Figure S1

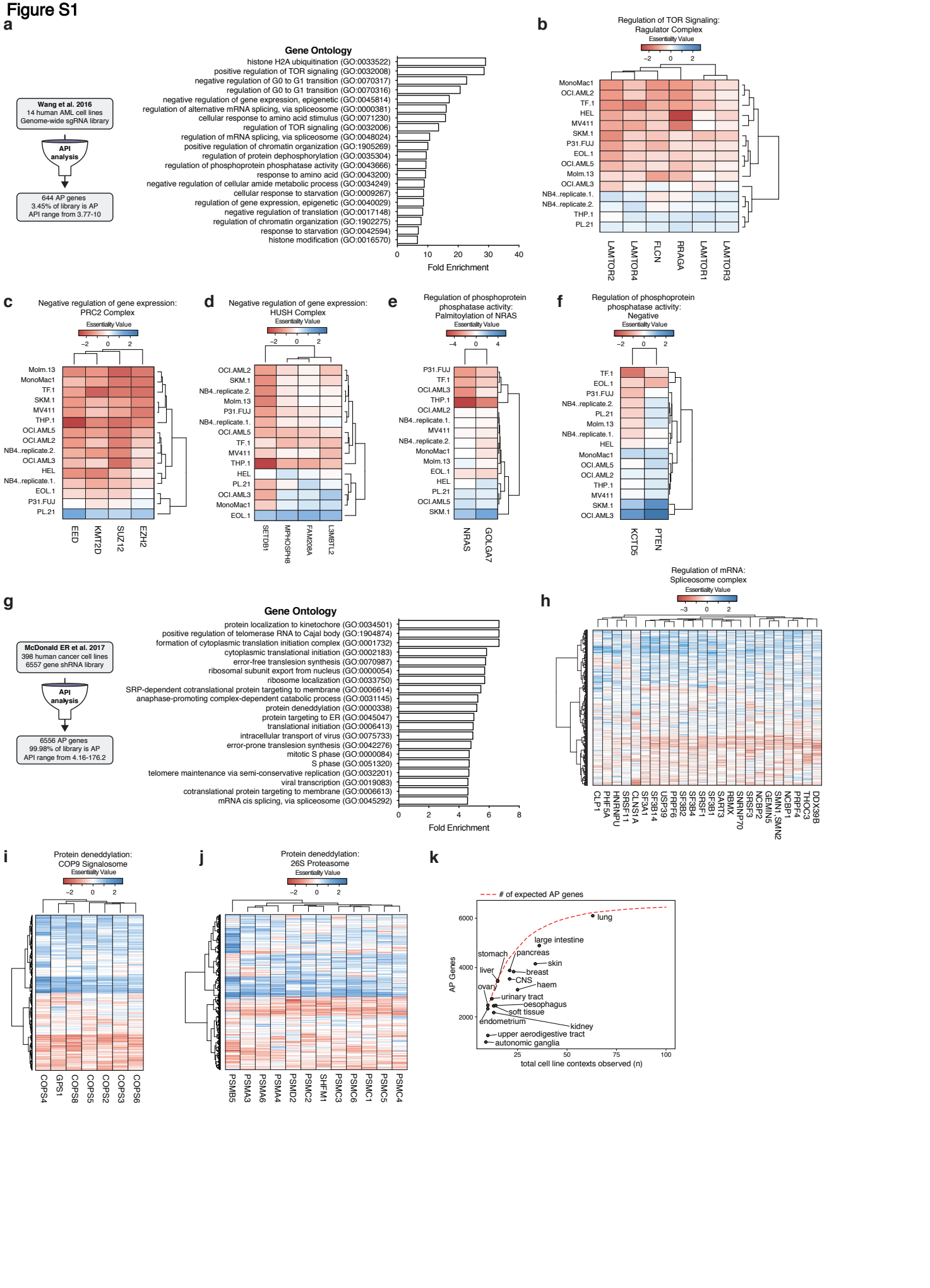

a
Wang et al. 2016
14 human AML cell lines
Genome-wide sgRNA library
API analysis
644 AP genes
3.45% of library is AP
API range from 3.77-10
Gene Ontology
histone H2A ubiquitination (GO:0033522)
positive regulation of TOR signaling (GO:0032008)
negative regulation of G0 to G1 transition (GO:0070317)
regulation of G0 to G1 transition (GO:0070316)
negative regulation of gene expression, epigenetic (GO:0045814)
regulation of alternative mRNA splicing, via spliceosome (GO:0000381)
cellular response to amino acid stimulus (GO:0071230)
regulation of TOR signaling (GO:0032006)
regulation of mRNA splicing, via spliceosome (GO:0048024)
positive regulation of chromatin organization (GO:1905269)
regulation of protein dephosphorylation (GO:0035304)
regulation of phosphoprotein phosphatase activity (GO:0043666)
response to amino acid (GO:0043200)
negative regulation of cellular amide metabolic process (GO:0034249)
cellular response to starvation (GO:0009267)
regulation of gene expression, epigenetic (GO:0040029)
negative regulation of translation (GO:0017148)
regulation of chromatin organization (GO:1902275)
response to starvation (GO:0042594)
histone modification (GO:0016570)
0 10 20 30 40
Fold Enrichment
b
Regulation of TOR Signaling: Ragulator Complex
Essentiality Value
−2 0 2
MonoMac1
OCI.AML2
TF.1
HEL
MV411
SKM.1
P31.FUJ
EOL.1
OCI.AML5
Molm.13
OCI.AML3
NB4..replicate.1.
NB4..replicate.2.
THP.1
PL.21
LAMTOR2 LAMTOR4 FLCN RRAGA LAMTOR1 LAMTOR3
c
Negative regulation of gene expression: PRC2 Complex
Essentiality Value
−2 0 2
Molm.13
MonoMac1
TF.1
SKM.1
MV411
THP.1
OCI.AML5
OCI.AML2
NB4..replicate.2.
OCI.AML3
HEL
NB4..replicate.1.
EOL.1
P31.FUJ
PL.21
EED KMT2D SUZ12 EZH2
d
Negative regulation of gene expression: HUSH Complex
Essentiality Value
−2 0 2
OCI.AML2
SKM.1
NB4..replicate.2.
Molm.13
P31.FUJ
NB4..replicate.1.
OCI.AML5
TF.1
MV411
THP.1
HEL
PL.21
OCI.AML3
MonoMac1
EOL.1
SETDB1 MPHOSPH8 FAM208A L3MBTL2
e
Regulation of phosphoprotein phosphatase activity: Palmitoylation of NRAS
Essentiality Value
−4 0 4
P31.FUJ
TF.1
OCI.AML3
THP.1
OCI.AML2
NB4..replicate.1.
MV411
NB4..replicate.2.
MonoMac1
Molm.13
EOL.1
HEL
PL.21
OCI.AML5
SKM.1
NRAS GOLGA7
f
Regulation of phosphoprotein phosphatase activity: Negative
Essentiality Value
−2 0 2
TF.1
EOL.1
P31.FUJ
NB4..replicate.2.
PL.21
Molm.13
NB4..replicate.1.
HEL
MonoMac1
OCI.AML5
OCI.AML2
THP.1
MV411
SKM.1
OCI.AML3
KCTD5 PTEN
g
McDonald ER et al. 2017
398 human cancer cell lines
6557 gene shRNA library
API analysis
6556 AP genes
99.98% of library is AP
API range from 4.16-176.2
Gene Ontology
protein localization to kinetochore (GO:0034501)
positive regulation of telomerase RNA to Cajal body (GO:1904874)
formation of cytoplasmic translation initiation complex (GO:0001732)
cytoplasmic translational initiation (GO:0002183)
error-free translesion synthesis (GO:0070987)
ribosomal subunit export from nucleus (GO:0000054)
ribosome localization (GO:0033750)
SRP-dependent cotranslational protein targeting to membrane (GO:0006614)
anaphase-promoting complex-dependent catabolic process (GO:0031145)
protein deneddylation (GO:0000338)
protein targeting to ER (GO:0045047)
translational initiation (GO:0006413)
intracellular transport of virus (GO:0075733)
error-prone translesion synthesis (GO:0042276)
mitotic S phase (GO:0000084)
S phase (GO:0051320)
telomere maintenance via semi-conservative replication (GO:0032201)
viral transcription (GO:0019083)
cotranslational protein targeting to membrane (GO:0006613)
mRNA cis splicing, via spliceosome (GO:0045292)
0 2 4 6 8
Fold Enrichment
h
Regulation of mRNA: Spliceosome complex
Essentiality Value
−3 0 2
CLP1 PHF5A HNRNPU SRSF11 CLNS1A SF3A1 SF3B14 USP39 PRPF6 SF3B2 SF3B4 SRSF1 SF3B1 SART3 RBMX SNRNP70 SRSF3 NCBP2 GEMIN5 SMN1.SMN2 NCBP1 PRPF4 THOC3 DDX39B
i
Protein deneddylation: COP9 Signalosome
Essentiality Value
−2 0 2
COPS4 GPS1 COPS8 COPS5 COPS2 COPS3 COPS6
j
Protein deneddylation: 26S Proteasome
Essentiality Value
−2 0 2
PSMB5 PSMA3 PSMA6 PSMA4 PSMD2 PSMC2 SHFM1 PSMC3 PSMC6 PSMC1 PSMC5 PSMC4
k
# of expected AP genes
AP Genes
6000
4000
2000
lung
large intestine
stomach
pancreas
skin
liver
breast
CNS
ovary
haem
urinary tract
oesophagus
soft tissue
endometrium
kidney
upper aerodigestive tract
autonomic ganglia
25 50 75 100
total cell line contexts observed (n)

