Feedback

Imatinib (LSM-1023)

Description | Datasets | Curated Data

Compound Information

Name	Imatinib
LINCS (ID)	LSM-1023
PubChem (CID)	5291
ChEBI (ID)	31690 , 45783
ChEMBL (ID)	CHEMBL1642 , CHEMBL2386595 , CHEMBL941
Alternative Names	CGP-57148B; Gleevec; Glivec; Imatinib; IMATINIB (3524741); Imatinib Mesilate; Imatinib Mesylate; IMATINIB (STI571); STI-571
SMILES	Show
InChI	Show



Find Similar Structures Similarity Search POWERED BY ChemAxon

95% Similar Molecules
90% Similar Molecules
80% Similar Molecules

Provide Feedback

Related LINCS Compounds by chemical structure (similarity ≥ 0.9)

LSM-43288
LSM-45329
LSM-44525

Predicted Physicochemical Properties

Molecular formula	C29H31N7O
Molecular weight	493.60g/mol
Lipinski 3	Fail
Lipinski 5	Pass
Bioavailability	Pass
Lead likeliness	Fail

cLogP	4.38
Rotatable bonds	7
H bond acceptors	7
H bond donors	2
TPSA	86.28
QED	0.40

OR

LINCS Center

- BroadT LINCS 3
- HMS LINCS 3

+ More

Bioassay Type

- KINOMEscan kinase-small molecule binding assay 3
- L1000 mRNA profiling assay 3

+ More

Clinical Phase

- Approved drug 1

+ More

Pharmacological Classification

- Protein kinase inhibitors 1
- Tyrosine kinase inhibitors 1

+ More

Mechanism of Action

- DNA topoisomerase II alpha inhibitor 1

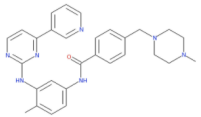
− Less

Search assays, cell lines, and perturbagens...

Filtered by: LSM-45329" OR "LSM-43288" OR "LSM-1023" OR "LSM-44525 *(lincsidentifier)* clear all

Total Small Molecules: 4

List view | Table view | Download



Imatinib

Synonyms: CGP-57148B; Gleevec; Glivec; Imatinib; IMATINIB (3524741); Imatinib Mesilate; Imatinib Mesylate; IMATINIB (STI571); STI-571

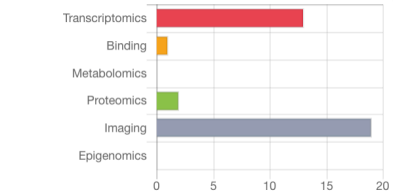
Max Phase: Approved drug

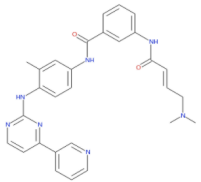
Mechanism of Action: Platelet-derived growth factor receptor beta inhibitor; Stem cell growth factor receptor inhibitor; Tyrosine-protein kinase ABL inhibitor Explore

Pharmacological Classification: Tyrosine kinase inhibitors; Protein kinase inhibitors Explore

Model Systems: 669 cell-lines used Show Explore

Datasets: Used in 32 Datasets Show Explore



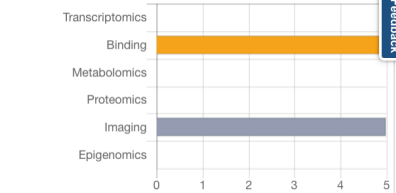


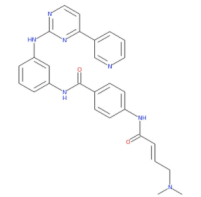
JNK-IN-8

Synonyms:

Model Systems: 14 cell-lines used Show Explore

Datasets: Used in 10 Datasets Show Explore



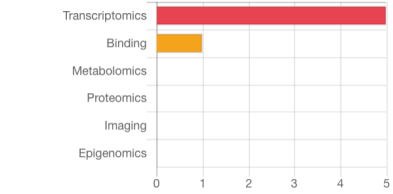


JNK-IN-2

Synonyms: ZG-10

Model Systems: 93 cell-lines used Show Explore

Datasets: Used in 6 Datasets Show Explore



Provide Feedback

Glioblastoma Multiforme (GBM)

- Most **common** and **aggressive** adult brain tumor
- Occurs primarily in ages of 45-70 years

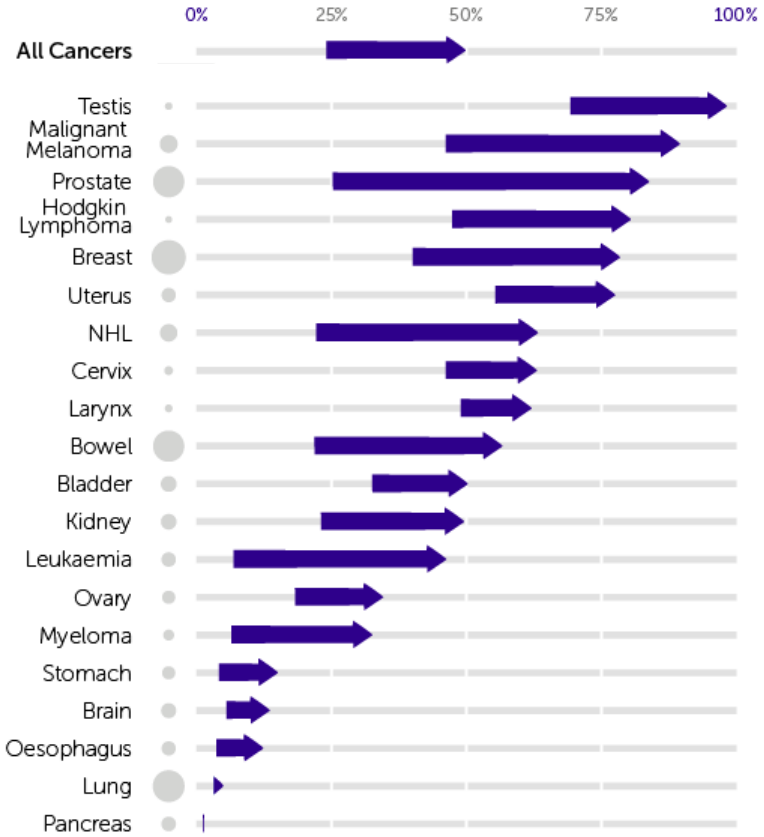
- Surgical resection followed by radiotherapy and temozolamide chemotherapy

- Annual incidence: 1 / 19,000
- 5-years survival rate **< 9.8%**

Little progress has been made in the survival of brain cancer patients

Changes in the 10-year survival

1971 → 2010



Quaresma et al. 2015

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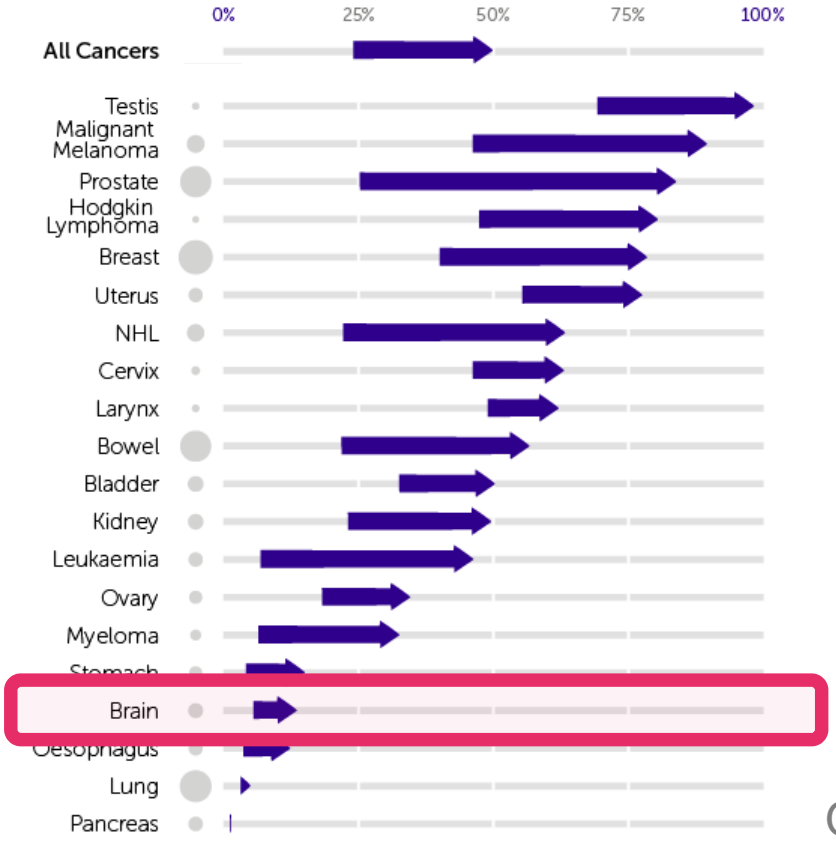
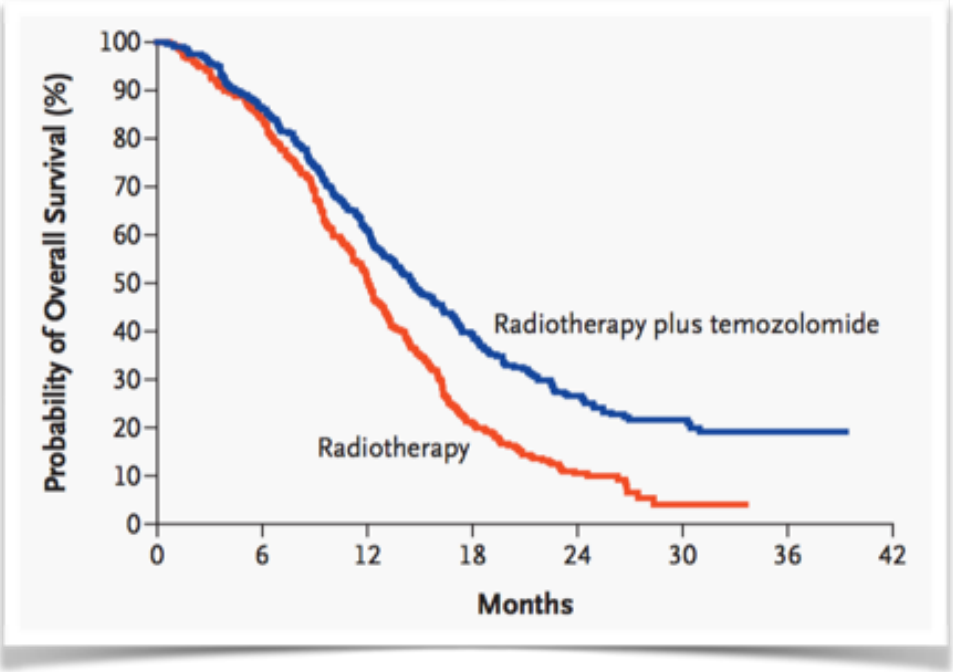


Brain Cancer

Quaresma et al. 2015

Current GBM Treatment is Ineffective



Standard of Care

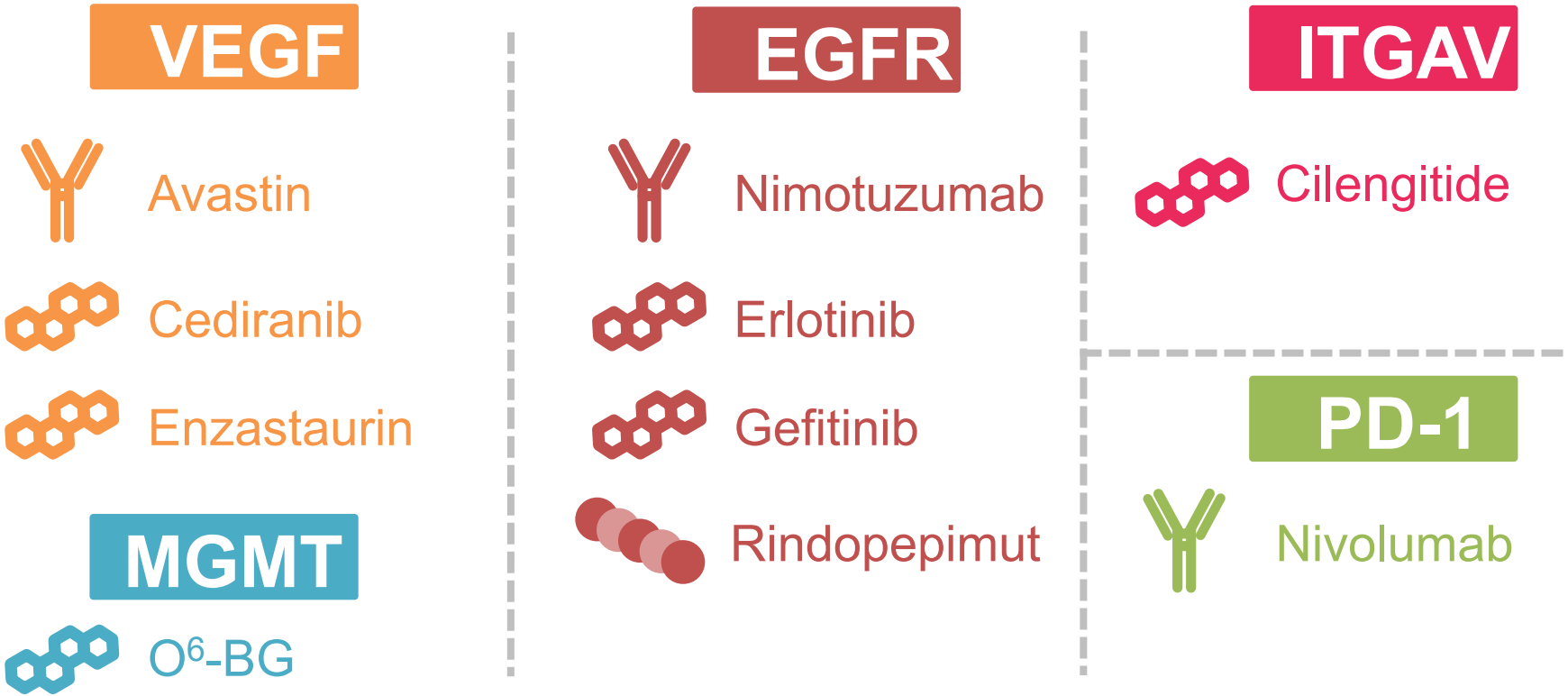
1. Maximal surgical resection
2. Radiotherapy
3. Temozolomide (TMZ) treatment

No early detection Biomarker

Temozolomide (2005) 2.5 month increase in survival
(14.6 vs 12.1 months)

Stupp et al. 2005

Targeted phase III trials have failed to improve overall survival of Glioblastoma patients



