

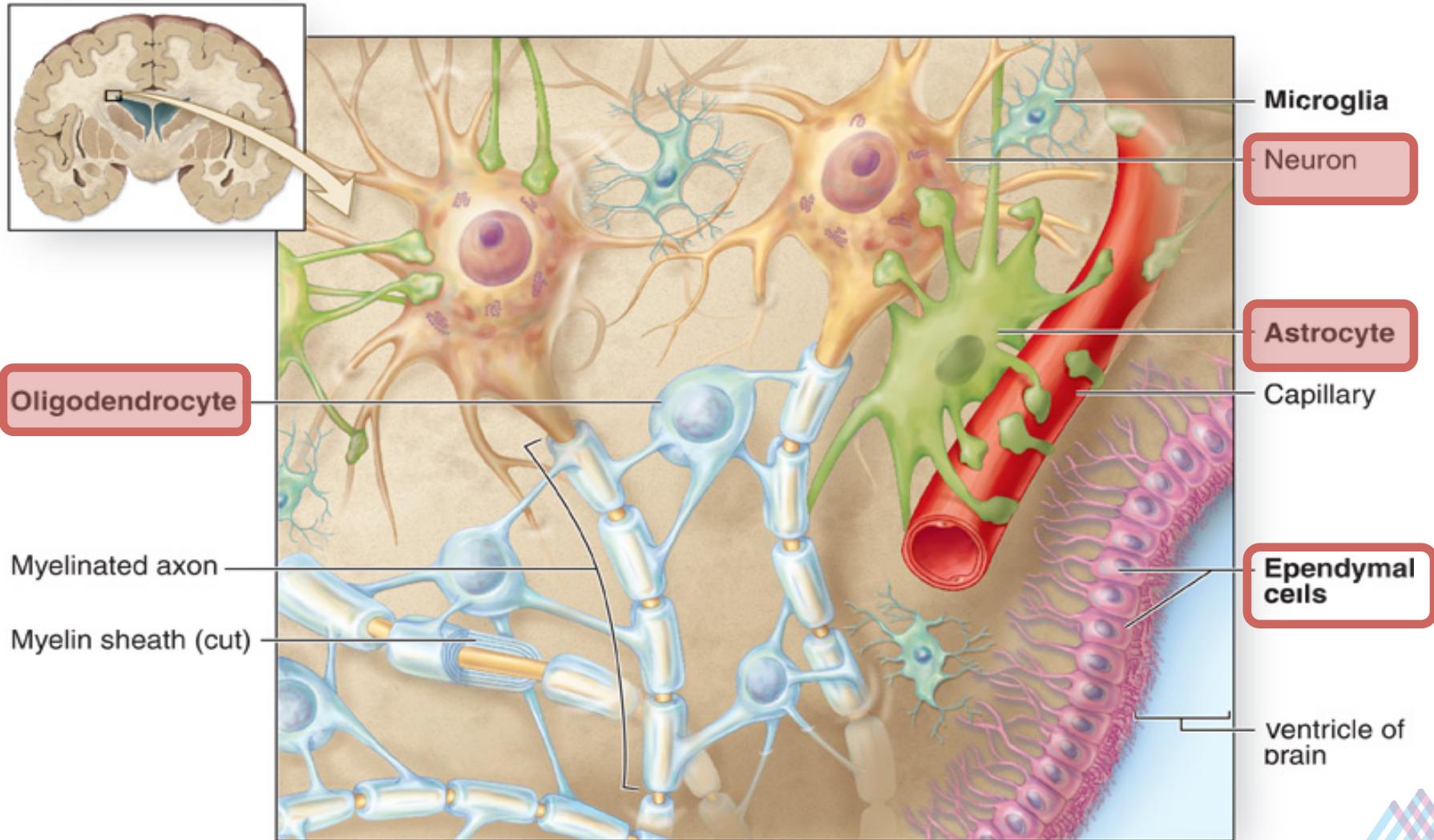


Differential Gene Expression In Glioblastoma Multiforme

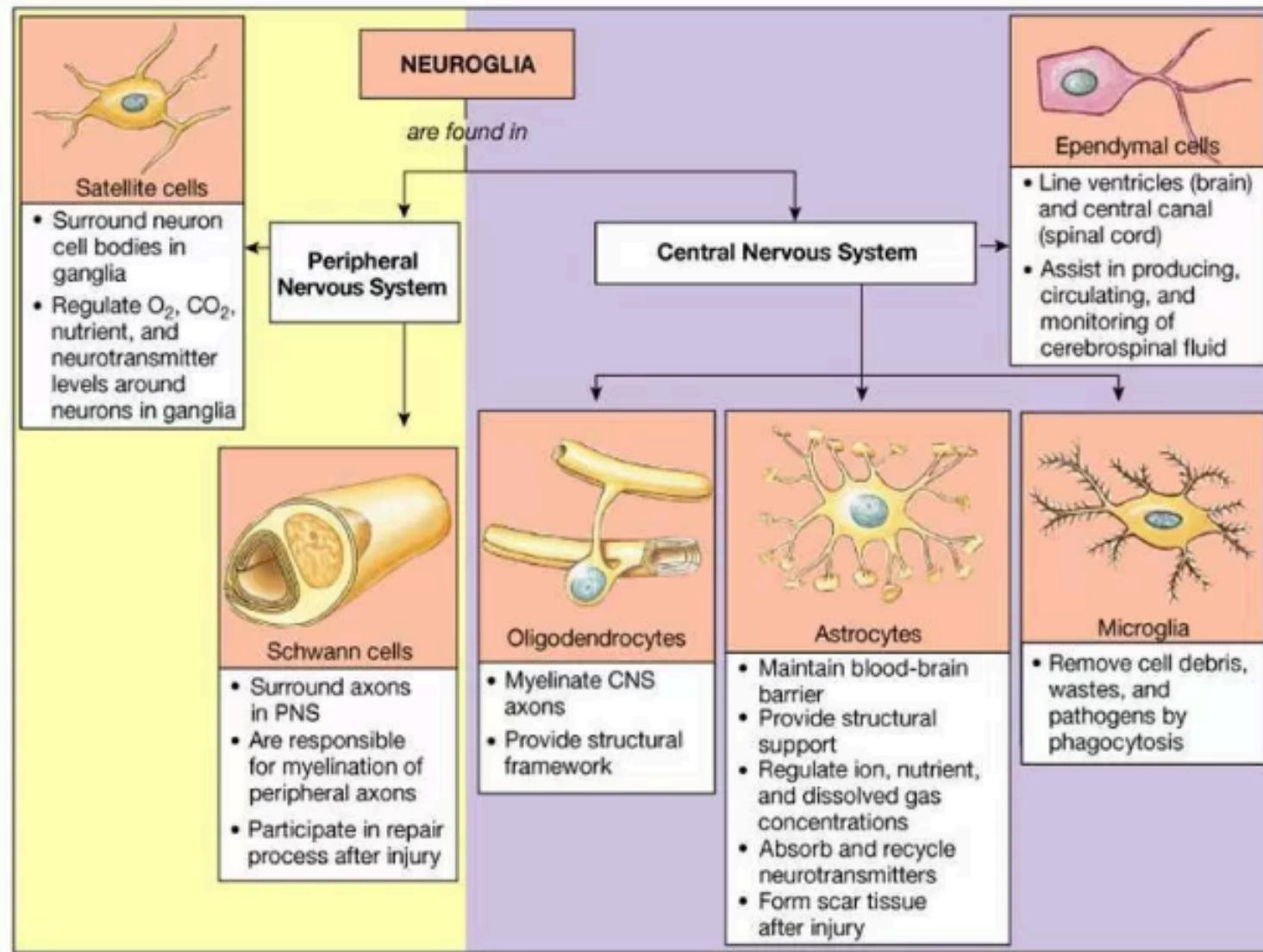
Caroline Monteiro

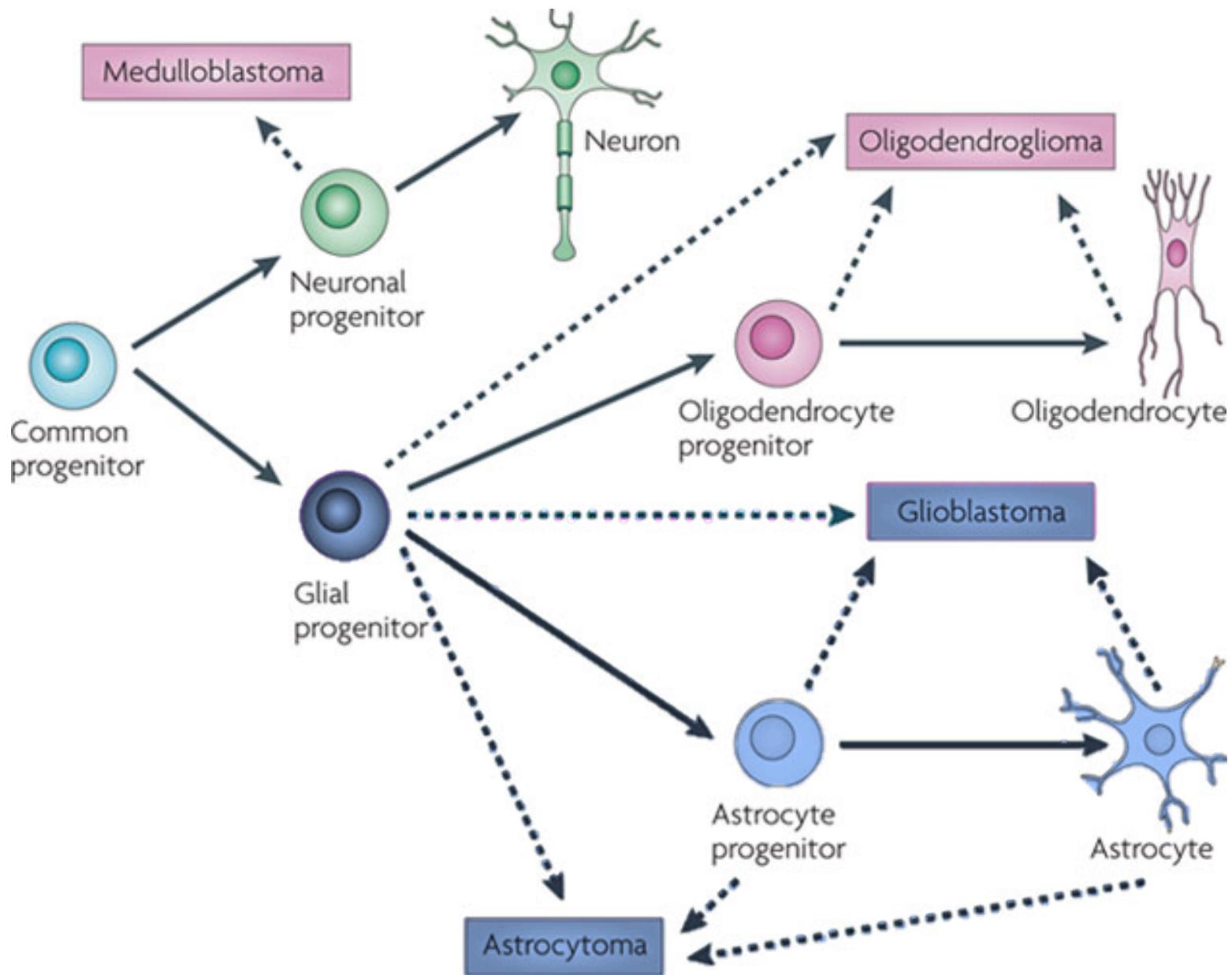
Etiology

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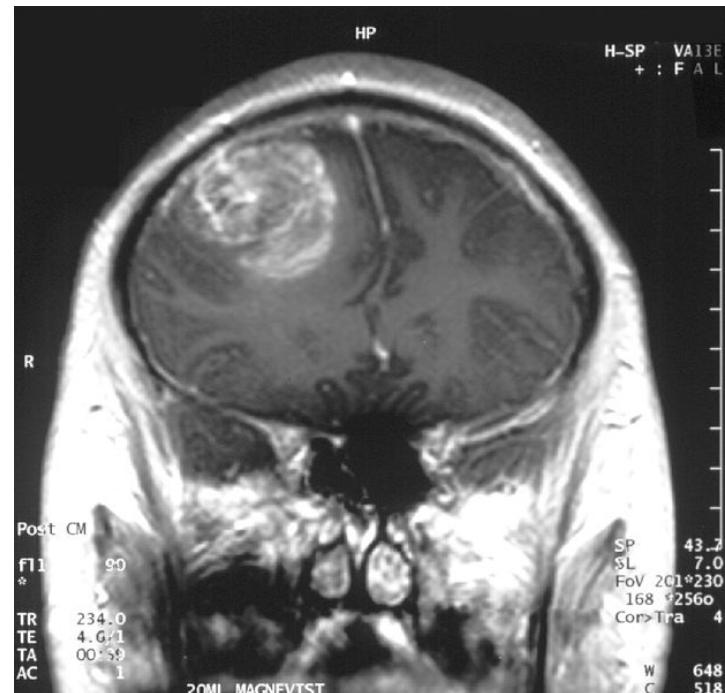
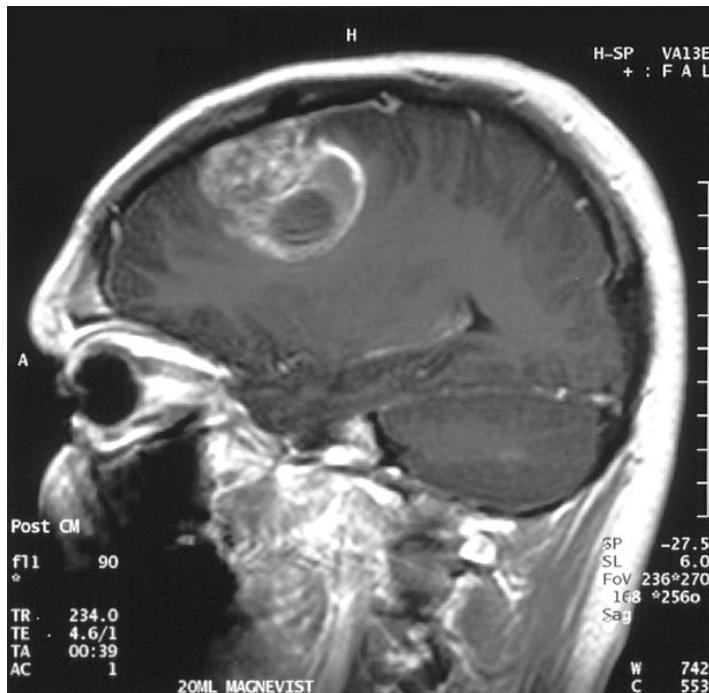


Function





Glioblastomas



Wikimedia commons



Glioma Survival



Subtypes



THE CANCER GENOME ATLAS
National Cancer Institute
National Human Genome Research Institute

Proneural

Neural

Classical

Mesenchymal



Putative GBM cells of origin:



TIC → BCPC
Sequential genetic alterations & clonal evolution

Primary GBM subtypes:

Classical

EGFR mutation/amplification/overexpression
PTEN loss/mutation
CDKN2A loss
NES overexpression
Notch & Shh pathways activation

Mesenchymal

NF1 loss/mutation
TP53 loss/mutation
PTEN loss/mutation
MET, CHI3L1, CD44, MERTK overexpression
TNF family & NF κ B pathways activation

Neural

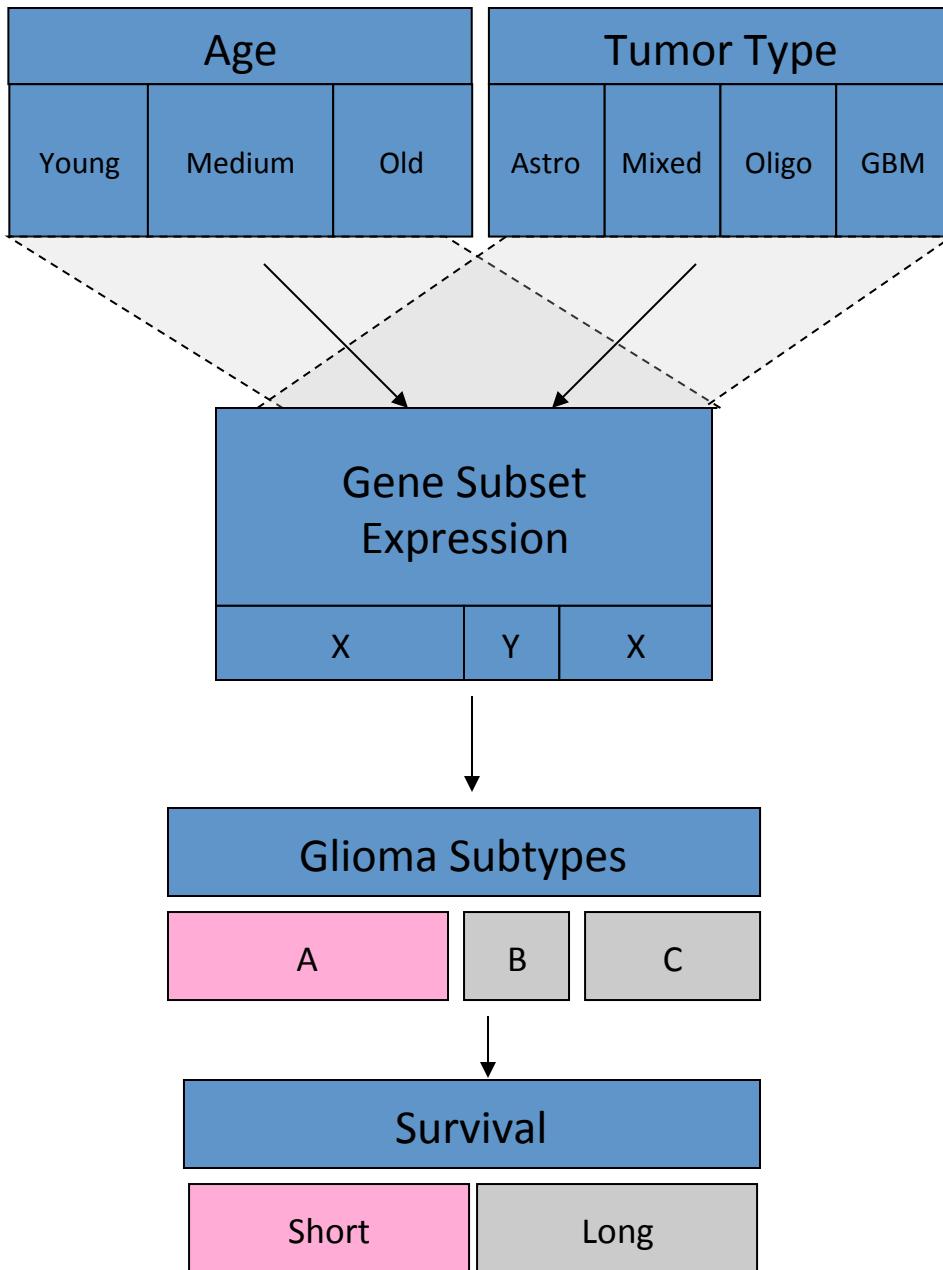
EGFR amplification/overexpression
Gene signature of normal brain
Neuron marker expression
(NEFL, GABRA1, SYT1, SLC12A5)
Remains to be better defined