Figure S2

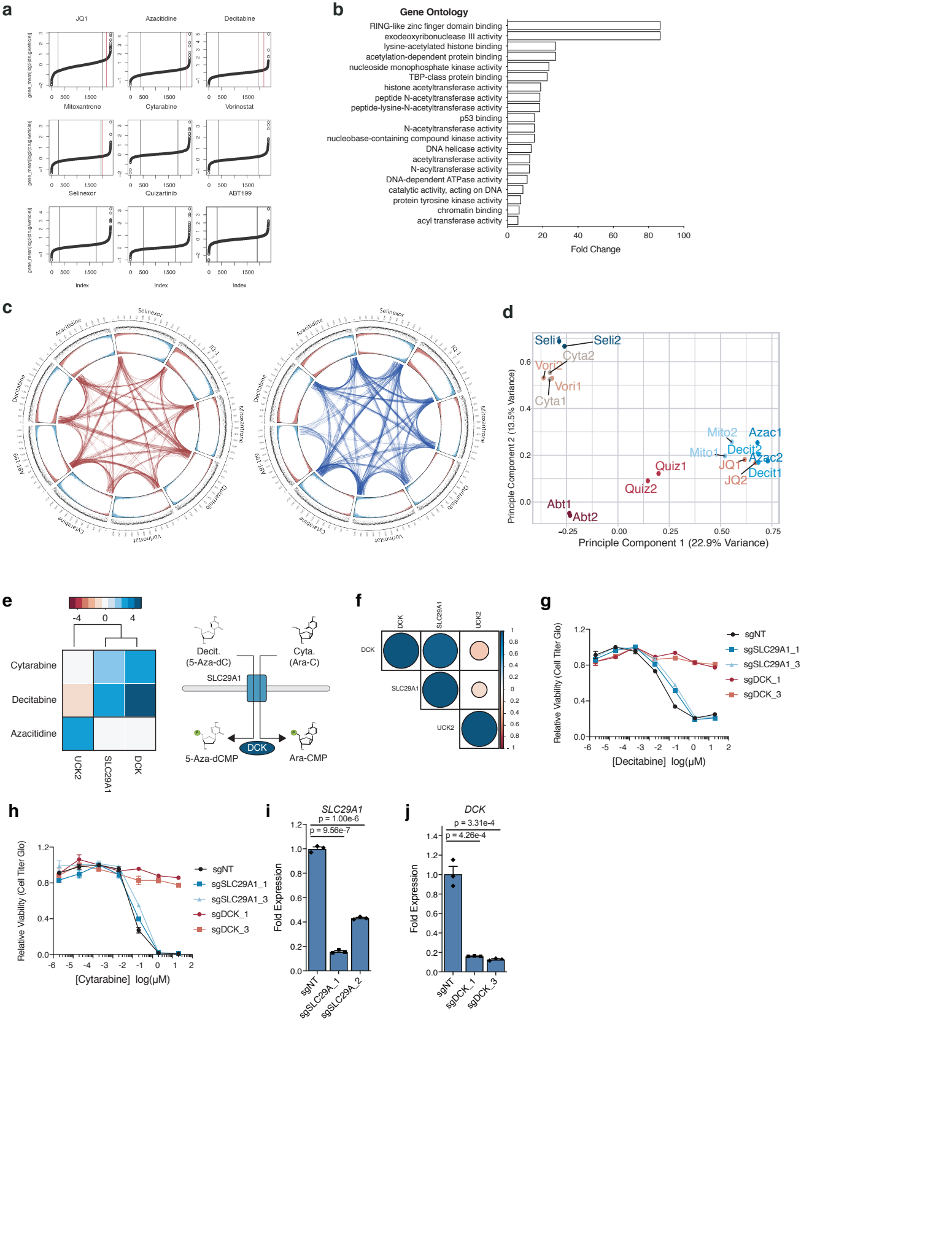
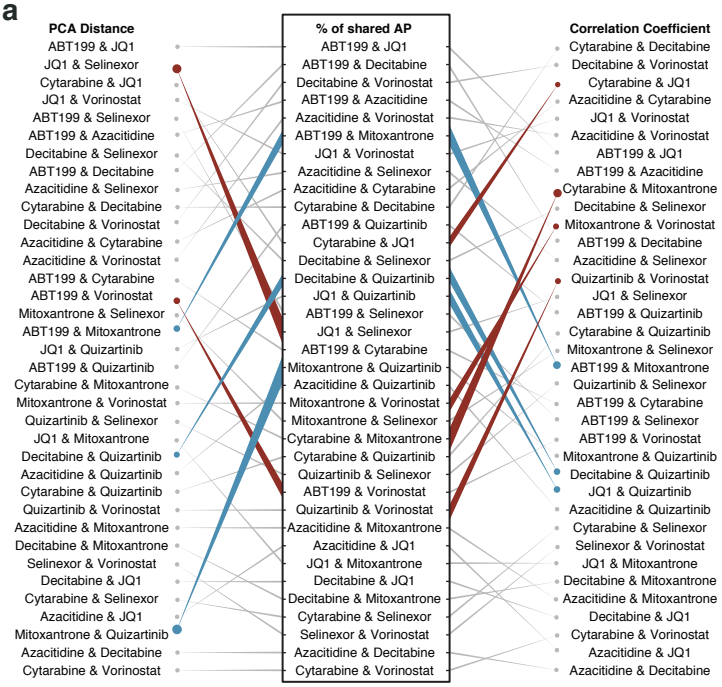

a
JQ1
Azacitidine
Decitabine
Mitoxantrone
Cytarabine
Vorinostat
Selinexor
Quizartinib
ABT199
Index
b
Gene Ontology
RING-like zinc finger domain binding
exodeoxyribonuclease III activity
lysine-acetylated histone binding
acetylation-dependent protein binding
nucleoside monophosphate kinase activity
TBP-class protein binding
histone acetyltransferase activity
peptide N-acetyltransferase activity
peptide-lysine-N-acetyltransferase activity
p53 binding
N-acetyltransferase activity
nucleobase-containing compound kinase activity
DNA helicase activity
acetyltransferase activity
N-acyltransferase activity
DNA-dependent ATPase activity
catalytic activity, acting on DNA
protein tyrosine kinase activity
chromatin binding
acyl transferase activity
Fold Change
c
d
Seli1
Seli2
Cyta2
Vori2
Vori1
Cyta1
Mito2
Azac1
Mito1
Decit2
Azac2
JQ1
Decit1
Quiz1
JQ2
Quiz2
Abt1
Abt2
Principle Component 2 (13.5% Variance)
Principle Component 1 (22.9% Variance)
e
Cytarabine
Decitabine
Azacitidine
UCK2
SLC29A1
DCK
Decit.
(5-Aza-dC)
Cyta.
(Ara-C)
5-Aza-dCMP
Ara-CMP
f
g
sgNT
sgSLC29A1_1
sgSLC29A1_3
sgDCK_1
sgDCK_3
Relative Viability (Cell Titer Glo)
[Decitabine] log(μM)
h
[Cytarabine] log(μM)
i
SLC29A1
p = 1.00e-6
p = 9.56e-7
Fold Expression
sgSLC29A_1
sgSLC29A_2
j
DCK
p = 3.31e-4
p = 4.26e-4
sgDCK_1
sgDCK_3