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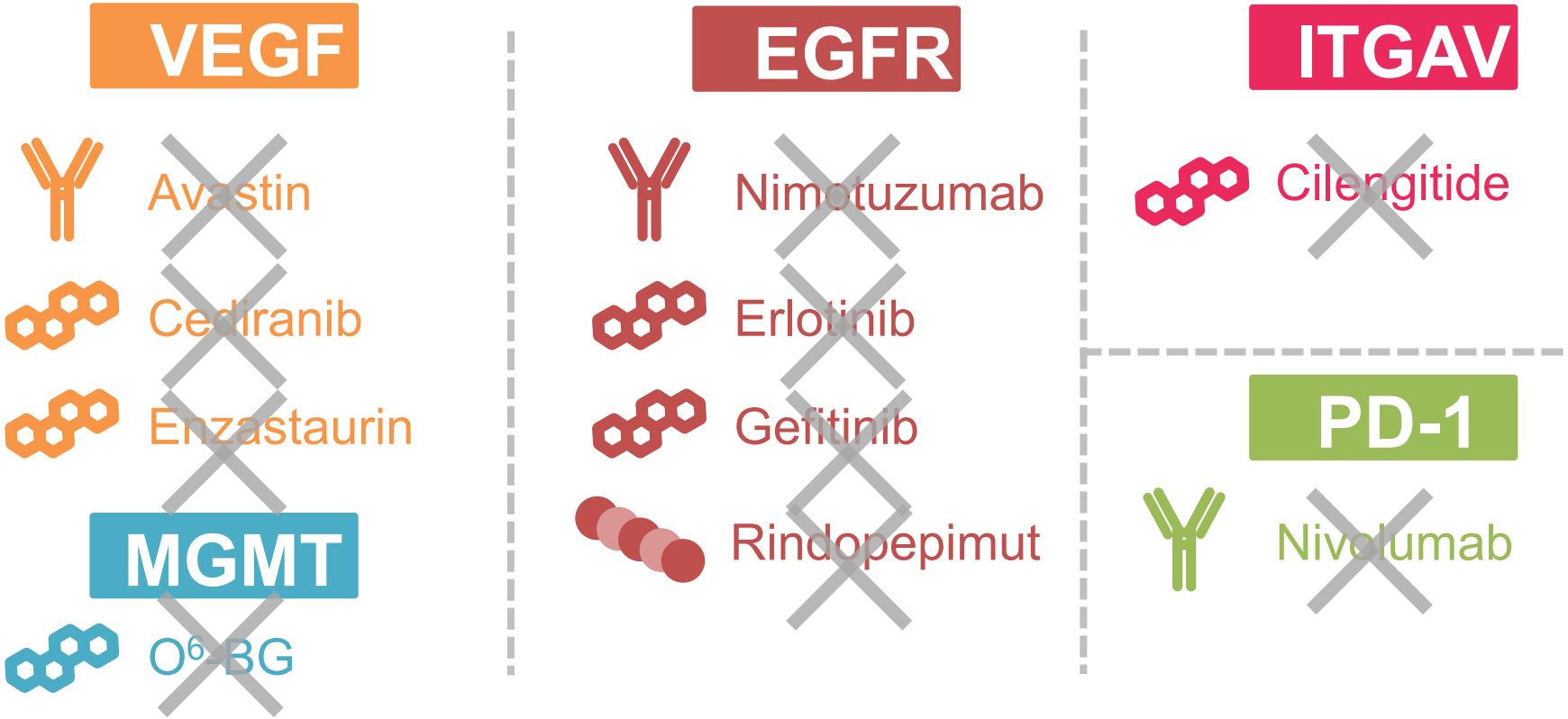
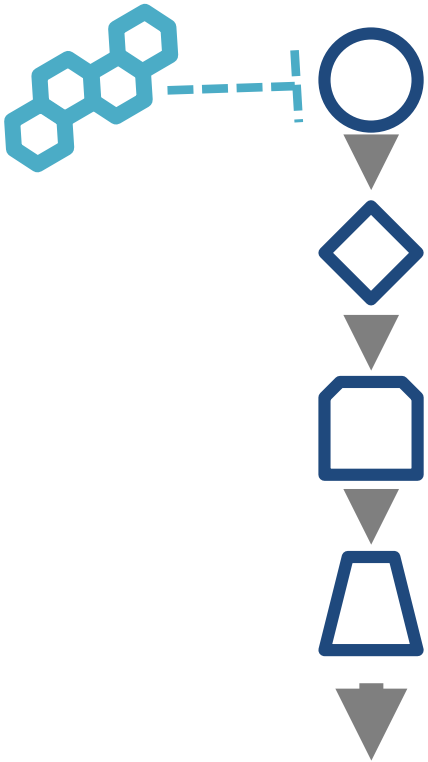


Tumors can adapt to targeted therapy by reprogramming signaling pathways resulting in resistance

Growth / Survival Signal

Tumors can adapt to targeted therapy by reprogramming signaling pathways resulting in resistance



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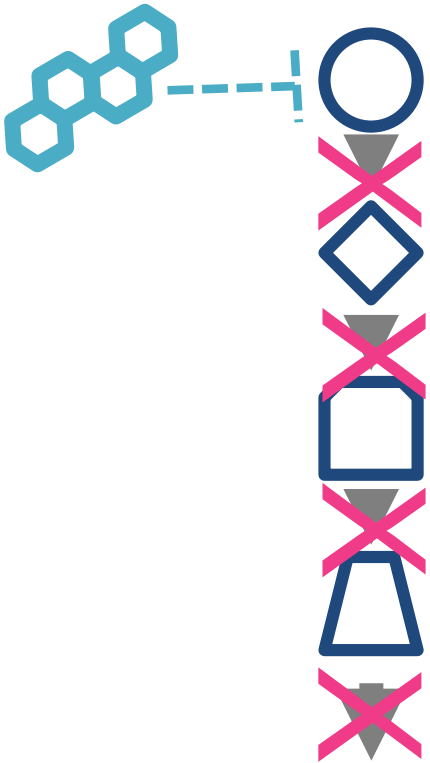

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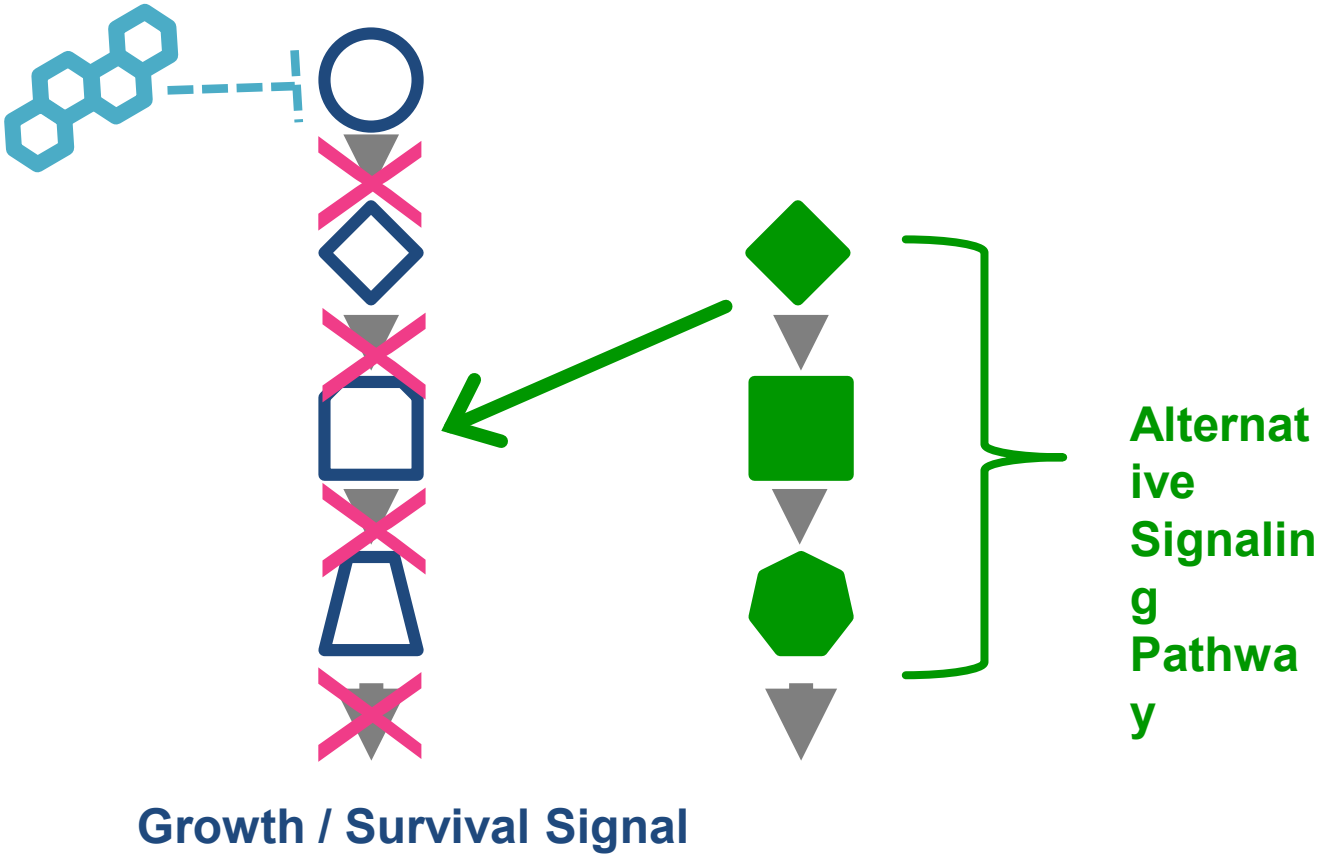

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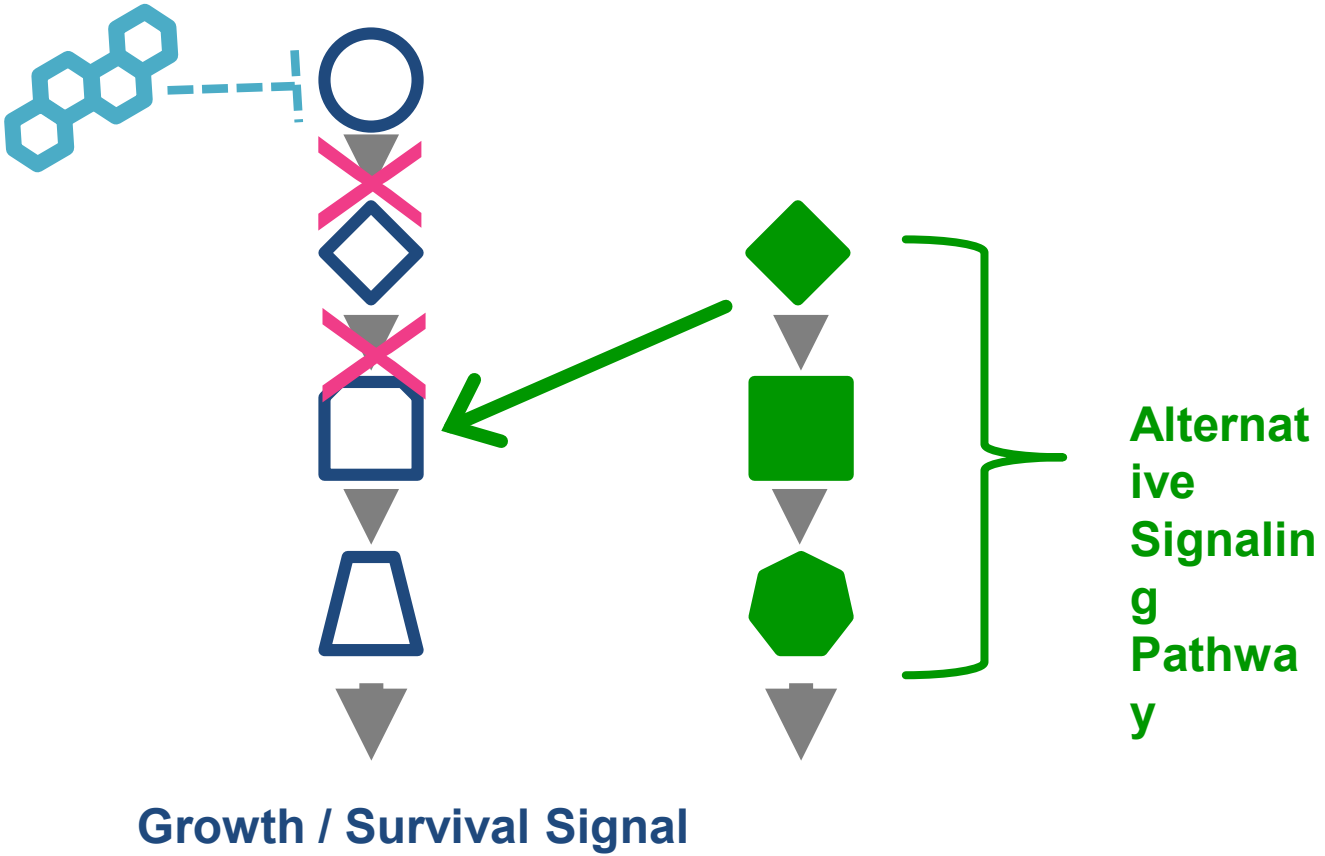

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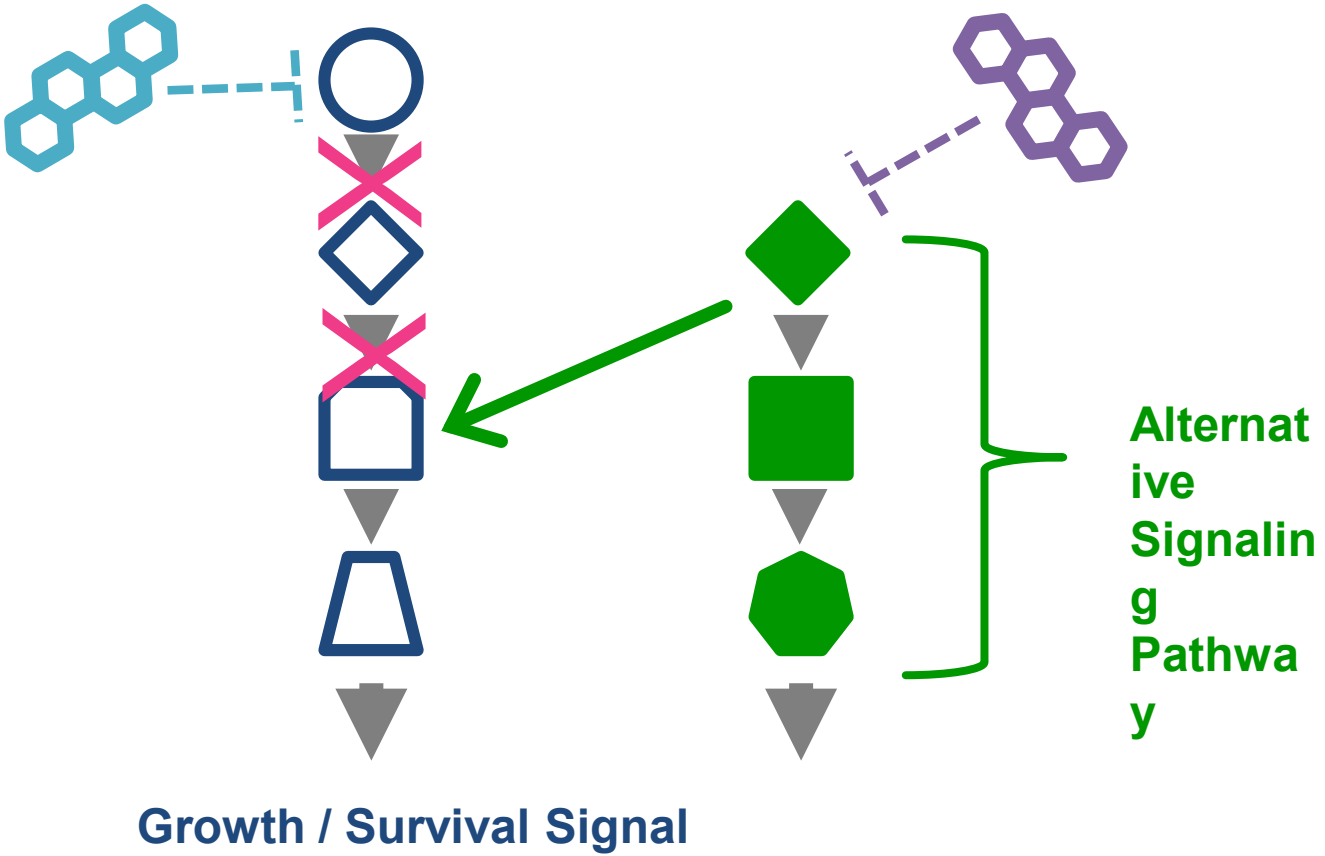

