FIG. 1

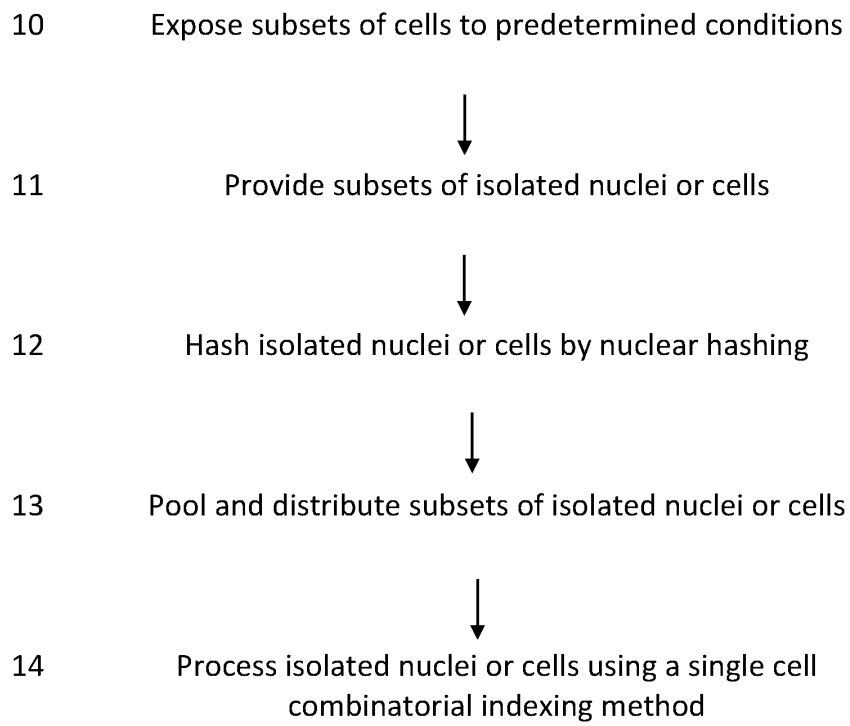

10
Expose subsets of cells to predetermined conditions
11
Provide subsets of isolated nuclei or cells
12
Hash isolated nuclei or cells by nuclear hashing
13
Pool and distribute subsets of isolated nuclei or cells
14
Process isolated nuclei or cells using a single cell combinatorial indexing method

FIG. 2

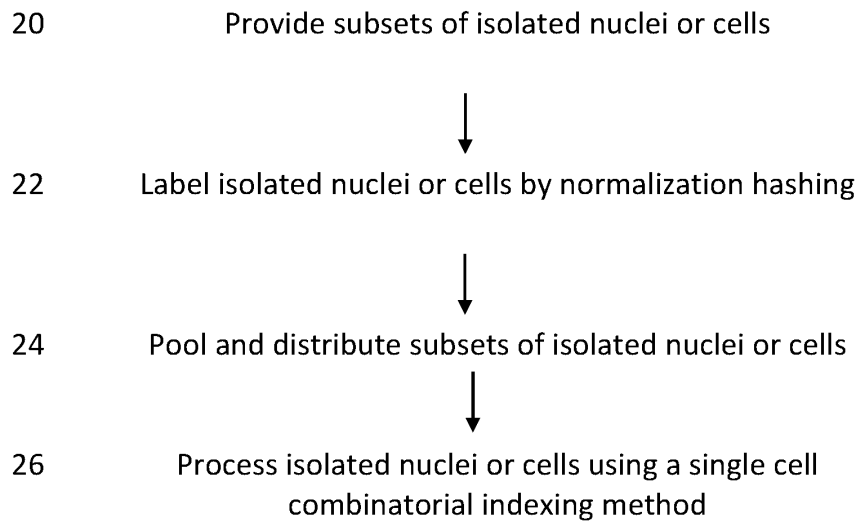

20
Provide subsets of isolated nuclei or cells
22
Label isolated nuclei or cells by normalization hashing
24
Pool and distribute subsets of isolated nuclei or cells
26
Process isolated nuclei or cells using a single cell combinatorial indexing method

FIG. 3

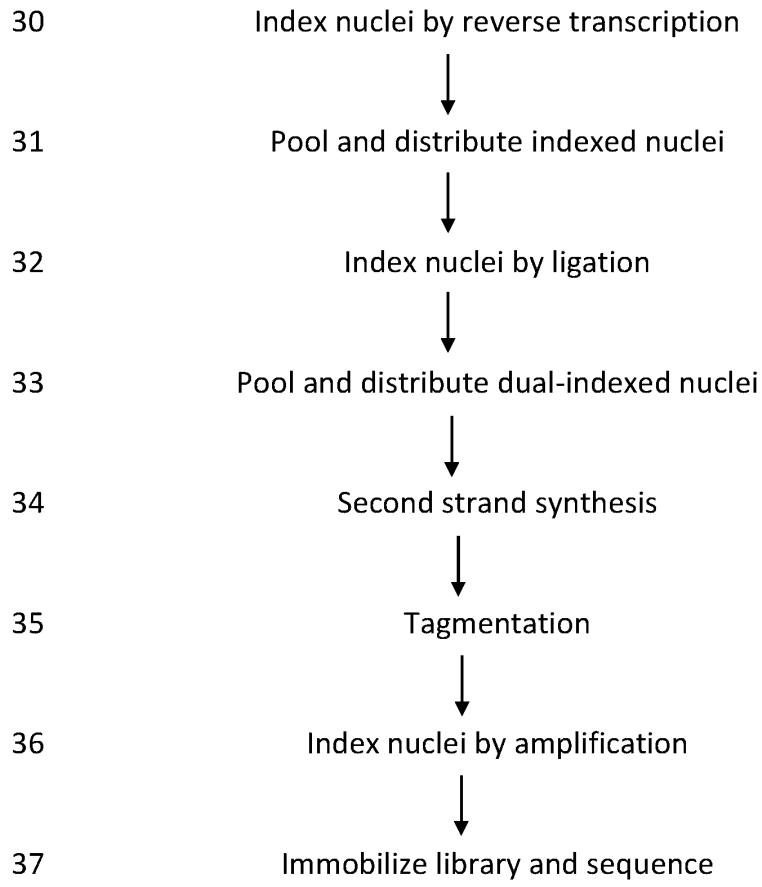

30
Index nuclei by reverse transcription
31
Pool and distribute indexed nuclei
32
Index nuclei by ligation
33
Pool and distribute dual-indexed nuclei
34
Second strand synthesis
35
Tagmentation
36
Index nuclei by amplification
37
Immobilize library and sequence

FIG. 4

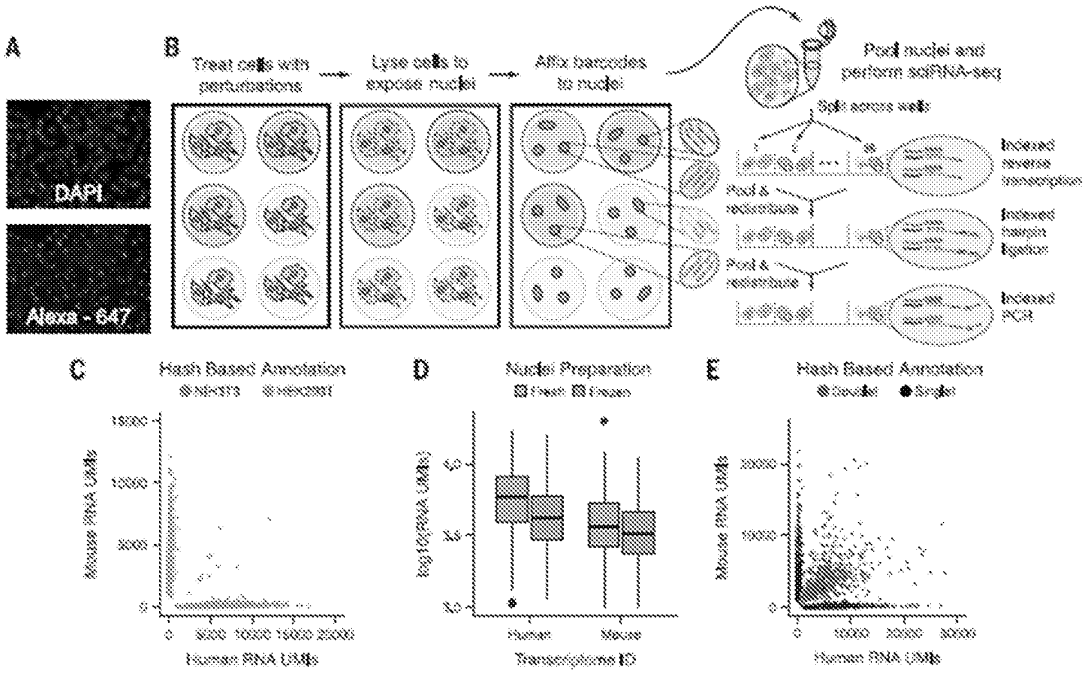

A
DAPI
Alexa - 647
B
Treat cells with perturbations
Lyse cells to expose nuclei
Affix barcodes to nuclei
Pool nuclei and perform scRNA-seq
Split across wells
Pool & redistribute
Pool & redistribute
Indexed reverse transcription
Indexed barcode ligation
Indexed PCR
C
Hash Based Annotation
Mouse RNA UMIs
Human RNA UMIs
D
Nuclei Preparation
Fixed
Frozen
log10(RNA UMIs)
Human
Mouse
Transcriptome ID
E
Hash Based Annotation
Doublet
Singlet
Mouse RNA UMIs
Human RNA UMIs