Proneural

PDGFRA amplification
IDH1 mutation
PIK3A/PIK3R1 mutations
TP53, CDKN2A & PTEN loss/mutation
Proneural marker expression
(SOX, DCX, DLL3, ASCL1, TCF4)
Oligodendrocytic marker expression
(PDGFRA, OLIG2, TCF3 and NKX2-2)
HIF, PI3 kinase & PDGFRA pathways activation

Grade II/III
Astrocytoma





- “Tiers” of classification can assist with discovery of downstream groups
- **Glioma Classification**
 - Histological Level
 - Clinical Level (Survival, Age, etc.)
 - Transcriptome (Gene Expression Level)
- **Gene Classification**
 - GO Hierarchy
 - Pathway Databases
 - Expression Level (Microarray Data)



UCLA Neuro-Oncology Center

- 5FC
- AMG 595
- AMG-595
- AVANDIA (Rosiglitazone Maleate)
- BCNU
- Carboplatin
- CCI-779
- CDX-110
- Celecoxib (Systemic)
- Chlorquine
- CPT -11 (CAMPTOSAR, Irinotecan)
- Dasatinib (BMS-354825, Sprycel)
- DCVax
- Etoposide (Eposin, Etopophos, Vepesid)
- GLIADEL Wafer
- IL-13
- Iressa (ZD-1839)
- Lapatinib (GW572016)
- MEDI4736
- Metformin
- Nivolumab
- Optune
- PEMBROLIZUMAB
- Rapamycin (Rapamune, Sirolimus)
- RTA 744
- Sorafenib
- Sulfasalazine (Azulfidine)
- TARCEVA (erlotinib HCl)
- TEMODAR Schering-Plough
- TOCA 511
- Topotecan (Systemic)
- VEGF Trap
- Vincristine
- XL184
- ZOCOR (simvastatin)
- Accutane Hoffmann-La Roche
- AMG-102
- Anti Neoplaston
- Avastin
- BiCNU Carmustine
- CC-223
- CCNU
- CDX-110 (RINDOPEPIMUT)
- Celldex
- Cilengitide (EMD 121974)
- CPT-11
- Dc vaccine
- Dendritic Cell Therapy
- GDC-0449
- Hydroxychloroquine
- IMC-3G3
- Irinotecan
- LOMUSTINE
- Mefloquine
- Methotrexate for Cancer (Systemic)
- Novocure TTF Therapy
- OSI-774
- Procarbazine
- Rindopepimut
- Simvastatin
- SU-101
- Sutent (Pfizer)
- Taxol
- TGF-B Anti-Sense
- TOCA FC
- Valcyte
- VEGF-Trap
- Vorinostat (SAHA)
- XL765
- AEE788 Novartis
- AMG-386
- AQ4N (Banoxantrone)
- Avastin (Bevacizumab) Genetech
- BMS-CA209143 NIVOLUMAB
- CC223
- CCNU Lomustine
- Ceenu
- Chloroquine
- Cisplatin
- Cytoxan
- DC Vax
- Disulfiram
- Gleevec (imatinib mesylate)
- Hydroxyurea
- Immune Therapy
- keytruda
- LY317615 (Enzastaurin)
- Memantine
- nilotinib
- ONARTUZUMAB vs PLACEBO
- PCV
- RAD001 Novartis (mTOR inhibitor)
- RMP-7
- Sirolimus
- SU5416 Sugen
- Tamoxifen
- TEMODAR
- Thalomid (thalidomide)
- TOCA INTRACRANIAL
- VB-111
- Velcade
- XL 765
- Zarnestra (tipifarnib)

* Published: Thursday, September 29, 2016 : 5:36:09 PM PT



Clinical trials:

Study Agent	IRB ID	Trial:Details
MEDI4736	15-001680	[ABTC 14-02]:
18-FDG	14-001460	[Ludwig LUD2013-006]:
5-FC (Flucytosine)	16-000600	Dr. Ellingson 18-FDG-PET (2016):
ACP-196	10-001147	[Tg 511-09-01]:
aCTL and IL-2	15-001667	[Acerta ACE-ST-209]:
AG881	11-000790	[aCTL Immunotherapy (Dr Liau)]:
CDX-110, Temozolomide	15-000792	Agios_AG881-C-002:
Lapatinib (GW572016), TMZ, RT	11-002220	[Celldex CDX110-05] :
Nivolumab, the combination of Nivolumab and ipilimumab	12-000493	[Lapatinib_Nghiemphu]:
Toca 511	14-000075	[BMS CA209143]:
VB-111	15-001608	[Tg 511-15-01]:
	15-001545	VBL VB-111-215 :



Methods

Glioblastoma



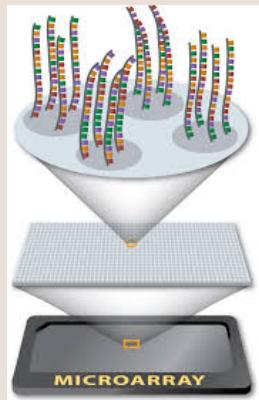
Dissociated Glioblastoma cells



Xenograft model



Samples



CEL files

```
if value == 0:  
    genes.append(gene)  
    genes.append(value)  
  
# convert data matrix to a one-dimensional array  
datamatrix = np.array(datamatrix)  
  
# log2 transformation  
datamatrix = np.log2(datamatrix)  
  
# quartile normalization  
# sortrowsmatrix = np.mean(np.sort(datamatrix, axis=0), axis=0)  
# for j in range(len(sortrowsmatrix)): sortrowsmatrix[j] = sortrowsmatrix[backsorted(j), :]  
  
# z-score  
datamatrix = stats.zscore(datamatrix, axis=0)  
  
# create folder for signatures  
signature_folder = os.path.join(signatures_folder, 'ILMN_1212612')  
os.makedirs(signature_folder, exist_ok=True)  
if not os.path.exists(signature_folder):  
    os.makedirs(signature_folder)  
  
# save matrix  
matrix_name = 'ILMN_1212612' + '_ILMN_1212612' + '_matrix.txt'  
np.savetxt(matrix_name, datamatrix, delimiter='\t', header='', footer='', comments='')
```

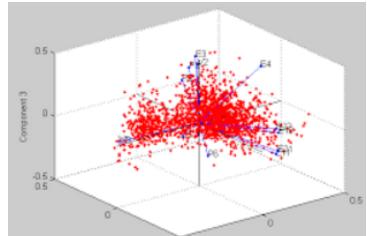
	GSM594001	GSM594002	GSM594003
ID_REF			
ILMN_1212602	7.184260	7.194550	7.161091
ILMN_1212603	7.196894	7.182783	7.178232
ILMN_1212605	7.344910	7.344303	7.441332
ILMN_1212607	7.210274	7.177601	7.242680
ILMN_1212610	7.155835	7.178343	7.172530
ILMN_1212612	7.186474	7.155083	7.153309

API

GEN3VA REPORT

Visualization

clustergrammer



Enrichment

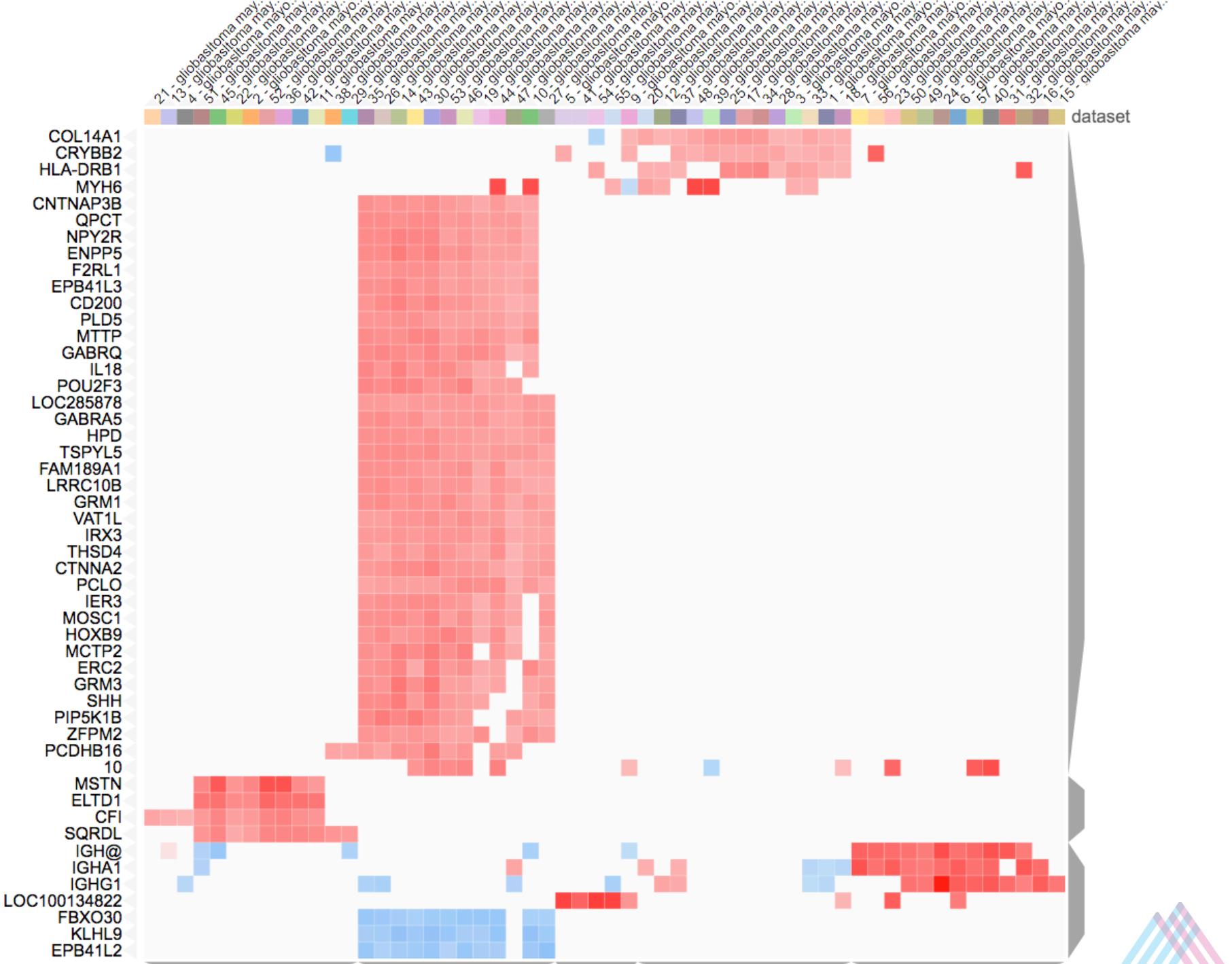
Enrichr

Prediction

L1000CDS²

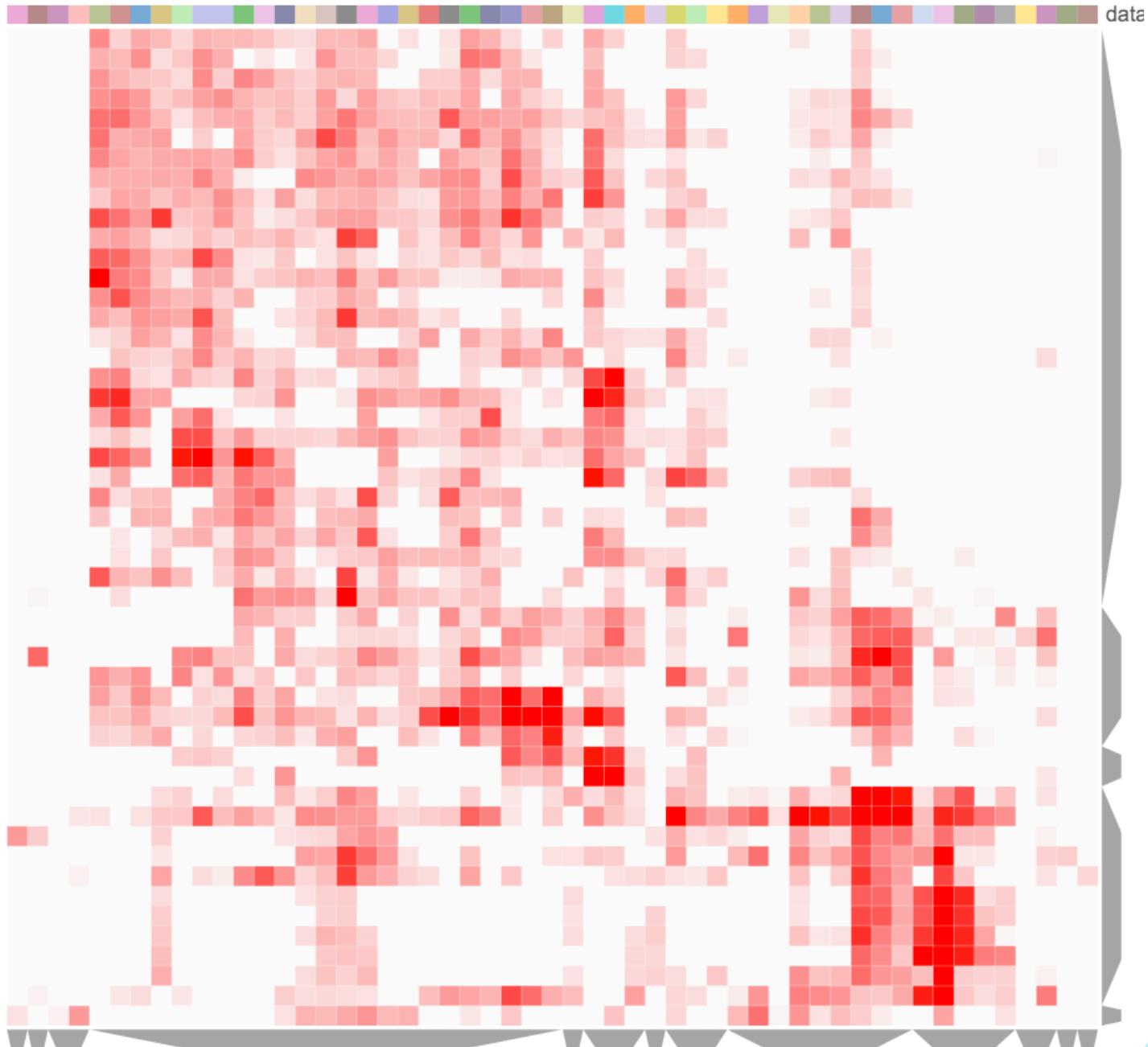
 GEN3VA REPORT





ENCODE TF ChIP-seq 2015

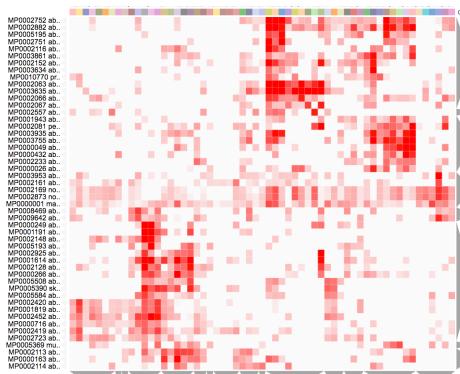
CTCF H54 hg19
CTCF WERI-Rb..
CTCF foreskin ..
CTCF SK-N-SH..
RAD21 H1-hES..
CTCF H1-hESC..
CTCF fibroblas..
CTCF A549 hg..
RAD21 A549 h..
CTCF MCF-7 h..
CTBP2 H1-hES..
CTCF fibroblas..
CTCF endothe..
CTCF medullo..
CTCF GM06990..
CTCF HCT116 ..
GATA2 endoth..
RAD21 HepG2 ..
RAD21 IMR-90..
UBTF K562 hg..
POLR2A MCF-7..
POLR2A MCF 1..
ZBTB7A ECC-1..
CTCF skin fibrob..
CTCF HGPS ce..
CTCF brain mm9
KDM5B H1-hES..
CHD1 H1-hESC..
EP300 osteobla..
EZH2 fibroblas..
CBX8 K562 hg..
SUZ12 K562 h..
EZH2 fibroblas..
SMC3 SK-N-SH..
RAD21 SK-N-S..
RAD21 MCF-7 ..
STAT1 HeLa-S..
STAT2 K562 h..
EZH2 skeletal ..
EZH2 B cell hg..
SUZ12 NT2-D1..
EZH2 astrocyte..
SUZ12 H1-hES..
REST Panc1 h..
REST U-87 MG..
REST MCF-7 h..
REST HCT116 ..
REST H1-hESC..
EZH2 keratinoc..
EZH2 myotube..