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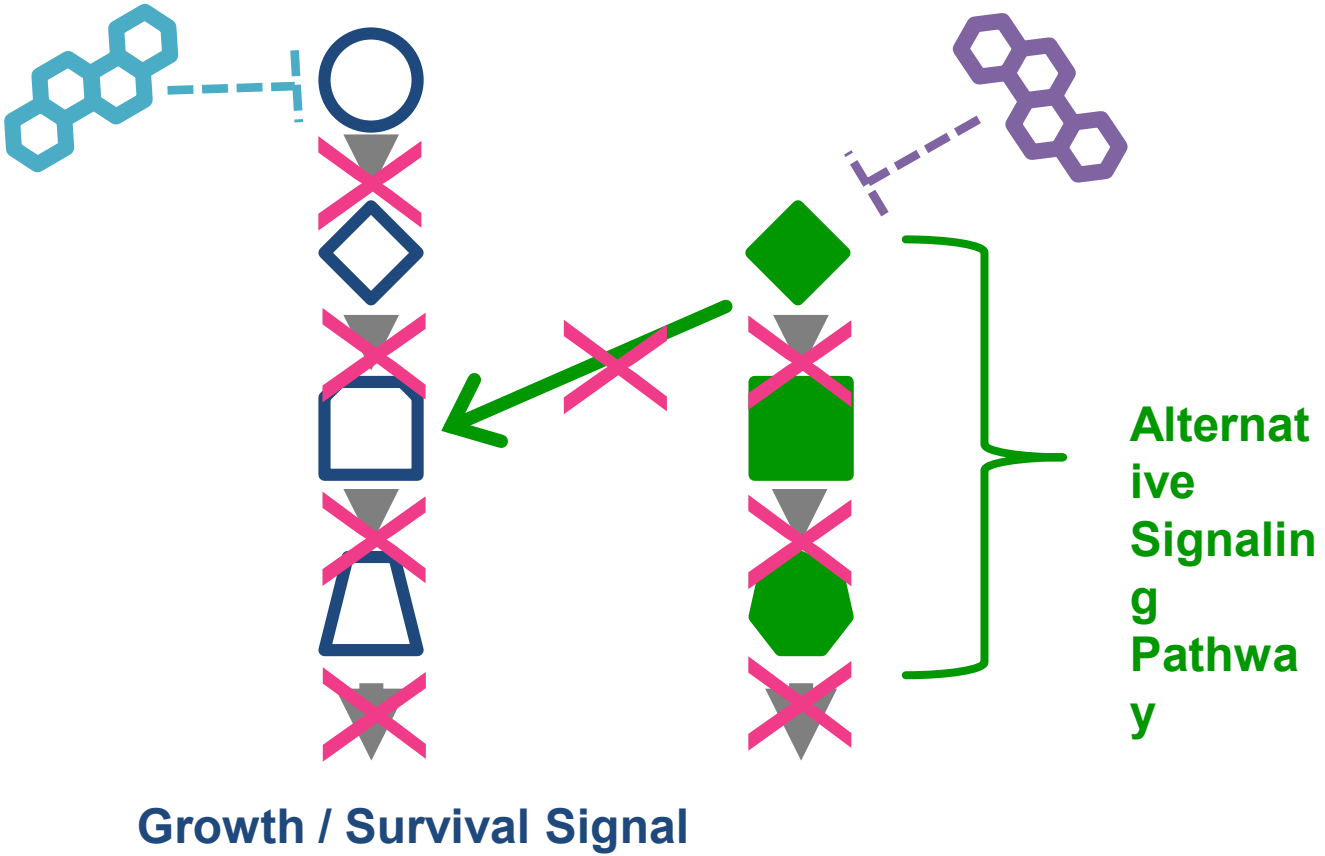
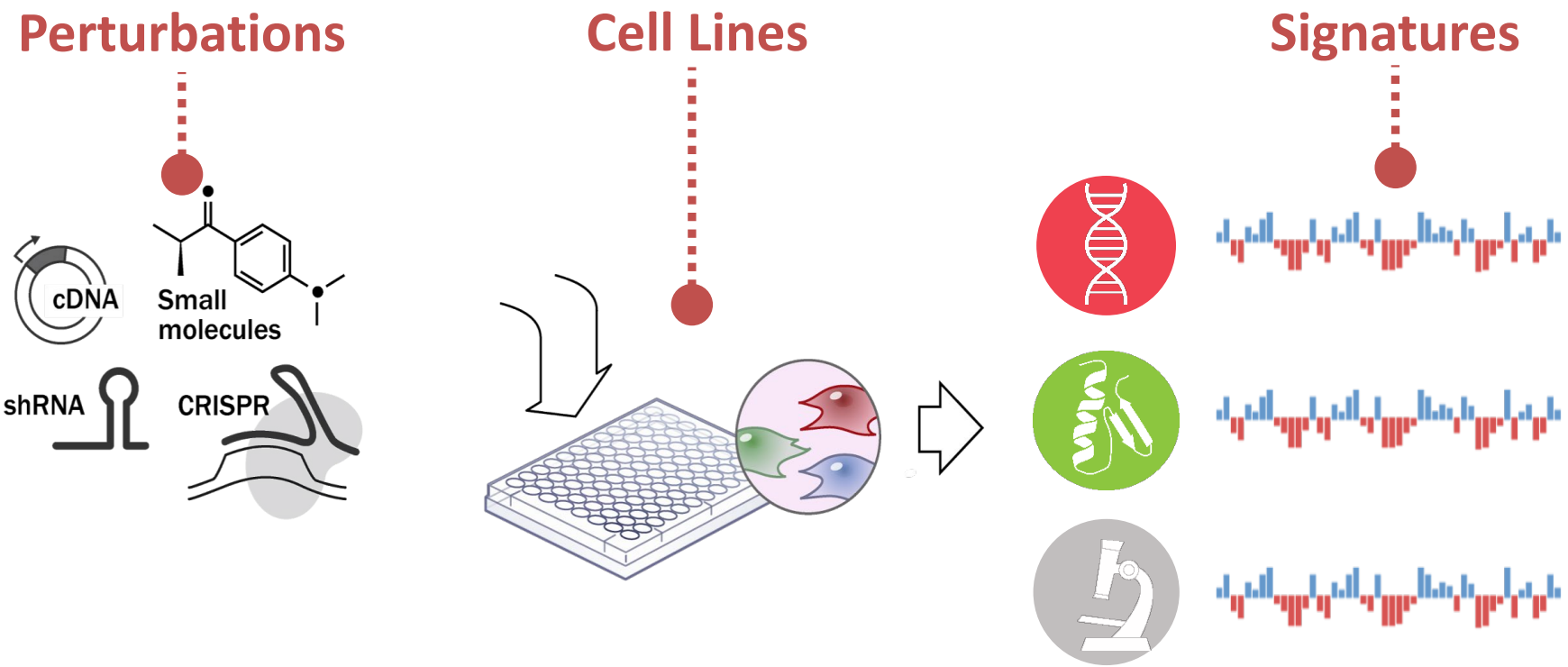
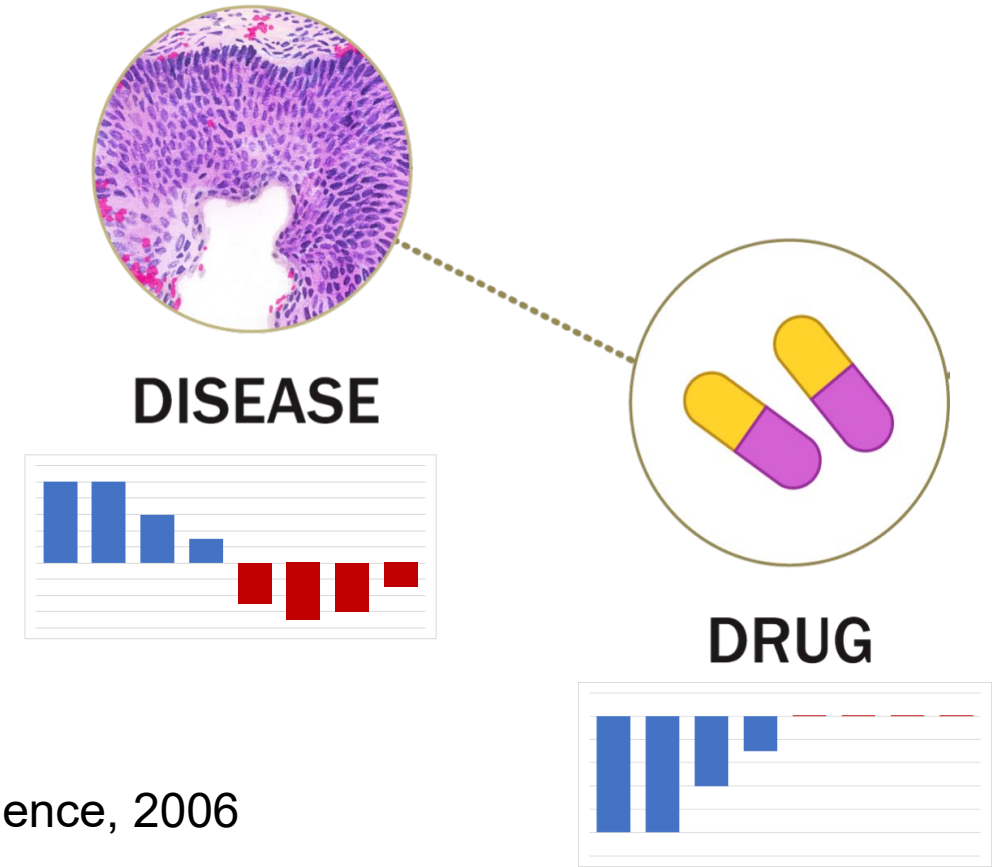


LINCS Signatures characterize diverse cellular responses upon perturbation



CMap concept: linking diseases to therapeutics



Lamb et al. Science, 2006

nature COMMUNICATIONS

ARTICLE

Received 7 Dec 2016 | Accepted 17 May 2017 | Published 12 Jul 2017

DOI: 10.1038/ncomms16022 OPEN

Reversal of cancer gene expression correlates with drug efficacy and reveals therapeutic targets

Bin Chen[1,*], Li Ma[2,*], Hyojung Paik[1,3], Marina Sirota[1], Wei Wei[2], Mei-Sze Chua[2], Samuel So[2] & Atul J. Butte[1]

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SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Systems biology–based drug repositioning identifies digoxin as a potential therapy for groups 3 and 4 medulloblastoma

Lei Huang[1]*, Sarah Garrett Injac[2,3]*, Kemi Cui[1], Frank Braun[2], Qi Lin[2], Yuchen Du[2], Huiyuan Zhang[2], Mari Kogiso[2], Holly Lindsay[2,3], Sibo Zhao[2,3], Patricia Baxter[2,3], Adesina Adekunle[4], Tsz-Kwong Man[3], Hong Zhao[1], Xiao-Nan Li[2,3†], Ching C. Lau[3†‡§], Stephen T. C. Wong[1†]

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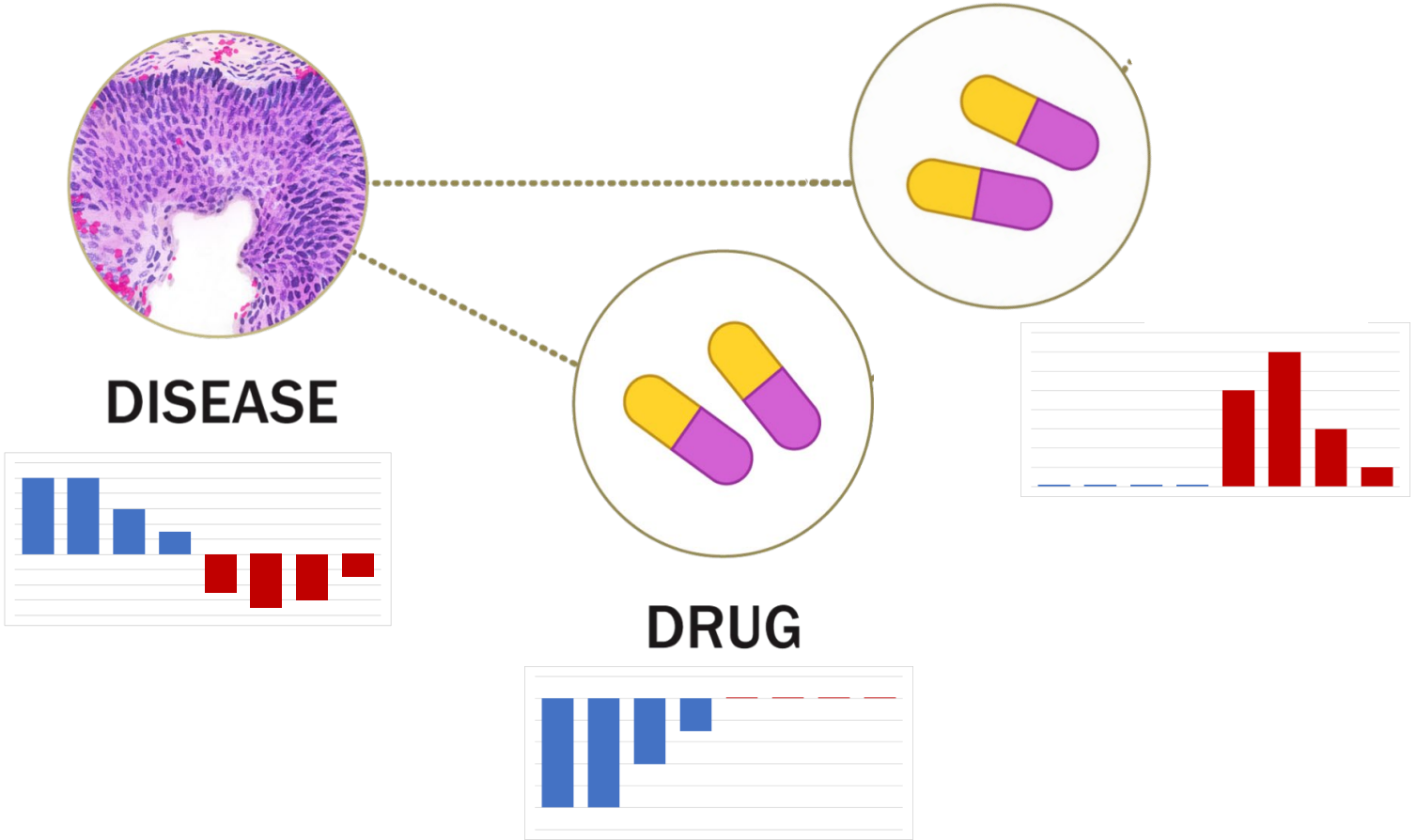
Integrated Systems and Technologies

Cancer Research

Novel Drug Candidates for the Treatment of Metastatic Colorectal Cancer through Global Inverse Gene-Expression Profiling

Vera van Noort[1,2], Sebastian Schölch[3], Murat Iskar[1], Georg Zeller[1], Kristina Ostertag[4], Christine Schweitzer[3], Kristin Werner[3], Jürgen Weitz[3], Moritz Koch[3], and Peer Bork[1,5]