FIG. 5

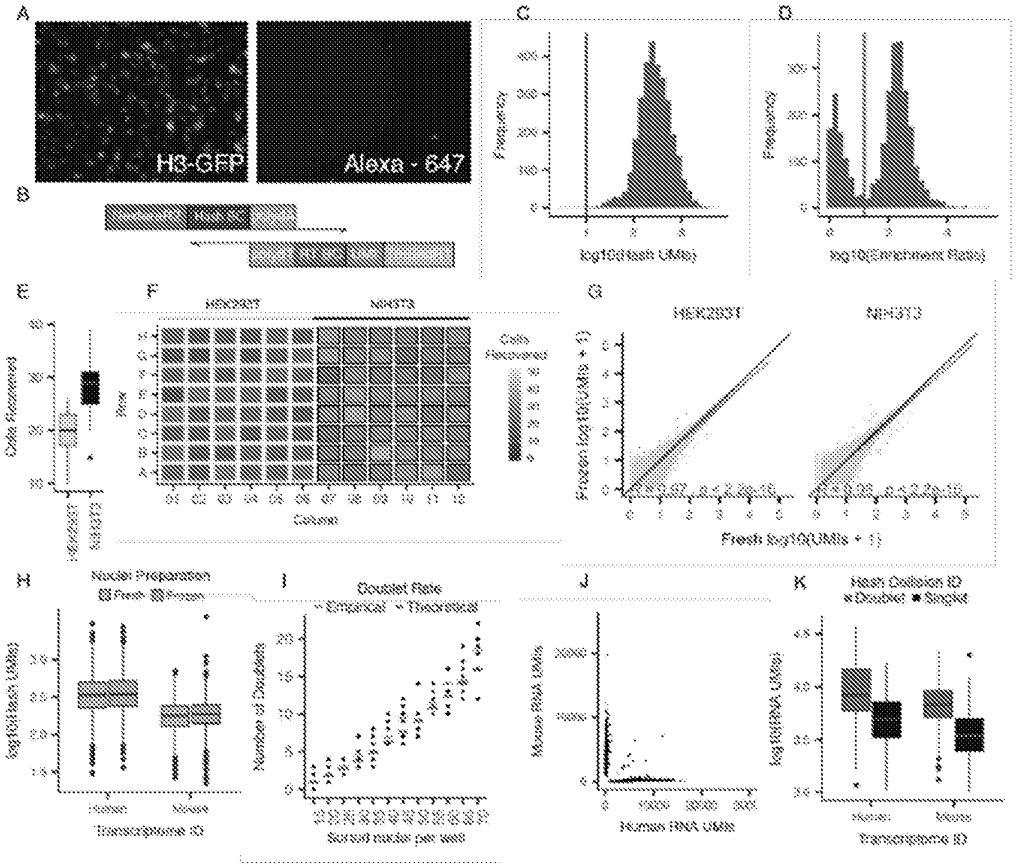

A
H3-GFP
Alexa - 647
B
C
Frequency
log10(Nash UMIs)
D
Frequency
log10(Enrichment Ratio)
E
Cells Recovered
F
HEK293T
NIH3T3
Row
Column
Cells
G
HEK293T
NIH3T3
Frozen log10(UMIs + 1)
Fresh log10(UMIs + 1)
H
Nuclei Preparation
Fresh
Frozen
log10(Nash UMIs)
Human
Mouse
Transcriptome ID
I
Doublet Rate
Empirical
Theoretical
Number of Doublets
Sorted nuclei per well
J
Mouse RNA UMIs
Human RNA UMIs
K
Nash Doublet ID
Doublet
Singlet
log10(UMIs)
Human
Mouse
Transcriptome ID

FIG. 6

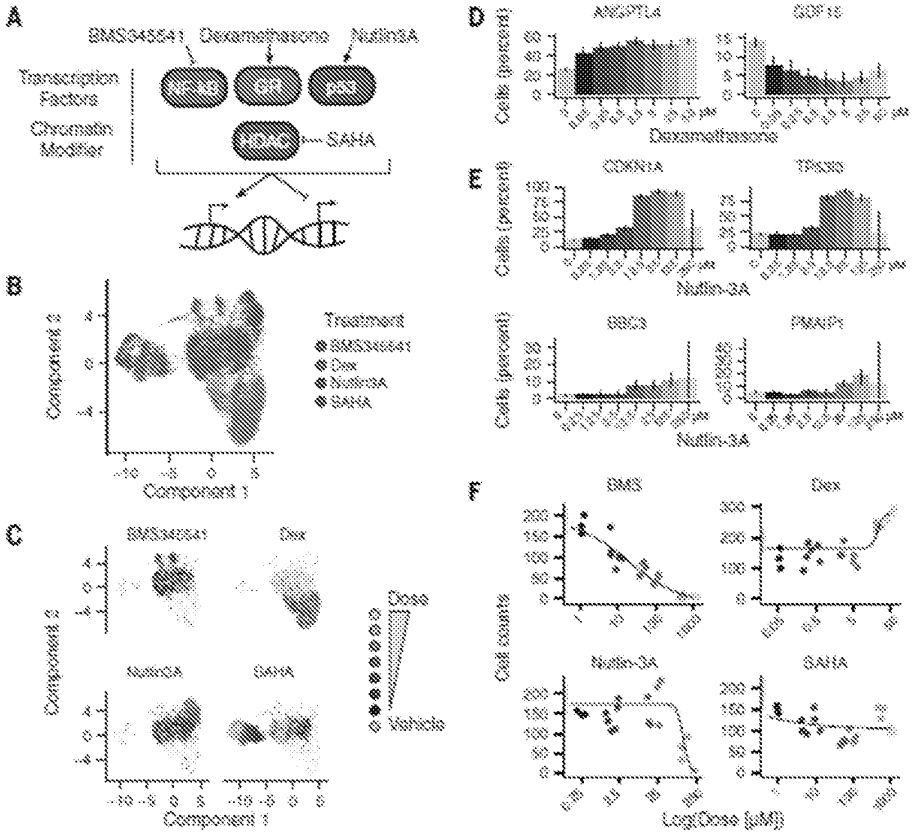

A
BMS345541
Dexamethasone
Nutlin3A
Transcription Factors
Chromatin Modifier
NFκB
GR
p53
HDAC
SAHA
B
Treatment
BMS345541
Dex
Nutlin3A
SAHA
Component 2
Component 1
C
BMS345541
Dex
Nutlin3A
SAHA
Dose
Vehicle
Component 2
Component 1
D
ANGPTL4
GDF15
Cells (percent)
Dexamethasone
E
CDKN1A
TP53I3
BBC3
PMAIP1
Cells (percent)
Nutlin-3A
F
BMS
Dex
Nutlin-3A
SAHA
Cell counts
Log(Dose (μM))

FIG. 7

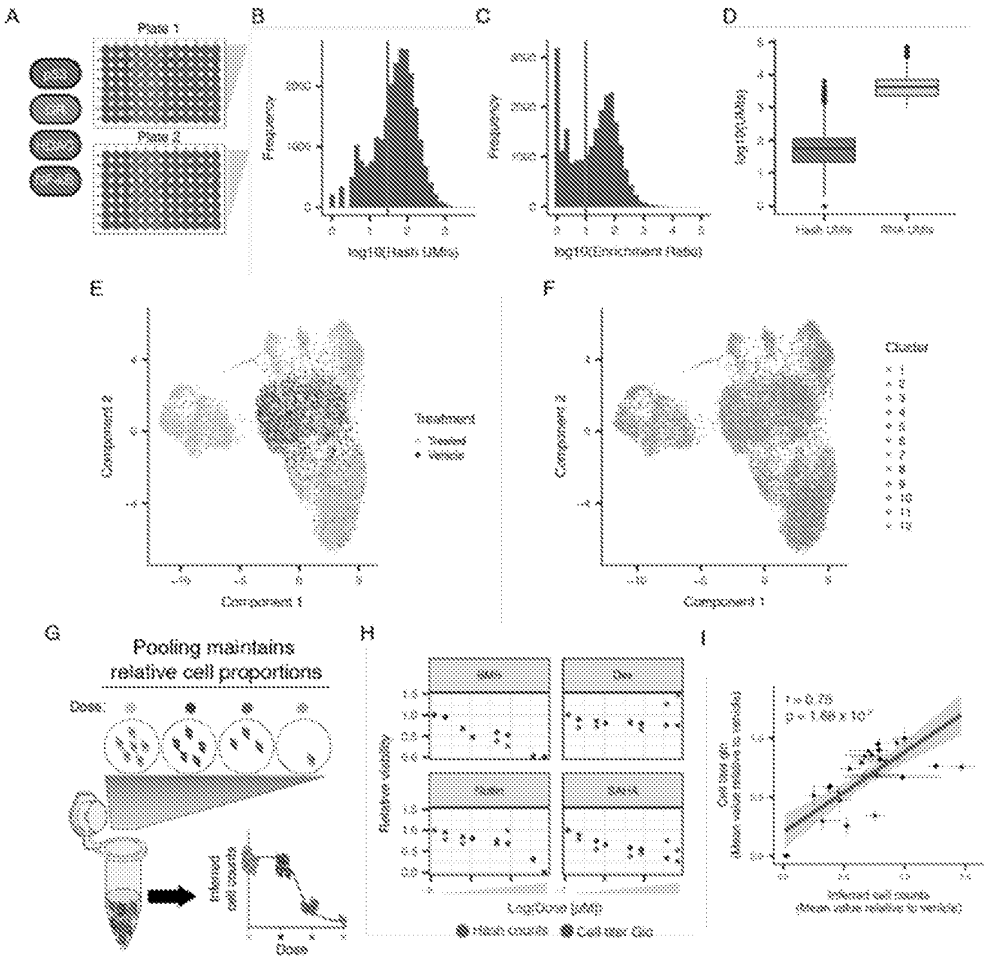

A
Plate 1
Plate 2
B
C
D
E
F
Component 1
Component 2
Treatment
Vehicle
Cluster
G
Pooling maintains
relative cell proportions
Dose
Dose
H
Relative viability
Log(Dose (nM))
I