Figure S3

a



b

Pair	% AP	Corr. Coeff.	Distance
ABT199 and JQ1	75.610	-0.198	30.685
ABT199 and Decitabine	69.231	-0.142	24.299
Decitabine and Vorinostat	62.500	-0.261	21.786
ABT199 and Azacitidine	60.000	-0.193	25.233
Azacitidine and Vorinostat	59.184	-0.231	21.367
ABT199 and Mitoxantrone	57.143	-0.038	18.217
JQ1 and Vorinostat	55.556	-0.238	26.077
Azacitidine and Selinexor	52.941	-0.138	23.697
Azacitidine and Cytarabine	52.830	-0.249	21.536
Cytarabine and Decitabine	52.632	-0.262	22.013
ABT199 and Quizartinib	52.459	-0.081	16.376
Cytarabine and JQ1	50.000	-0.254	26.144
Decitabine and Selinexor	46.429	-0.160	24.519
Decitabine and Quizartinib	45.313	0.217	12.141
JQ1 and Quizartinib	43.860	0.230	17.462
ABT199 and Selinexor	41.429	0.066	26.038
JQ1 and Selinexor	41.304	-0.105	27.506
ABT199 and Cytarabine	41.096	0.059	20.311
Mitoxantrone and Quizartinib	40.984	0.159	5.123
Azacitidine and Quizartinib	38.983	0.258	12.128
Mitoxantrone and Vorinostat	38.182	-0.149	15.291
Mitoxantrone and Selinexor	37.931	-0.075	19.184
Cytarabine and Mitoxantrone	37.500	-0.172	15.655
Cytarabine and Quizartinib	34.940	-0.077	10.698
Quizartinib and Selinexor	30.769	-0.020	14.803
ABT199 and Vorinostat	30.667	0.105	19.505
Quizartinib and Vorinostat	28.235	-0.124	10.271
Azacitidine and Mitoxantrone	25.532	0.508	7.570
JQ1 and Mitoxantrone	25.000	0.450	13.117
Azacitidine and JQ1	25.000	0.564	5.563
Decitabine and JQ1	23.529	0.525	6.399
Decitabine and Mitoxantrone	14.583	0.506	7.248
Cytarabine and Selinexor	10.000	0.370	5.727
Selinexor and Vorinostat	9.756	0.395	6.534
Azacitidine and Decitabine	7.143	0.681	1.650
Cytarabine and Vorinostat	4.396	0.544	0.807

Figure S4

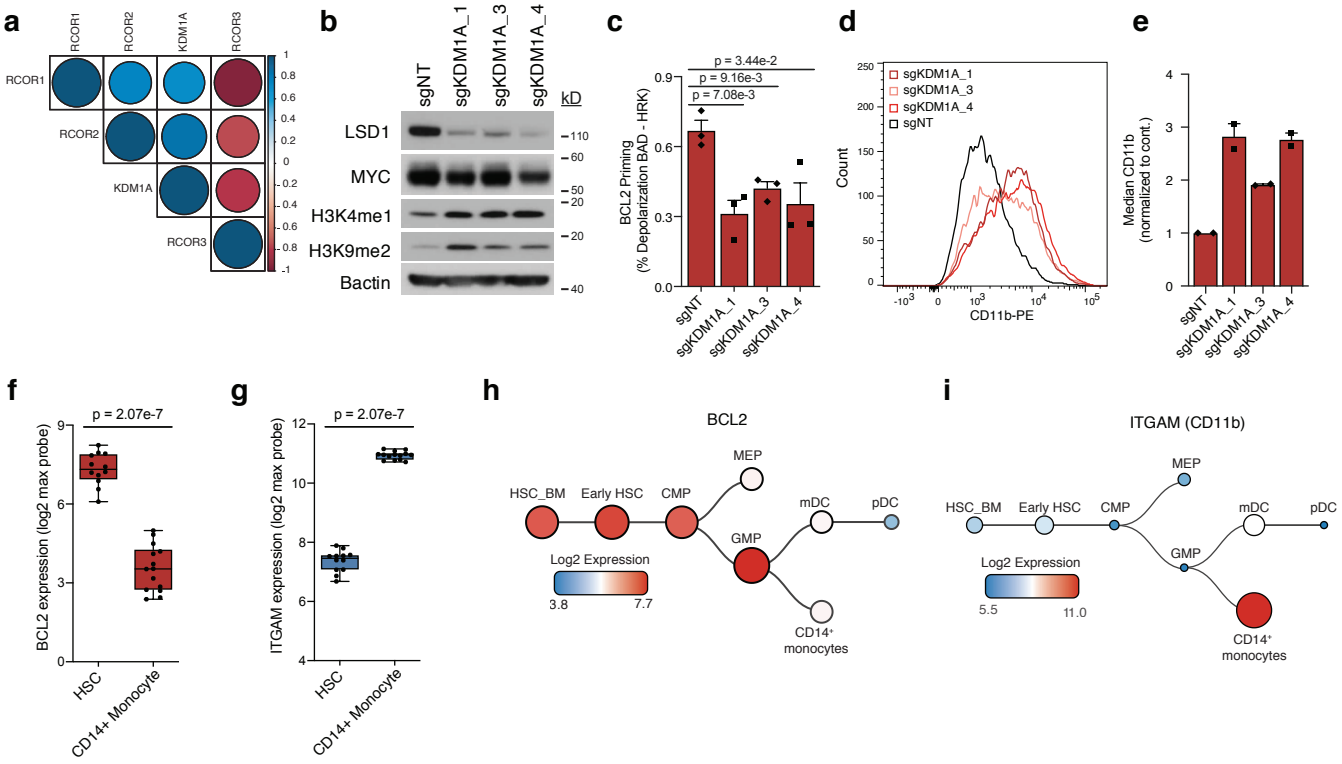

a
RCOR1
RCOR2
KDM1A
RCOR3
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
b
sgNT
sgKDM1A_1
sgKDM1A_3
sgKDM1A_4
kD
LSD1
MYC
H3K4me1
H3K9me2
Bactin
110
60
50
20
20
40
c
p = 3.44e-2
p = 9.16e-3
p = 7.08e-3
BCL2 Priming
(% Depolarization BAD - HRK)
sgNT
sgKDM1A_1
sgKDM1A_3
sgKDM1A_4
d
sgKDM1A_1
sgKDM1A_3
sgKDM1A_4
sgNT
Count
CD11b-PE
e
Median CD11b
(normalized to cont.)
sgNT
sgKDM1A_1
sgKDM1A_3
sgKDM1A_4
f
p = 2.07e-7
BCL2 expression (log2 max probe)
HSC
CD14+ Monocyte
g
p = 2.07e-7
ITGAM expression (log2 max probe)
HSC
CD14+ Monocyte
h
BCL2
HSC_BM
Early HSC
CMP
MEP
GMP
mDC
pDC
Log2 Expression
3.8
7.7
CD14+
monocytes
i
ITGAM (CD11b)
HSC_BM
Early HSC
CMP
MEP
GMP
mDC
pDC
Log2 Expression
5.5
11.0
CD14+
monocytes

