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

Acknowledgements

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- Rimpi Khurana

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- Stephan Schürer

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http://bd2k-lincs.org/#/about#team
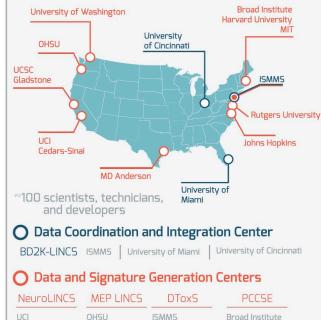
sschurer@miami.edu

LINCS
BY THE NUMBERS

15 INSTITUTIONS

University of Washington
Broad Institute Harvard University MIT
OHSU
University of Cincinnati
UCSC Gladstone
ISMMS
Rutgers University
Johns Hopkins
UCI Cedars-Sinai
MD Anderson
University of Miami

~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

⬇ LINCS Data Portal
Slicr
Ⓐ HMS LINCS Database

⬇ iLINCS
Ⓐ piLINCS
Harmonizome

OmicsIntegrator
L1000CDS
Enrichr
SEP - L1000
Breast Cancer Browser

30 MORE TOOLS

⬇ Download LINCS Datasets   Ⓐ Analyze LINCS Datasets
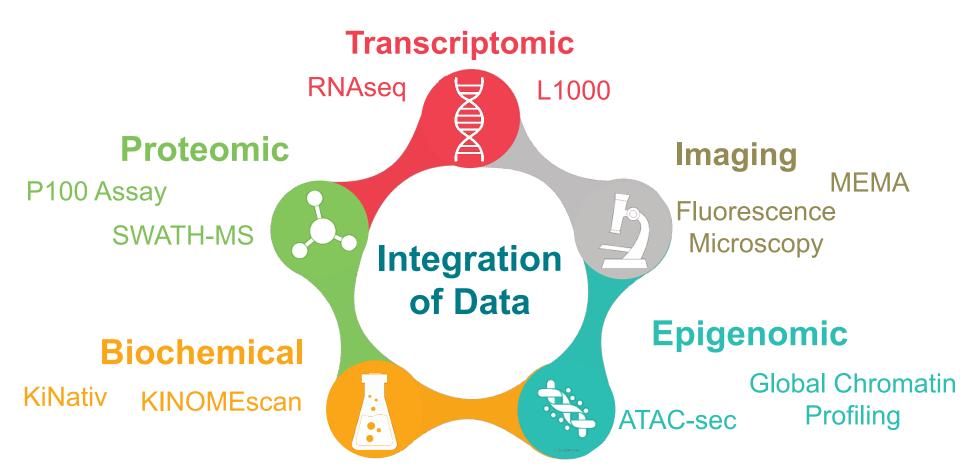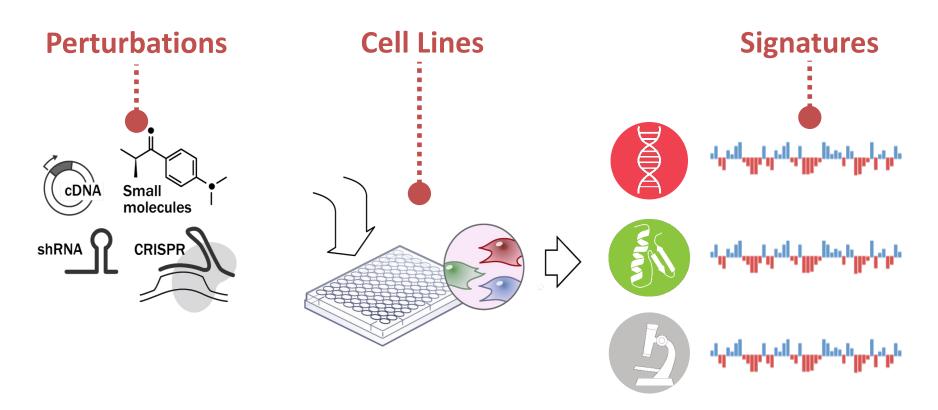
LINCS Project generates diverse multidimensional data

Transcriptomic
RNAseq
L1000

Imaging
MEMA
Fluorescence
Microscopy

Proteomic
P100 Assay
SWATH-MS

Integration of Data

Epigenomic
Global Chromatin Profiling
ATAC-sec

Biochemical
KiNativ
KINOMEscan

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**
06 Subject Areas	Imaging	85 Datasets
12 Centers	Transcriptomics	12 Datasets
06 Projects	Proteomics	9 Datasets
11 Biological Processes	Epigenomics	4 Datasets
	Metabolomics	1 Datasets

KINOMEscan kinase-small molecule binding assay

163 Datasets

KiNativ kinase-small molecule binding assay	30 Datasets
Bead-based immunoassay for protein state	3 Datasets
ELISA protein secretion profiling assay	3 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
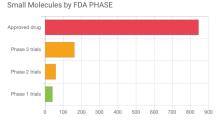
Search can be performed by a wide set of annotations such as mechanism of actions Cyclin-dependent kinase 2 inhibitor, MESH terms CARCINOMA, EFO terms CYSTIC FIBROSIS and cells MCF7.
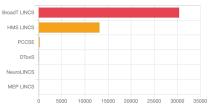
Advanced Search

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.
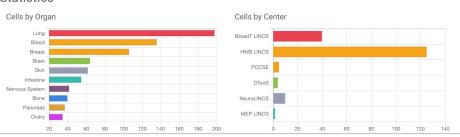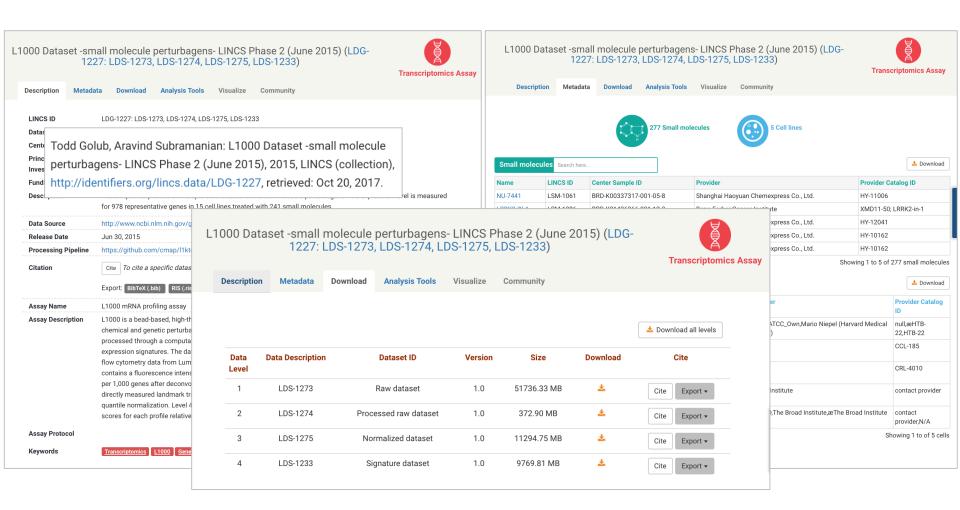
Explore Annotations