FIG. 8

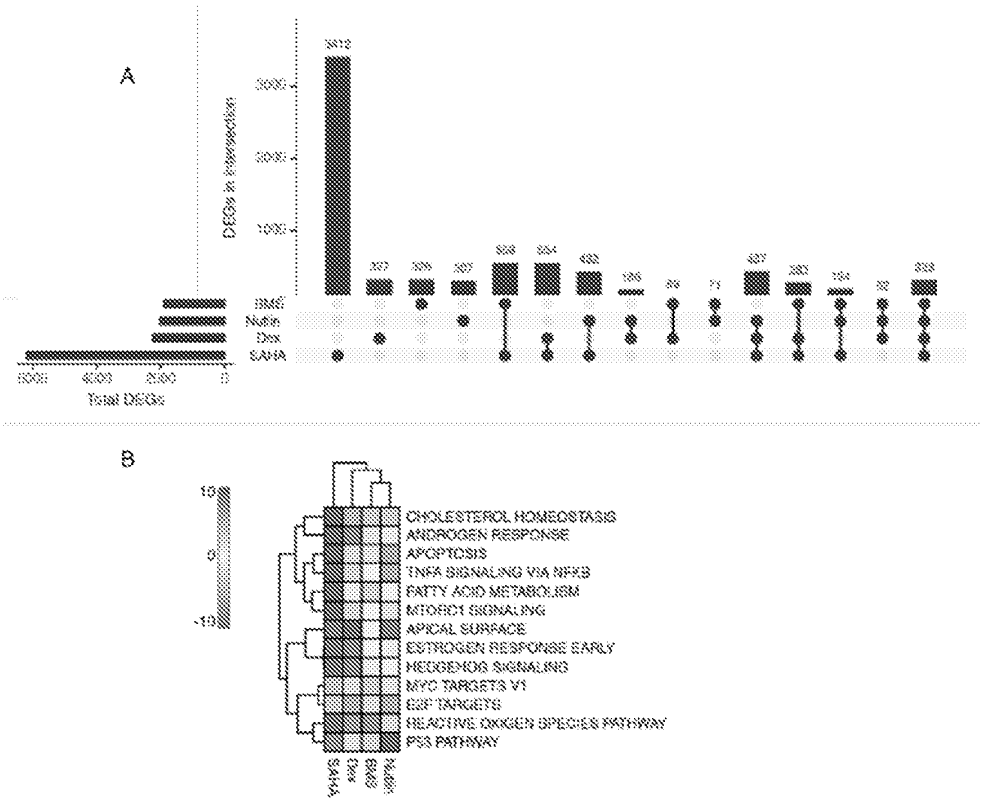

A
DEGs in Intersection
Total DEGs
B
CHOLESTEROL HOMEOSTASIS
ANDROGEN RESPONSE
APOPTOSIS
TNFA SIGNALING VIA NFKB
FATTY ACID METABOLISM
MTORC1 SIGNALING
APICAL SURFACE
ESTROGEN RESPONSE EARLY
HEDGEHOG SIGNALING
MYC TARGETS V1
E2F TARGETS
REACTIVE OXIGEN SPECIES PATHWAY
P53 PATHWAY

FIG. 9

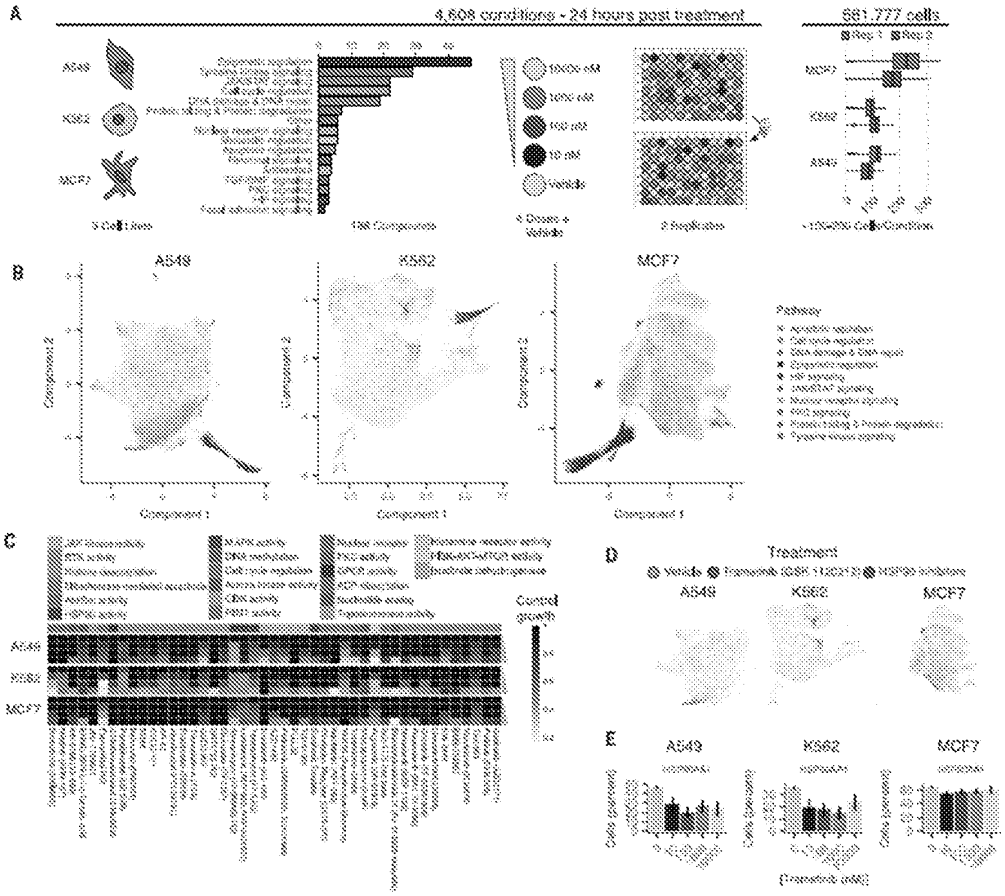

A
4,608 conditions - 24 hours post treatment
661,777 cells
A549
K562
MCF7
B
A549
K562
MCF7
Component 1
Component 2
Component 3
C
Control growth
D
Treatment
Vehicle
A549
K562
MCF7
E
A549
K562
MCF7

FIG. 10

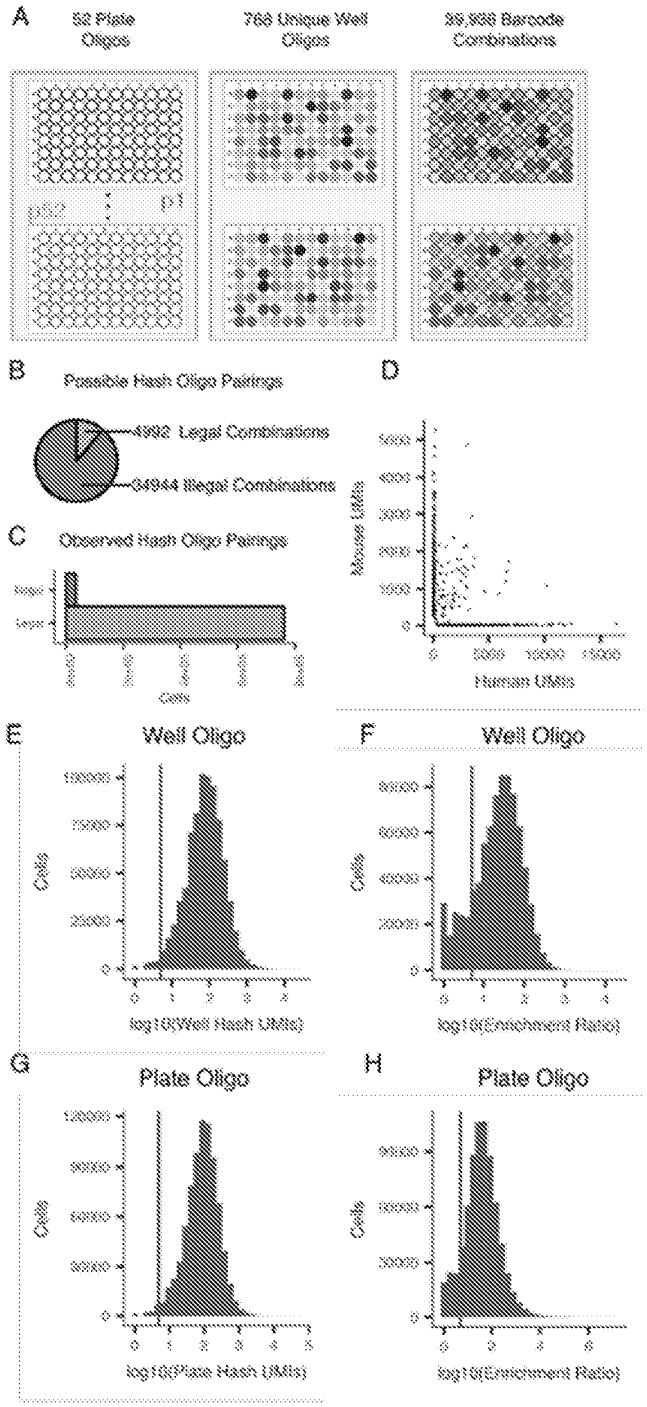

A
92 Plate Oligos
768 Unique Well Oligos
96,936 Barcode Combinations
p2
p1
B
Possible Hash Oligo Pairings
4992 Legal Combinations
94944 Illegal Combinations
C
Observed Hash Oligo Pairings
Cells
D
Mouse UMIs
Human UMIs
E
Well Oligo
Cells
log10(Well Hash UMIs)
F
Well Oligo
Cells
log10(Enrichment Ratio)
G
Plate Oligo
Cells
log10(Plate Hash UMIs)
H
Plate Oligo
Cells
log10(Enrichment Ratio)