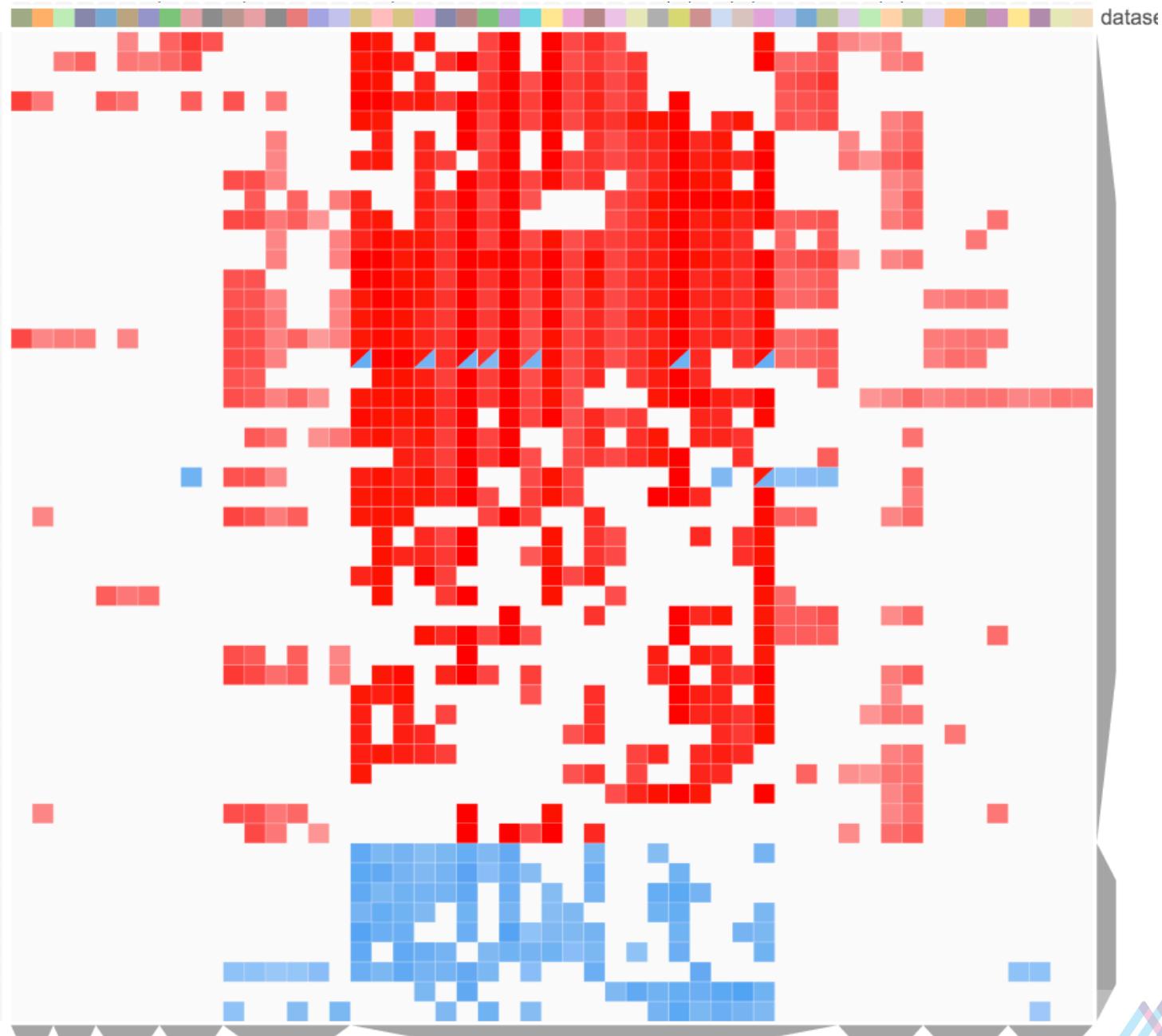
This horizontal bar chart displays the distribution of 59 samples across various molecular phenotypes. The phenotypes are listed on the left, and the count of samples for each phenotype is indicated by the length of the red bars.

MP ID	MP Term	Count
MP0002169	No abnormal phenotype	55
MP0002873	Normal phenotype	46
MP0002752	Abnormal somatic nervous	45
MP0002882	Abnormal neuron morphology	31
MP0001614	Abnormal blood vessel	29
MP0003635	Abnormal synaptic transmission	23
MP0003935	Abnormal craniofacial development	23
MP0002063	Abnormal learning/memory/ cond	21

MGI Mammalian Phenotype Level 4



 Enrichr

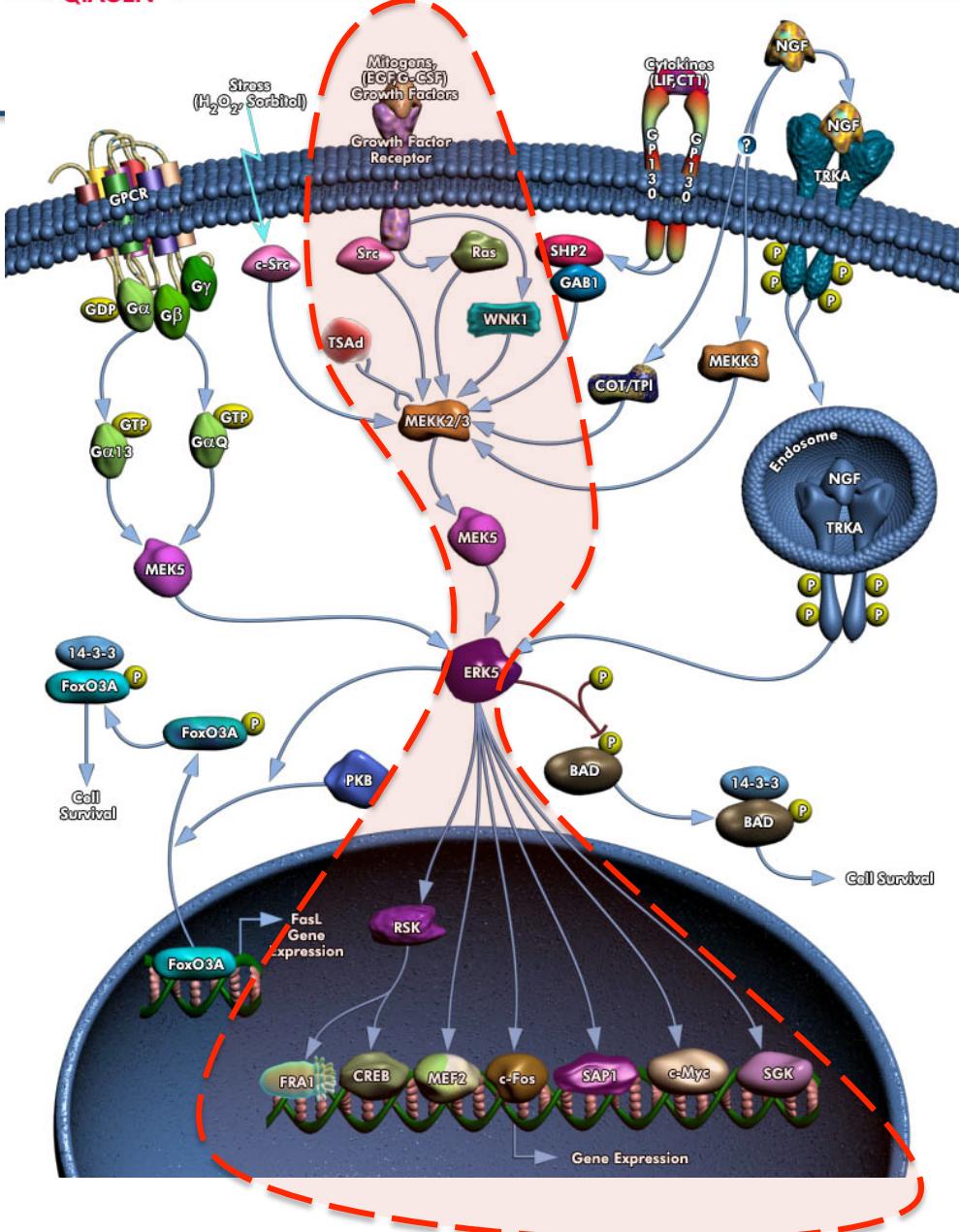


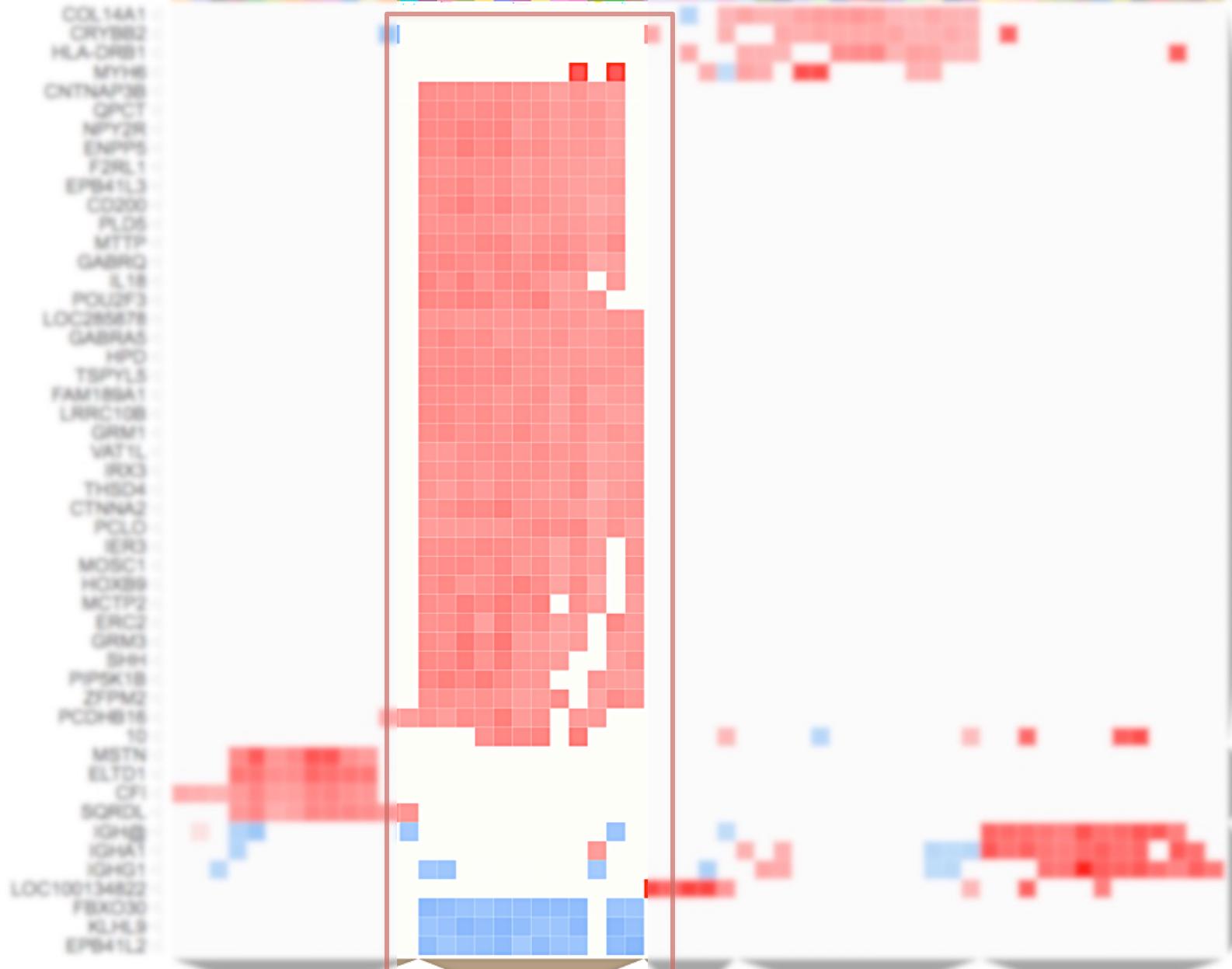
XMD-892

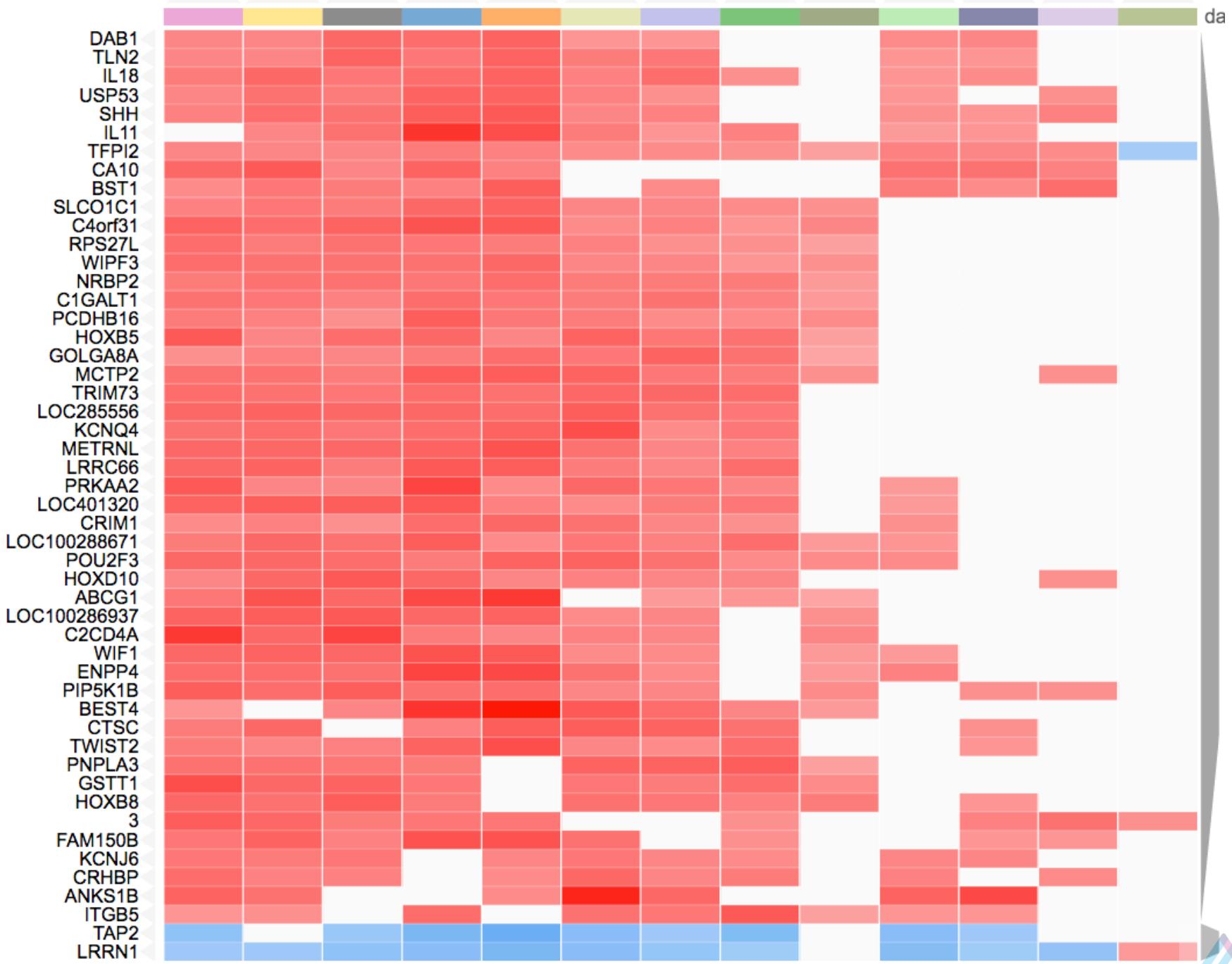


ERK5 Signaling

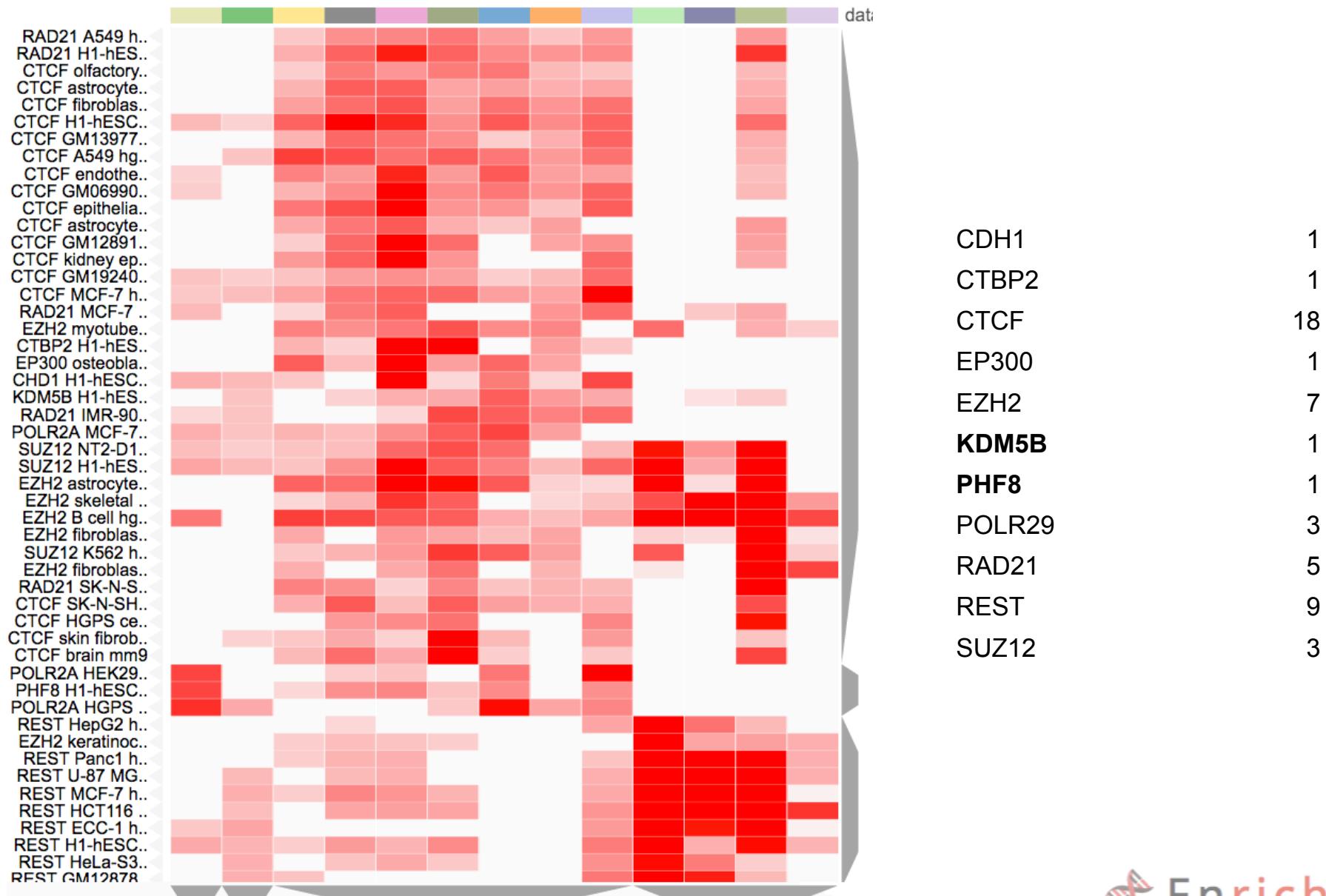
- ERK5/BMK1 inhibitor
- Blocks growth factor-induced activation of cellular BMK1 and reduces BMK1 activity in in vitro kinase assays.
- Inhibits proliferation in a variety of cancer cell lines.
 - blocks tumor cell proliferation and tumor-associated angiogenesis.