Figure S5

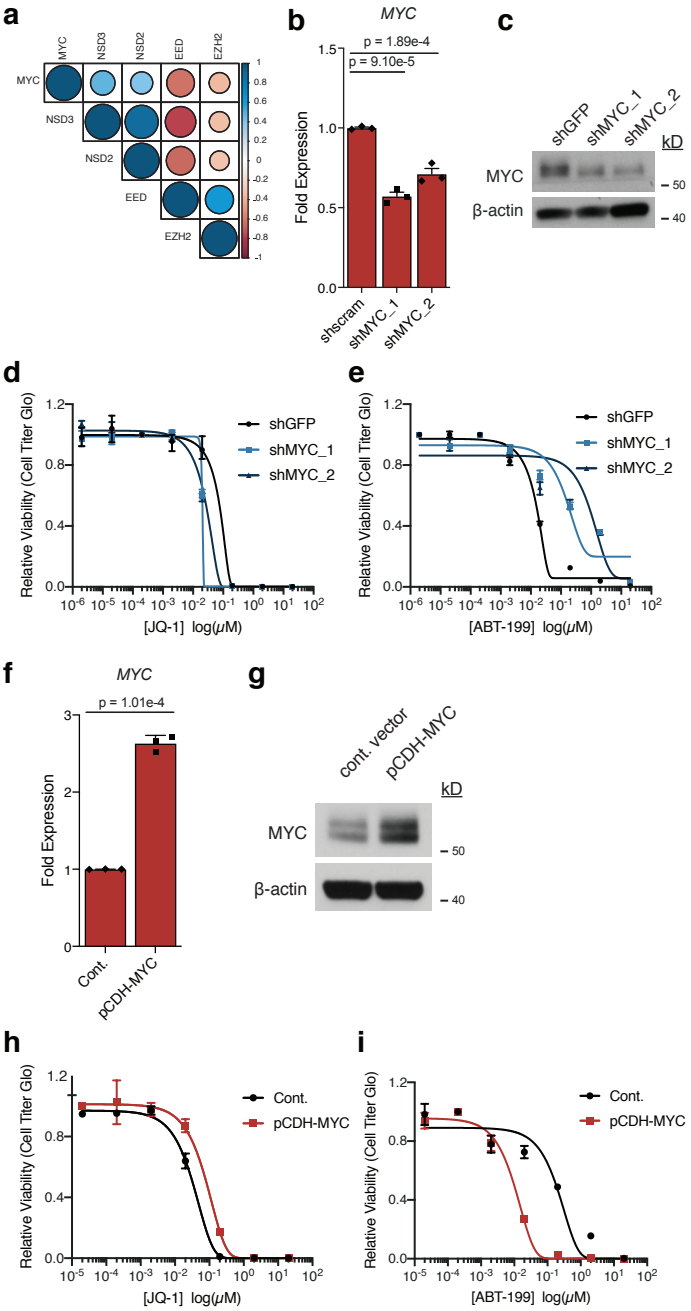

a
MYC
NSD3
NSD2
EED
EZH2
b
MYC
p = 1.89e-4
p = 9.10e-5
Fold Expression
shscram
shMYC_1
shMYC_2
c
shGFP
shMYC_1
shMYC_2
kD
MYC
β-actin
50
40
d
Relative Viability (Cell Titer Glo)
shGFP
shMYC_1
shMYC_2
[JQ-1] log(μM)
e
Relative Viability (Cell Titer Glo)
shGFP
shMYC_1
shMYC_2
[ABT-199] log(μM)
f
MYC
p = 1.01e-4
Fold Expression
Cont.
pCDH-MYC
g
cont. vector
pCDH-MYC
kD
MYC
β-actin
50
40
h
Relative Viability (Cell Titer Glo)
Cont.
pCDH-MYC
[JQ-1] log(μM)
i
Relative Viability (Cell Titer Glo)
Cont.
pCDH-MYC
[ABT-199] log(μM)