FIG. 11

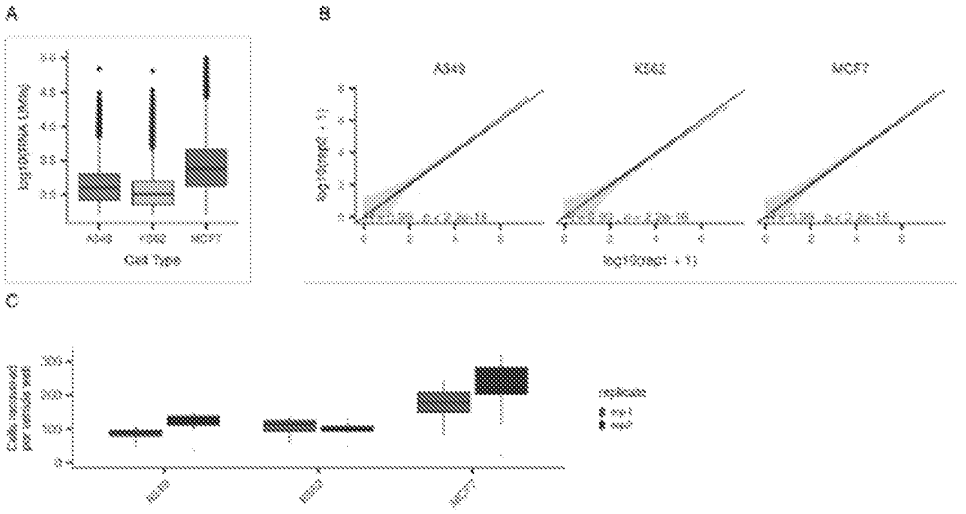


FIG. 12

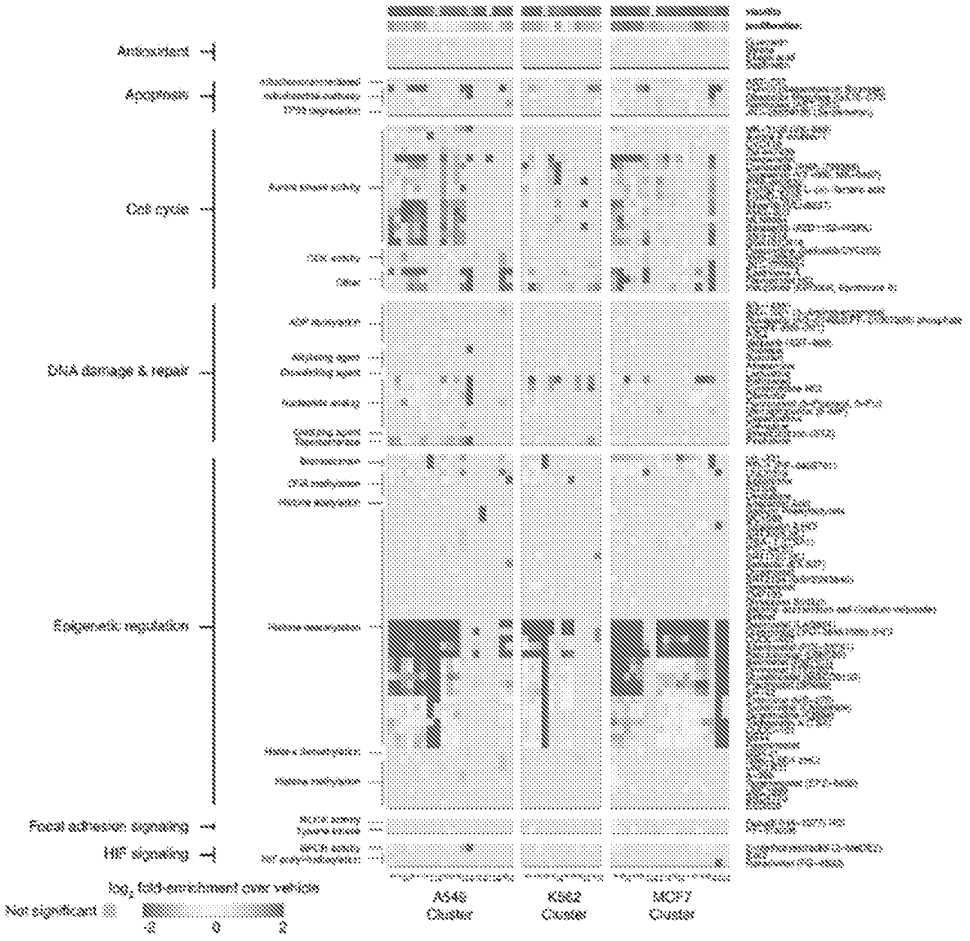

Antioxidant
Apoptosis
Cell cycle
DNA damage & repair
Epigenetic regulation
Focal adhesion signaling
HIF signaling
log2 fold-enrichment over vehicle
Not significant
-2
0
2
A549 Cluster
K562 Cluster
MCF7 Cluster