Similar approach for combination therapies



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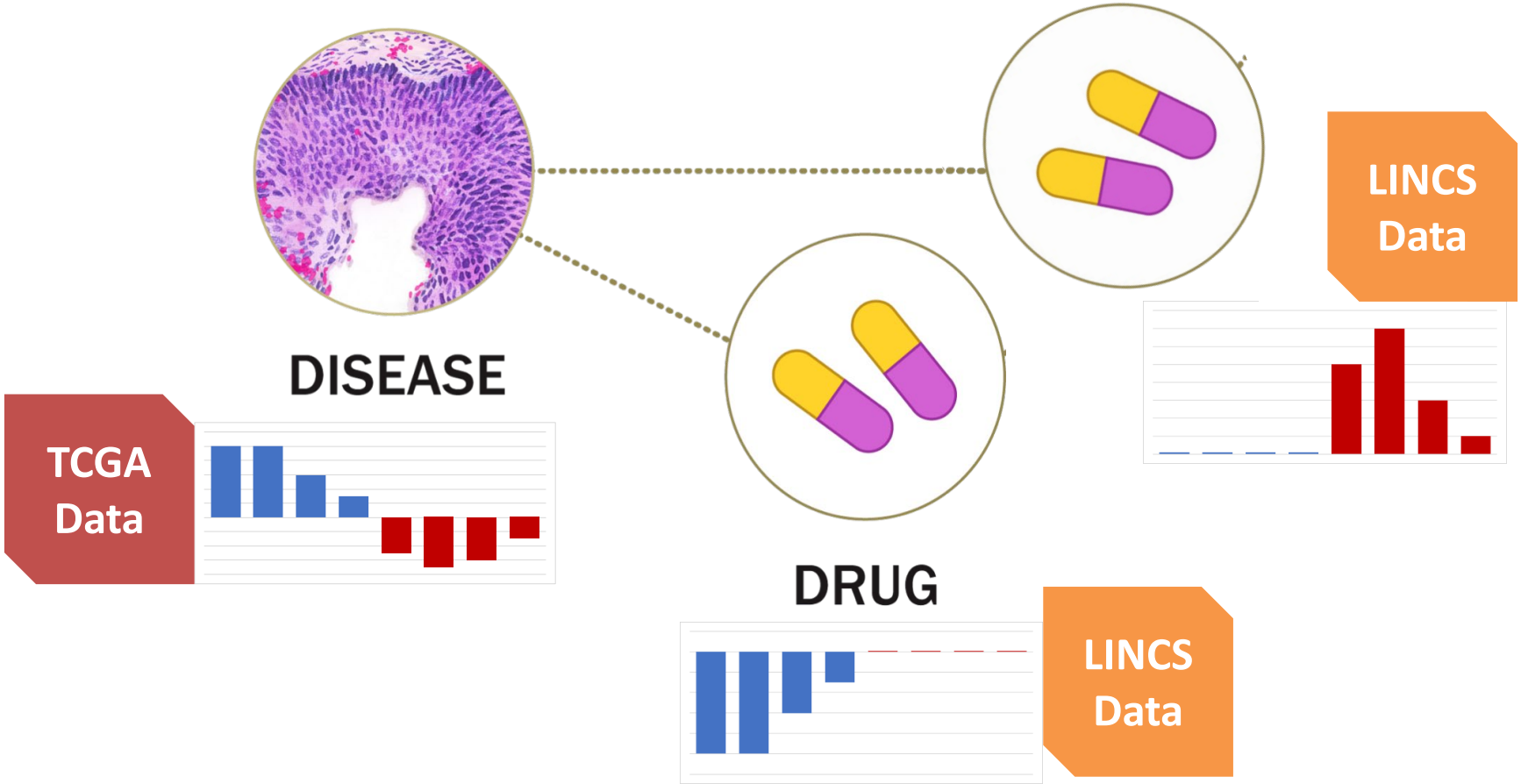
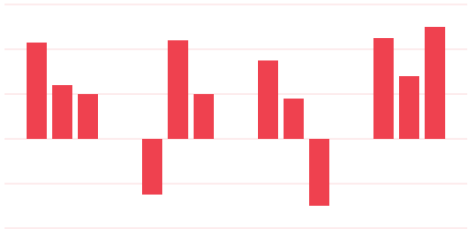
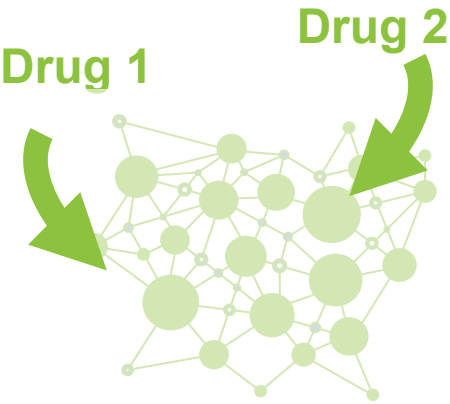


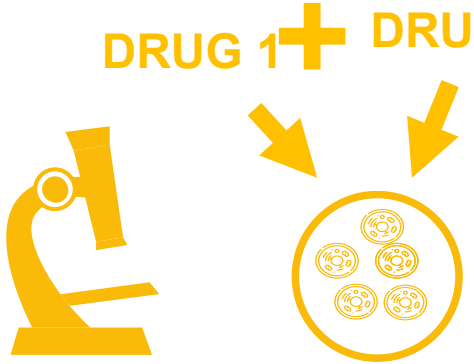
1 One Signature per Compound



2 Identify Drug Combinations



3 Validate in vitro / in vivo

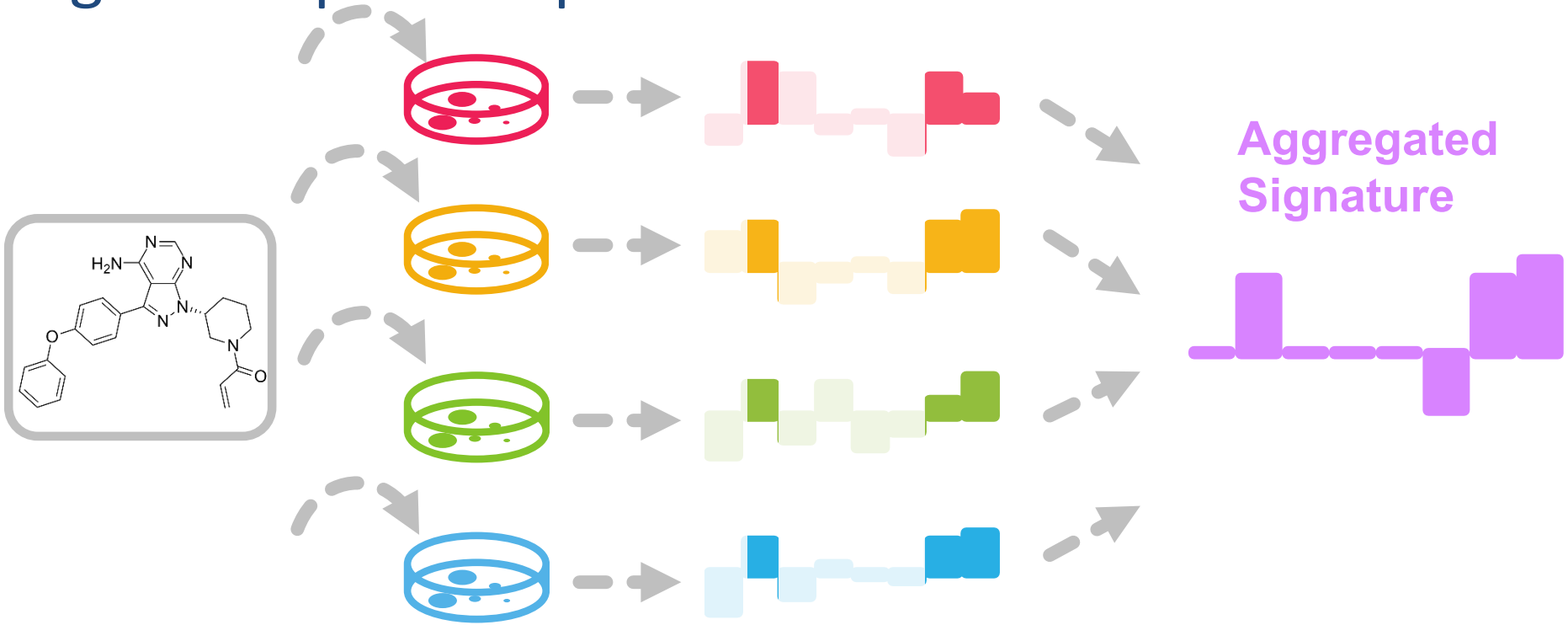


1 One Signature per Compound

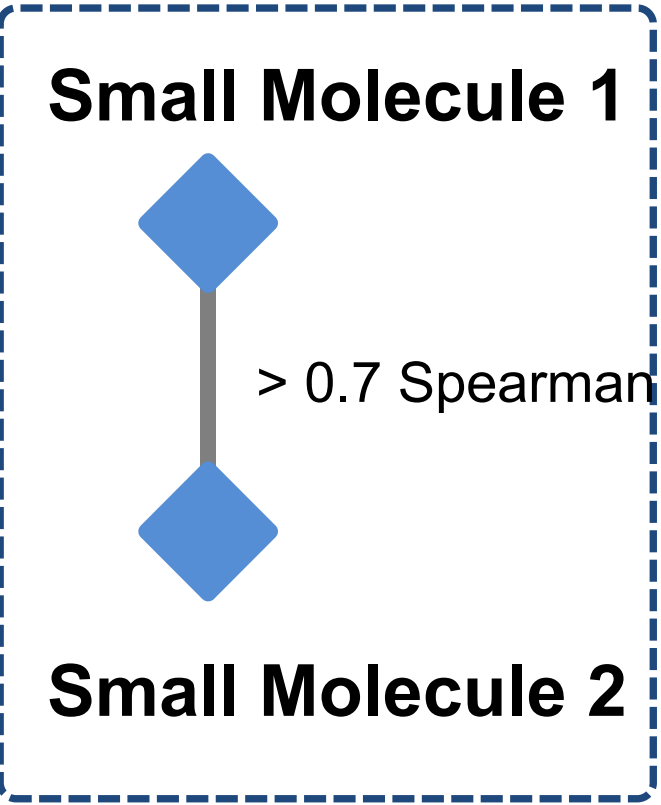
2 Identify Drug Combinations

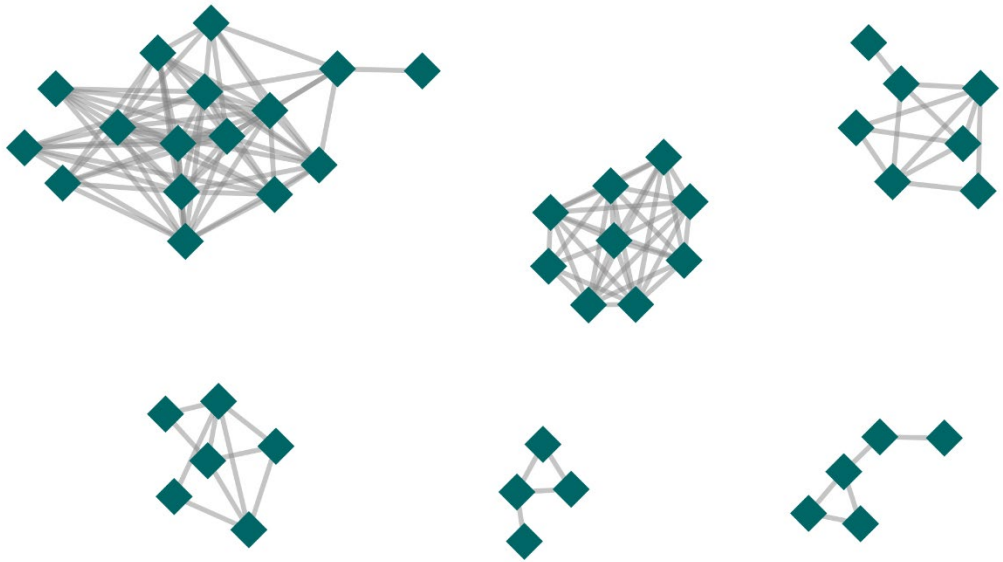
3 Validate in vitro / in vivo

Collapse the gene expression profiles into one signature per compound



Compounds with same Mechanism of Action form distinct networks





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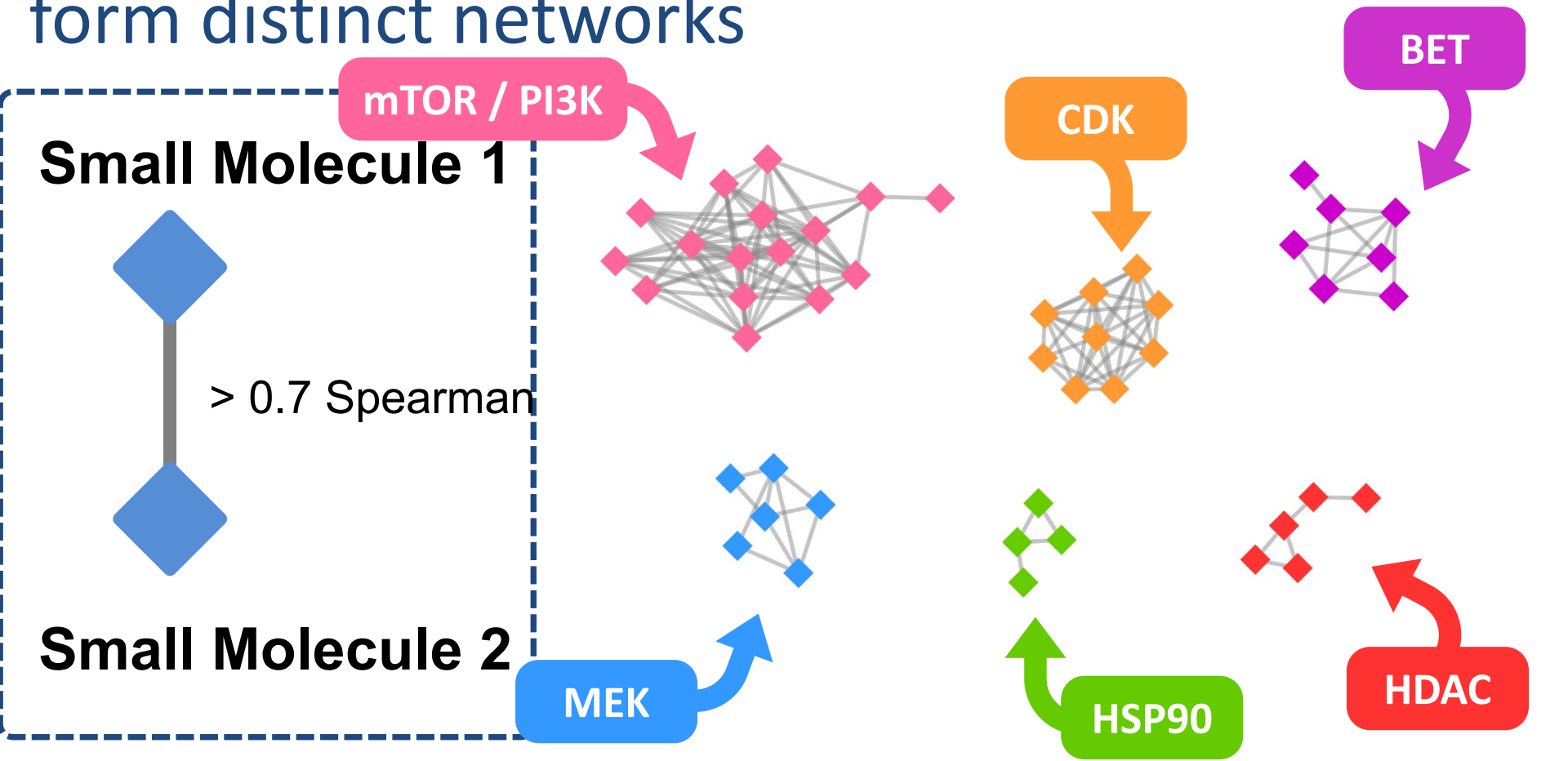

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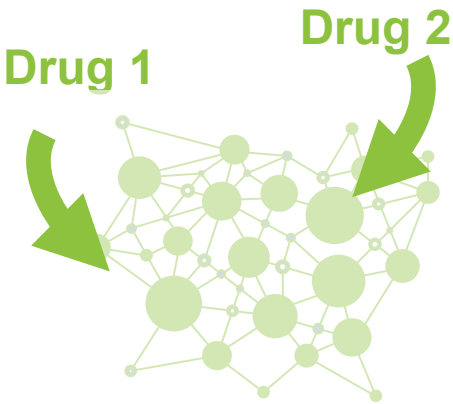
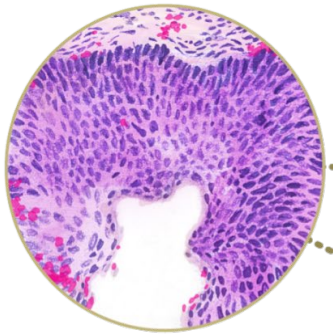