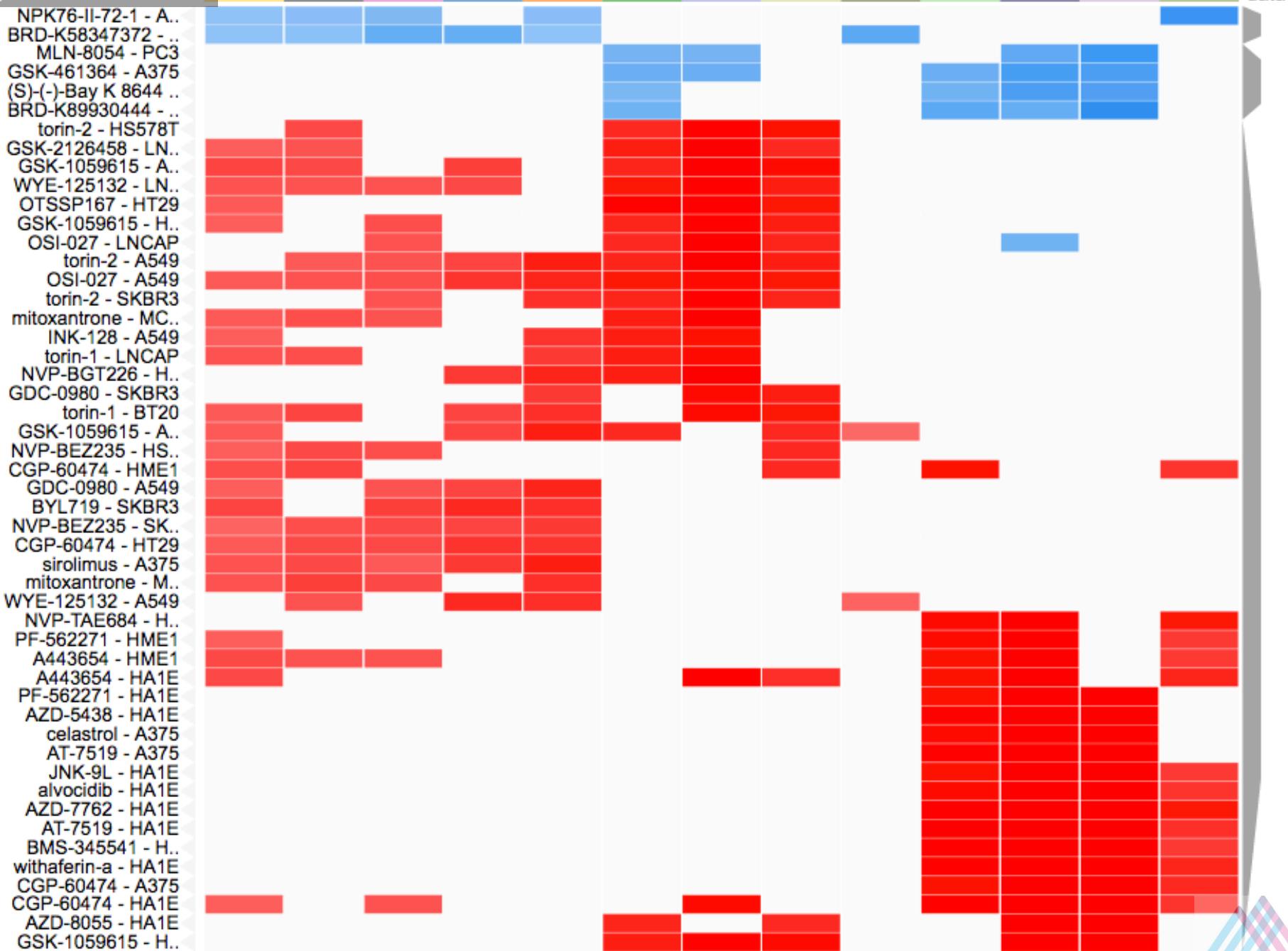


ENCODE TF ChIP-seq 2015



MGI Mammalian Phenotype Level 4

MP ID	MP Term	13 Samples
MP0003635	Abnormal synaptic transmission	12
MP0000001	Mammalian phenotype	12
MP0002873	Normal phenotype	11
MP0002169	No abnormal phenotype detected	
MP0002063	Abnormal learning/memory/conditioning	
MP0002752	Abnormal somatic nervous system morphology	9
MP0001501	Abnormal sleep pattern	8
MP0002114	Abnormal axial skeleton morphology	7
MP0001970	Abnormal pain threshold	7
MP0002067	Abnormal sensory capabilities/reflexes/nociception	7
MP0002066	Abnormal motor capabilities/coordination/movement	7
MP0004085	Abnormal heartbeat	6
MP0002733	Abnormal thermal nociception	6
MP0002272	Abnormal nervous system electrophysiology	6
MP0002882	Abnormal neuron morphology	6
MP0002152	Abnormal brain morphology	6
MP0002081	Perinatal lethality	5
MP0000613	Abnormal salivary gland morphology	5
MP0002557	Abnormal social/conspecific interaction	5
MP0003755	Abnormal palate morphology	4



BRD-K58347372 (LSM-4668)

Molecular Formula: C₅₅H₅₄N₆O₁₃

Molecular Mass: 1007.04966

ALogP: 5.563

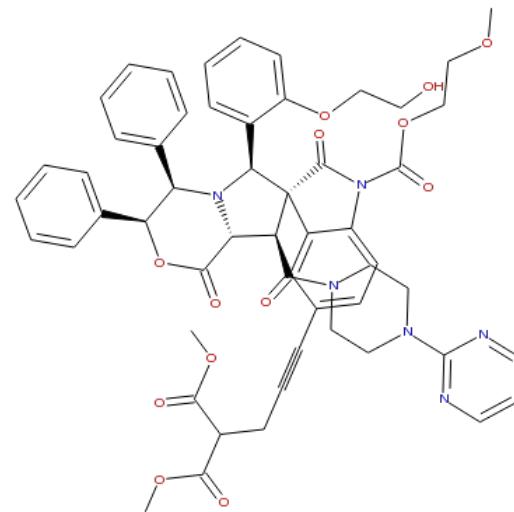
PSA: 216.77

HBA: 17

HBD: 1

N Aromatic Rings: 5

Rotatable Bonds: 19



1 to 10 of 143

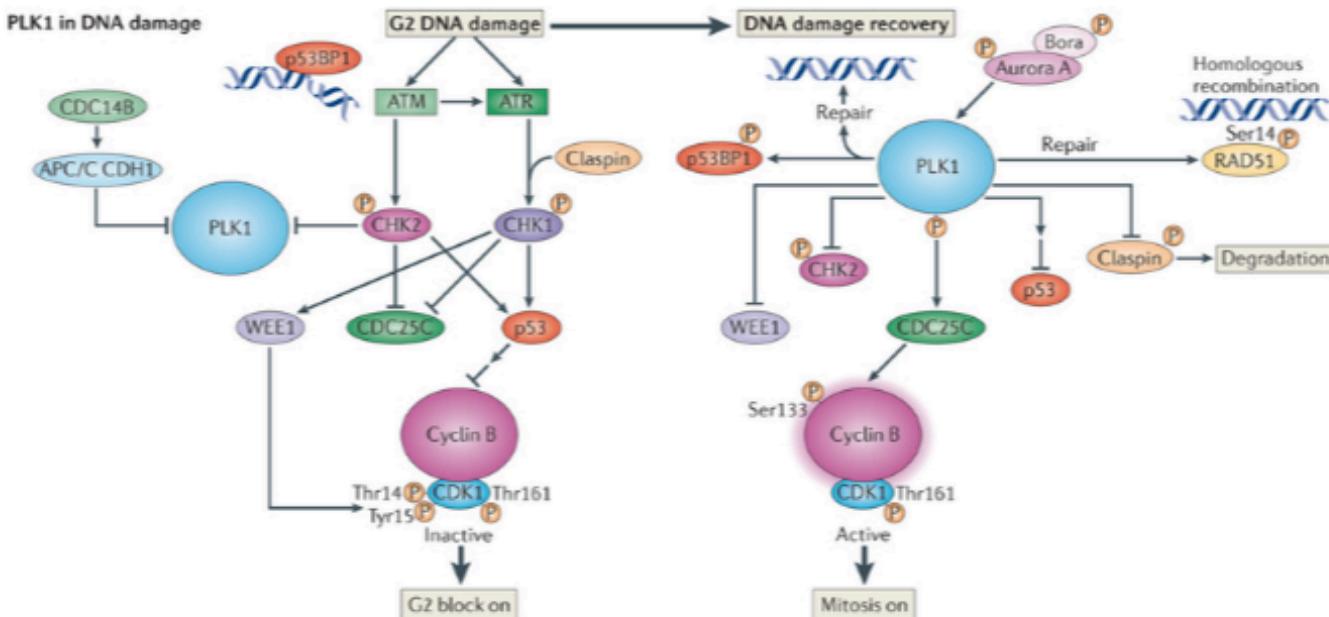
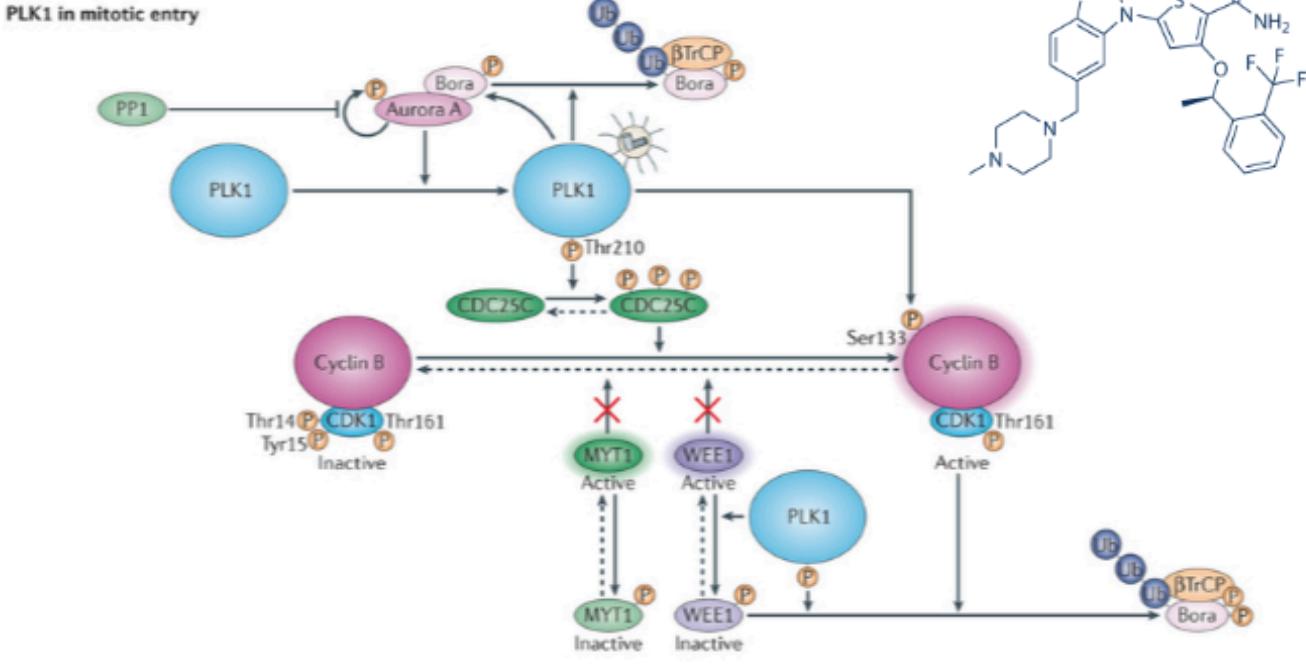
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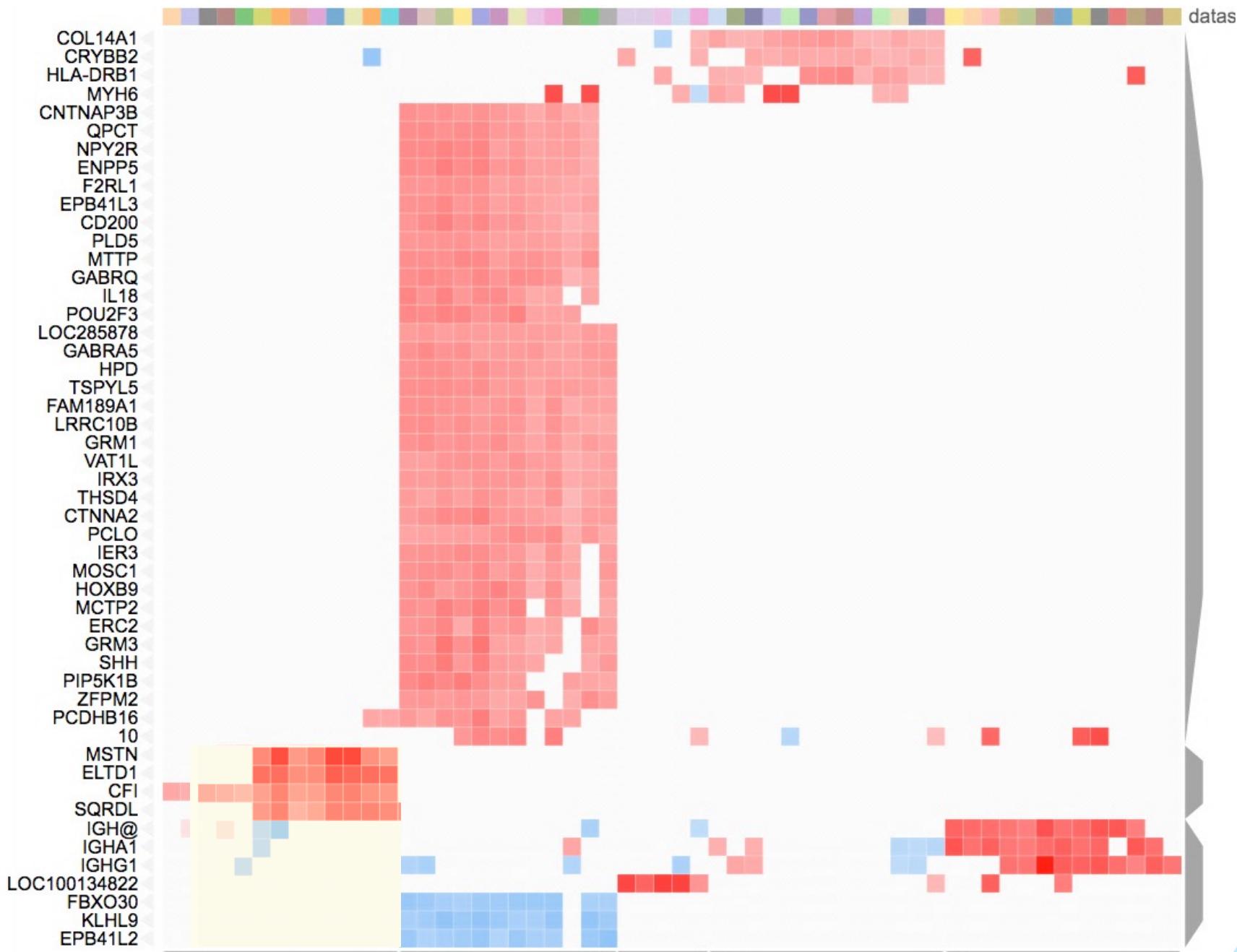
Activity ▾

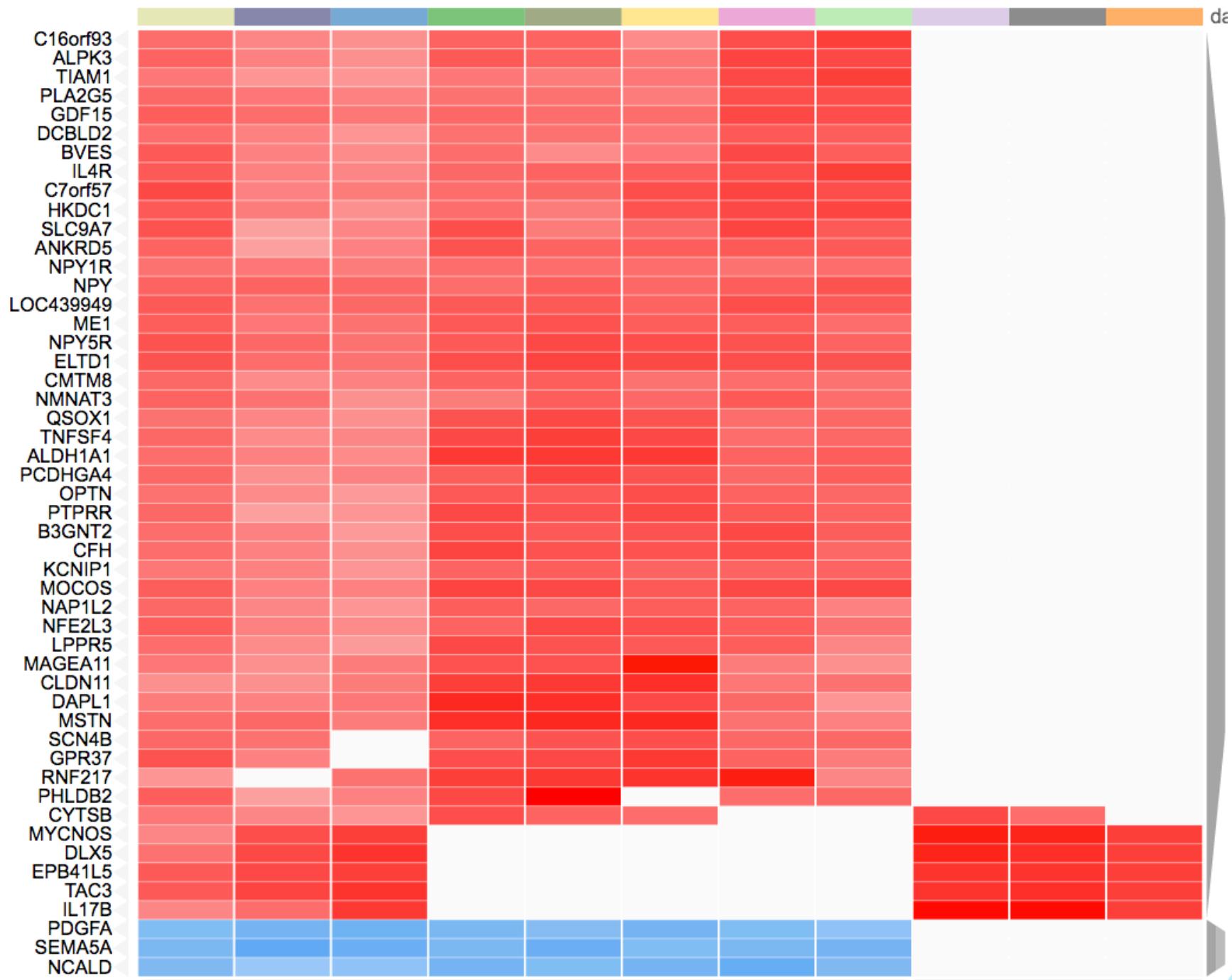
Activity	Substance SID	BioAssay AID	BioAssay Name
Active	85845731	651661	Luminescence Cell-Based Primary HTS to identify inhibitors of the oncprotein EWS/Fli transcriptional activity Measured in Cell-Based System Using Plate Reader - 7014-01_Inhibitor_SinglePoint_HTS_Activity
Active	85845731	686920	Luminescence Cell-Based Primary HTS to identify inhibitors of the oncprotein EWS/Fli transcriptional activity Measured in Cell-Based System Using Plate Reader - 7014-01_Inhibitor_Dose_CherryPick_Activity
Active	85845731	720587	Luminescence cell-based Retest at Dose assay to determine EWS/Fli1 dependent A673 mammalian cell cytotoxicity Measured in Cell-Based System Using Plate Reader - 7014-03_Inhibitor_Dose_CherryPick_Activity