FIG. 12, continued

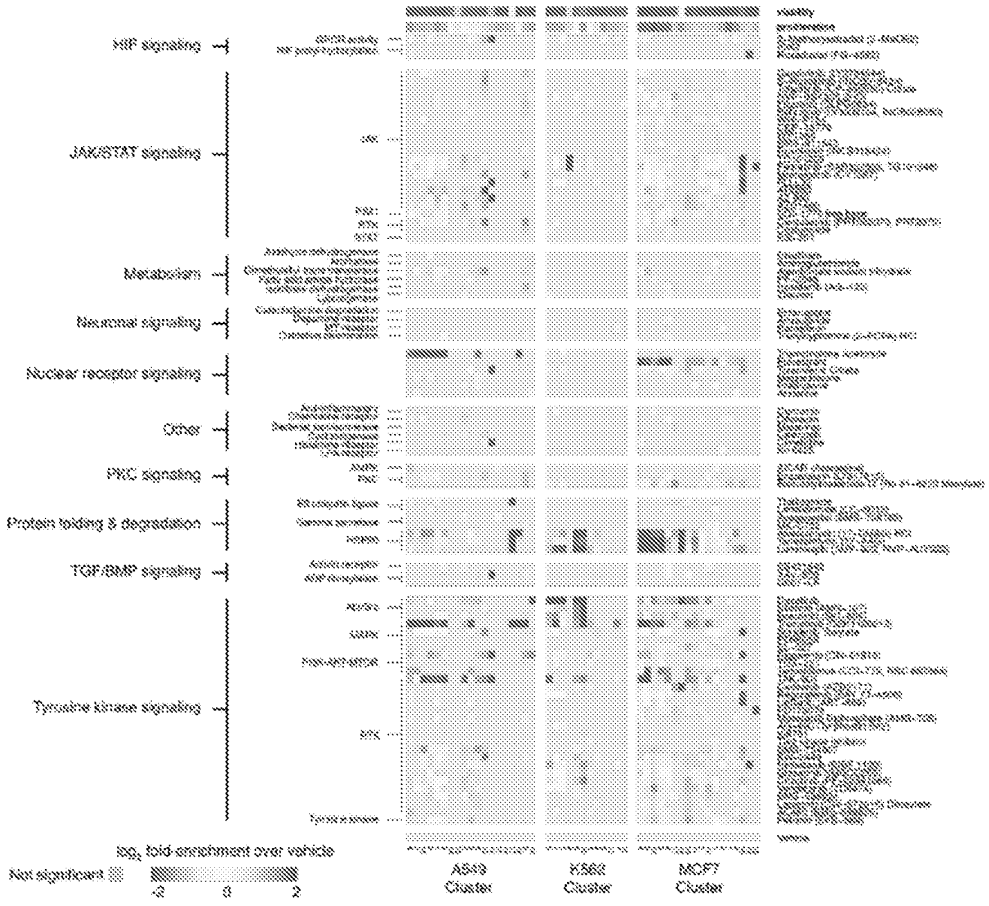


FIG. 13

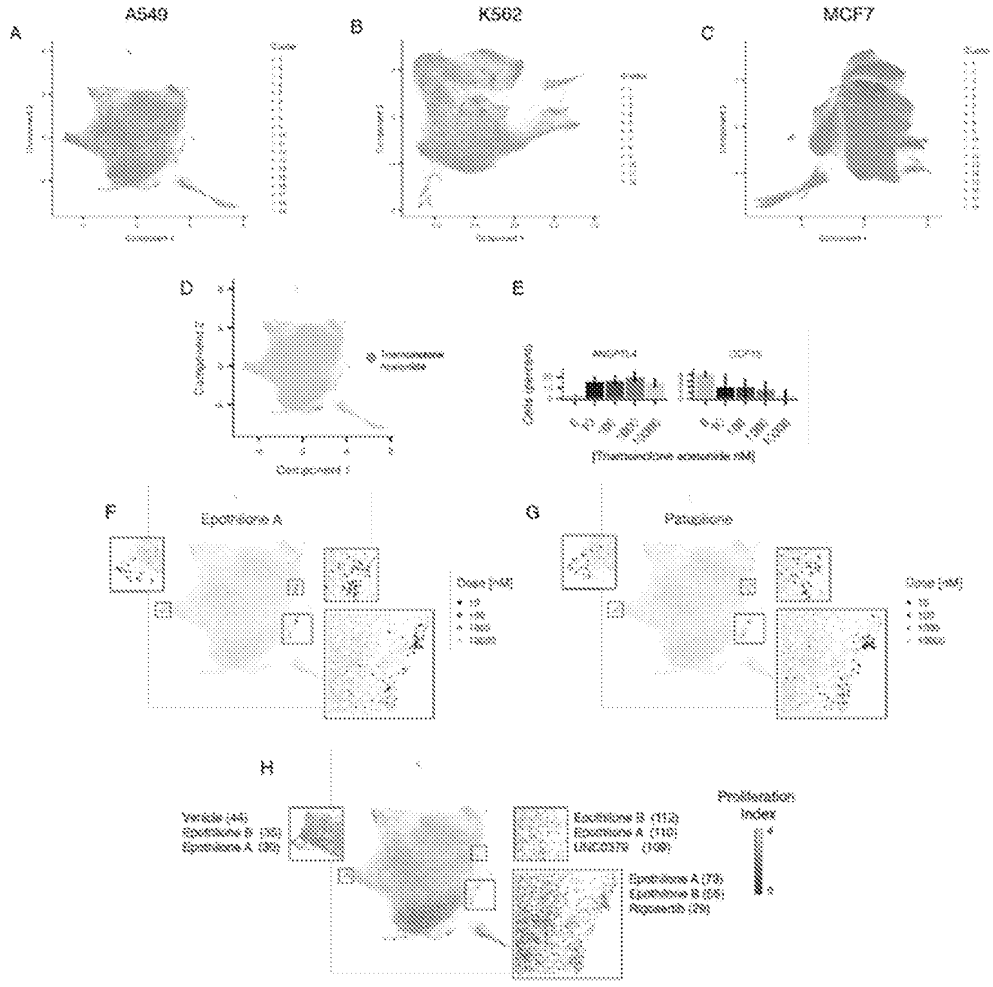

A549
K562
MCF7
A
B
C
D
E
F
G
H
Epothilone A
Paclitaxel
Vehicle (44)
Epothilone B (36)
Epothilone A (38)
Epothilone B (113)
Epothilone A (110)
DMSO/EtOH (108)
Epothilone A (78)
Epothilone B (55)
Rigosertib (29)
Proliferation Index

FIG. 14

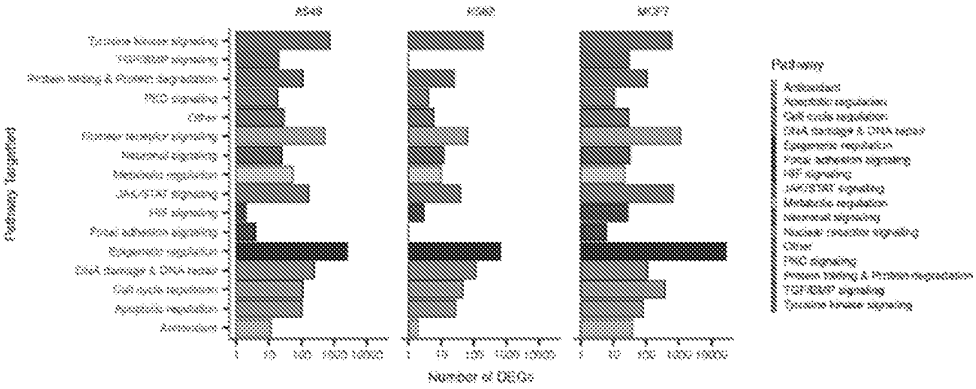

A549
H460
MCF7
Pathway
Antioxidant
Apoptotic regulation
Cell cycle regulation
DNA damage & DNA repair
Epigenetic regulation
Focal adhesion signaling
HIF signaling
JAK/STAT signaling
Metabolic regulation
Neuronal signaling
Nuclear receptor signaling
Other
PKC signaling
Protein folding & Protein degradation
TGF/BMP signaling
Tyrosine kinase signaling
Number of DEGs

FIG. 15

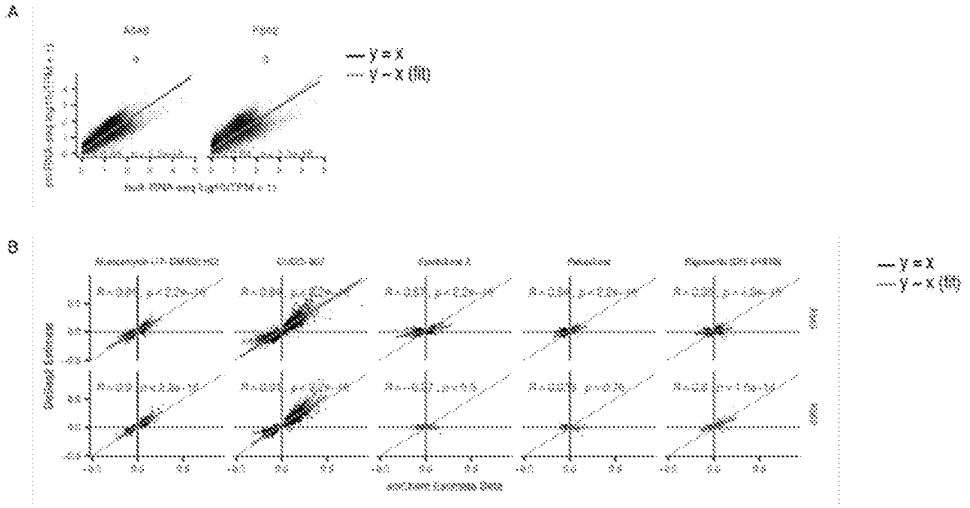

A
A549
H460
y = x
y ~ x (fit)
A549 RNA-seq Log2(TPM + 1)
B
Docking Distance
Docked Ligand Energy
y = x
y ~ x (fit)

FIG. 16

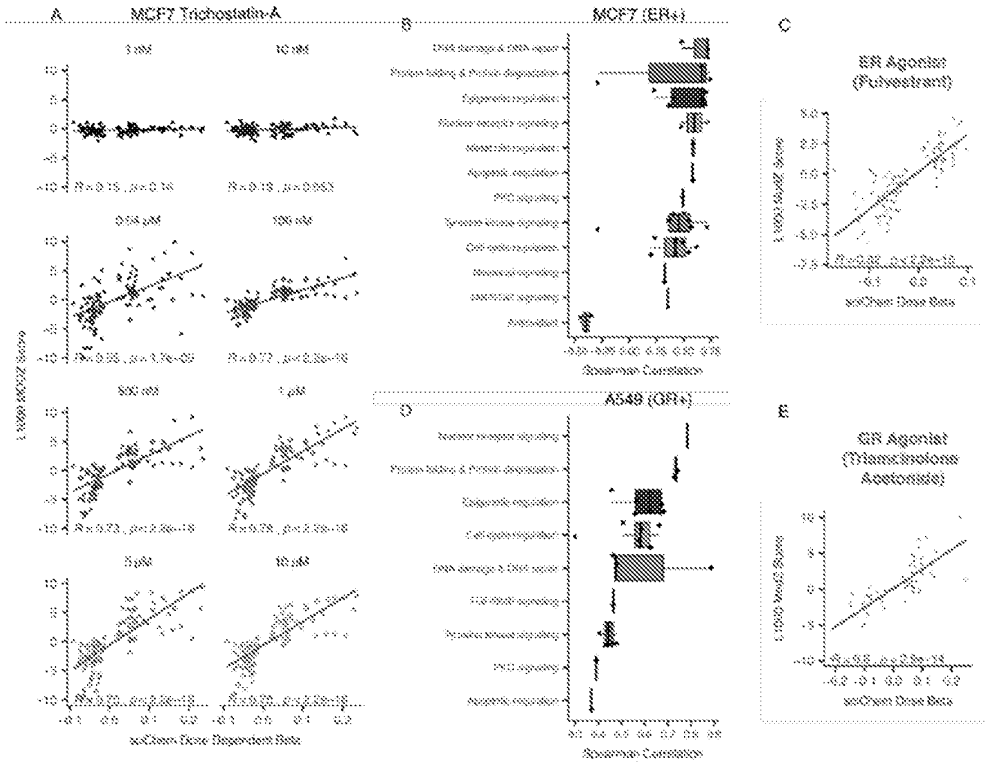
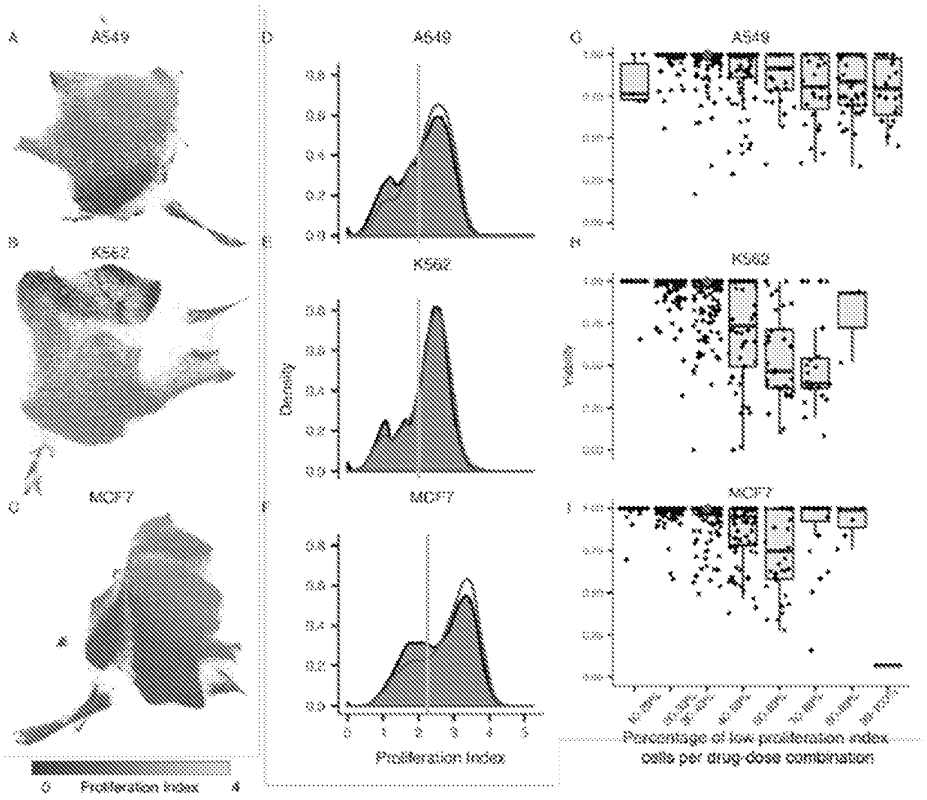