Figure S6

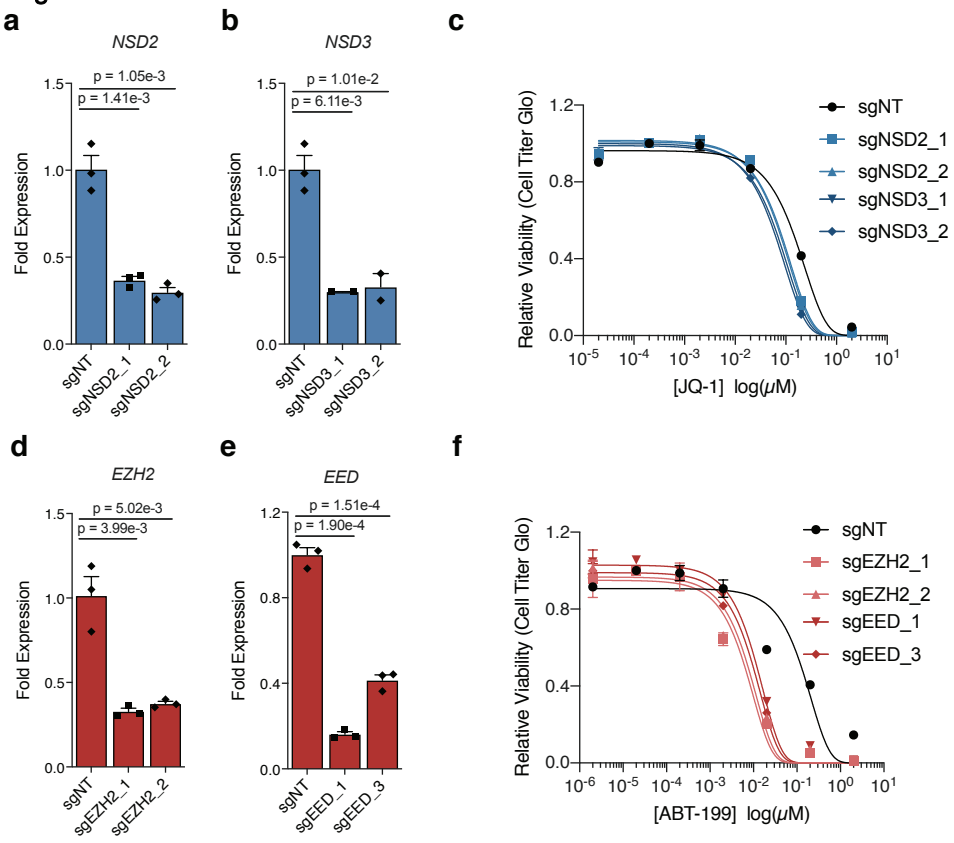

a
NSD2
p = 1.05e-3
p = 1.41e-3
Fold Expression
sgNT
sgNSD2_1
sgNSD2_2
b
NSD3
p = 1.01e-2
p = 6.11e-3
Fold Expression
sgNT
sgNSD3_1
sgNSD3_2
c
Relative Viability (Cell Titer Glo)
[JQ-1] log(μM)
sgNT
sgNSD2_1
sgNSD2_2
sgNSD3_1
sgNSD3_2
d
EZH2
p = 5.02e-3
p = 3.99e-3
Fold Expression
sgNT
sgEZH2_1
sgEZH2_2
e
EED
p = 1.51e-4
p = 1.90e-4
Fold Expression
sgNT
sgEED_1
sgEED_3
f
Relative Viability (Cell Titer Glo)
[ABT-199] log(μM)
sgNT
sgEZH2_1
sgEZH2_2
sgEED_1
sgEED_3