GSK-461364

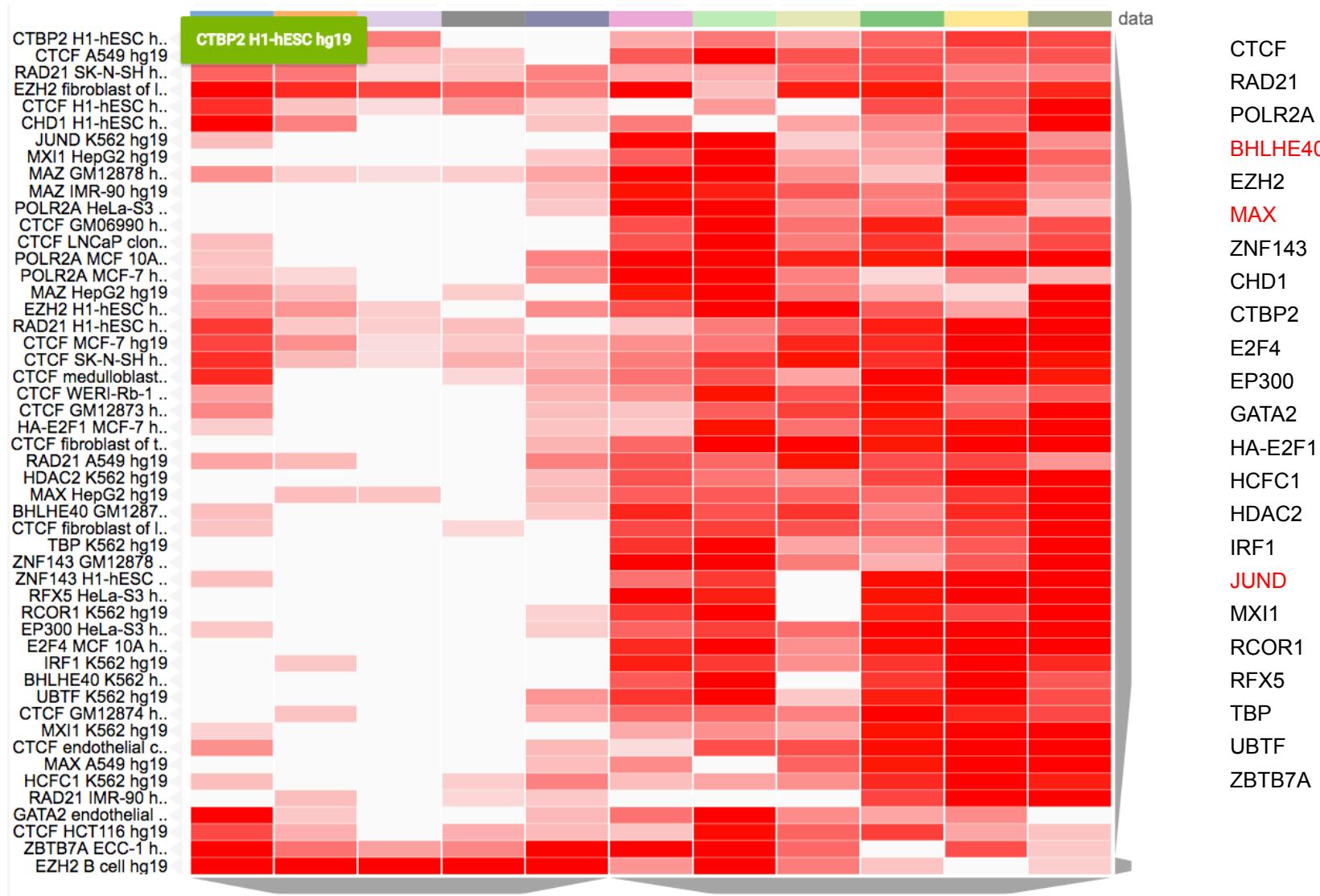
- PLK1 inhibitor
- Potent inhibitor of cell proliferation
- Silencing of WT p53 increases this antiproliferative activity.



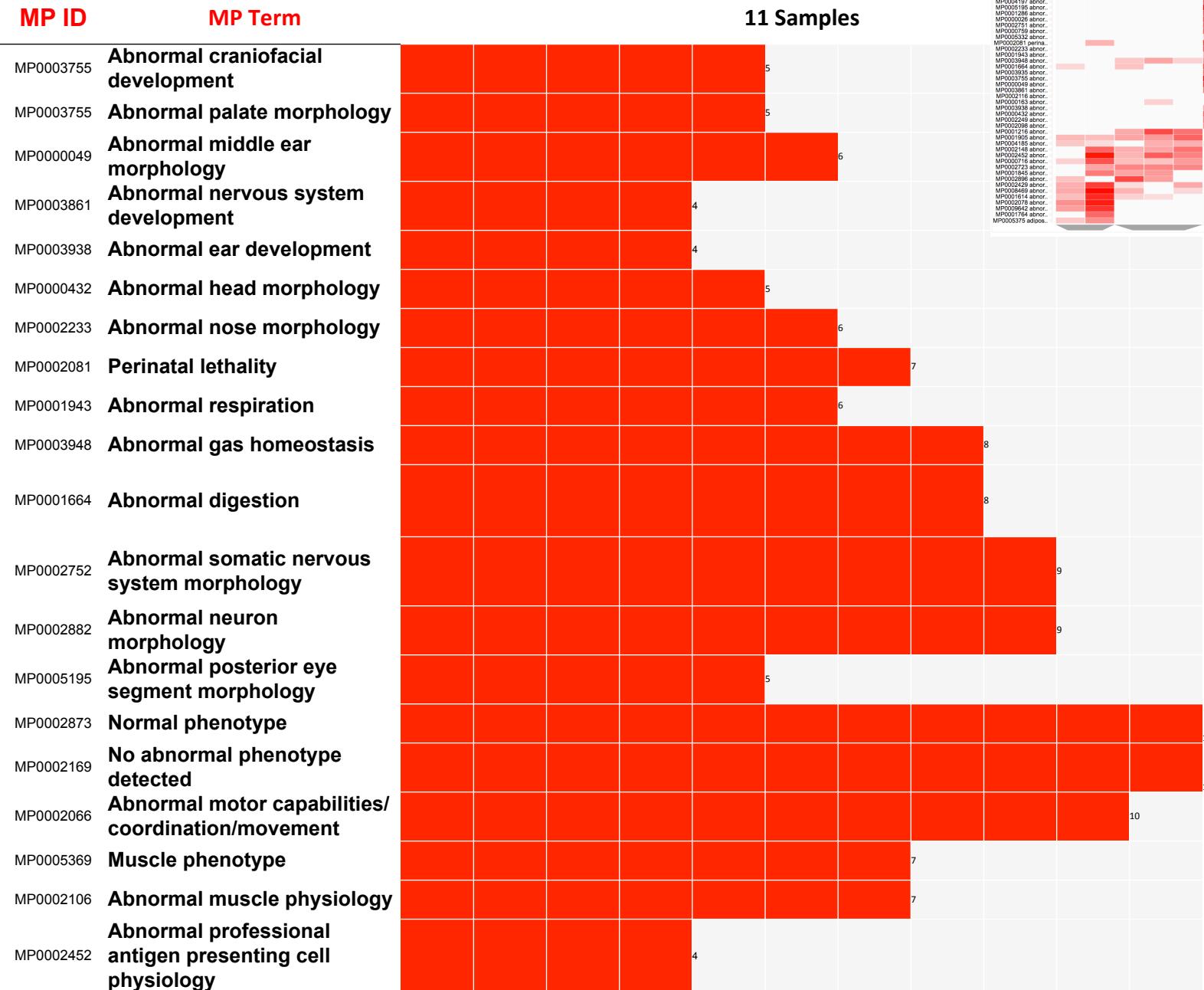




ENCODE TF ChIP-seq 2015

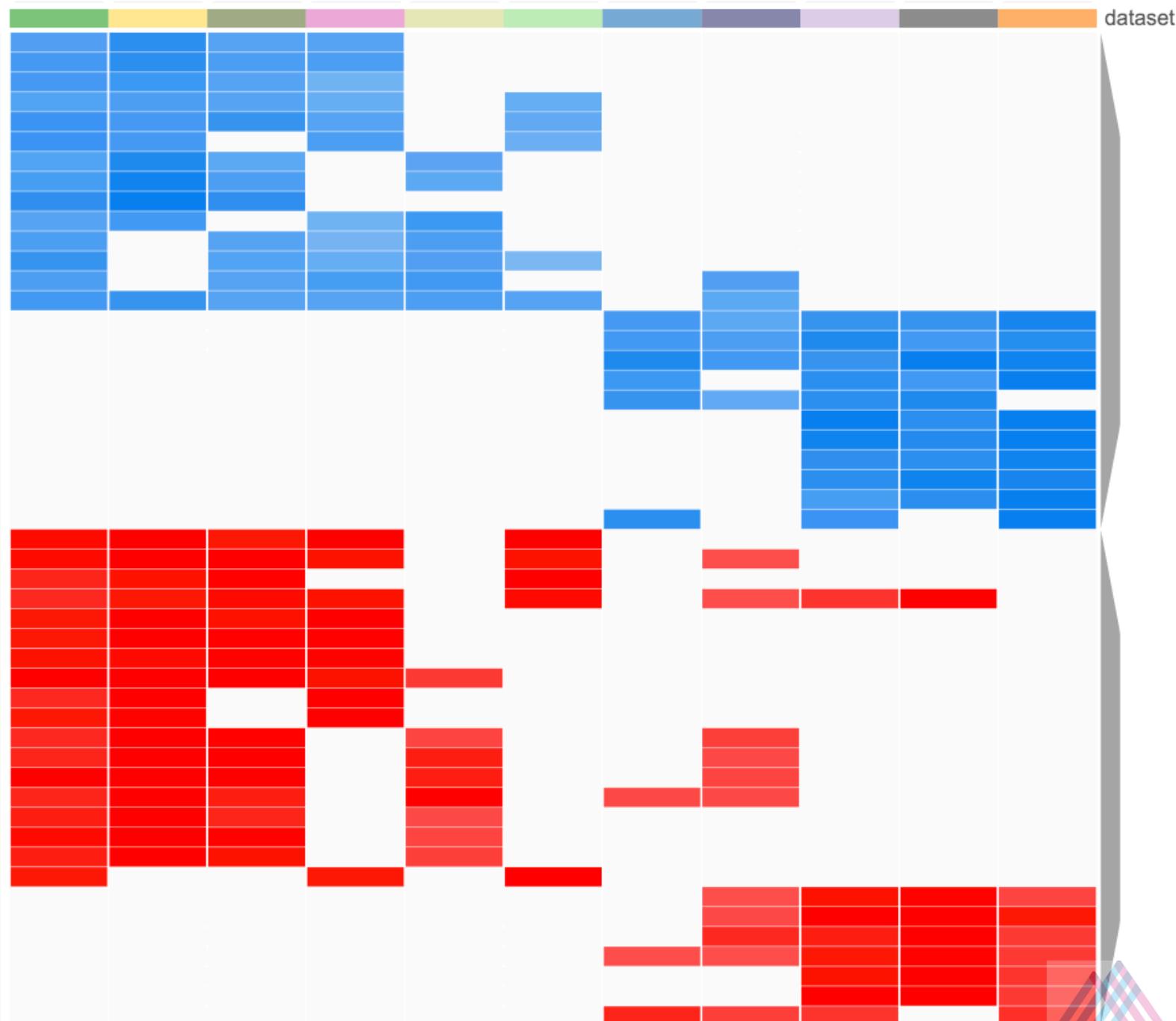


MGI Mammalian Phenotype Level 4



L1000CDS²

XMD-1150 - HS578T
 B3063 - HA1E
 CC-401 - PC3
 A443654 - HEPG2
 BRD-K00313977 - ..
 NU-7026 - HA1E
 NCGC00238427-0..
 NCGC00242337-0..
 withaferin-a - PC3
 TG-101348 - PC3
 TG101348 - SKME..
 NVP-TAE684 - SK..
 BRD-K18953385 - ..
 wortmannin - ASC
 wortmannin - A549
 SKATOLE - VCAP
 nilotinib - MCF10A
 CX-5461 - A549
 GSK-690693 - HT29
 BAS 00535043 - H..
 ""Ingenol 3, 20-dib..
 B675700.cdx - HC..
 MLN2238 - HCC515
 BRD-K61717269 - ..
 tremulacin - MCF7
 BMS-387032 - LN..
 BRD-K20755323 - ..
 JW-7-24-1 - A375
 CGP-60474 - A549
 WZ-4-145 - LNCAP
 nintedanib - LNCAP
 BRD-K45818044 - ..
 PKCbeta inhibitor - ..
 dinaciclib - HEPG2
 CGP-60474 - HE..
 DCC-2036 - MCF7
 4-(aminomethyl)be..
 NP-000732 - HCC..
 ED CSC 15 - SW..
 IOX2 - HCC515
 BRD-K08448573 - ..
 BRD-U43867373 - ..
 AZD-8330 - MCF..
 mitoxantrone - HS5..
 celastrol - A375
 mitoxantrone - A375
 HG-5-113-01 - A375
 A443654 - A375
 PF-431396 - A375
 ""7-hydroxy-2,3,4,..



Wortmannin

- Inhibitor PI3Ks
- PX-866 is a derivate of wortmannin
- Failed a Phase II study of PX-866 in recurrent glioblastoma.
 - Stabilized disease.
 - Did not account for subtypes.

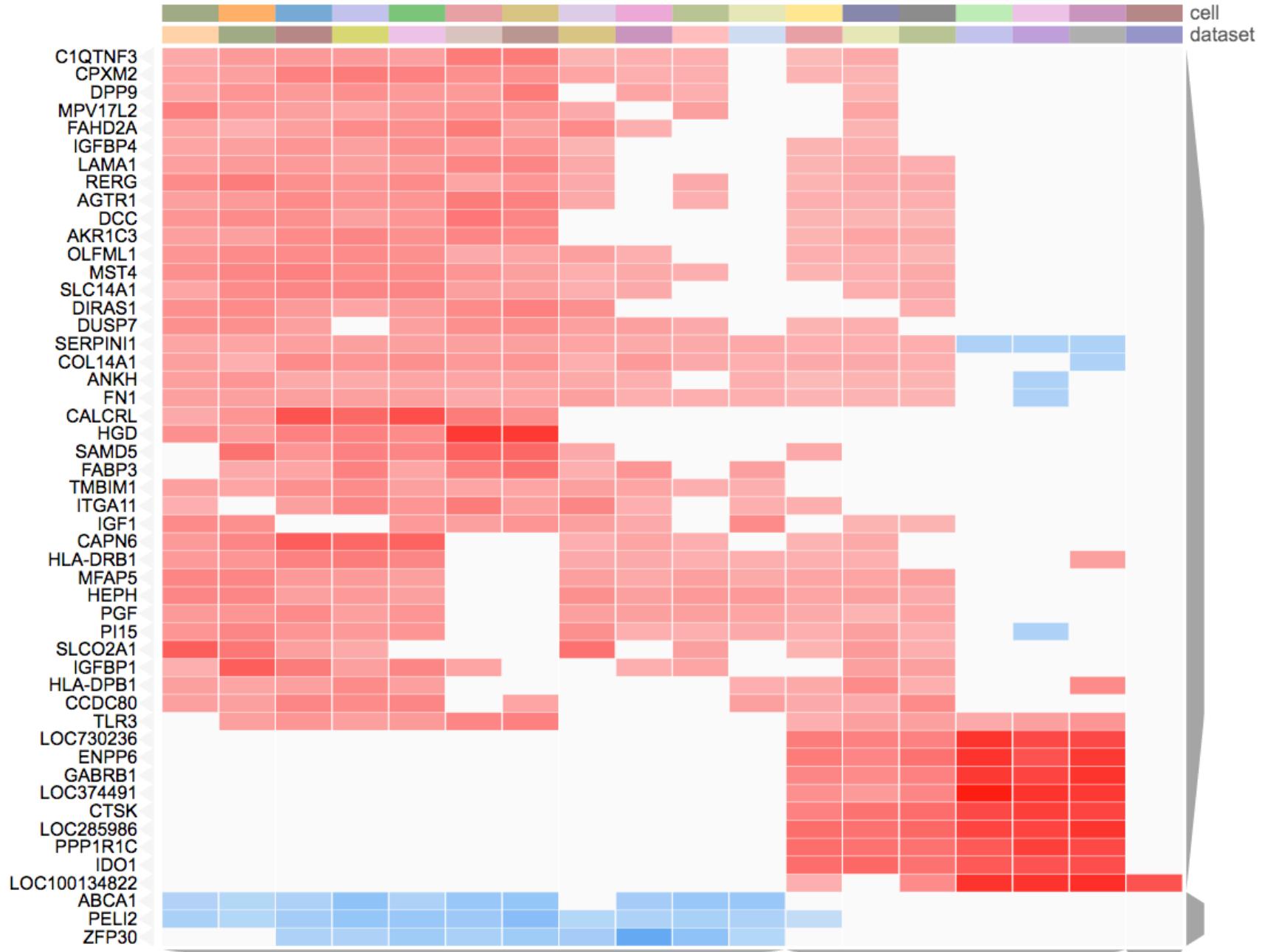


Steroid metabolite of the fungi *Penicillium funiculosum*

Wortmannin is a known and potent PI3K inhibitor; as such, it was shown to have detrimental influence on memory and impair spatial learning abilities.