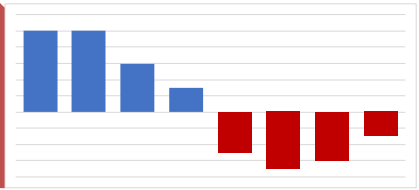
3 Validate in vitro / in vivo

Glioblastoma disease signature from TCGA



DISEASE

TCGA Data

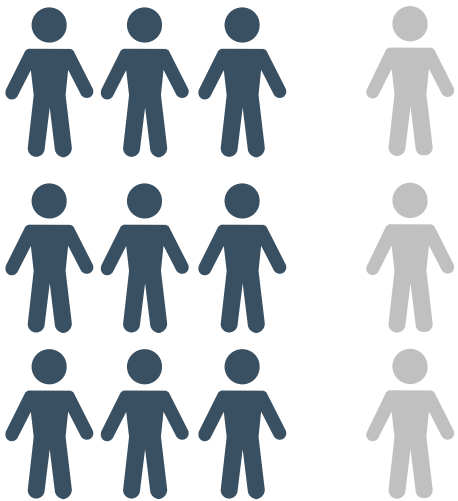


LINCS Data

DRUG

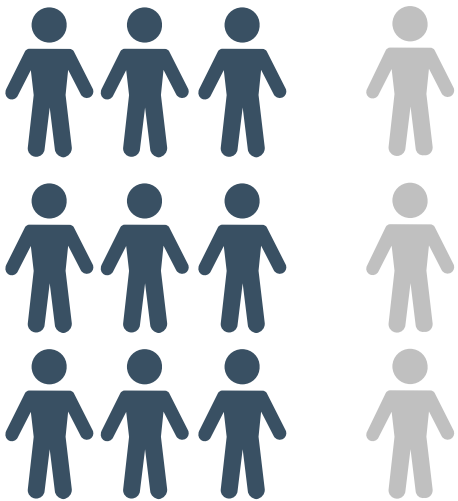
LINCS Data

Identify Differentially Expressed Genes in Glioblastoma Samples



Glioblastoma Samples and Controls
(from TCGA)

Identify Differentially Expressed Genes in Glioblastoma Samples



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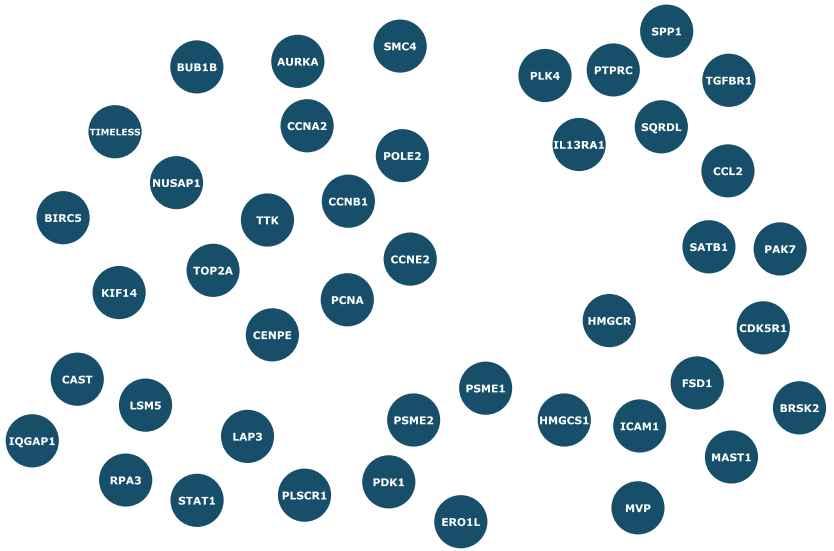
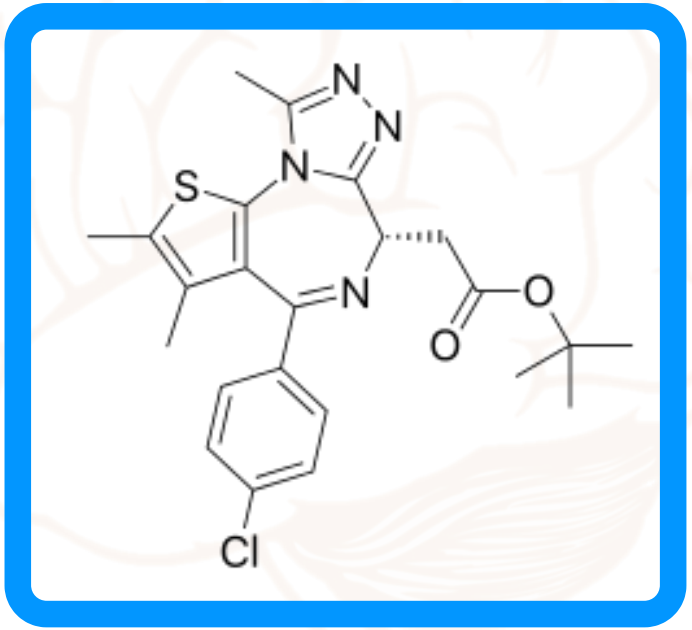


Differentially Expressed Genes in Glioblastoma

JQ1 is a potent Bromodomain inhibitor

- **JQ1 reduces proliferation and survival of glioblastoma PDXs**
- **Bromodomains:**
  Readers of lysine acetylation
- **Many cancers are sensitive to bromodomain inhibitors**



Resistance after Bromodomain inhibition emerges in multiple cancer types

Breast Cancer

Response and resistance to BET bromodomain inhibitors in triple-negative breast cancer

Shaokun Shu[1,2*], Charles Y. Lin[1,2*], Housheng Hansen He[1,2,3,4,5*], Robert M. Witwicki[1,2*], Doris P. Tabassum[1], Justin M. Roberts[1], Michalina Janiszewska[1,2], Sung Jin Huh[1,2], Yi Liang[4], Jeremy Ryan[1,2], Ernest Doherty[1,6], Hisham Mohammed[7], Hao Guo[3], Daniel G. Stover[1,2], Muhammad B. Ekram[1,2], Guillermo Peluffo[1,2], Jonathan Brown[1,2], Clive D'Santos[7], Ian E. Krop[1,2], Deborah Dillon[1,8], Michael McKeown[1,2], Christopher Ott[1,2], Jun Qi[1,2], Min Ni[1,2], Prakash K. Rao[9], Melissa Duarte[9], Shwu-Yuan Wu[10], Cheng-Ming Chiang[10], Lars Anders[11], Richard A. Young[11], Eric P. Winer[1,2], Antony Letai[1,2], William T. Barry[2,3], Jason S. Carroll[7], Henry W. Long[1,9], Myles Brown[1,2,9], X. Shirley Liu[3,9,12], Clifford A. Meyer[3], James E. Bradner[1,2,12] & Kornelia Polyak[1,2,9,12]

Colorectal Cancer

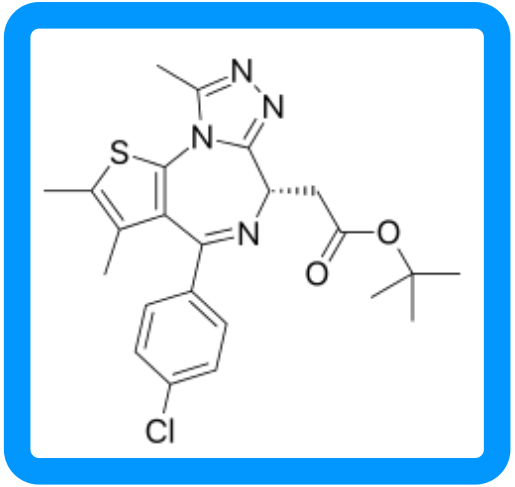
Loss of TRIM33 causes resistance to BET bromodomain inhibitors through MYC- and TGF-β–dependent mechanisms

Xiarong Shi[a], Valia T. Mihaylova[a], Leena Kuruvilla[a], Fang Chen[a], Stephen Viviano[a], Massimiliano Baldassarre[a], David Sperandio[b], Ruben Martinez[b], Peng Yue[b], Jamie G. Bates[b], David G. Breckenridge[b], Joseph Schlessinger[a,1], Benjamin E. Turk[a,1], and David A. Calderwood[a,c,1]

Leukemia

BET inhibitor resistance emerges from leukaemia stem cells

Chun Yew Fong[1,2,3], Omer Gilan[1,2], Enid Y. N. Lam[1], Alan F. Rubin[4,5], Sarah Ftouni[1], Dean Tyler[1,2], Kym Stanley[1], Devbarna Sinha[1], Paul Yeh[1,2,3], Jessica Morison[6], George Giotopoulos[6], Dave Lugo[7], Philip Jeffrey[7], Stanley Chun-Wei Lee[8], Christopher Carpenter[9], Richard Gregory[7], Robert G. Ramsay[1,2], Steven W. Lane[10], Omar Abdel-Wahab[8], Tony Kouzarides[11], Ricky W. Johnstone[1,2], Sarah-Jane Dawson[1,2], Brian J. P. Huntly[6], Rab K. Prinjha[7], Anthony T. Papenfuss[1,2,4,5] & Mark A. Dawson[1,2,3]



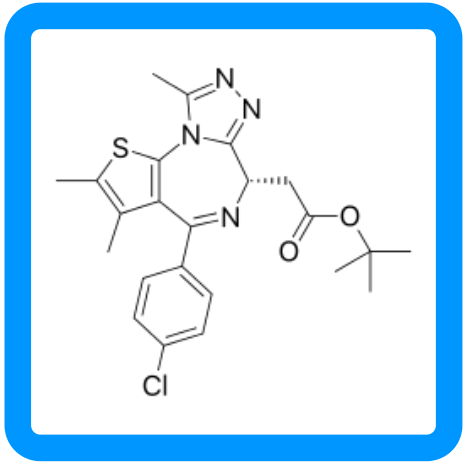
JQ1

Ovarian Cancer

Resistance to BET Bromodomain Inhibitors Is Mediated by Kinome Reprogramming in Ovarian Cancer

Alison M. Kurimchak,[1] Claude Shelton,[1] Kelly E. Duncan,[1] Katherine J. Johnson,[1] Jennifer Brown,[1] Shane O'Brien,[2] Rashid Gabbasov,[2,4] Lauren S. Fink,[1] Yuesheng Li,[1] Nicole Lounsbury,[3] Magid Abou-Gharbia,[3] Wayne E. Childers,[3] Denise C. Connolly,[2] Jonathan Chernoff,[1] Jeffrey R. Peterson,[1] and James S. Duncan[1,*]

Identify a small molecule that would be effective in combination with JQ1

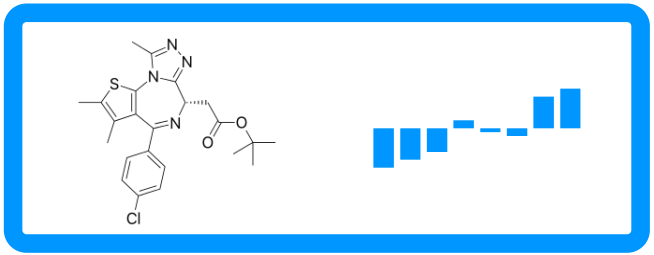


JQ1

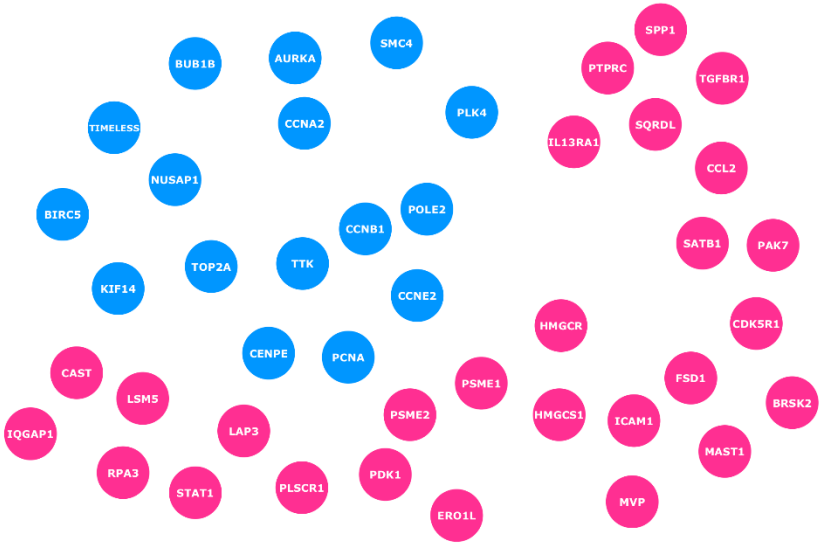
+

?

Identify compounds that induce orthogonal gene expression

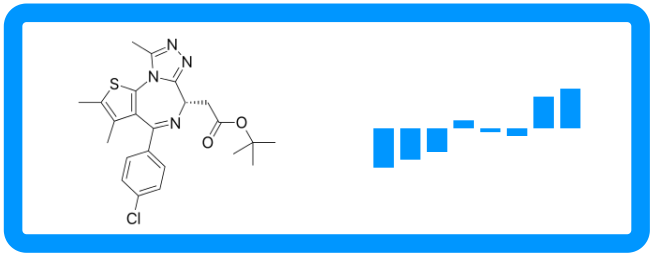


JQ1



Differentially Expressed Genes in Glioblastoma

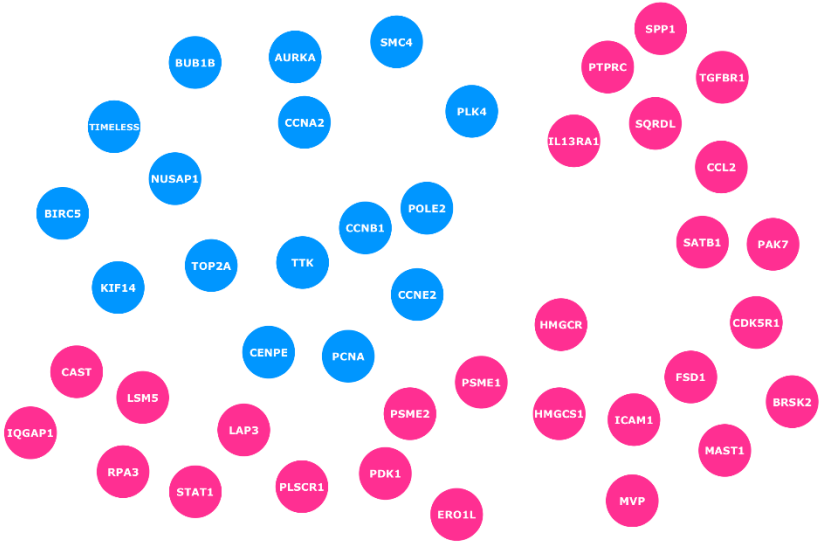
Identify compounds that induce orthogonal gene expression