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.
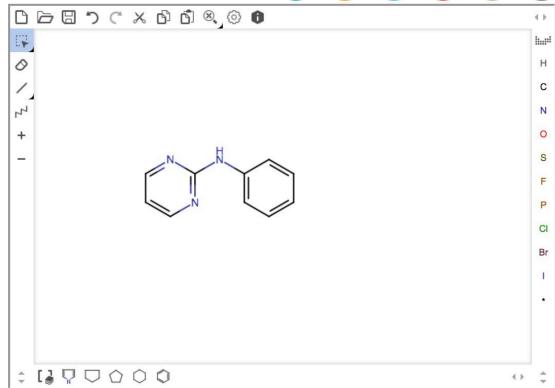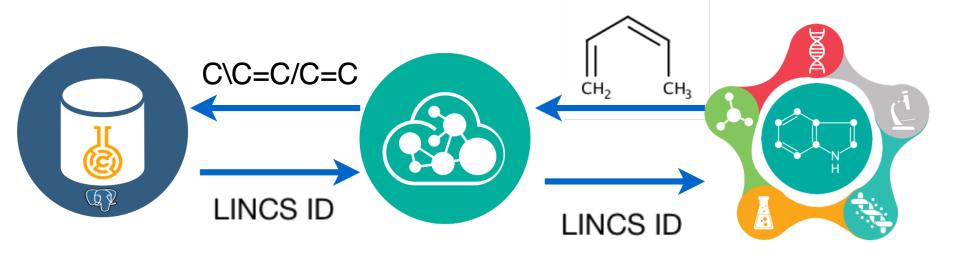
Statistics

Cells by Organ

Cells by Center

Substructure Search   Similarity Search

LDP Chemical Structure Search Engine

SMDB

JChem Postgres Cartridge

API Servlet

Structure Search

Marvin JS or direct

LINCS Data Portal | Small Molecules

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

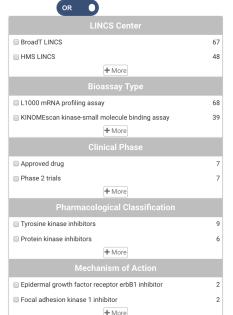|	
☐ Epidermal growth factor receptor erbB1 inhibitor	2
☐ Focal adhesion kinase 1 inhibitor	2

+ 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 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 ↗**

Transcriptomics | Binding | Metabolomics | Proteomics | Imaging | Epigenomics
(0, 5, 10, 15, 20)

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 ↗**

Transcriptomics | Binding | Metabolomics | Proteomics | Imaging | Epigenomics
(0, 5, 10, 15, 20)

TAE-684

Synonyms: NVP-TAE684

Model Systems: 637 cell-lines used **Show ⌄** **Explore ↗**

Datasets: Used in 28 Datasets **Show ⌄** **Explore ↗**

Transcriptomics | Binding | Metabolomics | Proteomics | Imaging | Epigenomics
(0, 10, 20, 30)

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 ↗**

Transcriptomics | Binding | Metabolomics | Proteomics | Imaging

Provide Feedback

LINCS Data Portal | Small Molecules

Search assays, cell lines, and perturbagens...

Total Small Molecules: 7

List view **Table view** **Download**

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**

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 ⧉**

Transcriptomics / Binding / Metabolomics / Proteomics / Imaging / Epigenomics

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 ⧉**

Transcriptomics / Binding / Metabolomics / Proteomics / Imaging / Epigenomics

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 ⧉**
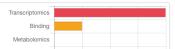**Pharmacological Classification**: Angiogenesis inhibitors; Protein kinase inhibitors **Explore ⧉**
Model Systems: 1115 cell-lines used **Show ⌄** **Explore ⧉**
Datasets: Used in 13 Datasets **Show ⌄** **Explore ⧉**

Transcriptomics / Binding / Metabolomics / Proteomics / Imaging / Epigenomics

Osimertinib
Synonyms: AZD-9291; AZD-9291 MESYLATE; HG-14-8-02; Osimertinib; Osimertinib Mesylate; Tagrisso
Max Phase: Approved drug

Transcriptomics / Binding / Metabolomics

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

Related LINCS Compounds by chemical structure (similarity ≥ 0.9)

LSM-43288
LSM-45329
LSM-44525

Predicted Physicochemical Properties

Molecular formula	C29H31N7O		cLogP	4.38
Molecular weight	493.60g/mol		Rotatable bonds	7
Lipinski 3	Fail		H bond acceptors	7
Lipinski 5	Pass		H bond donors	2
Bioavailability	Pass		TPSA	86.28
Lead likeliness	Fail		QED	0.40

Provide Feedback

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
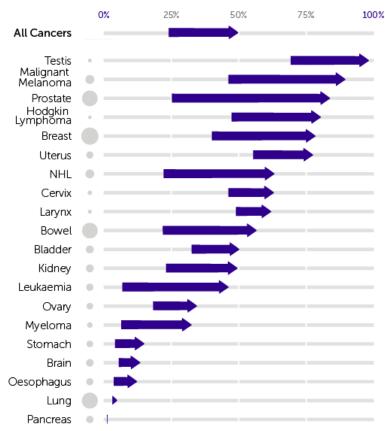
- Surgical resection followed by radiotherapy and temozolamide chemotherapy