Figure S7

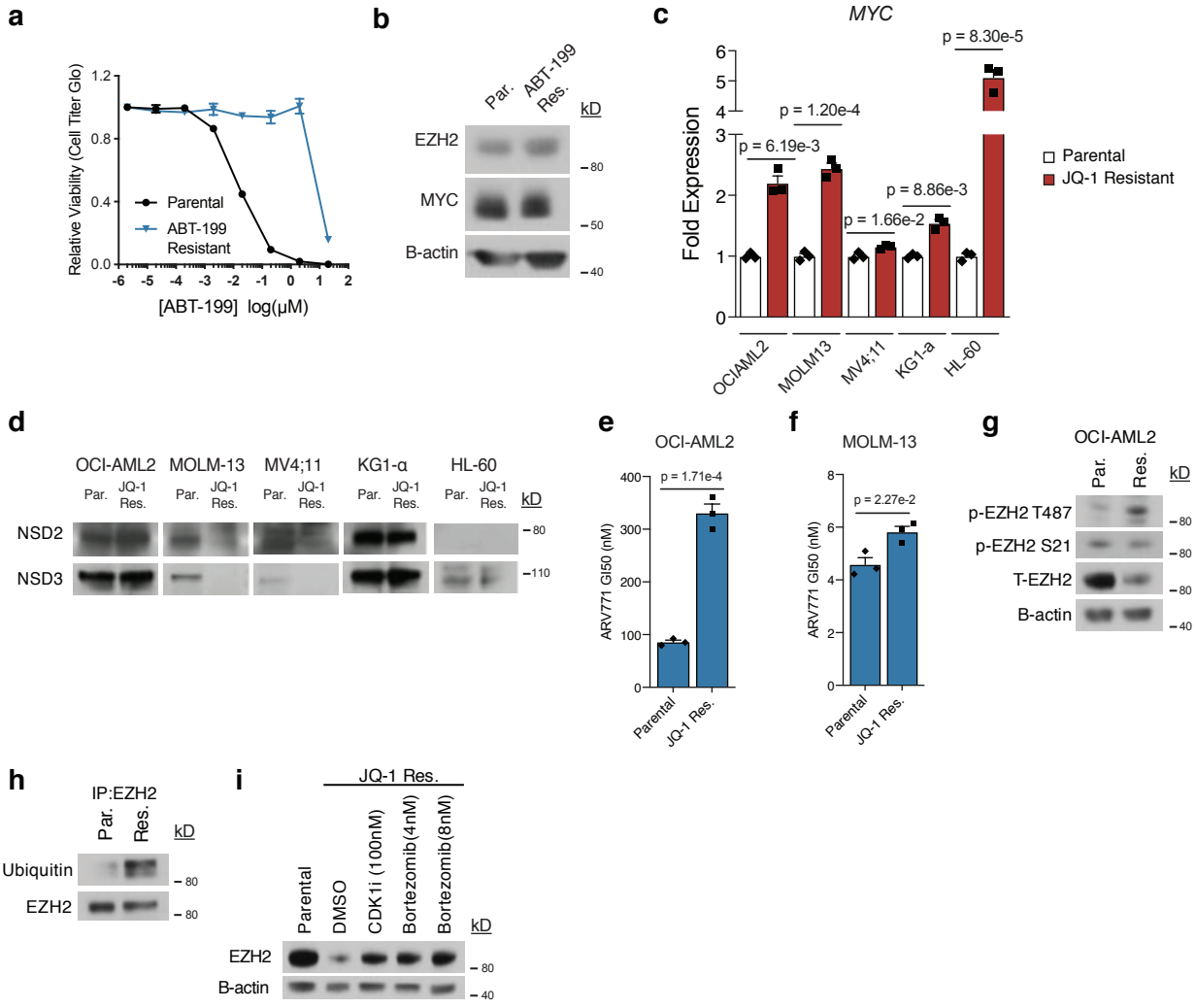

a
Relative Viability (Cell Titer Glo)
Parental
ABT-199 Resistant
[ABT-199] log(μM)
b
Par.
ABT-199 Res.
kD
EZH2
MYC
B-actin
c
MYC
Fold Expression
p = 6.19e-3
p = 1.20e-4
p = 1.66e-2
p = 8.86e-3
p = 8.30e-5
Parental
JQ-1 Resistant
OCIAML2
MOLM13
MV4;11
KG1-a
HL-60
d
OCI-AML2
MOLM-13
MV4;11
KG1-α
HL-60
Par.
JQ-1 Res.
kD
NSD2
NSD3
e
OCI-AML2