JQ1

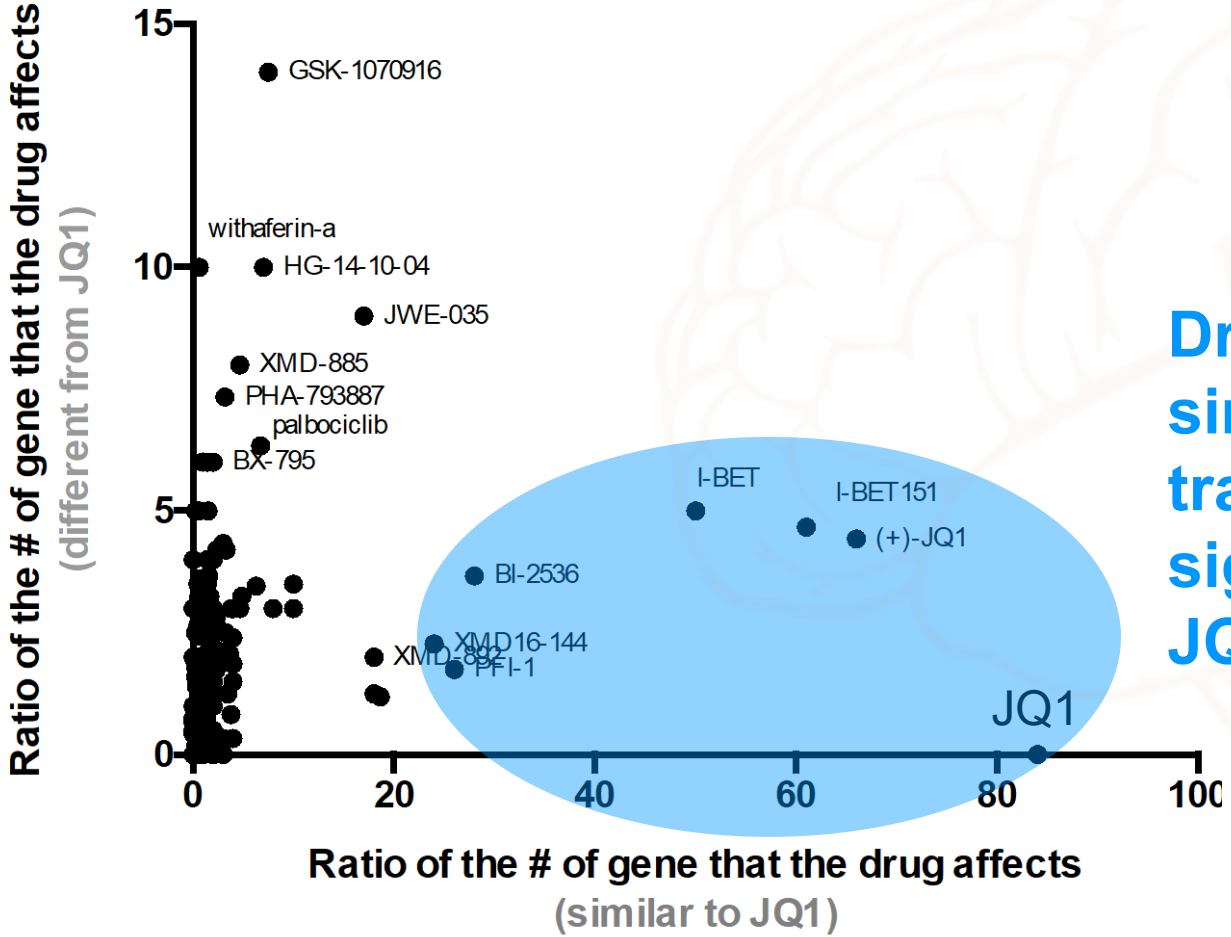
Compound

??



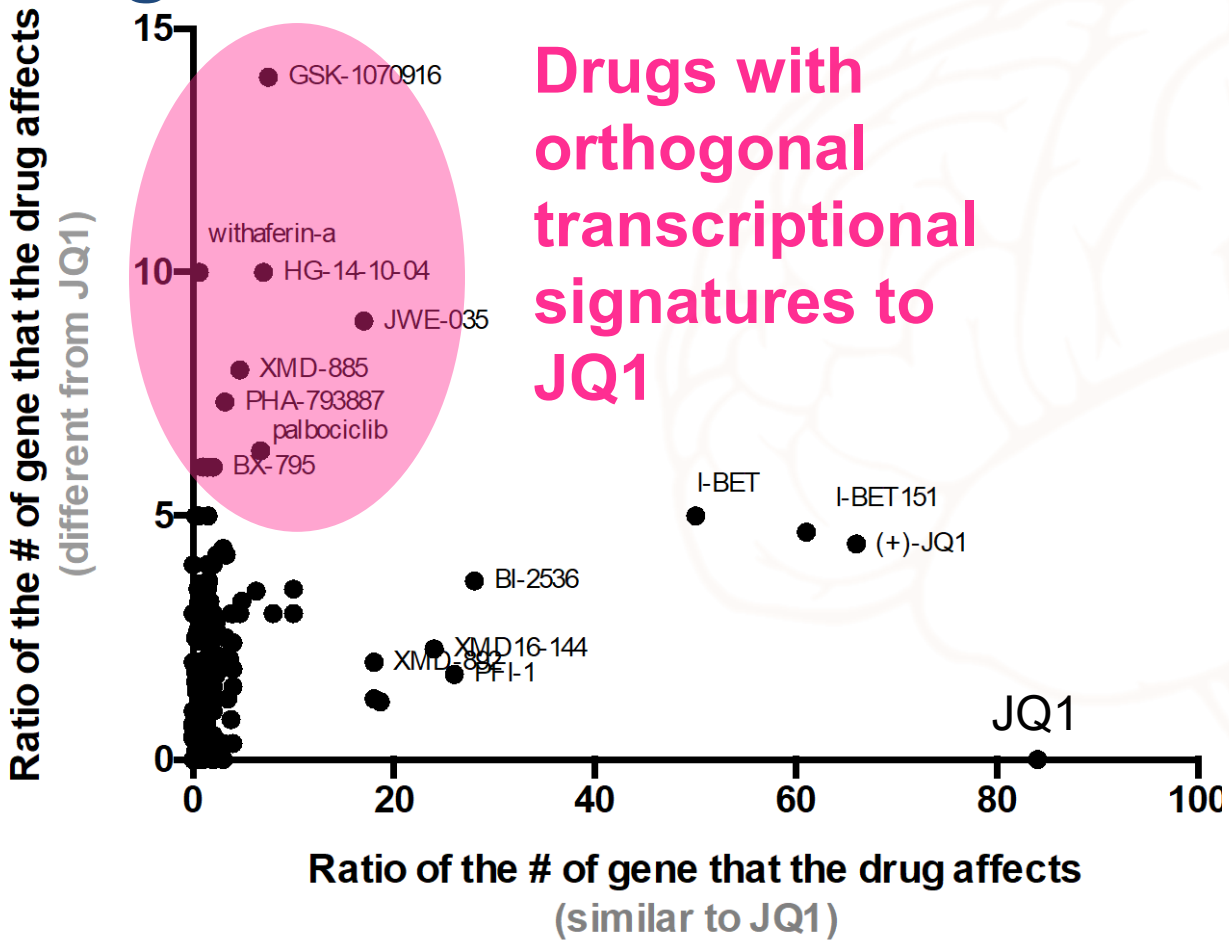
Differentially Expressed Genes in Glioblastoma

All Drugs were ranked based on similarity to JQ1

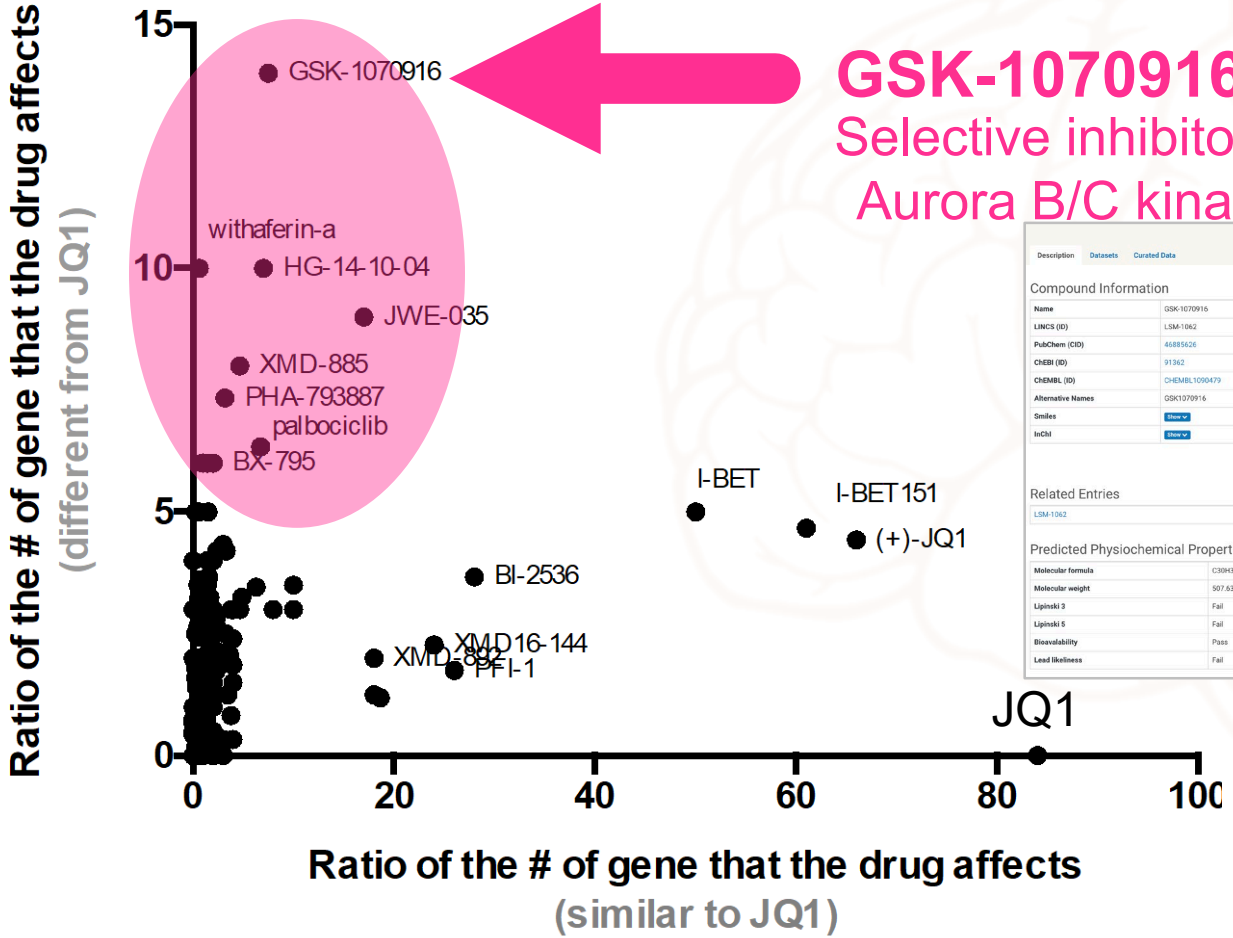


Drugs with similar transcriptional signatures to JQ1

All Drugs were ranked based on similarity to JQ1

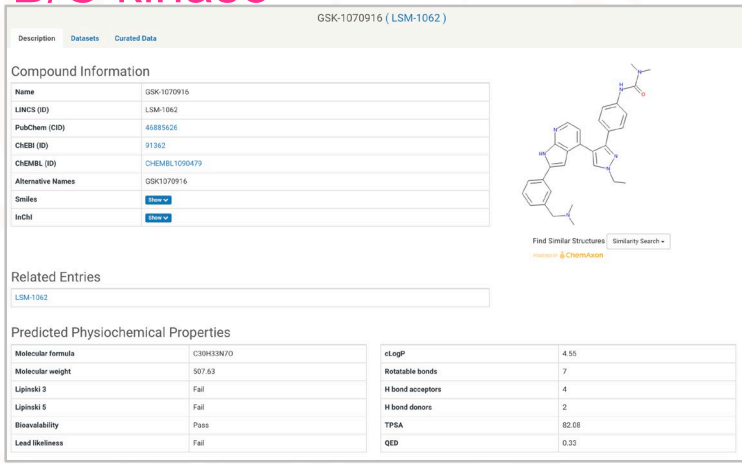


All Drugs were ranked based on similarity to JQ1



GSK-1070916

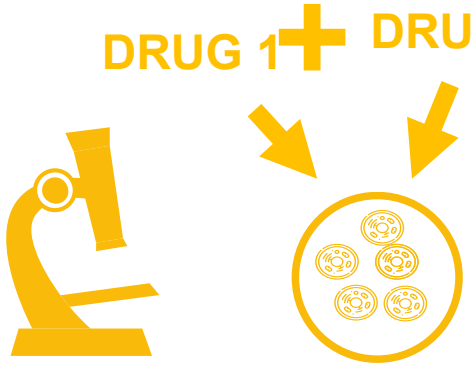
Selective inhibitor of
Aurora B/C kinase