A
MCF7 Trichostatin A
1 nM
10 nM
100 nM
1 µM
5 µM
10 µM
1,000 MoA Score
Log10 Dose Dependent Beta
B
MCF7 (ER+)
Spearman Correlation
C
GR Agonist
(Fulvestrant)
D
A549 (GR+)
E
GR Agonist
(Triamcinolone
Acetonide)

FIG. 17


A
A549
B
K562
C
MCF7
0
Proliferation Index
1
D
A549
E
K562
F
MCF7
Density
0.0
0.2
0.4
0.6
0.8
0
1
2
3
4
5
Proliferation Index
G
A549
H
K562
I
MCF7
Viability
Percentage of low proliferation index cells per drug-dose combination

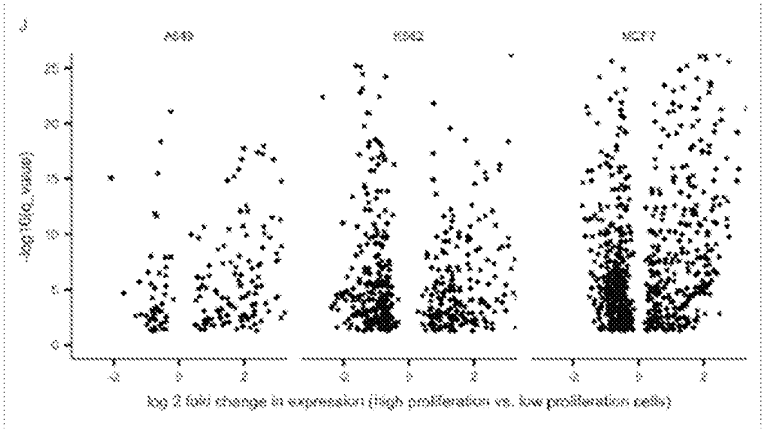

J
A549
K562
MCF7
-log10(p_value)
log 2 fold change in expression (high proliferation vs. low proliferation cells)

FIG. 18

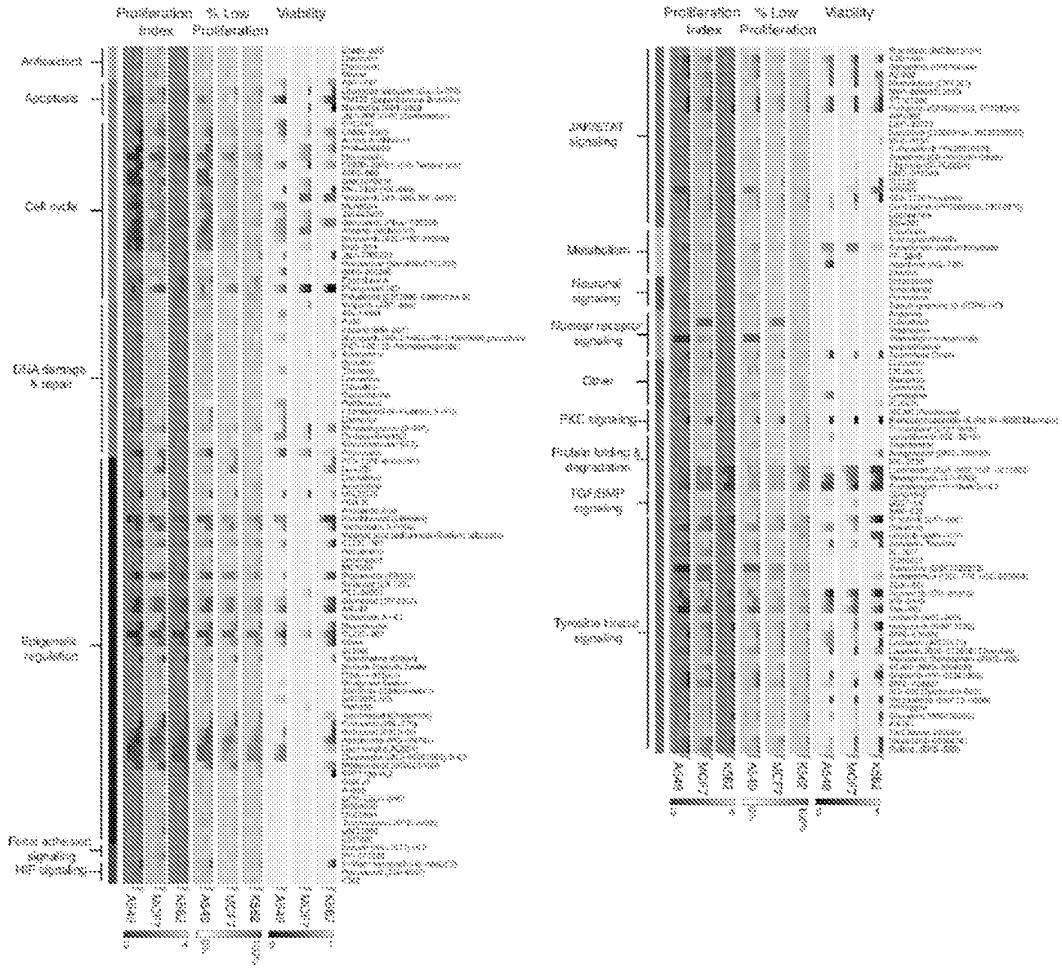

Proliferation Index
% Low Proliferation
Viability
Antioxidant
Apoptosis
Cell cycle
DNA damage & repair
Epigenetic regulation
Focal adhesion signaling
MIF signaling
Metabolism
Neuronal signaling
Other
PKC signaling
Protein folding & degradation
RAS/MAP signaling
Tyrosine kinase signaling
A549
MCF7
PC9
A549
MCF7
PC9
A549
MCF7
PC9