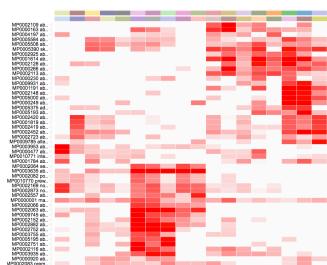






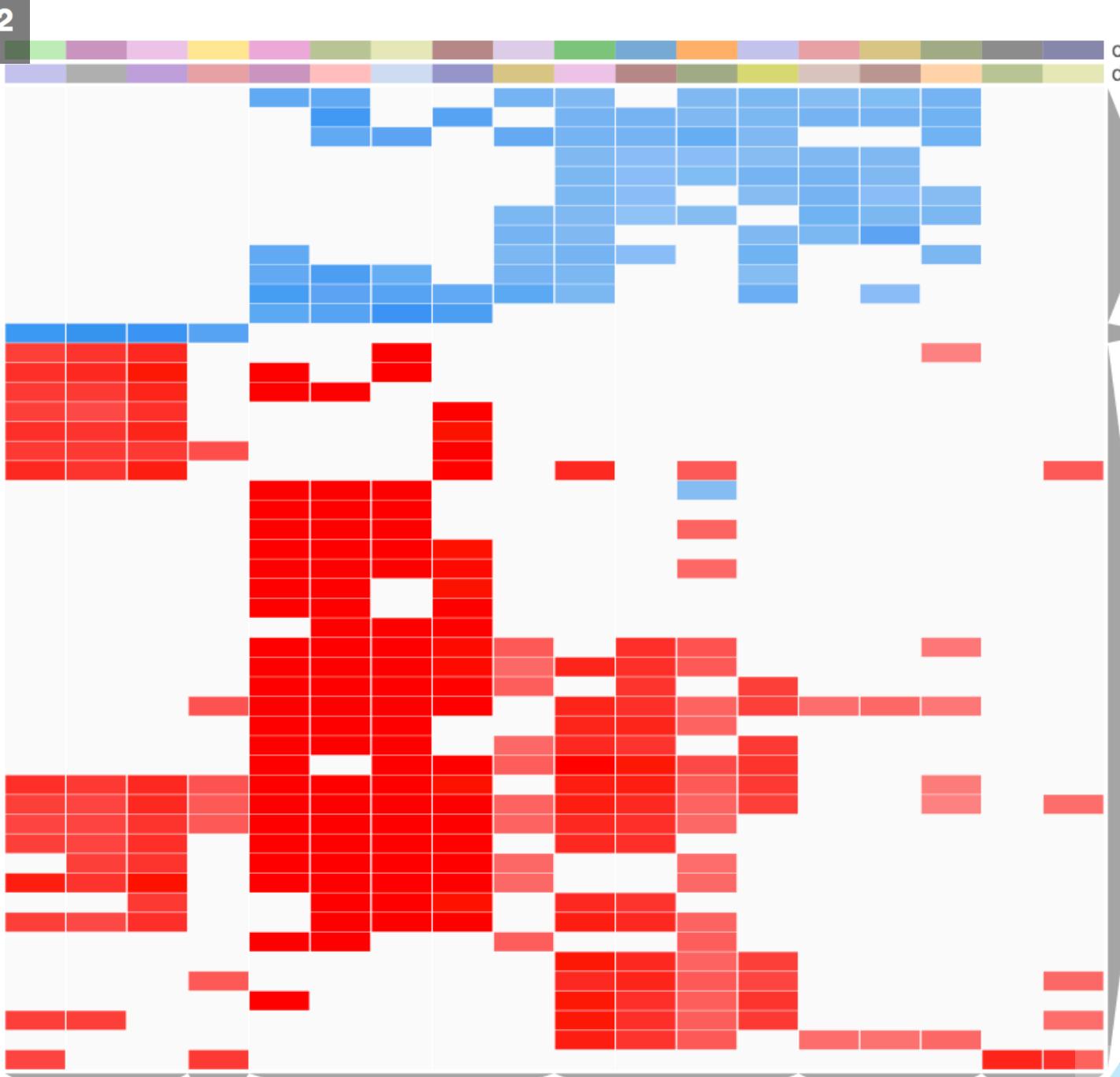
MGI Mammalian Phenotype Level 4

MP ID	MP Term	18 Samples																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18
MP0000001	Mammalian phenotype																	
MP0002873	Normal phenotype														15			
MP0005508	Abnormal skeleton morphology														14			
MP0002169	No Abnormal phenotype detected														14			
MP0005584	Abnormal enzyme/coenzyme activity														13			
MP0002452	Abnormal professional antigen presenting cell physiology														11			
MP0005390	Skeleton phenotype														11			
MP0002116	Abnormal craniofacial bone morphology																	10
MP0003935	Abnormal craniofacial development																	10
MP0000266	Abnormal heart morphology																	9
MP0002128	Abnormal blood circulation																	9
MP0002152	Abnormal brain morphology																	9
MP0002882	Abnormal neuron morphology																	9
MP0002752	Abnormal somatic nervous system morphology																	9
MP0003635	Abnormal synaptic transmission																	9
MP0002113	Abnormal skeleton development																	8
MP0000163	Abnormal cartilage morphology																	8
MP0002063	Abnormal learning/memory/conditioning																	8
MP0001191	Abnormal skin condition														6			



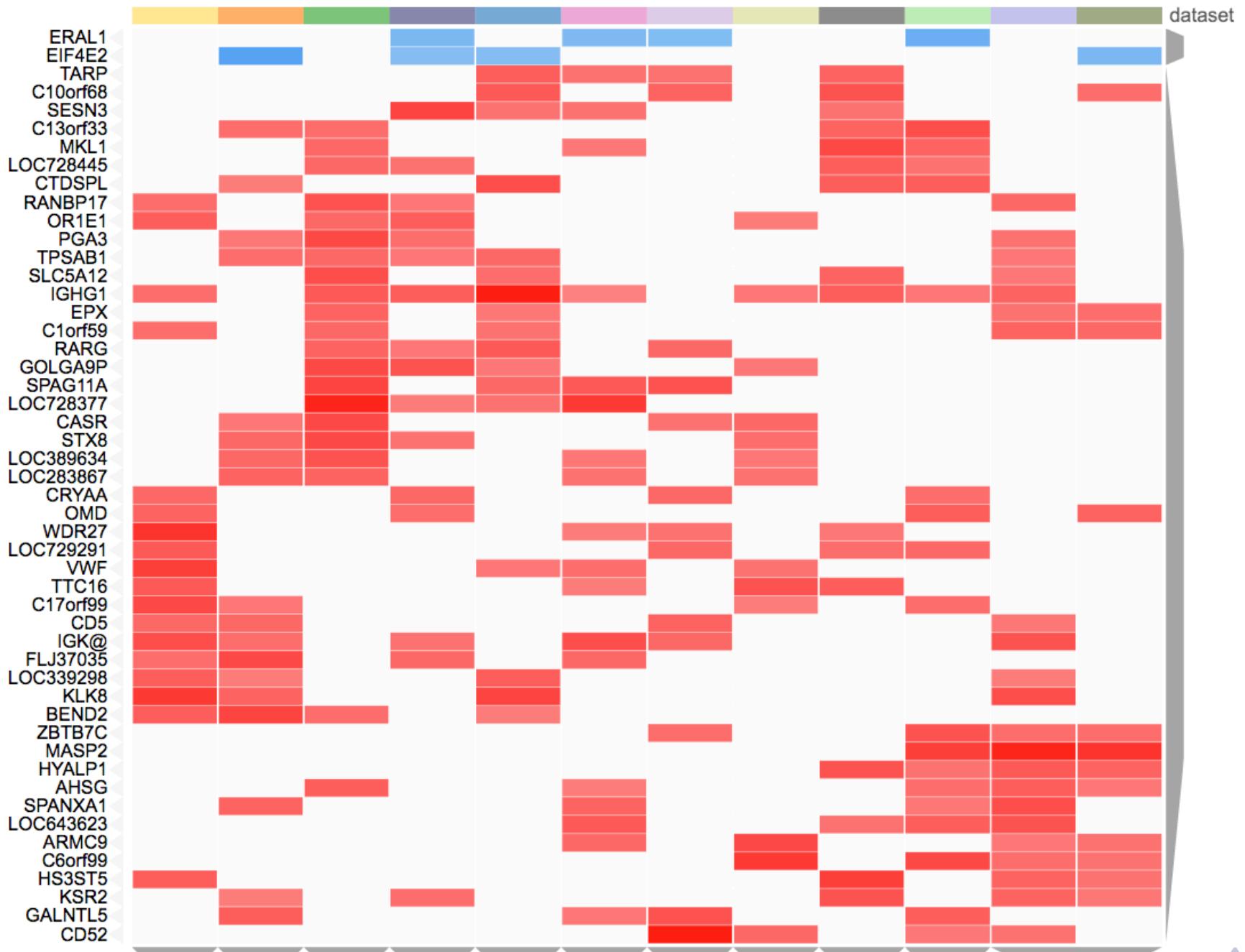
L1000CDS²cel
dat

I-BET151 - HEPG2
XMD-892 - HEPG2
XMD-892 - HA1E
BRD-A36471396 - ..
BI-2536 - SKBR3
BRD-K41996876 - ..
I-BET - HEPG2
CYCLOHEXIMIDE - ..
garcinol - HA1E
SB-525334 - HA1E
QL-XI-92 - HA1E
BRD-K72029282 - ..
CYT387 - BT20
mitoxantrone - MDA..
AZD-7762 - HA1E
BMS-345541 - A375
A443654 - HME1
PF-431396 - A549
WZ-3105 - A549
A443654 - HA1E
AS-601245 - HCC..
BMS-387032 - A375
A443654 - A375
alvocidib - HS578T
celastrol - A375
BMS-387032 - HS5..
mitoxantrone - HME1
AT-7519 - PC3
mitoxantrone - HA1E
AZD-5438 - HA1E
AT-7519 - A375
CGP-60474 - A549
WZ-3105 - PC3
alvocidib - A375
AT-7519 - HCC515
CGP-60474 - A375
CGP-60474 - HA1E
alvocidib - HA1E
BMS-345541 - HA1E
AT-7519 - HA1E
withaferin-a - HA1E
BMS-387032 - HA1E
JNK-9L - HA1E
chelerythrine chlori..
mitoxantrone - MCF..
WZ-3105 - A375
mitoxantrone - A549
BMS-387032 - HCC..
alvocidib - MCF10A
BRD-K98426715 - ..



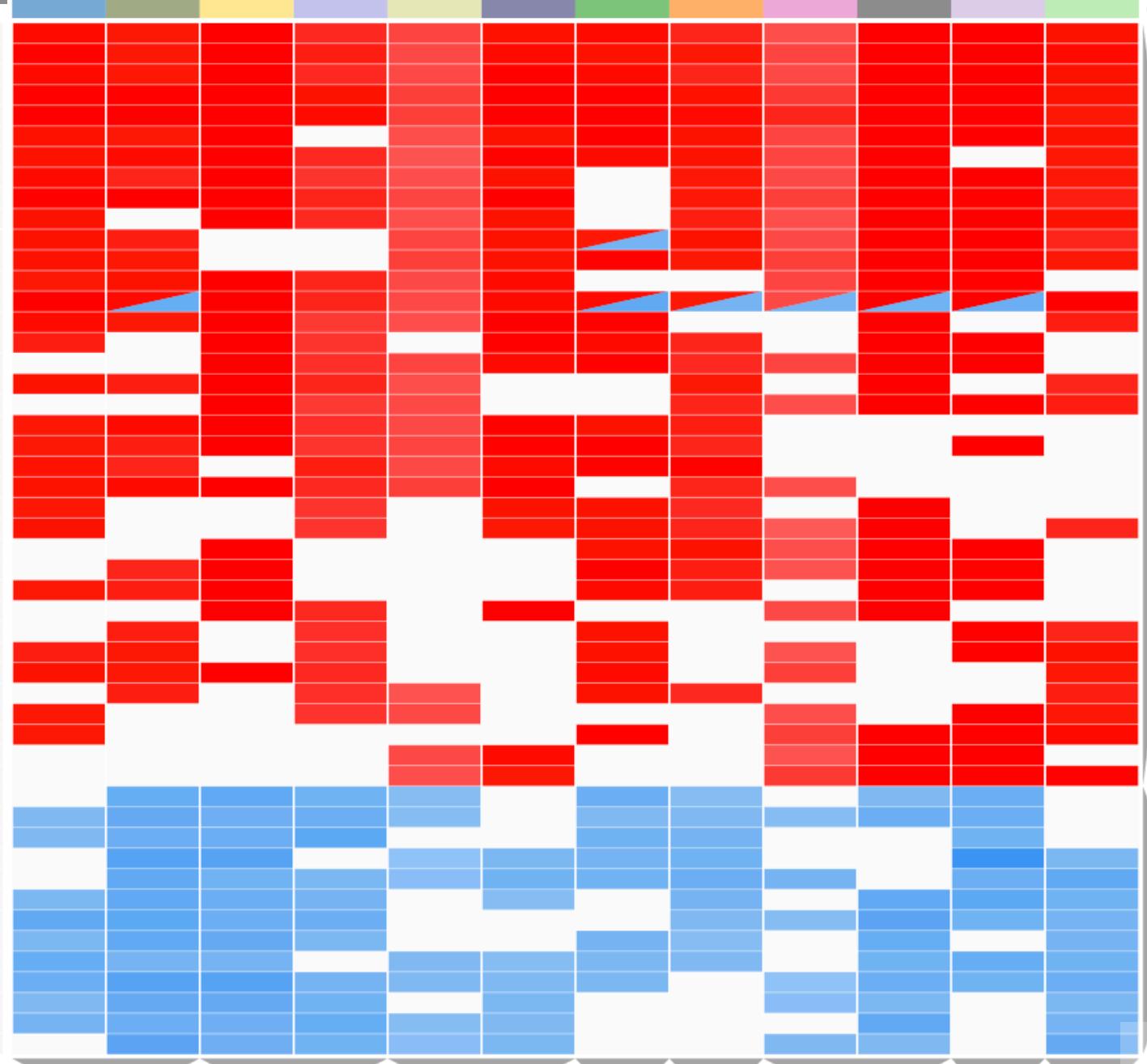
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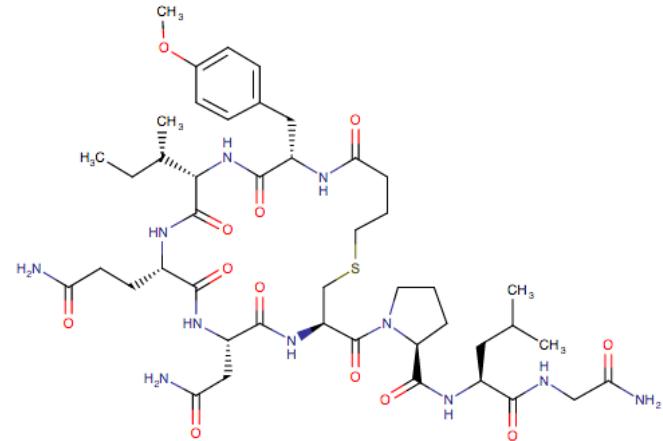
CGP-60474 - HA1E
alvocidib - HA1E
AZD-5438 - HA1E
BMS-345541 - H..
withaferin-a - HA1E
CGP-60474 - A549
mitoxantrone - H..
AT-7519 - HA1E
A443654 - HA1E
BMS-387032 - H..
CGP-60474 - PC3
AT-7519 - PC3
AZD-7762 - HA1E
JNK-9L - HA1E
A443654 - HME1
A443654 - A375
WZ-3105 - PC3
mitoxantrone - H..
PF-562271 - HA1E
celastrol - HME1
celastrol - A375
BMS-345541 - HS5..
NVP-TAE684 - H..
alvocidib - HME1
AT-7519 - HME1
WZ-3105 - A549
AT-7519 - A375
CGP-60474 - A375
PF-431396 - A375
BMS-387032 - HS5..
AT-7519 - HS578T
BMS-387032 - HC..
CGP-60474 - HS5..
CYT387 - PC3
AT-7519 - HCC515
AZD-5438 - PC3
Y-39983 - PC3
ST4049616 - A549
Prestw-550 - A549
Flubendazol - MCF7
Acetylcysteine - PC3
ODQ - VCAP
BRD-K87426499 - ..
5377525 - A549
BRD-K53592093 - ..
AT-CSC-18 BRD-K..
H-5832 - VCAP
2378-0086 - VCAP
7643453 - VCAP
ST4066738 - VCAP



H-5832 | Carbetocin

- Long-acting oxytocin analogue.
- In the peripheral nervous system acts as:
 - Antihemorrhagic
 - Uterotonic
- In obstetrics:

Used to control postpartum hemorrhage and bleeding after giving birth.
- There is evidence of Carbetocin produced **antidepressant-like changes in behavior** via activation of oxytocin receptors in the CNS.