- Annual incidence: 1 / 19,000
- 5-years survival rate **< 9.8%**
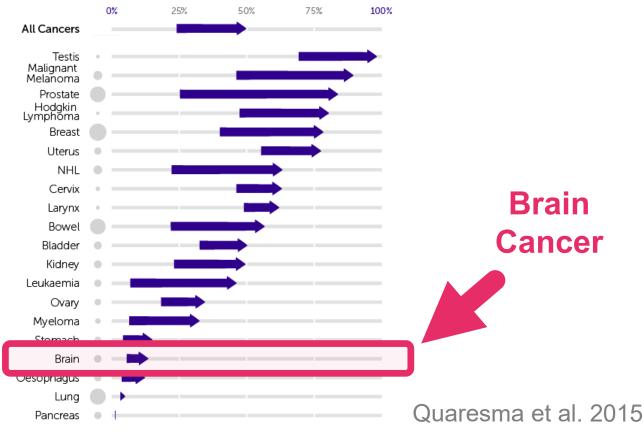
Little progress has been made in the survival of brain cancer patients

Changes in the 10-year survival

1971 → 2010

Quaresma et al. 2015

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

Changes in the 10-year survival
1971 ➡ 2010

Brain Cancer

Quaresma et al. 2015
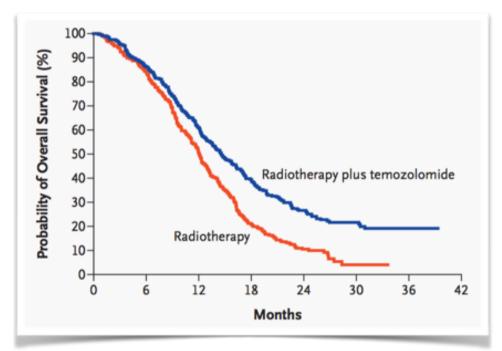
Current GBM Treatment is Ineffective

Probability of Overall Survival (%) vs Months — Radiotherapy plus temozolomide; Radiotherapy

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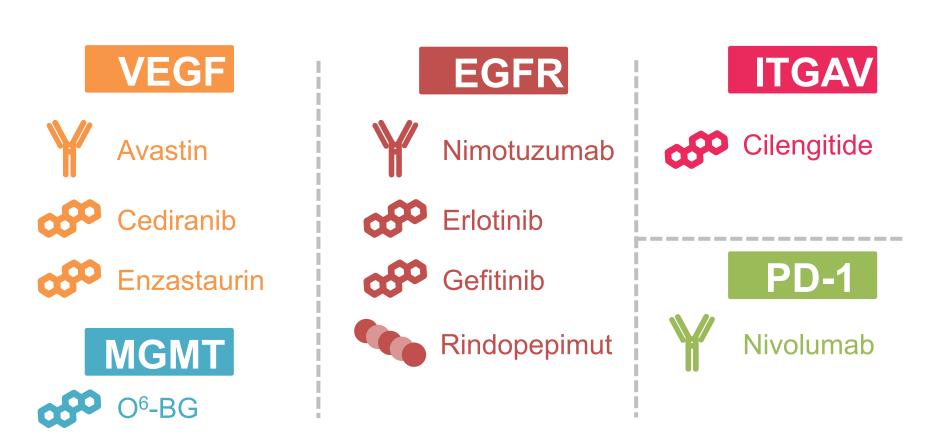
1. Maximal surgical resection
2. Radiotherapy
3. Temozolomide (TMZ) treatment

No early detection Biomarker
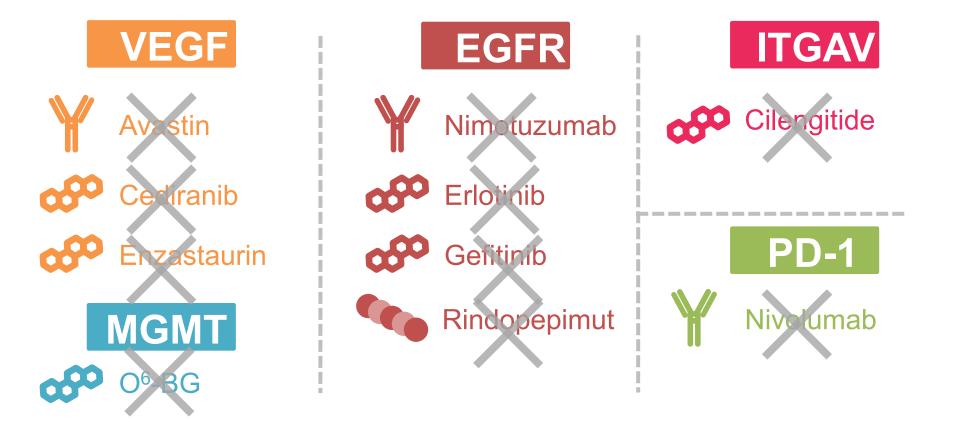
Temozolomide (2005)   2.5 month increase in survival
(14.6 vs 12.1 months)

Stupp et al. 2005

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

VEGF
- Avastin
- Cediranib
- Enzastaurin

MGMT
- O^6-BG

EGFR
- Nimotuzumab
- Erlotinib
- Gefitinib
- Rindopepimut

ITGAV
- Cilengitide

PD-1
- Nivolumab

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

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

Growth / Survival Signal

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

Growth / Survival Signal

Alternative Signaling Pathway

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Alternative Signaling Pathway

Growth / Survival Signal

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

Alternative Signaling Pathway

Growth / Survival Signal

LINCS Signatures characterize diverse cellular responses upon perturbation

CMap concept: linking diseases to therapeutics

Lamb et al. Science, 2006

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]

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

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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],
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SCIENTIFIC REPORTS

Personalised drug repositioning for Clear Cell Renal Cell Carcinoma using gene expression

Karel K. M. Koudijs[1], Anton G. T. Terwisscha van Scheltinga[1], Stefan Böhringer[2], Kirsten J. M. Schimmel[1] & Henk-Jan Guchelaar[1]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