FIG. 19

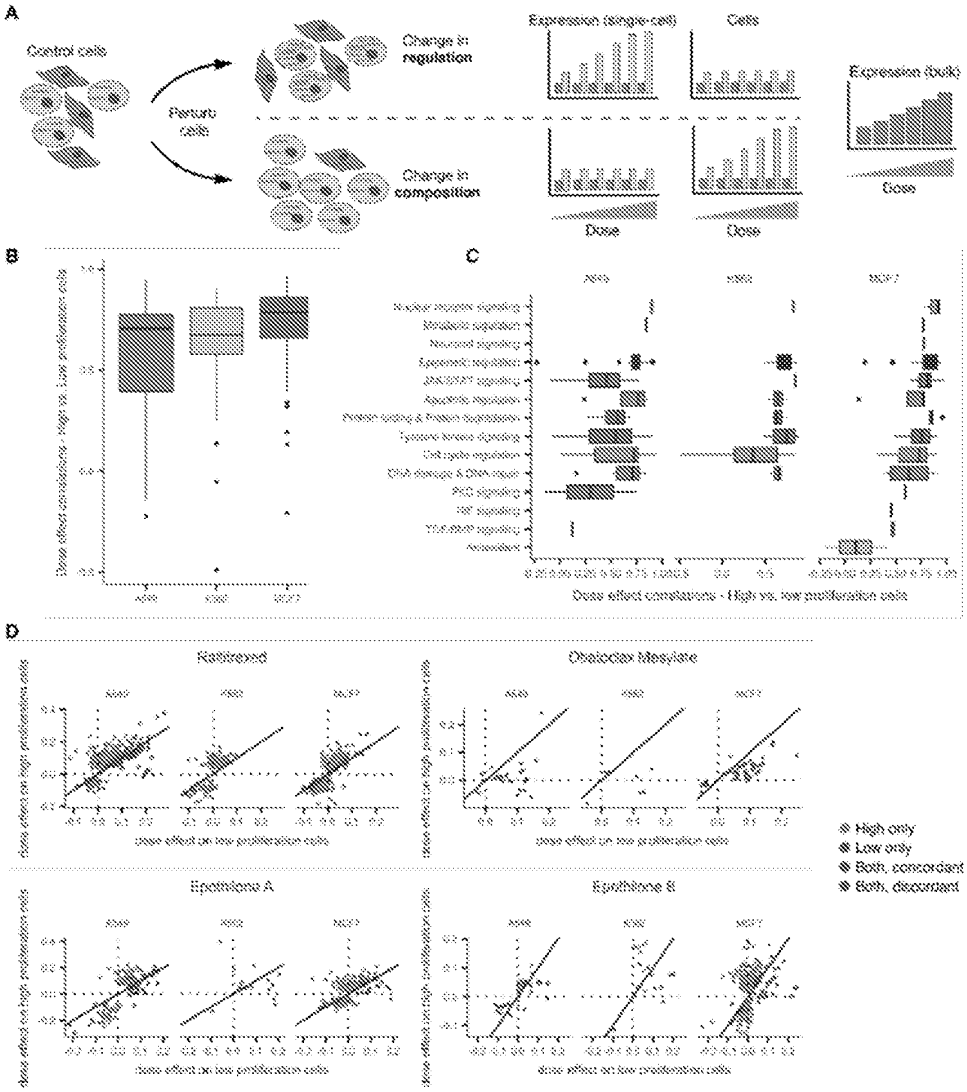

A
Control cells
Perturb cells
Change in regulation
Change in composition
Expression (single-cell)
Cells
Dose
Dose
Expression (bulk)
Dose
B
C
Dose effect correlations - High vs. low proliferation cells
D
Raltitrexed
Olaparib Mesylate
Epothilone A
Epothilone B
Dose effect on high proliferation cells
Dose effect on low proliferation cells
High only
Low only
Both, concordant
Both, discordant