References

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[An integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR and NF1](#)

Roel G.W. Verhaak, Katherine A. Hoadley, [...], and The Cancer Genome Atlas Research Network

[Assessing the antidepressant-like effects of carbetocin, an oxytocin agonist, using a modification of the forced swimming test](#)

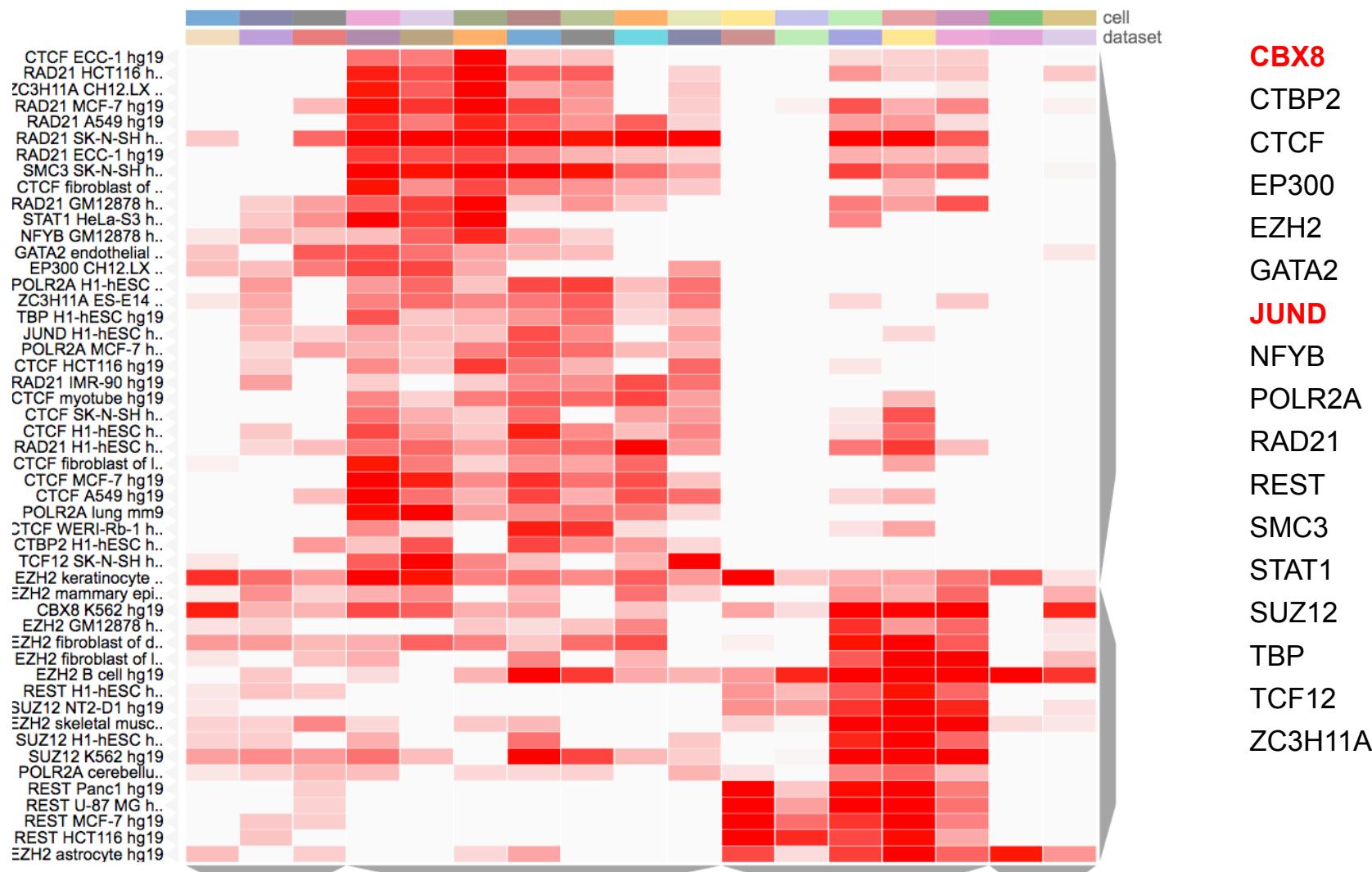
Chaviaras S¹, Mak P, Ralph D, Krishnan L, Broadbear JH.

<http://www.cyberounds.com/cmecontent/art467.html?pf=yes>

<http://www.abta.org/brain-tumor-information/types-of-tumors/glioma.html?referrer=https://www.google.com/>



ENCODE TF ChIP-seq 2015



The END



**ENCODE
& CHEA
TF**

MCG Mammalian Phenotype Level 4

	top 10	MP00	
CBX2			Abnormal fertility/ fecundity 7 samples
CBX8			Abnormal response to 5
CHD1			Abnormal innate 9
CREBBP			immunity
CTCF			Abnormal immune 7
EP300			cell
ESR1			Abnormal adaptive 8
EZH2			immunity
FOSL1			Abnormal blood 5
FOSL2			homeostasis
FOXA2			No abnormal 8
GATA2			phenotype
MAFK			Mammalian 11
SPI			Phenotype
STAT5A			Abnormal eye 2
SUZ12			electrophysiology
ZEB1			



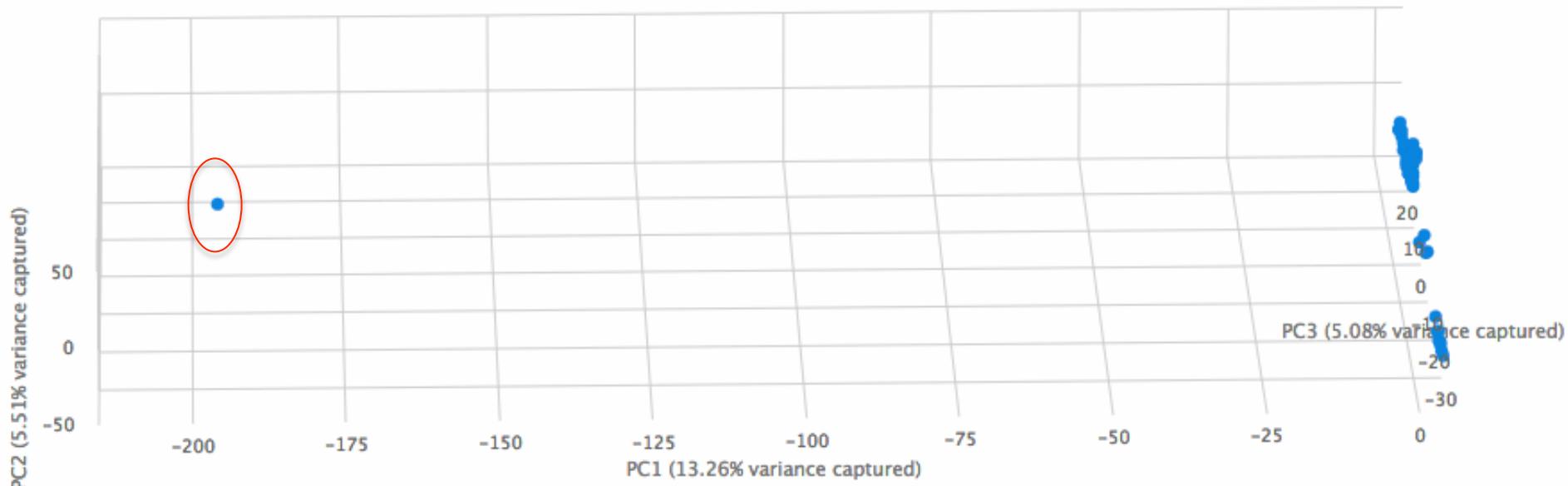


PCA PLOTS

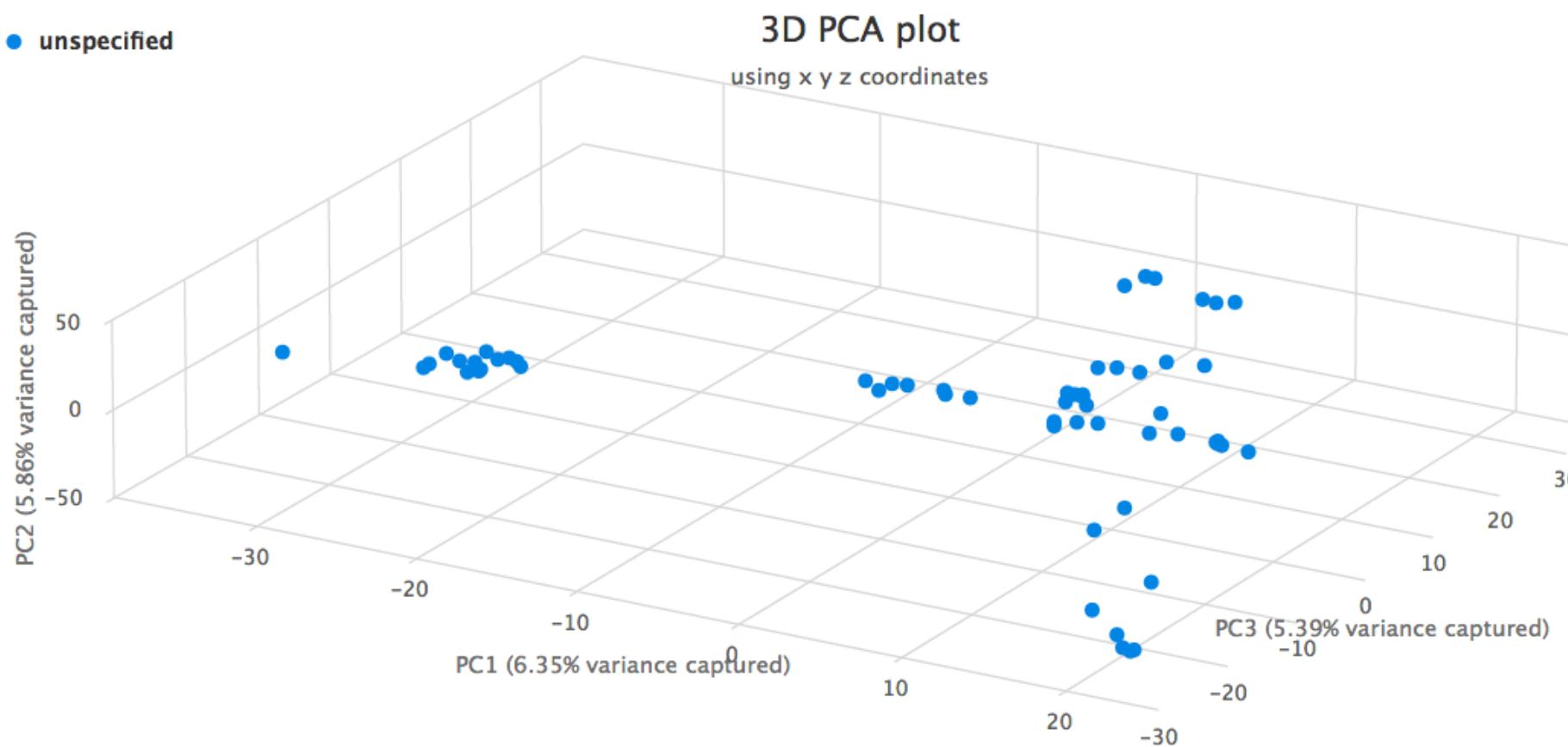


fied

3D PCA plot
using x y z coordinates



● unspecified

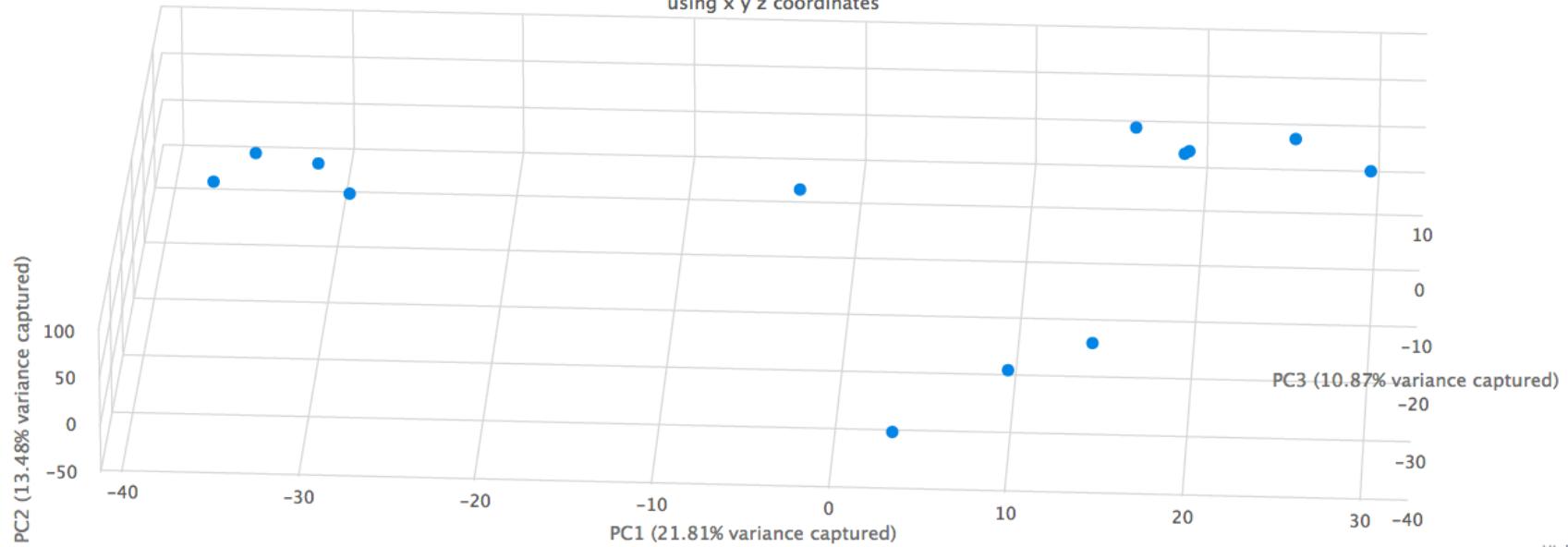


≡

● unspecified

3D PCA plot

using x y z coordinates



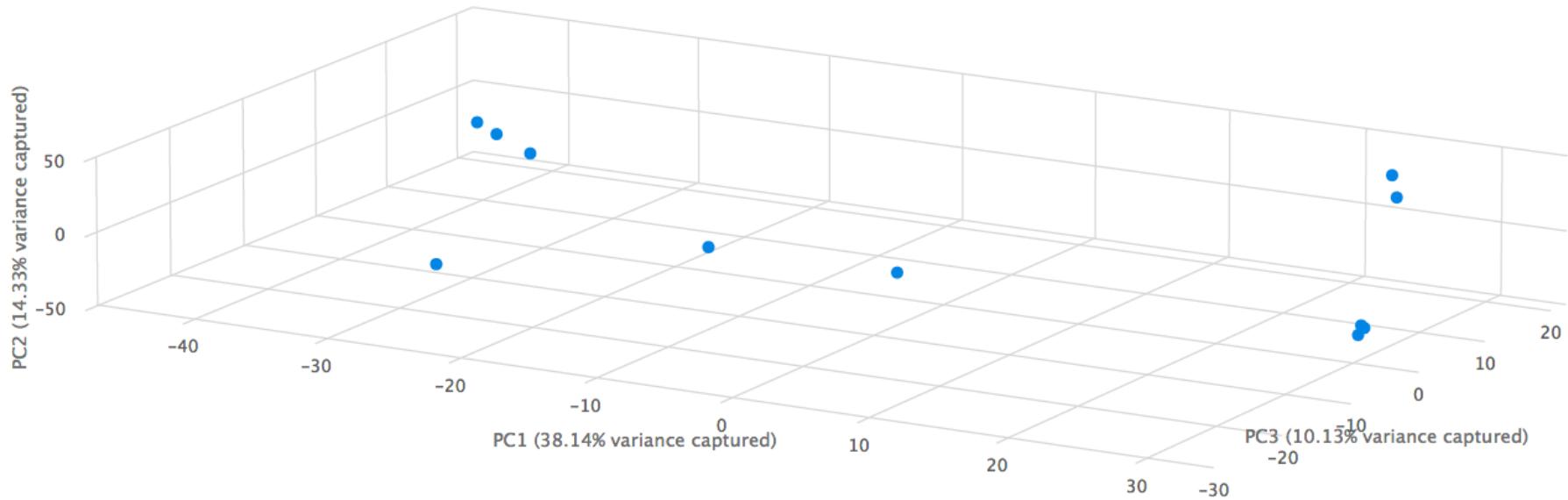
PCA

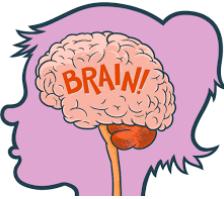
Interactive 3D principal component analysis of gene signatures. You can rotate the visualization and mouse over the data points.