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SCIENTIFIC REP⚙RTS

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CANCER

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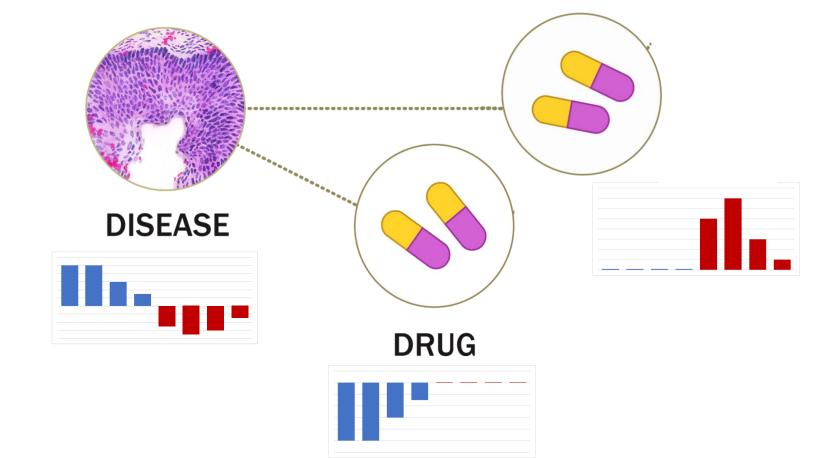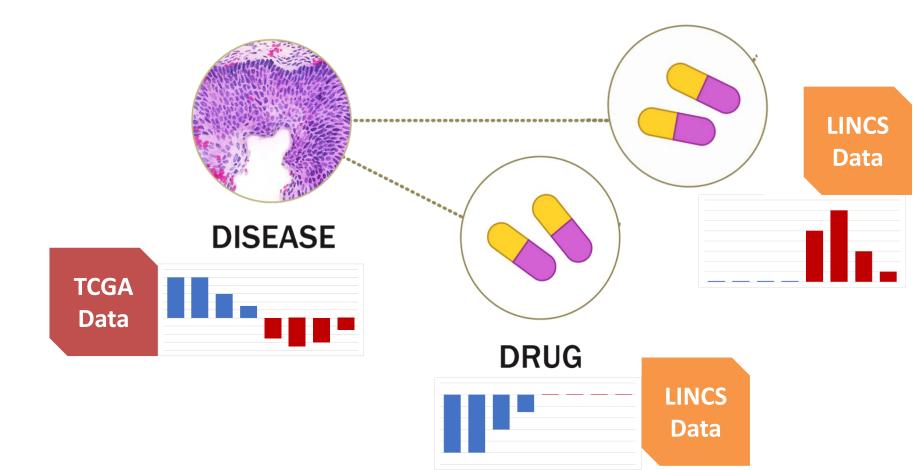
Novel Drug Candidates for the Treatment of Metastatic Colorectal Cancer through Global Inverse Gene-Expression Profiling 🔄
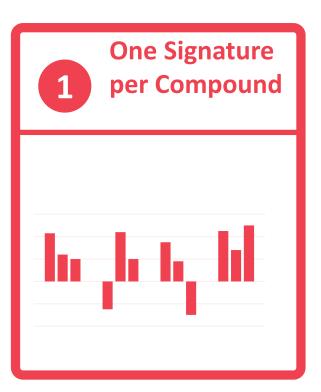
Vera van Noort[1,2], Sebastian Schölch[3], Murat Iskar[1], Georg Zeller[1], Kristina Ostertag[4], Christine Schweitzer[3], Kristin Werner[3], Jürgen Weitz[3], Moritz Koch[3], and Peer Bork[1,5]
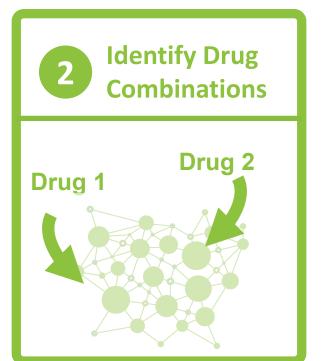
Similar approach for combination therapies
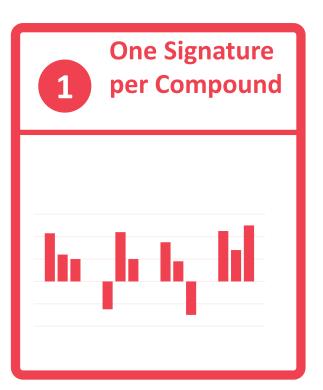
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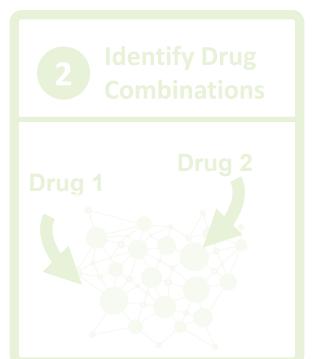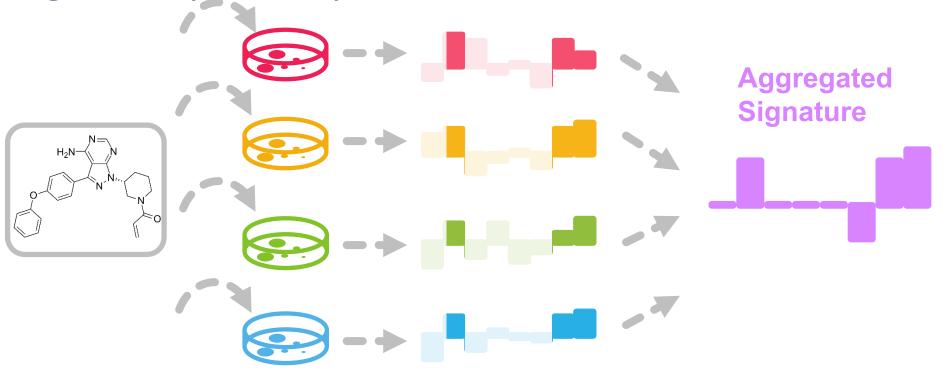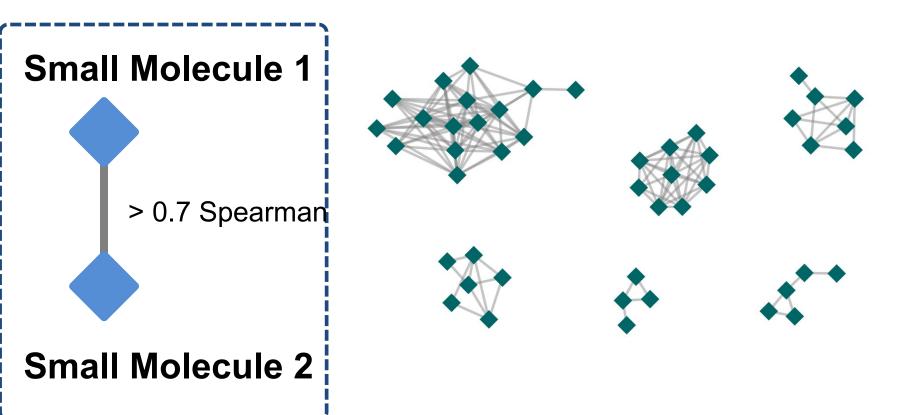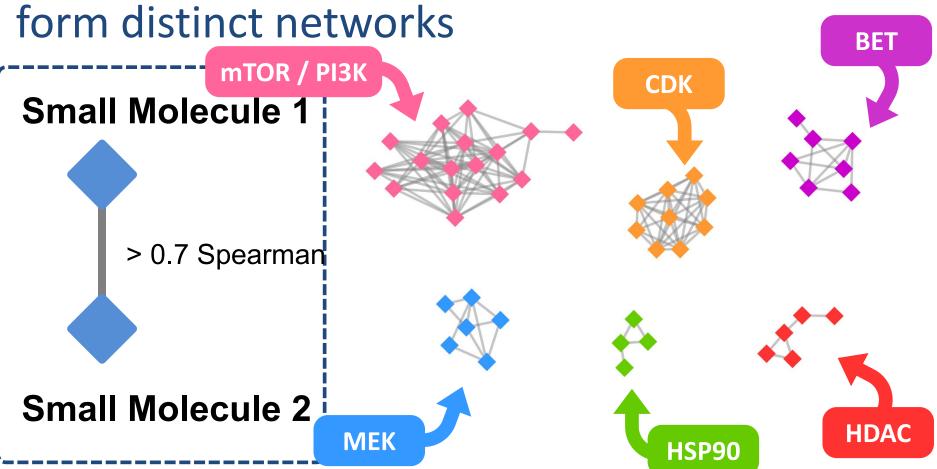
Collapse the gene expression profiles into one signature per compound