p = 1.71e-4
ARV771 GI50 (nM)
Parental
JQ-1 Res.
f
MOLM-13
p = 2.27e-2
ARV771 GI50 (nM)
Parental
JQ-1 Res.
g
OCI-AML2
Par.
Res.
kD
p-EZH2 T487
p-EZH2 S21
T-EZH2
B-actin
h
IP:EZH2
Par.
Res.
kD
Ubiquitin
EZH2
i
JQ-1 Res.
Parental
DMSO
CDK1i (100nM)
Bortezomib (4nM)
Bortezomib (8nM)
kD
EZH2
B-actin

Figure S8

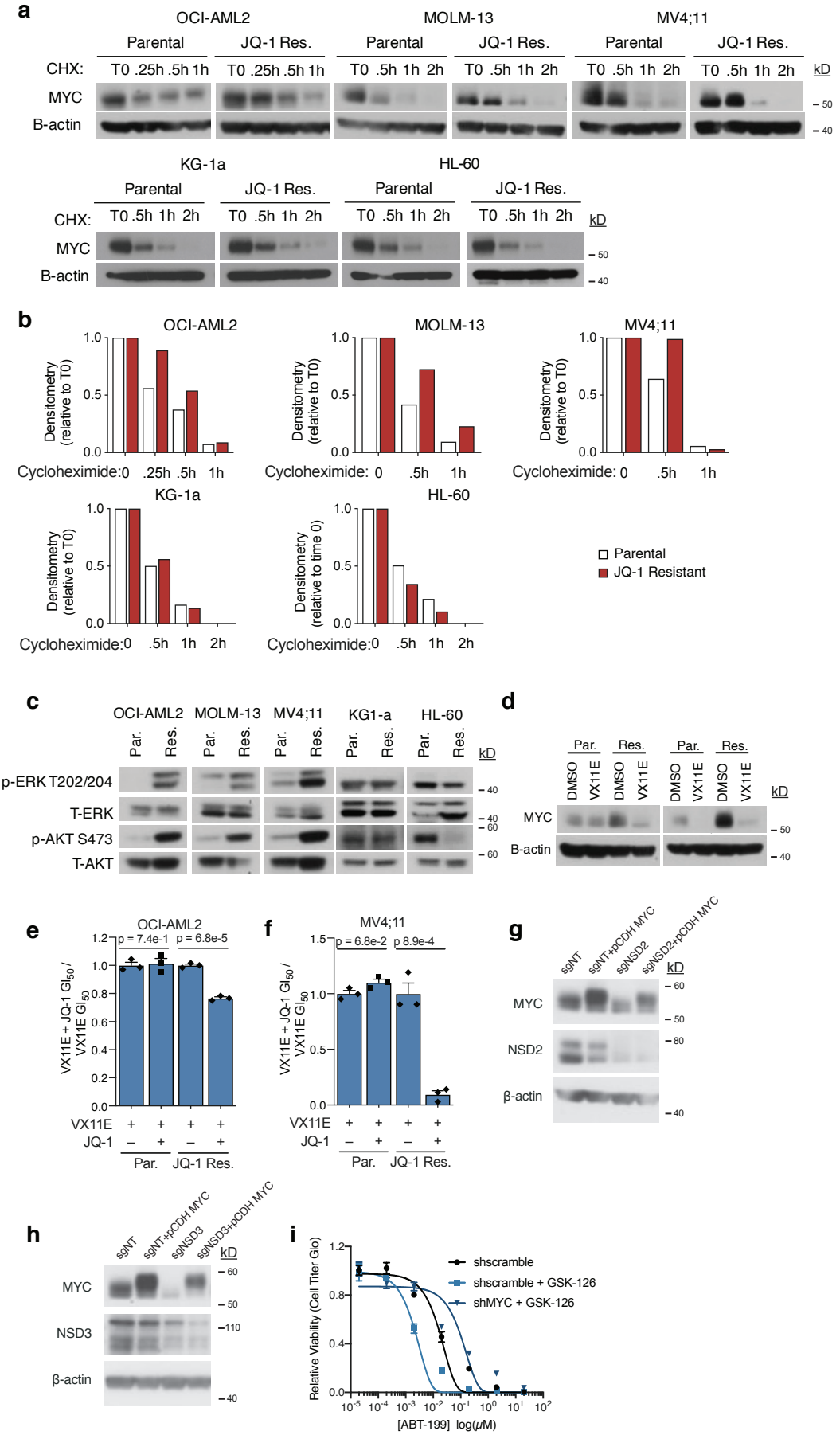
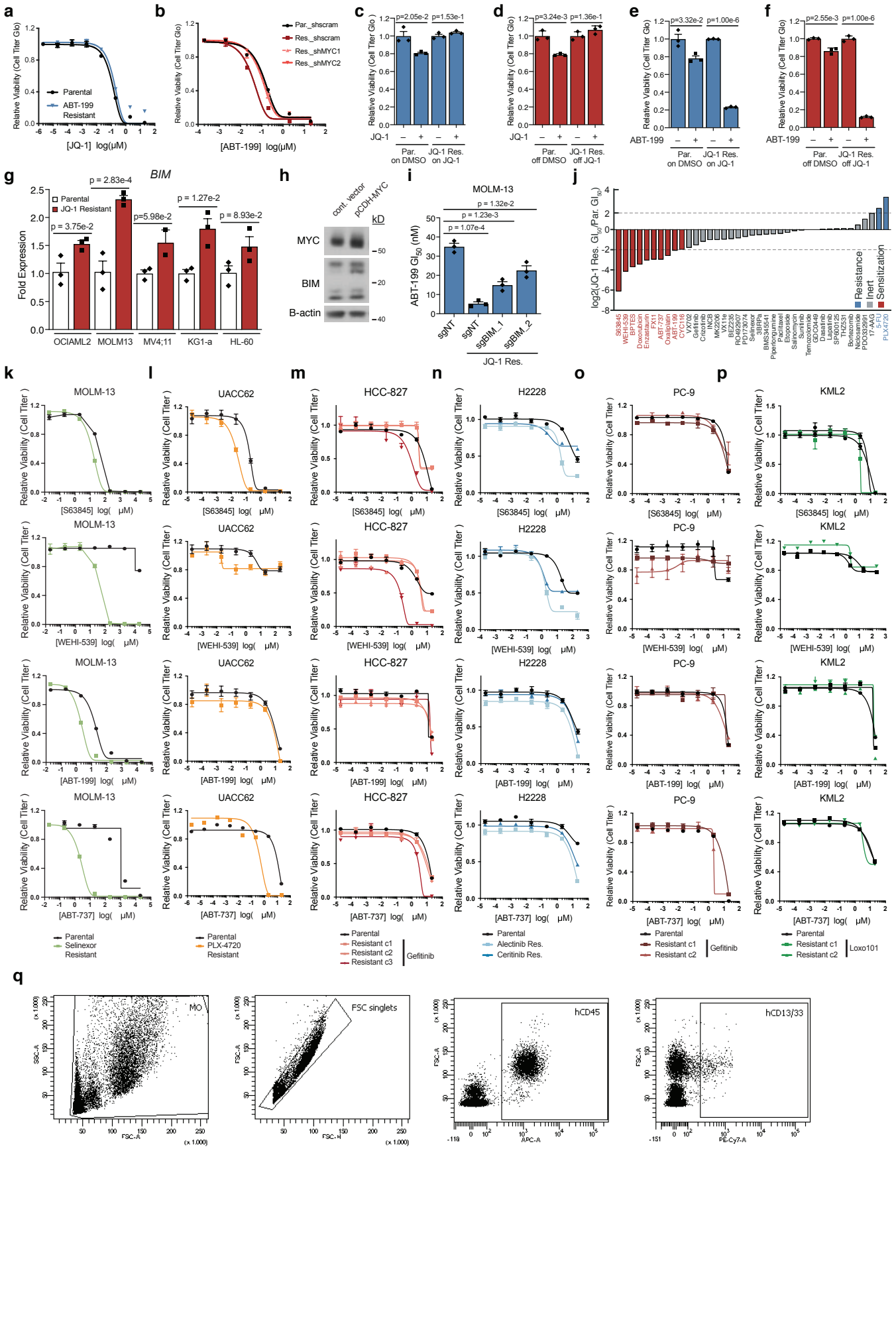