● unspecified

3D PCA plot

using x y z coordinates

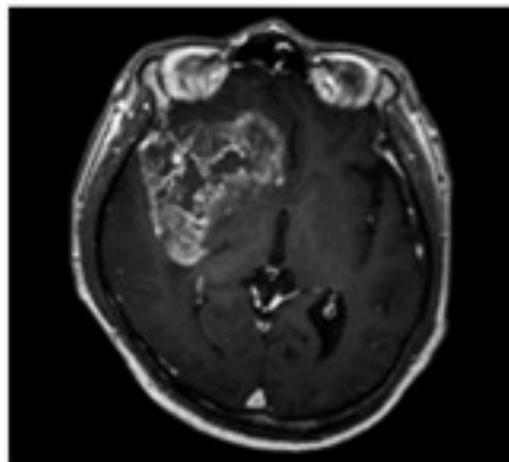




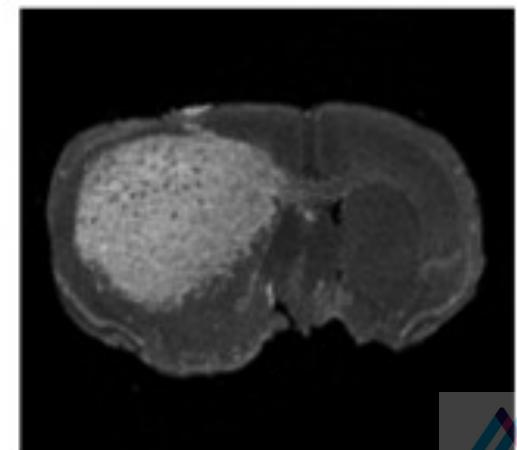
Methods



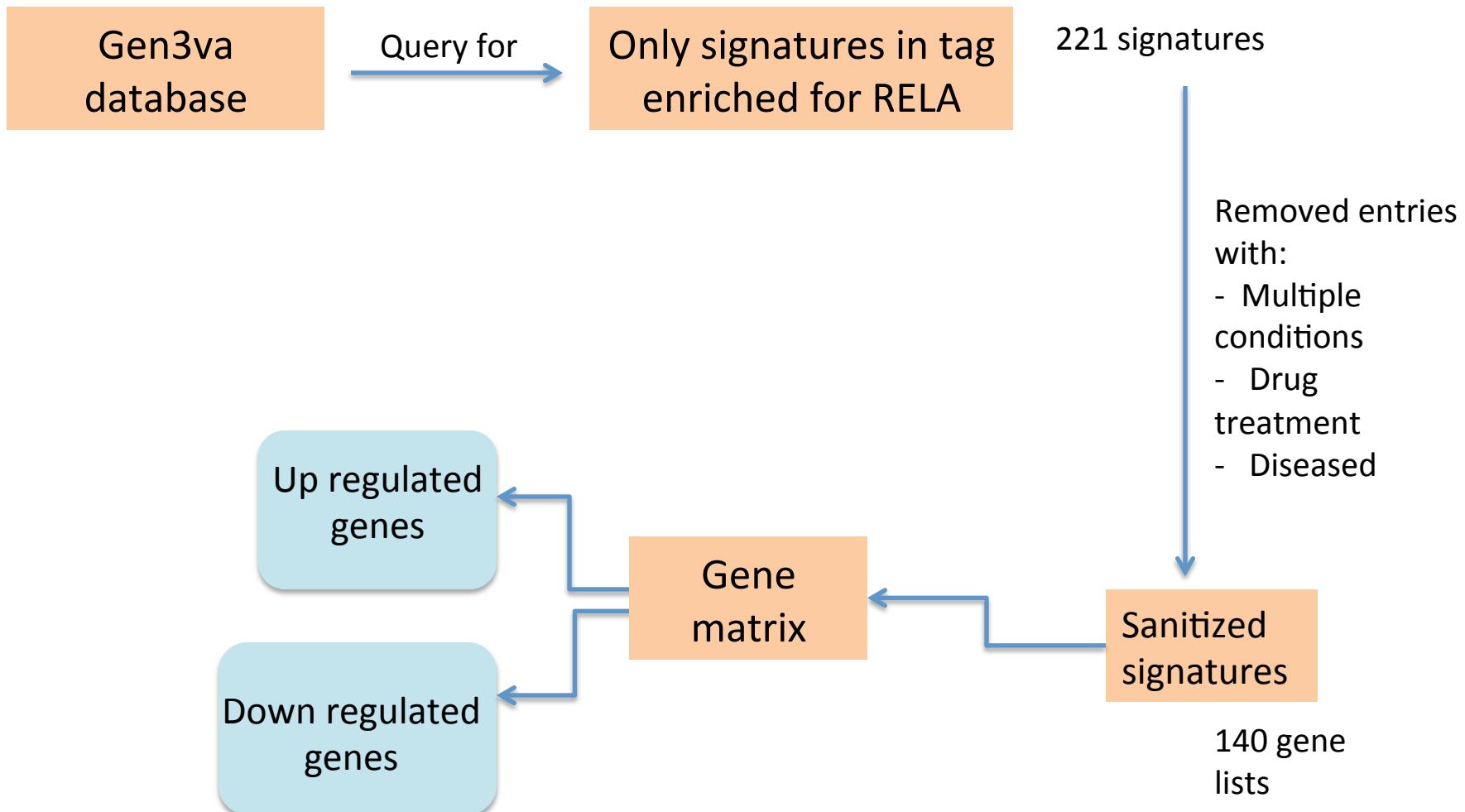
Patient's glioblastoma



"AVATAR" model

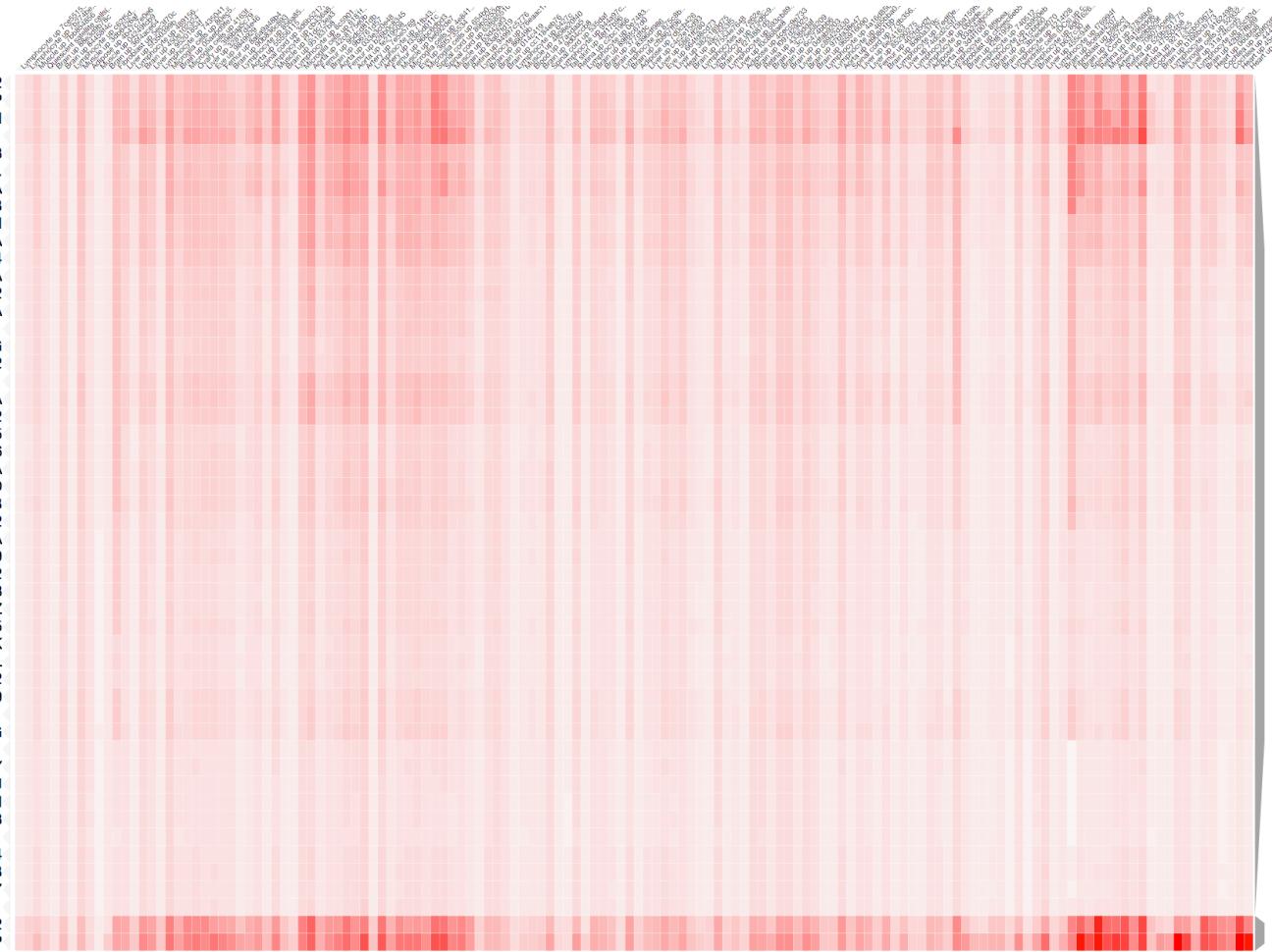


Gene Expression data from Coursera Aging tag

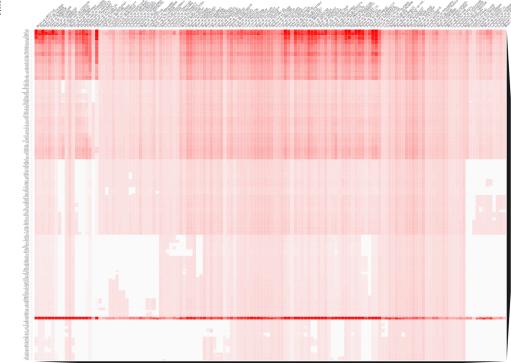


Up regulated

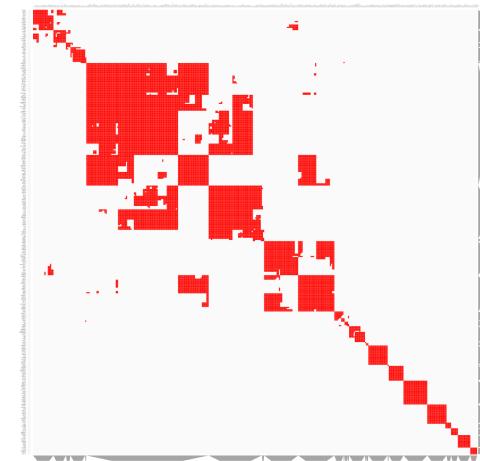
MMD2
GFAP
PCSK1N
BRSK1
ATP1A3
CHCH..
GRINA
CKB
NCDN
ITPKA
CD74
HPCA
NTSR2
RAB3A
APLP1
PRKCG
RPL12
SPOON1
MYL12A
NPC2
ICAM5
CPNE6
ALDOA
ATP5D
PYGB
ATP5J2
C1QA
RPS29
MLF2
RPS28
DGKZ
UBL5
CCK
FTL
BAI2
ERP29
ENO1
BSG
CTXN1
CALY
CLU
PKM
ITIH3
AP2M1
STMN4
SEC61B
TOMM7
CAPNS1
CNIH2
PSAP



Top 50



~ 400 gene matrix

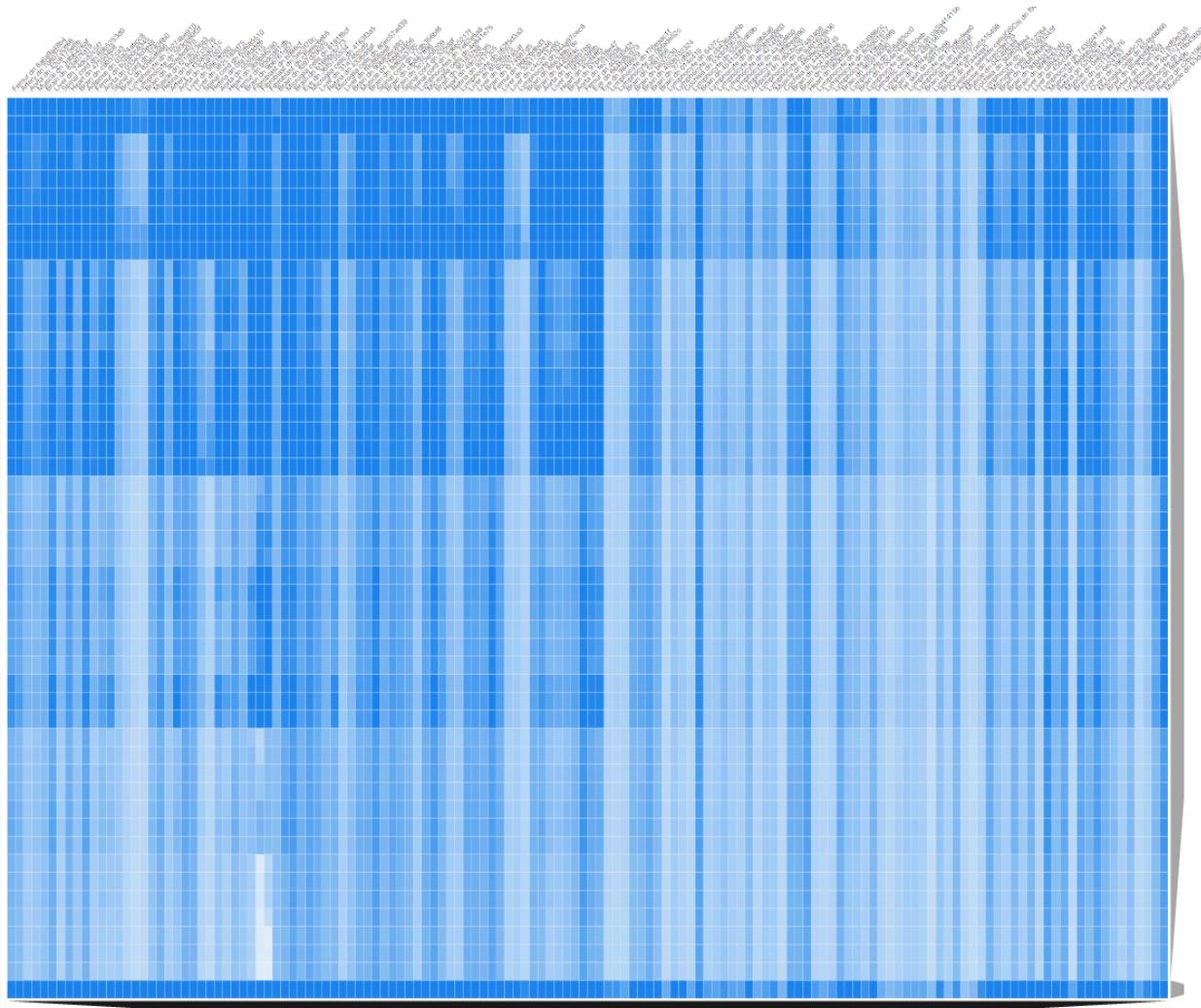


Row similarity matrix

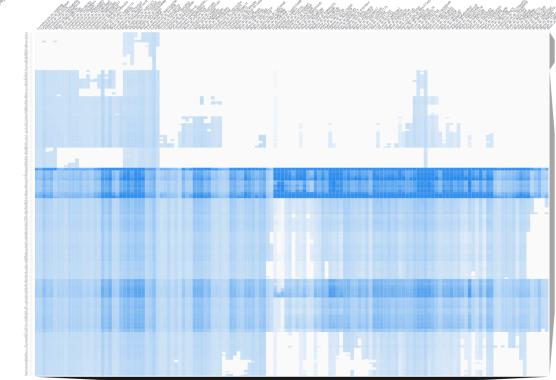


Down regulated genes

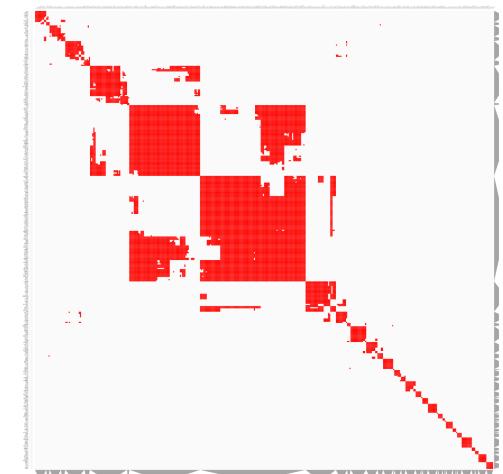
CHGB
GPM6A
RBM3
LRRK58
GPRASP1
RPS25
SERINC1
PLP1
RPS6
EIF3E
SNAP25
RPS23
FGF13
YWHAZ
SNAP91
RAP1GAP2
MDH1
MAP2K1
ZFAND6
DYNLT3
UBA3
STMN1
RPS3
TMCC2
LAMP5
GLRX3
FOXP1
ATP6V1D
NAP1L5
PGM2L1
AP1AR
ACSL4
SAT1
SNX3
ZNF330
YWHAH
RPS8
TCP1
TCP11L2
VSNL1
TBCA
SERINC3
PPP2CB
RPS4Y1
NRSN1
GOLGA7
NCKAP1
CCT4
NEDD8
NPXT1



Top 50

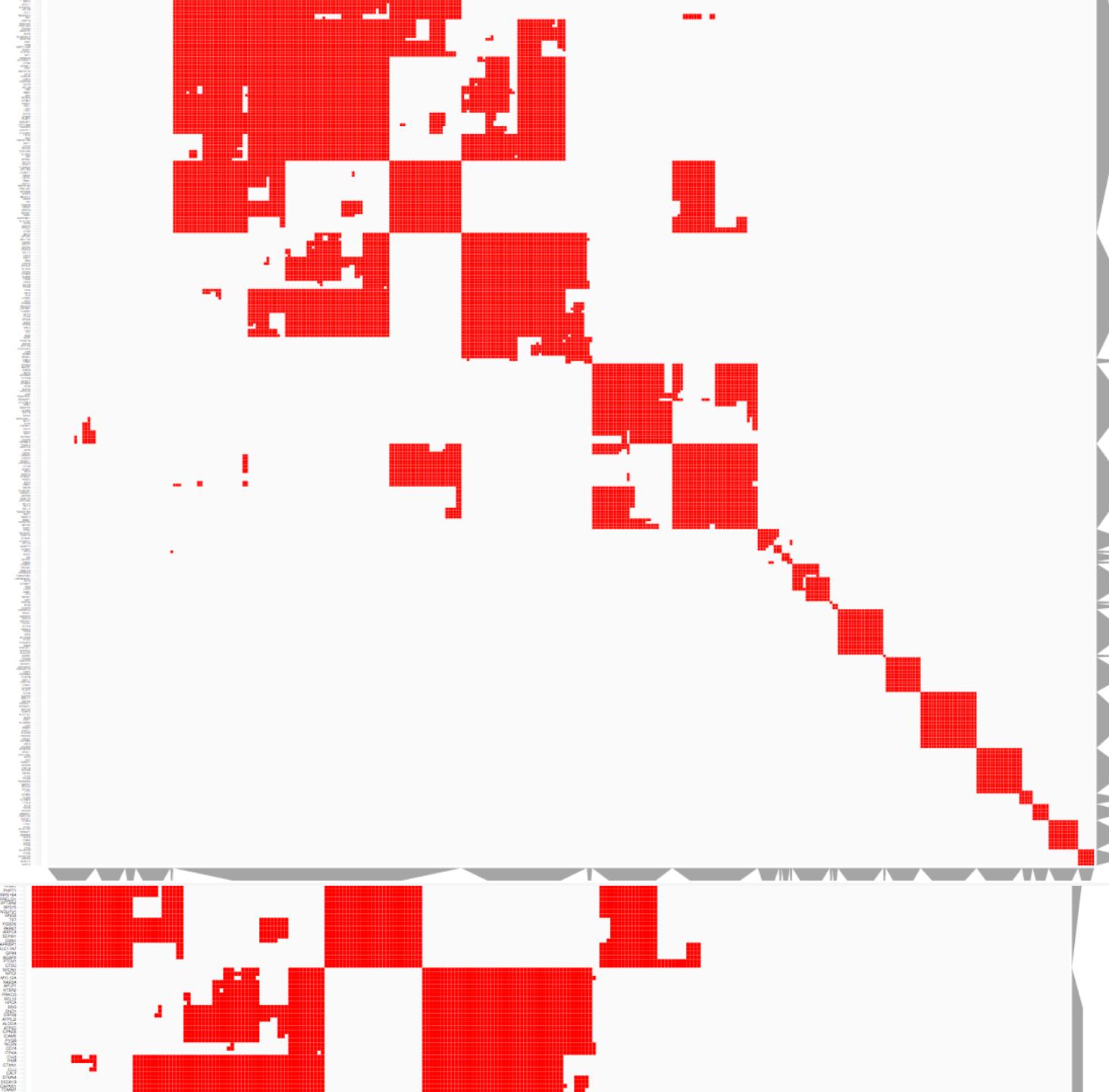


~ 400 gene matrix



Row similarity matrix





GOPI
MSP016A
SPT01
N01
S01
P01
S01 Part
S01
MSP016A
L01
AM01
S01
MSP11A
S01
P01
S01
B01
A01
C01
D01
E01
F01
G01
H01
I01
J01
K01
L01
M01
N01
O01
P01
Q01
R01
S01
T01
U01
V01
W01
X01
Y01
Z01