Aggregated Signature

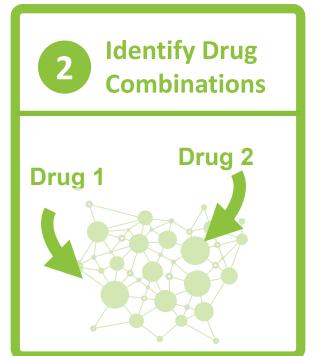# Compounds with same Mechanism of Action form distinct networks

Compounds with same Mechanism of Action form distinct networks

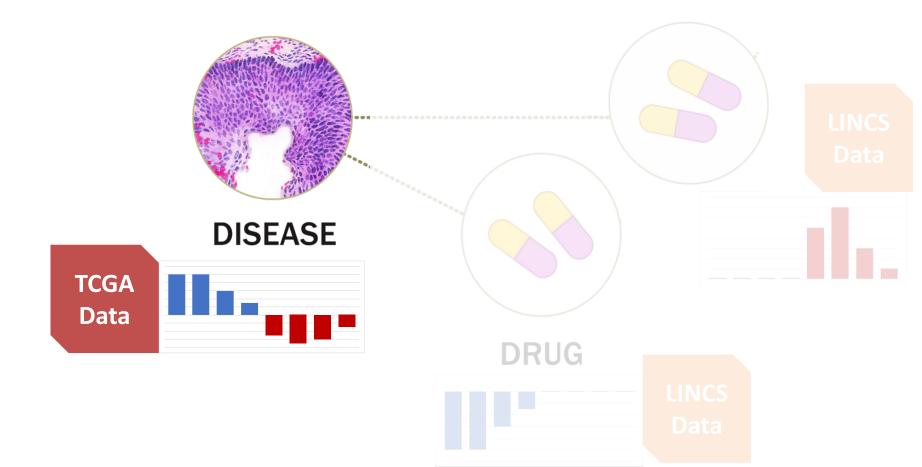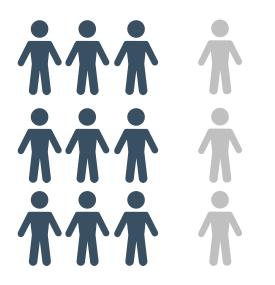

Small Molecule 1

Small Molecule 2

> 0.7 Spearman

mTOR / PI3K

CDK

BET

MEK

HSP90

HDAC

1 One Signature per Compound

2 Identify Drug Combinations

Drug 1

Drug 2

3 Validate in vitro / in vivo

DRUG 1 + DRUG 2

Glioblastoma disease signature from TCGA
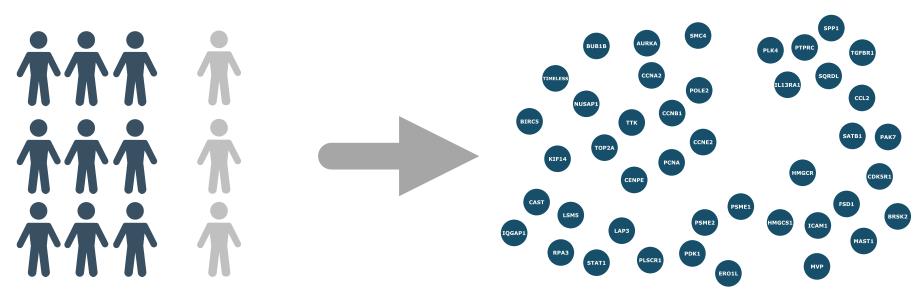
Identify Differentially Expressed Genes in Glioblastoma Samples

**Glioblastoma Samples
and Controls**
(from TCGA)

Identify Differentially Expressed Genes in Glioblastoma Samples
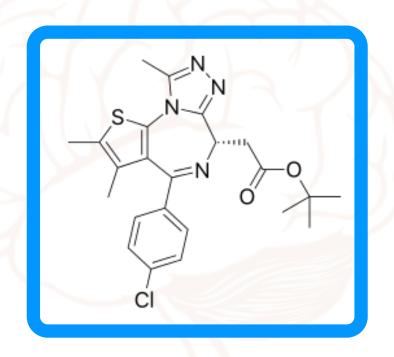
Glioblastoma Samples
and Controls
(from TCGA)

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

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[2], Hao Guo[2], Daniel G. Stover[1,2], Muhammad B. Ekram[1,2], Guillermo Peluffo[1,2], Jonathan Brown[1,2], Clive D'Santos[2], 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[1,6], Myles Brown[1,2,9], X. Shirley Liu[1,9,12], Clifford A. Meyer[3], James E. Bradner[1,2,12] & Kornelia Polyak[1,2,9,12]