1 One Signature per Compound

2 Identify Drug Combinations

3 Validate in vitro / in vivo



Treat Glioblastoma PDX cells with JQ1 and / or GSK-1070916

JQ1

AND / OR

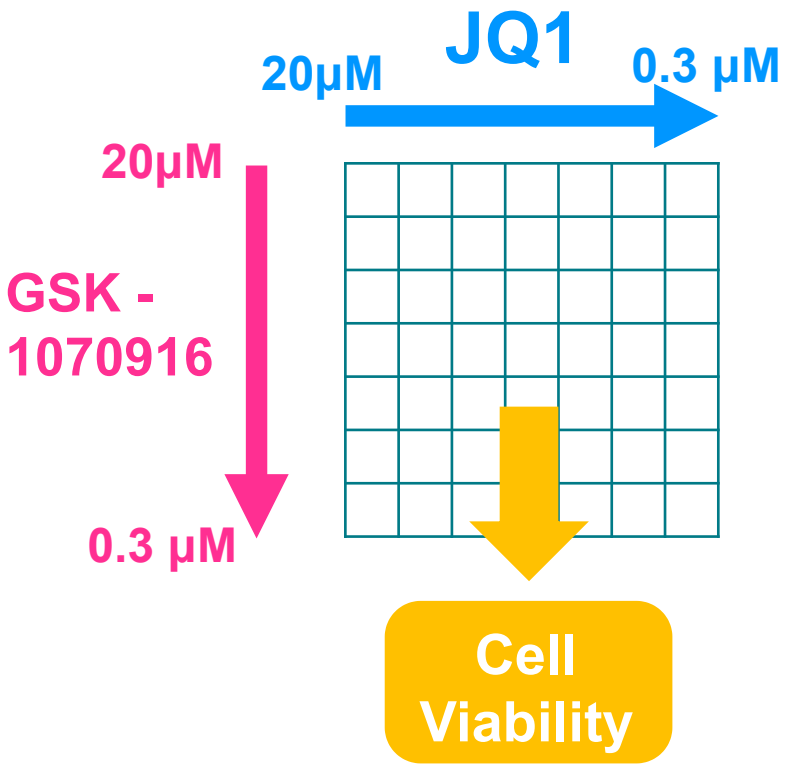
GSK1070916

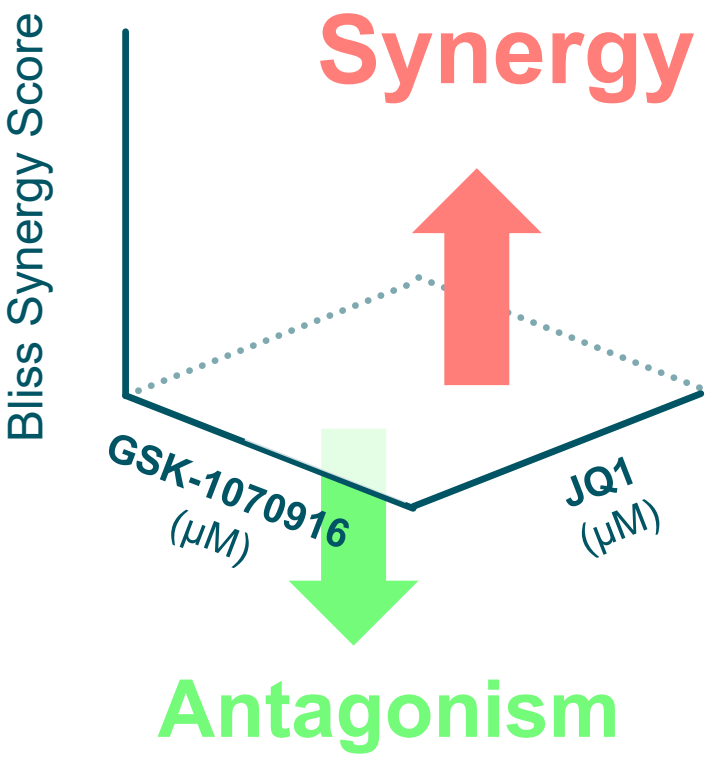
Glioblastoma PDXs

Quantify ATP

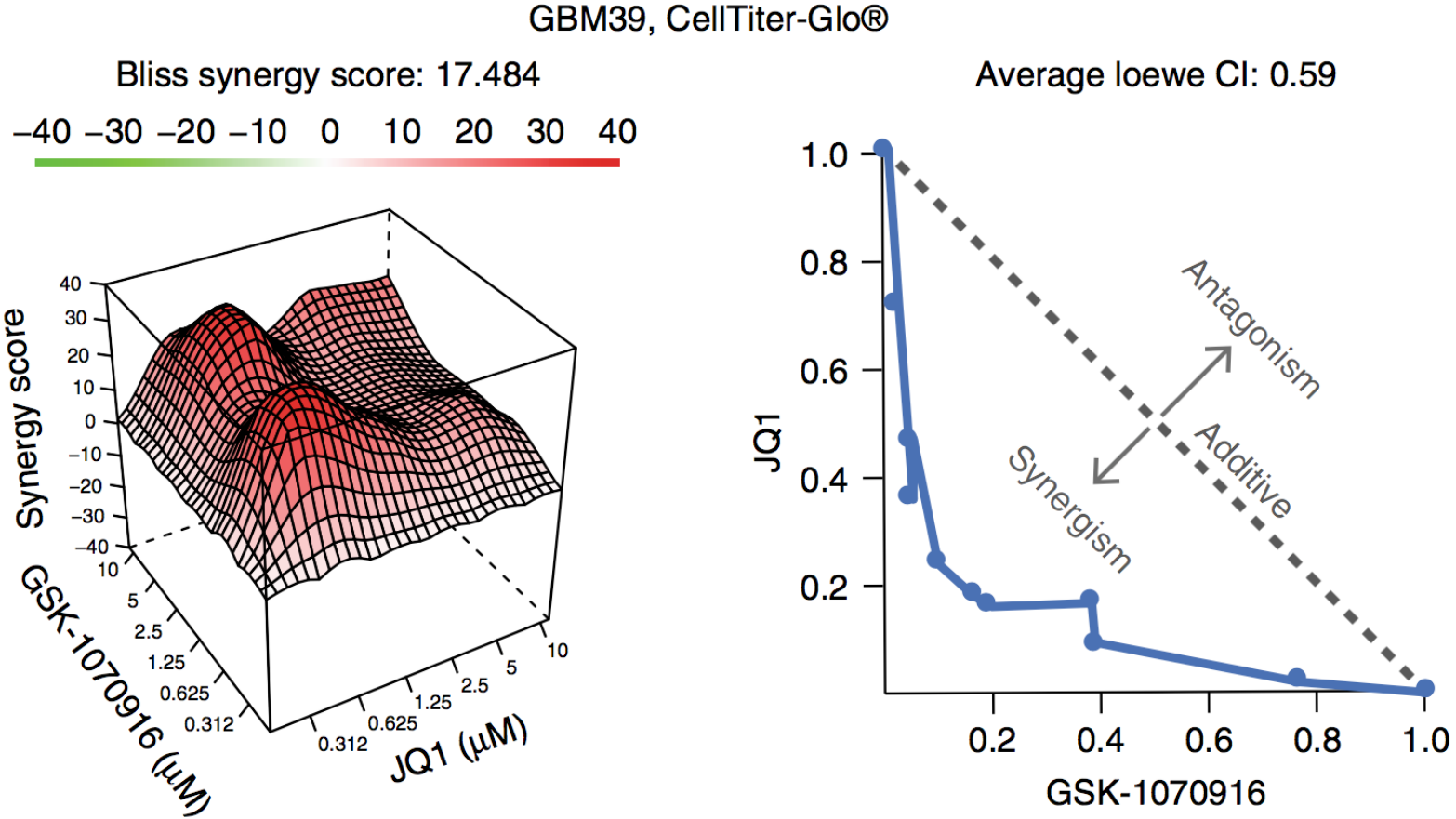
(Cell Titer Glo)

Bliss independence analysis of cell- viability combination response

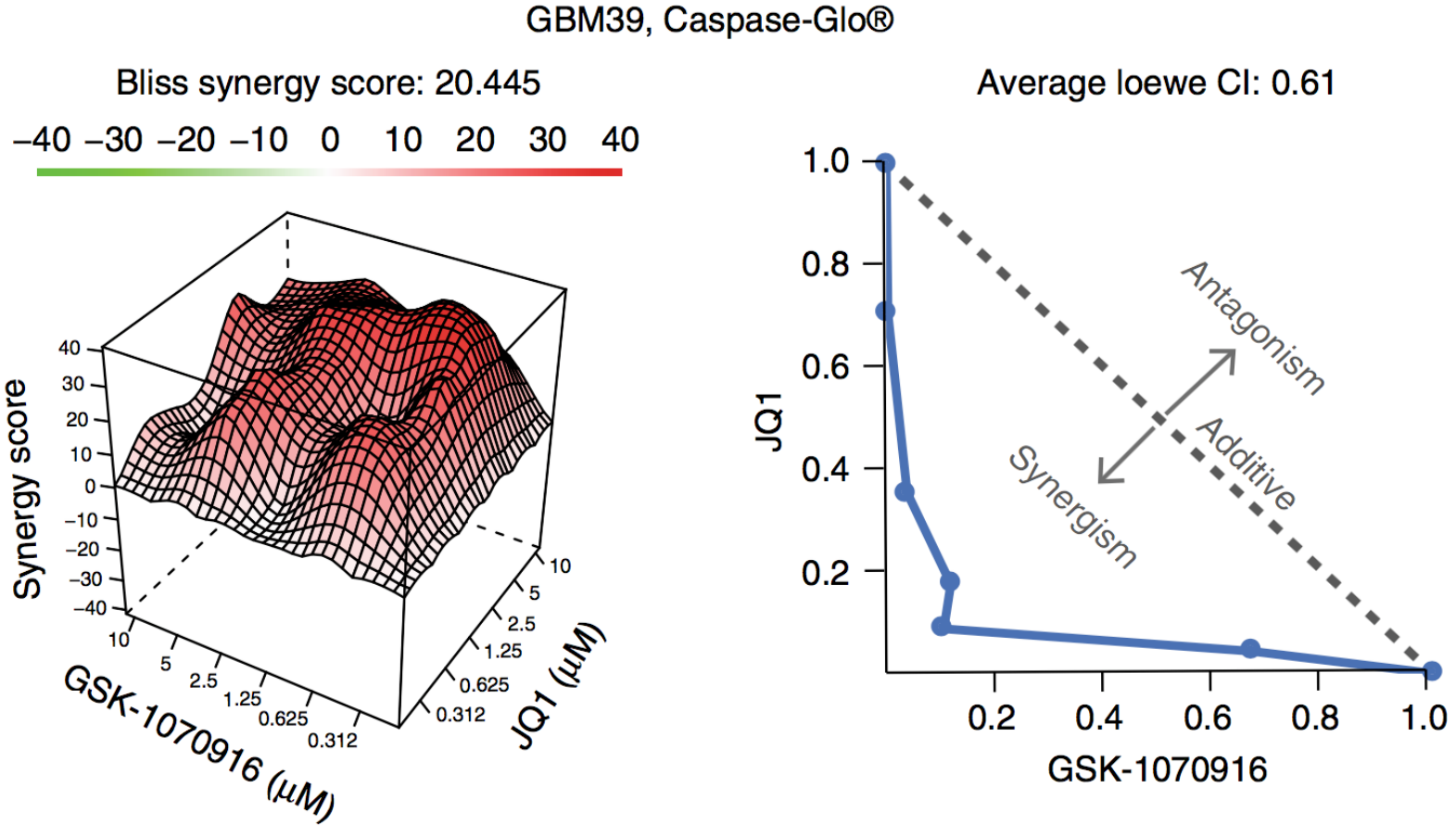




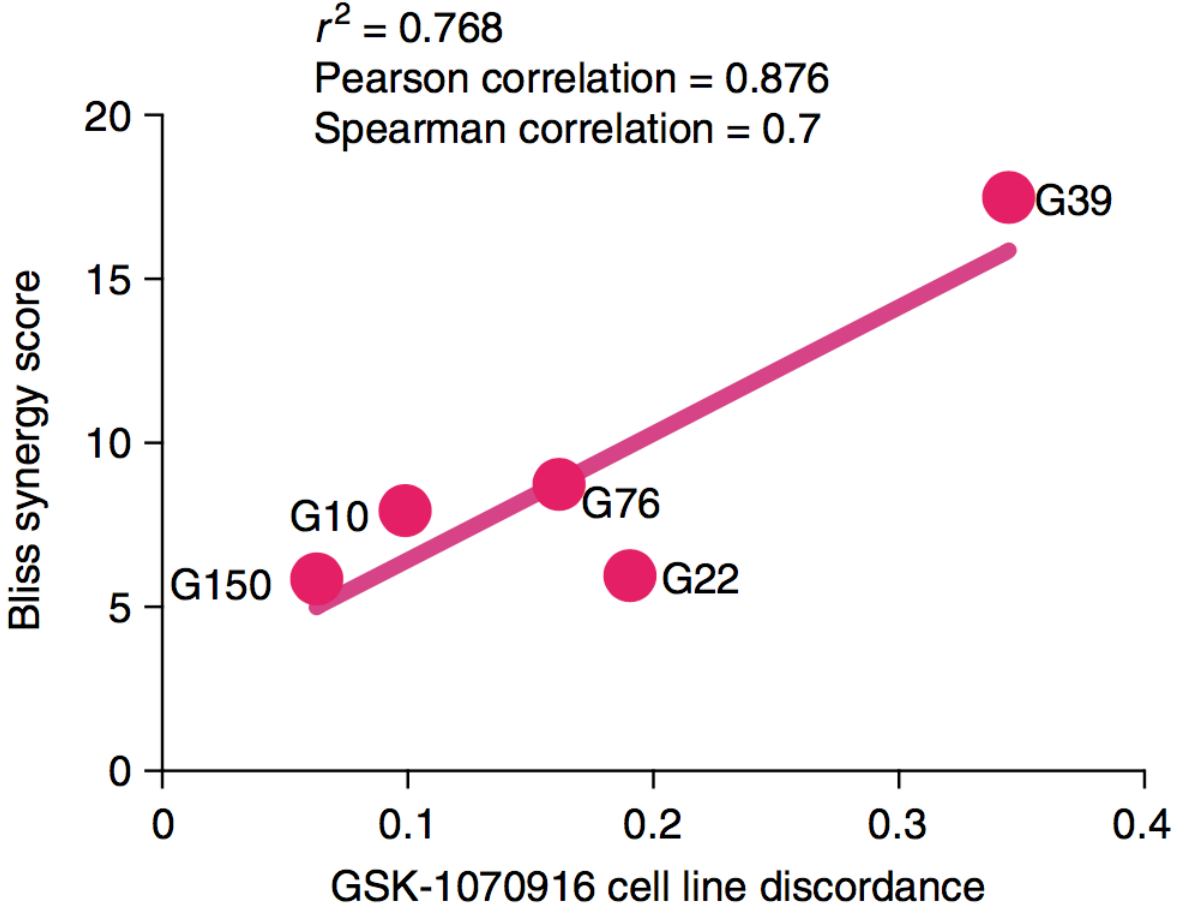
JQ1 + GSK-1070916 synergize in reducing cell viability

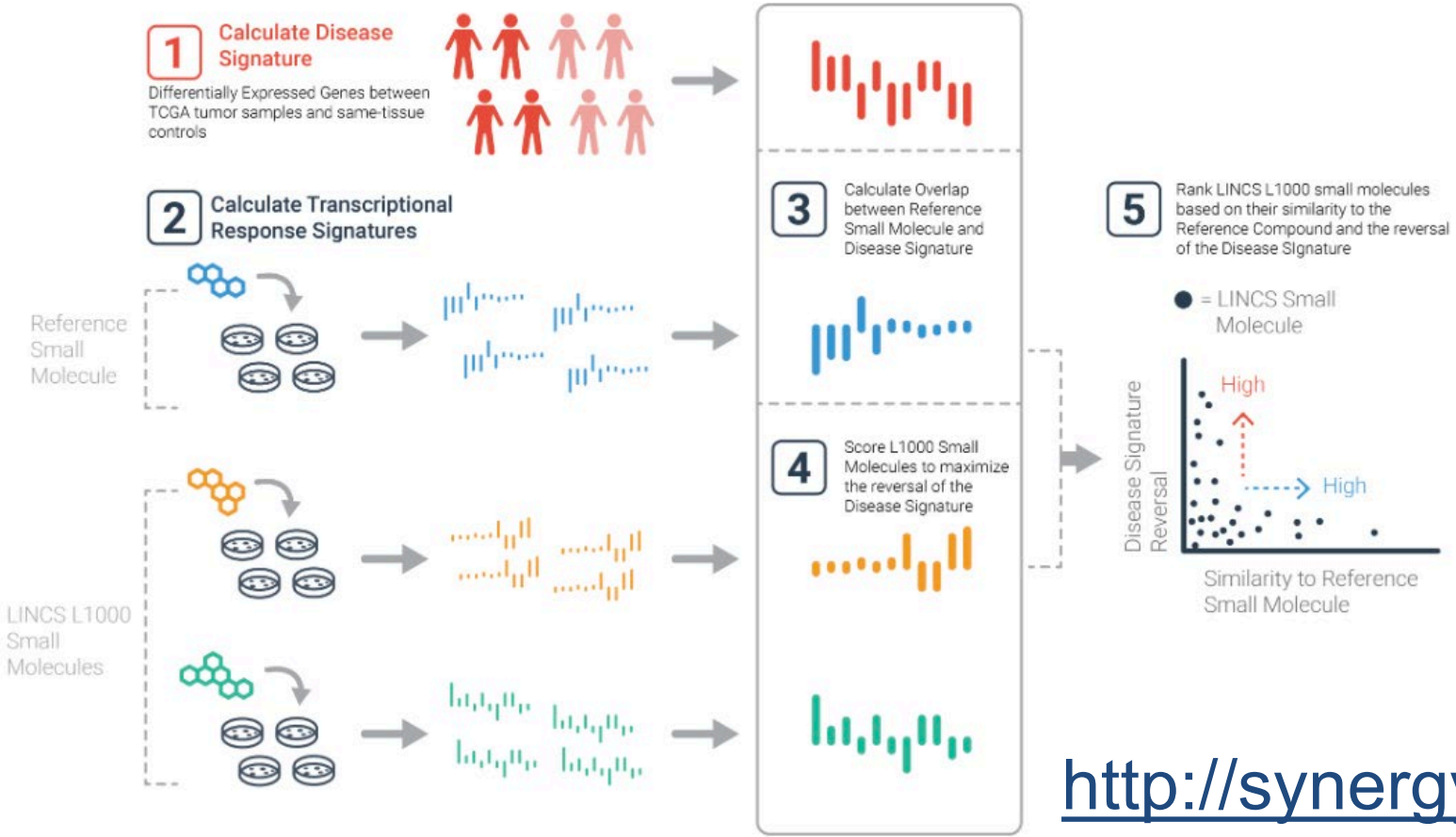


JQ1 + GSK-1070916 synergize in Glioblastoma cell death



Synergistic response correlates with discordance





http://synergyseq.com/

Download Synergy Plot Data | Download Drug Signatures

Drug	Disease_Same	Disease_Opp	Disease_Discordance	Reference_Drug_Orthogonality	Drug_Repurposing_Hub	CLUE	Manual
GSK-1070916	0.07	1.00	1	0.0892857142857143	Aurora kinase inhibitor	Aurora kinase inhibitor	N/A
HG-14-10-04	0.07	0.71	0.714285714285714	0.0833333333333333	N/A	N/A	potent and specific ALK inhibitor
JWE-035	0.07	0.64	0.642857142857143	0.202380952380952	N/A	Aurora kinase inhibitor	N/A
palbociclib	0.21	1.36	0.452380952380952	0.0803571428571429	CDK inhibitor	CDK inhibitor	N/A
PHA-793887	0.21	1.57	0.523809523809524	0.0378787878787879	CDK inhibitor	CDK inhibitor	N/A
withaferin-a	0.07	0.71	0.714285714285714	0.0076530612244898	N/A	N/A	Inhibits NF-_B activation
XMD-885	0.07	0.57	0.571428571428571	0.0555555555555556	MAP kinase inhibitor	Leucine rich repeat kinase inhibitor	N/A