a
OCI-AML2
MOLM-13
MV4;11
Parental
JQ-1 Res.
CHX:
T0 .25h .5h 1h
T0 .5h 1h 2h
kD
MYC
B-actin
50
40
KG-1a
HL-60
b
Densitometry (relative to T0)
Densitometry (relative to time 0)
Cycloheximide:0 .25h .5h 1h
Cycloheximide: 0 .5h 1h
Cycloheximide:0 .5h 1h 2h
Parental
JQ-1 Resistant
c
OCI-AML2 MOLM-13 MV4;11 KG1-a HL-60
Par. Res.
p-ERK T202/204
T-ERK
p-AKT S473
T-AKT
d
DMSO VX11E
MYC
B-actin
e
OCI-AML2
p = 7.4e-1
p = 6.8e-5
VX11E + JQ-1 GI50 / VX11E GI50
VX11E
JQ-1
f
MV4;11
p = 6.8e-2
p 8.9e-4
g
sgNT
sgNT+pCDH MYC
sgNSD2
sgNSD2+pCDH MYC
NSD2
β-actin
h
sgNSD3
sgNSD3+pCDH MYC
NSD3
i
shscramble
shscramble + GSK-126
shMYC + GSK-126
Relative Viability (Cell Titer Glo)
[ABT-199] log(μM)

Figure S9


a
Relative Viability (Cell Titer Glo)
Parental
ABT-199 Resistant
[JQ-1] log(μM)
b
Par._shscram
Res._shscram
Res._shMYC1
Res._shMYC2
[ABT-199] log(μM)
c
p=2.05e-2
p=1.53e-1
JQ-1
Par. on DMSO
JQ-1 Res. on JQ-1
d
p=3.24e-3
p=1.36e-1
Par. off DMSO
JQ-1 Res. off JQ-1
e
p=3.32e-2
p=1.00e-6
ABT-199
f
p=2.55e-3
p=1.00e-6
g
BIM
Fold Expression
p = 3.75e-2
p = 2.83e-4
p=5.98e-2
p = 1.27e-2
p = 8.93e-2
OCIAML2
MOLM13
MV4;11
KG1-a
HL-60
h
cont. vector
pCDH-MYC
kD
MYC
BIM
B-actin
i
MOLM-13
ABT-199 GI50 (nM)
p = 1.32e-2
p = 1.23e-3
p = 1.07e-4
sgNT
sgBIM_1
sgBIM_2
JQ-1 Res.
j
log2(JQ-1 Res. GI50/Par. GI50)
Resistance
Inert
Sensitization
k
MOLM-13
[S63845] log(μM)
[WEHI-539] log(μM)
[ABT-199] log(μM)
[ABT-737] log(μM)
Parental
Selinexor Resistant
l
UACC62
PLX-4720 Resistant
m
HCC-827
Resistant c1
Resistant c2
Resistant c3
Gefitinib
n
H2228
Alectinib Res.
Ceritinib Res.
o
PC-9
p
KML2
Loxo101
q
MO
FSC singlets
hCD45
hCD13/33