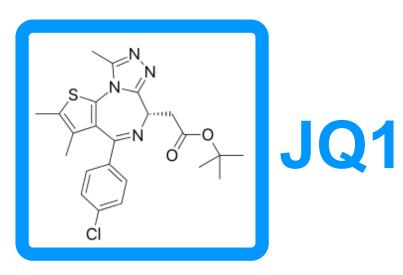## Loss of TRIM33 causes resistance to BET bromodomain inhibitors through MYC- and TGF-β–dependent mechanisms

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]

BET inhibitor resistance emerges from leukaemia stem cells

Chun Yew Fong[1,2,3], Omer Gilan[1,2], Enid Y. N. Lam[3], Alan F. Rubin[4,5], Sarah Ftouni[3], Dean Tyler[1,2], Kym Stanley[3], 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[1,2,3], Brian J. P. Huntly[6], Rab K. Prinjha[7], Anthony T. Papenfuss[1,2,4,5] & Mark A. Dawson[1,2,3]
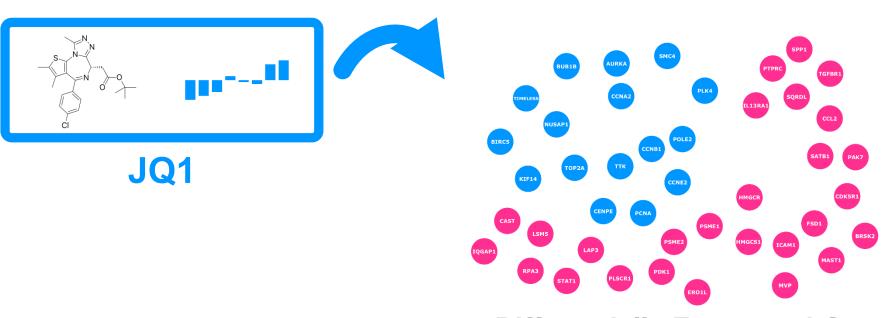
JQ1

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
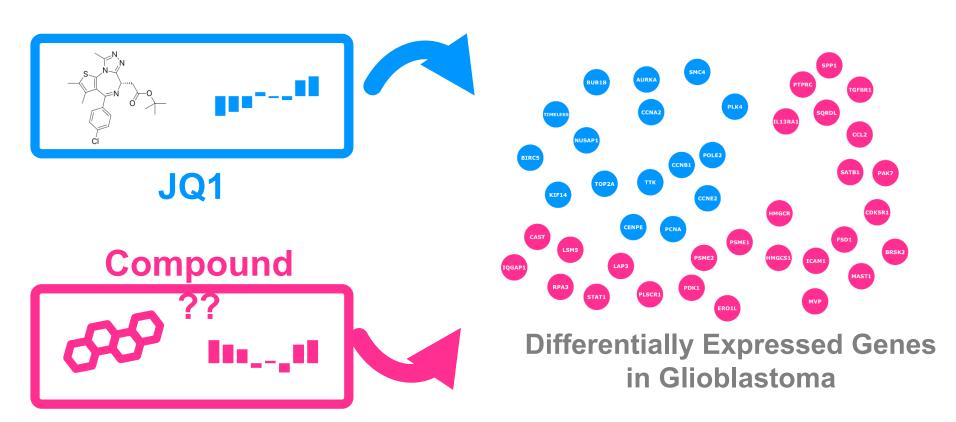
JQ1 + ?

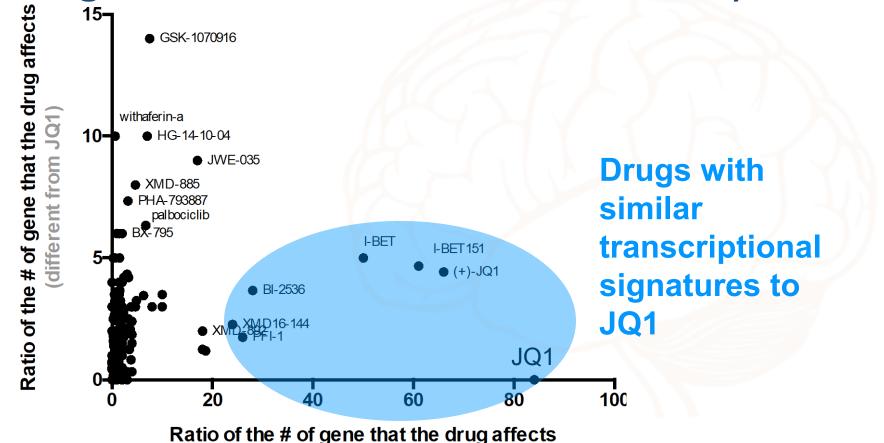# Identify compounds that induce orthogonal gene expression

JQ1

Differentially Expressed Genes in Glioblastoma

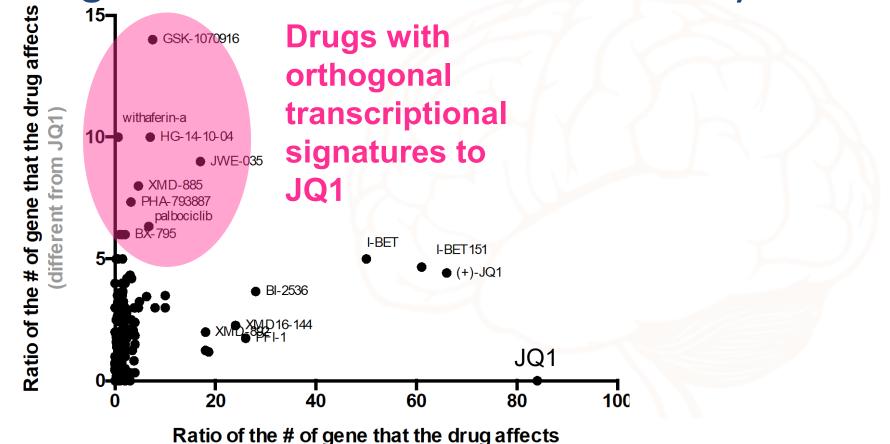Identify compounds that induce orthogonal gene expression