PDX GBM Group 3

PDX GBM Group 4

nature COMMUNICATIONS

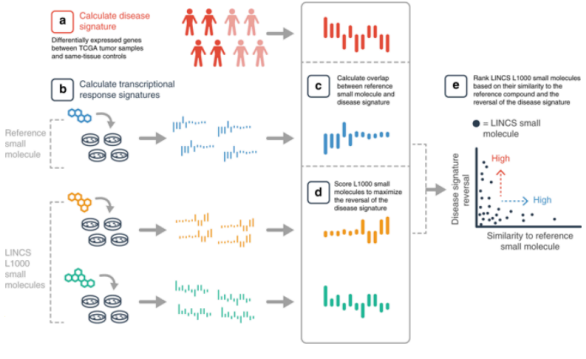
Article | OPEN | Published: 14 December 2018

Drug and disease signature integration identifies synergistic combinations in glioblastoma

Vasileios Stathias, Anna M. Jermakowicz, Marie E. Maloof, Michele Forlin, Winston Walters, Robert K. Suter, Michael A. Durante, Sion L. Williams, J. William Harbour, Claude-Henry Volmar, Nicholas J. Lyons, Claes Wahlestedt, Regina M. Graham, Michael E. Ivan, Ricardo J. Komotar, Jann N. Sarkaria, Aravind Subramanian, Todd R. Golub, Stephan C. Schürer & Nagi G. Ayad

Nature Communications **9**, Article number: 5315 (2018) | Download Citation

Fig. 1



View in article | Full size image »

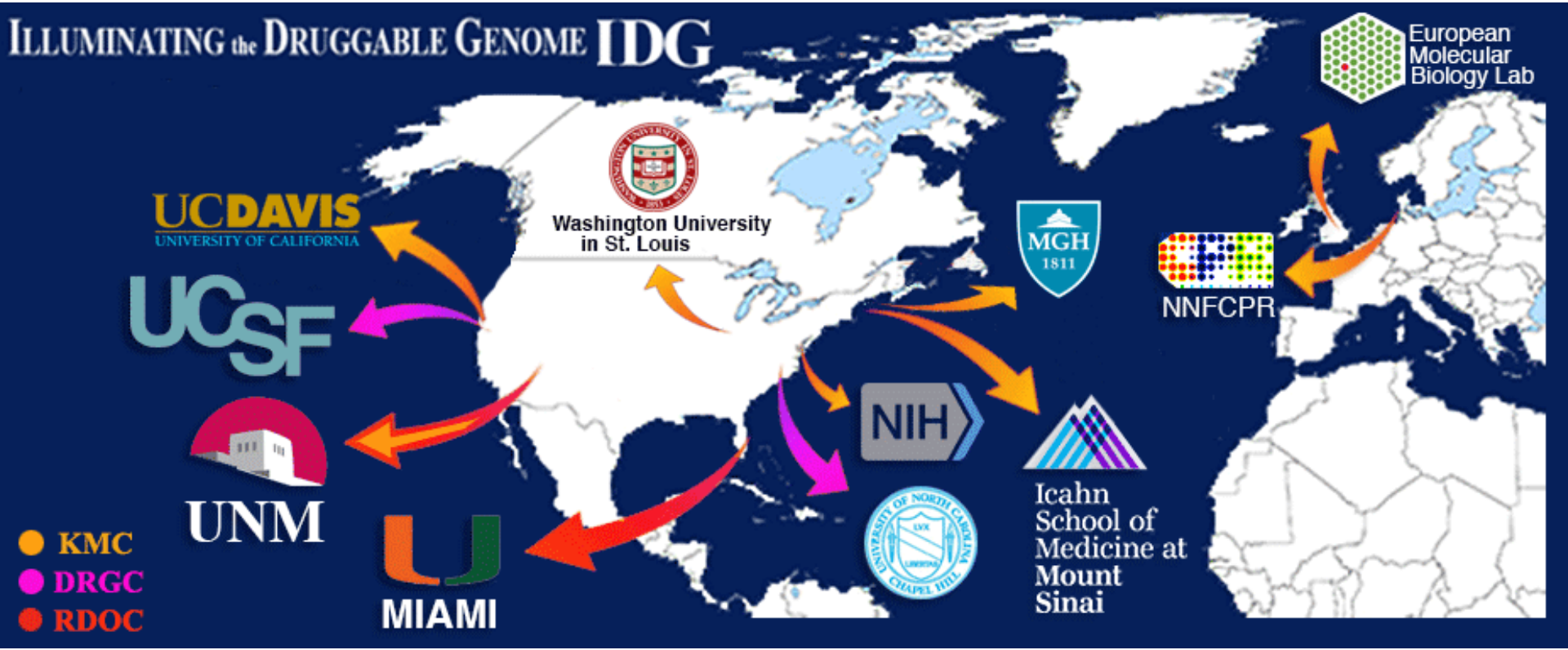
Abstract

Glioblastoma (GBM) is the most common primary adult brain tumor.

Take away (why did I show this)

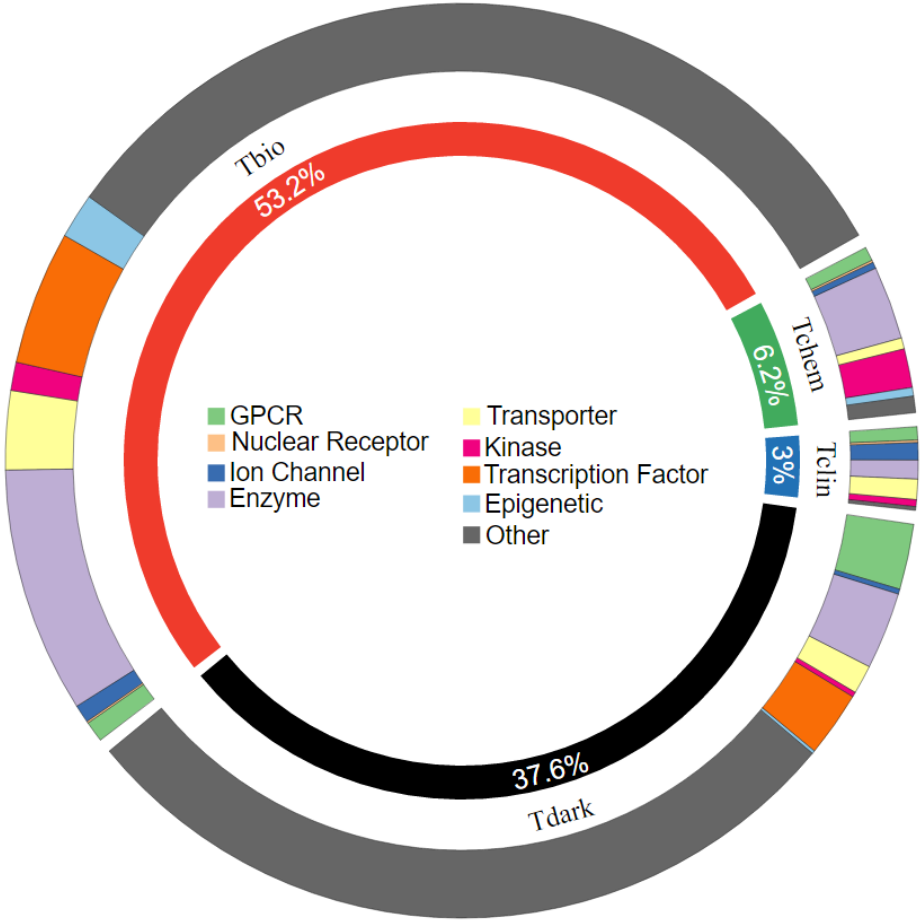
- Use LINCS data (http://lincsportal.ccs.miami.edu)
- Representation of chemical structures by transcriptional consensus signatures
- Systems-level data driven approach – vs target-driven approach
- Current work: combining transcriptional signatures with with chemical structure-based signatures

Illuminating the Druggable Genome (IDG)



http://druggablegenome.net

Target Development Level (TDL)



- Most protein classification schemes are based on structural and functional criteria.
- For therapeutic development, it is useful to understand how much and what types of data are available for a given protein, thereby highlighting well-studied and understudied targets.
- Proteins annotated as drug targets are **Tclin**
- Proteins for which *potent* small molecules are known are **Tchem**
- Proteins for which biology is better understood are **Tbio**
- Proteins that lack antibodies, publications or Gene RIFs are **Tdark**

nature REVIEWS DRUG DISCOVERY

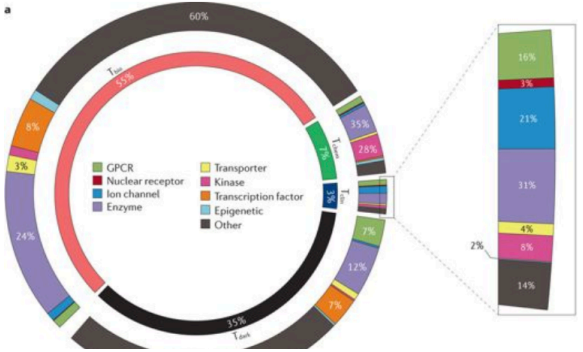
Analysis | Published: 23 March 2018

Unexplored therapeutic opportunities in the human genome

Tudor I. Oprea, Cristian G. Bologa, Søren Brunak, Allen Campbell, Gregory N. Gan, Anna Gaulton, Shawn M. Gomez, Rajarshi Guha, Anne Hersey, Jayme Holmes, Ajit Jadhav, Lars Juhl Jensen, Gary L. Johnson, Anneli Karlson, Andrew R. Leach, Avi Ma'ayan, Anna Malovannaya, Subramani Mani, Stephen L. Mathias, Michael T. McManus, Terrence F. Meehan, Christian von Mering, Daniel Muthas, Dac-Trung Nguyen, John P. Overington, George Papadatos, Jun Qin, Christian Reich, Bryan L. Roth, Stephan C. Schürer, Anton Simeonov, Larry A. Sklar, Noel Southall, Susumu Tomita, Ilinca Tudose, Oleg Ursu, Dušica Vidović, Anna Waller, David Westergaard, Jeremy J. Yang & Gergely Zahoránszky-Köhalmi - Show fewer authors

Nature Reviews Drug Discovery **17**, 317–332 (2018) | Download Citation

Figure 1: Target development level categories applied to the human proteome.



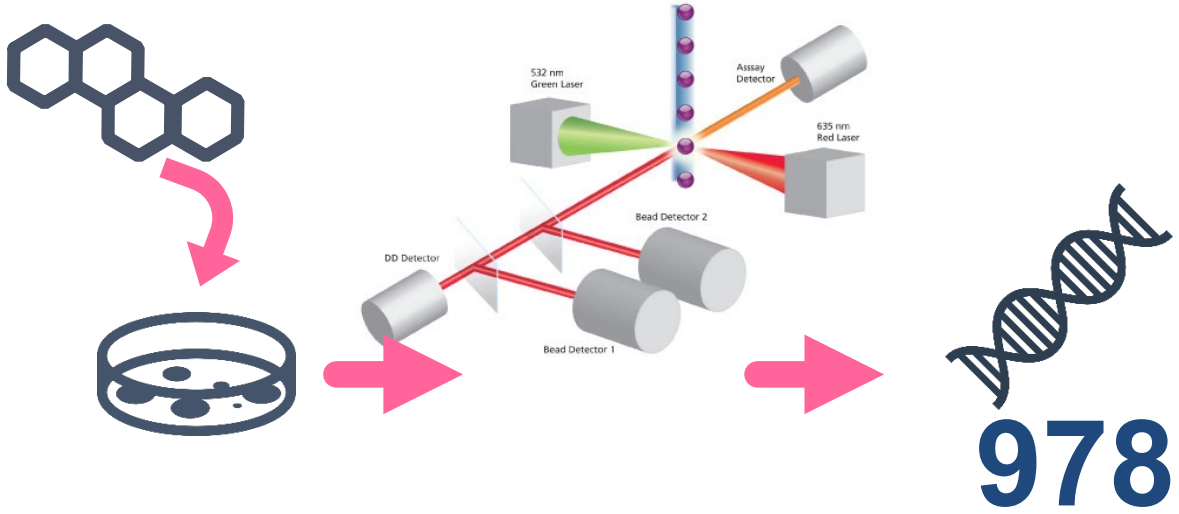
Additional slides

L1000 Gene Expression Platform

1753 Compounds

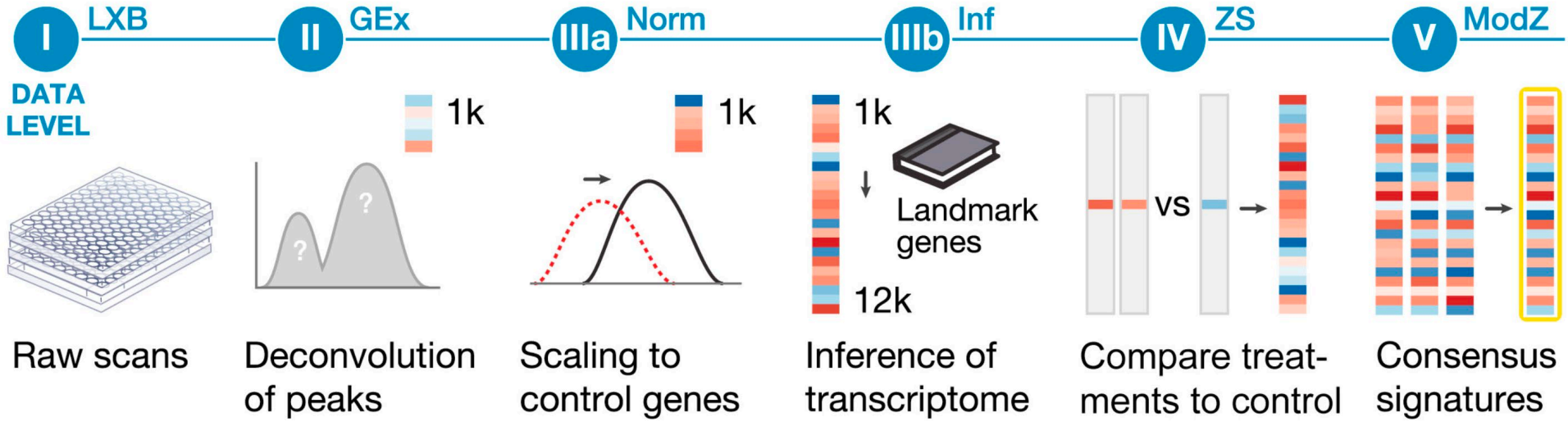
>50 Cell Lines

2 Timepoints



Aravind Subramanian et al, Cell, **2017**

L1000 Computational Processing Pipeline



Aravind Subramanian et al, Cell, **2017**

t-SNE Clustering of 4515 TCGA RNA-seq tumor samples

Cancer Subtype
- BRCA
- COAD
- GBM
- HNSC
- KIRC
- LUAD
- LUSC
- READ
- UCEC
- OV

Head and neck squamous cell carcinoma

Lung adenocarcinoma

Lung squamous cell carcinoma