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

Drugs with orthogonal transcriptional signatures to JQ1

Y-axis: Ratio of the # of gene that the drug affects (different from JQ1)
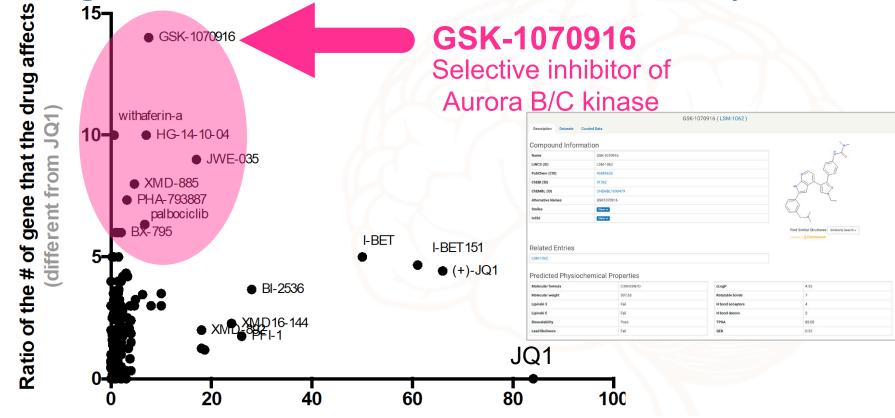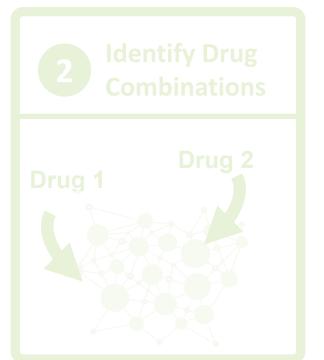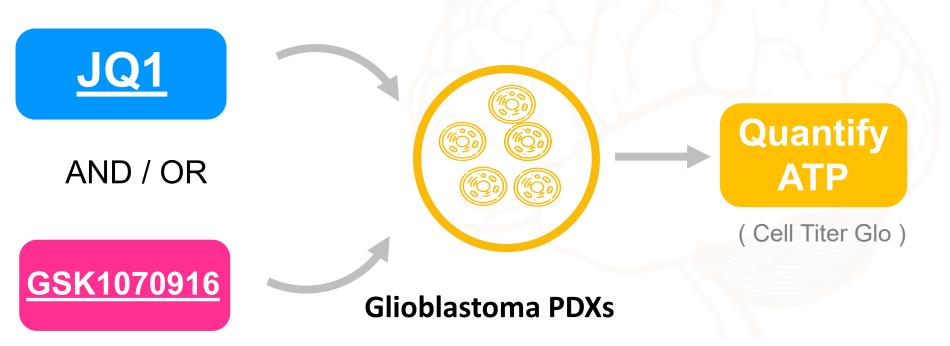
X-axis: Ratio of the # of gene that the drug affects (similar to JQ1)

Labeled points:
- GSK-1070916
- withaferin-a
- HG-14-10-04
- JWE-035
- XMD-885
- PHA-793887
- palbociclib
- BX-795
- I-BET
- I-BET 151
- (+)-JQ1
- BI-2536
- XMD16-144
- XMD-892
- PFI-1
- JQ1

All Drugs were ranked based on similarity to JQ1

GSK-1070916
Selective inhibitor of
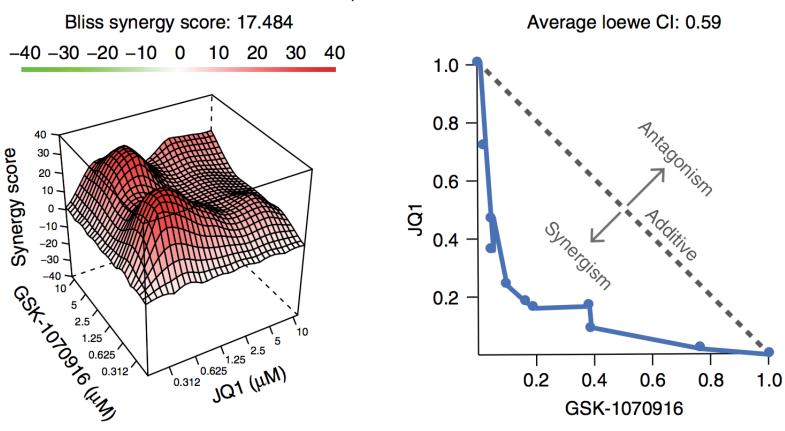Aurora B/C kinase
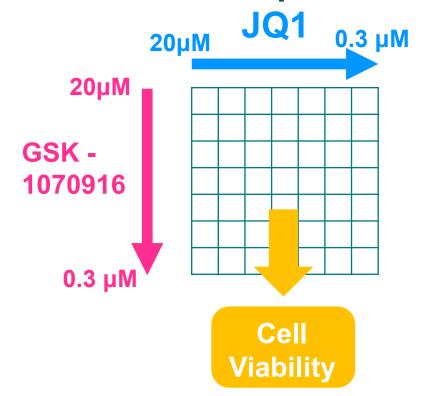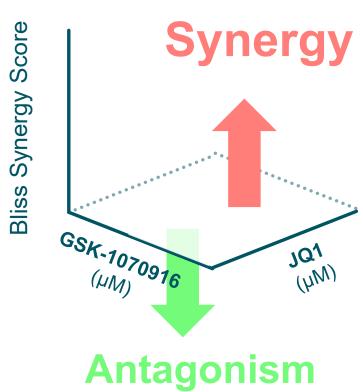
Bliss independence analysis of cell- viability combination response
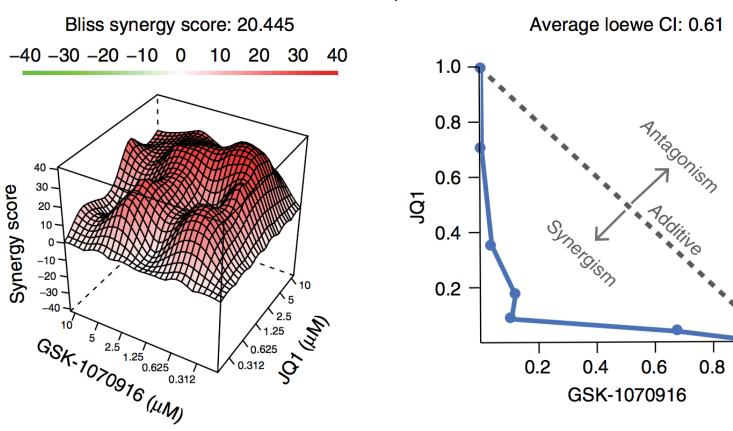
JQ1 + GSK-1070916 synergize in reducing cell viability
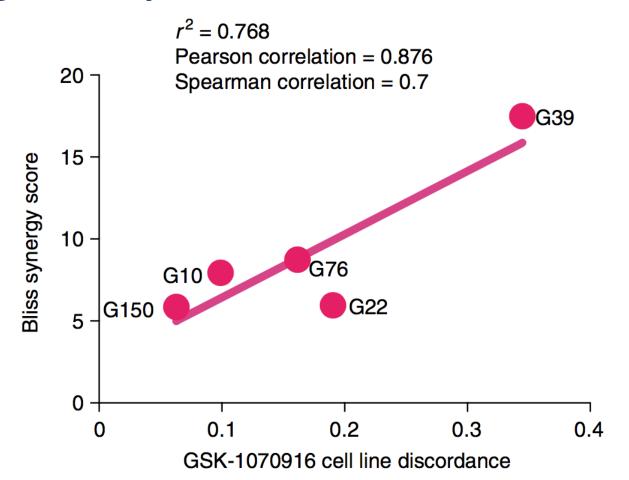
GBM39, CellTiter-Glo®

Bliss synergy score: 17.484

Average loewe CI: 0.59

JQ1 + GSK-1070916 synergize in Glioblastoma cell death

GBM39, Caspase-Glo®

Synergistic response correlates with discordance

http://synergyseq.com/
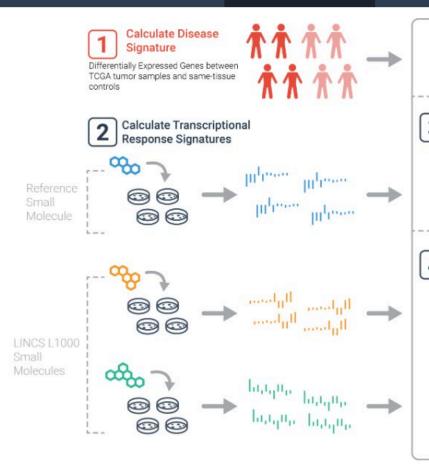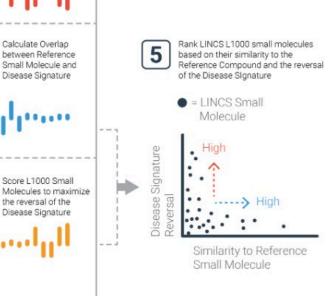
Download Synergy Plot Data   **Download Drug Signatures**

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

				333333	N/A	N/A	potent and specific ALK inhibitor
				30952	N/A	Aurora kinase inhibitor	N/A

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3 Citations   **11** Altmetric   Article metrics »

| Sections | **Figures** | References |

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 ✉

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)](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
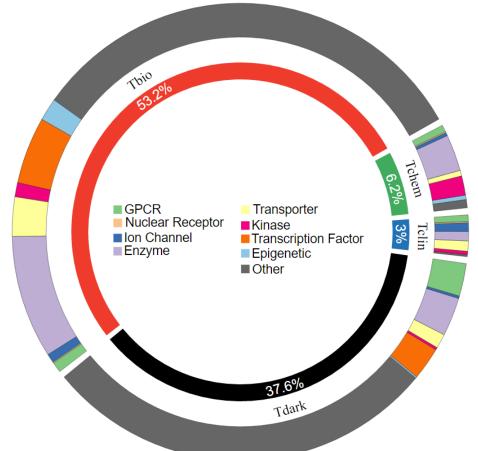
Illuminating the Druggable Genome (IDG)

http://druggablegenome.net

Target Development Level (TDL)

- GPCR
- Nuclear Receptor
- Ion Channel
- Enzyme
- Transporter
- Kinase
- Transcription Factor
- Epigenetic
- Other

Tbio 53.2%

Tchem 6.2%

Tclin 3%

Tdark 37.6%

- 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**

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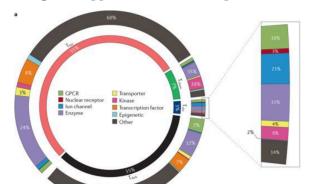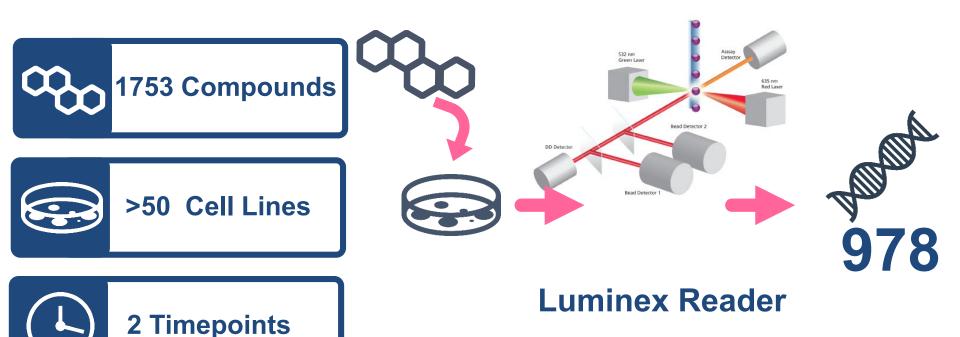
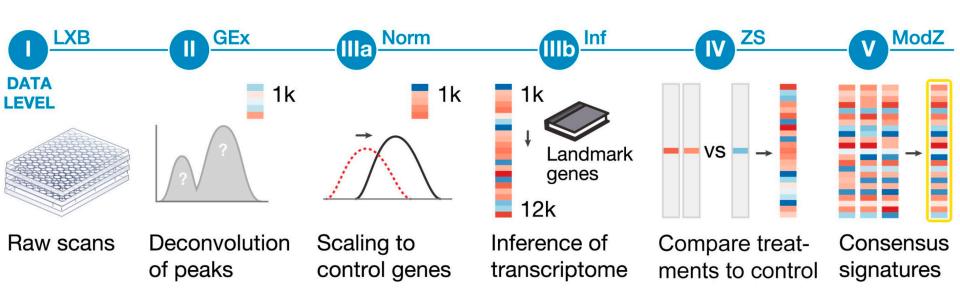**Figure 1: Target development level categories applied to the human proteome.**

Additional slides

L1000 Gene Expression Platform

1753 Compounds

>50 Cell Lines

2 Timepoints

Luminex Reader

978

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