FIG. 20

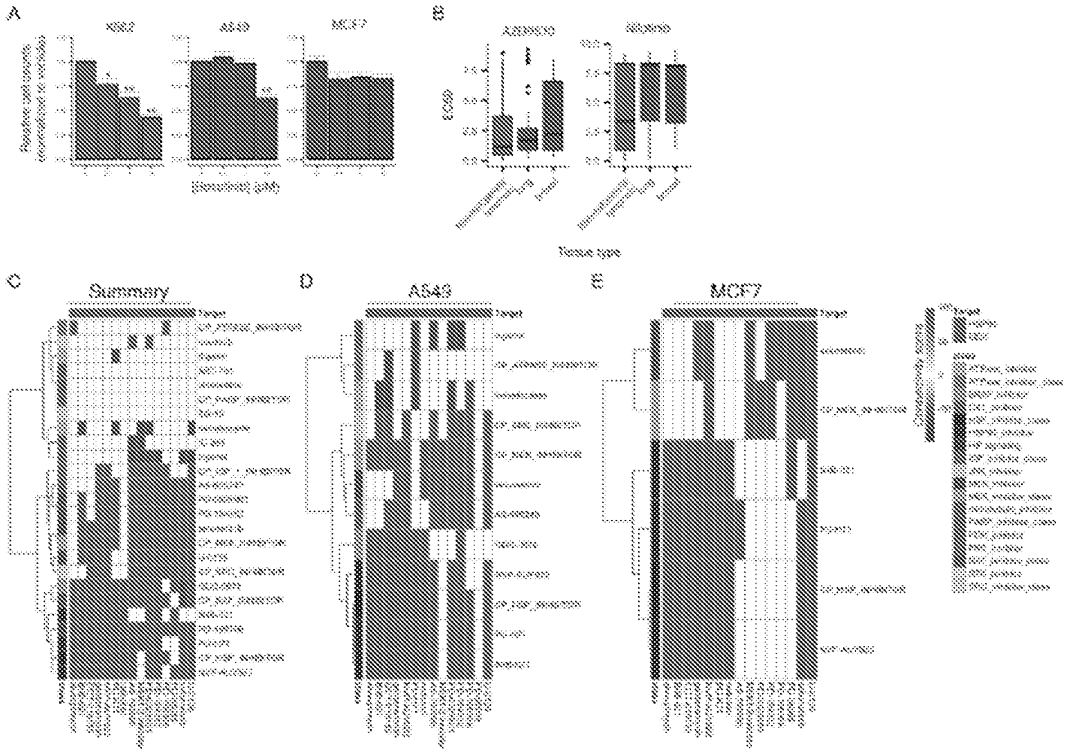


FIG. 21

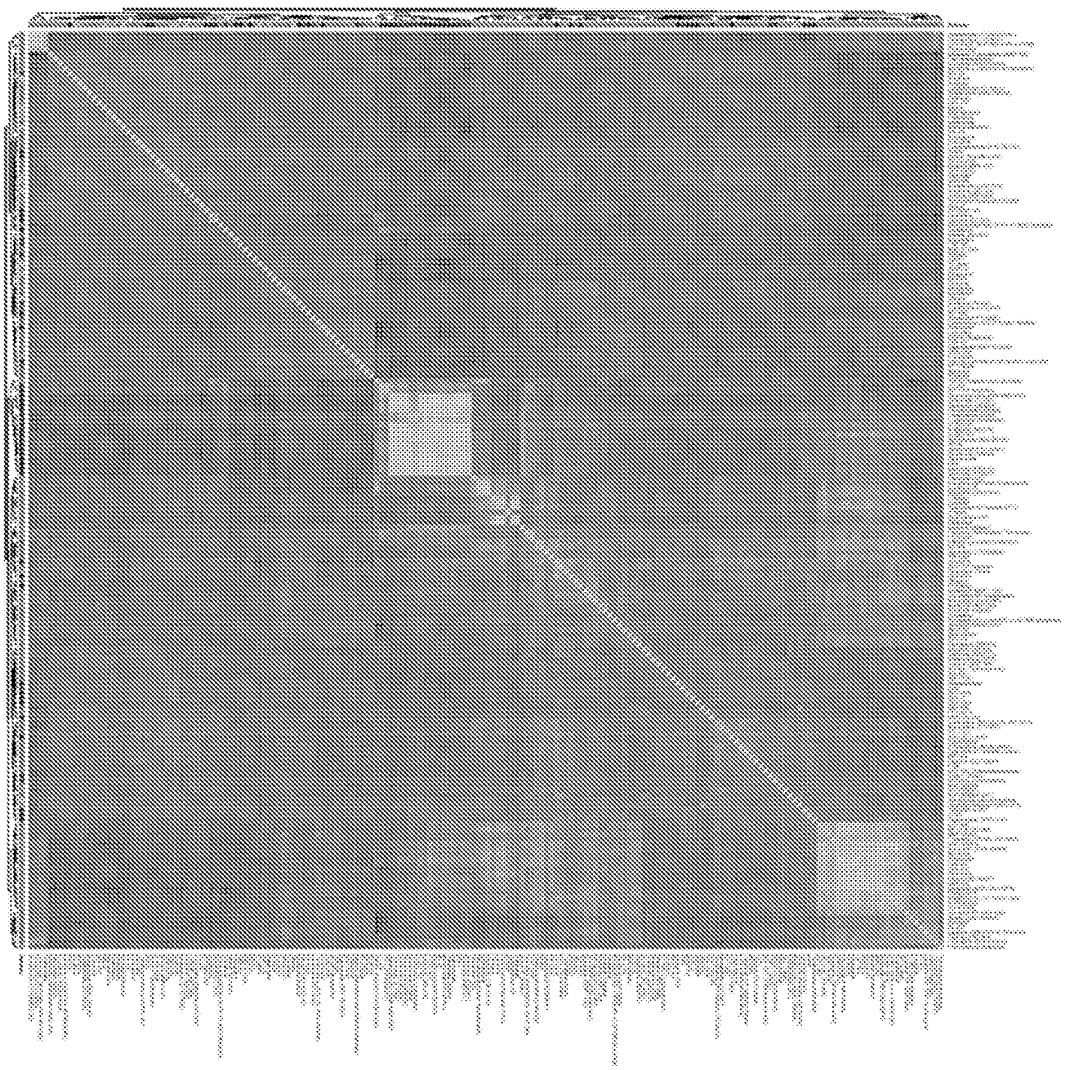


FIG. 22

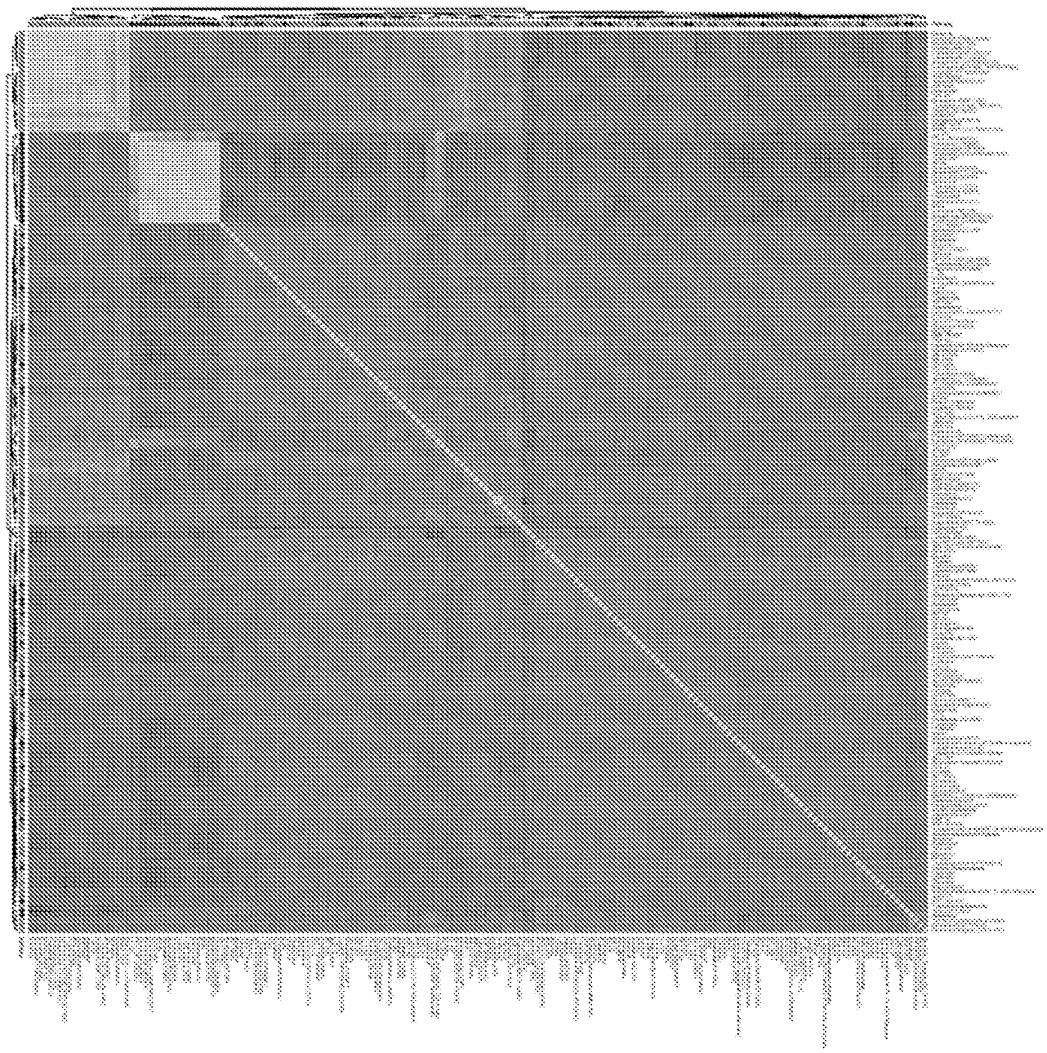


FIG. 23

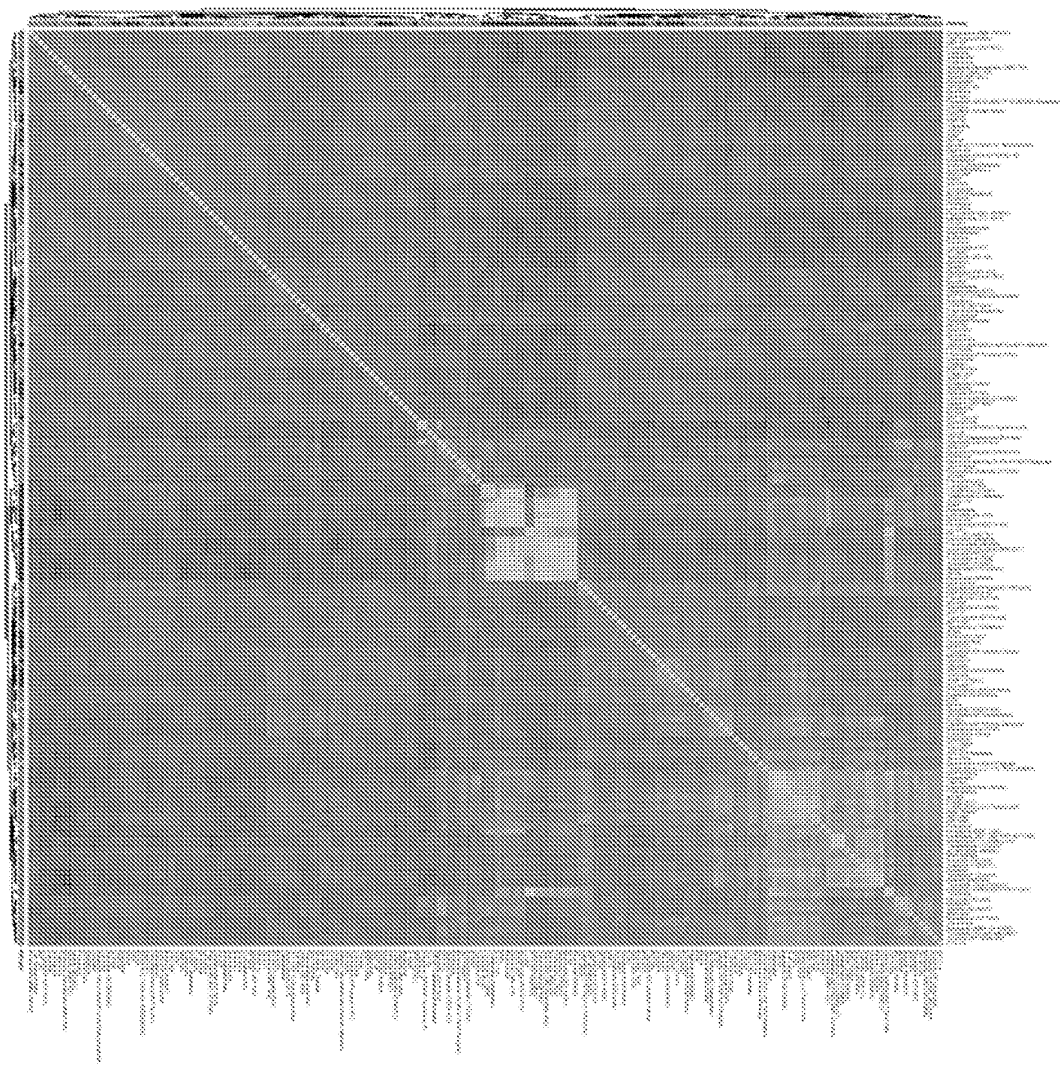


FIG. 24

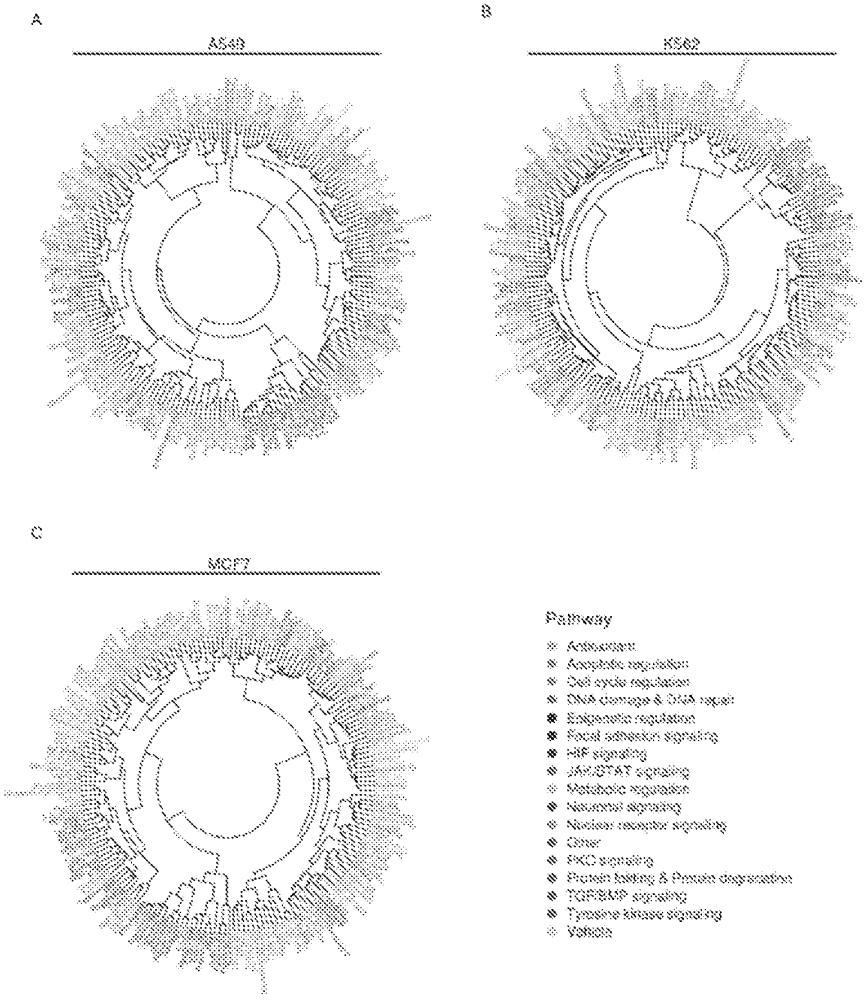

A
A549
B
K562
C
MCF7
Pathway
Antioxidant
Apoptotic regulation
Cell cycle regulation
DNA damage & DNA repair
Epigenetic regulation
Focal adhesion signaling
HIF signaling
JAK/STAT signaling
Metabolic regulation
Neuronal signaling
Nuclear receptor signaling
Other
PKC signaling
Protein folding & Protein degradation
TGFBMP signaling
Tyrosine kinase signaling
Vesicle

FIG. 25

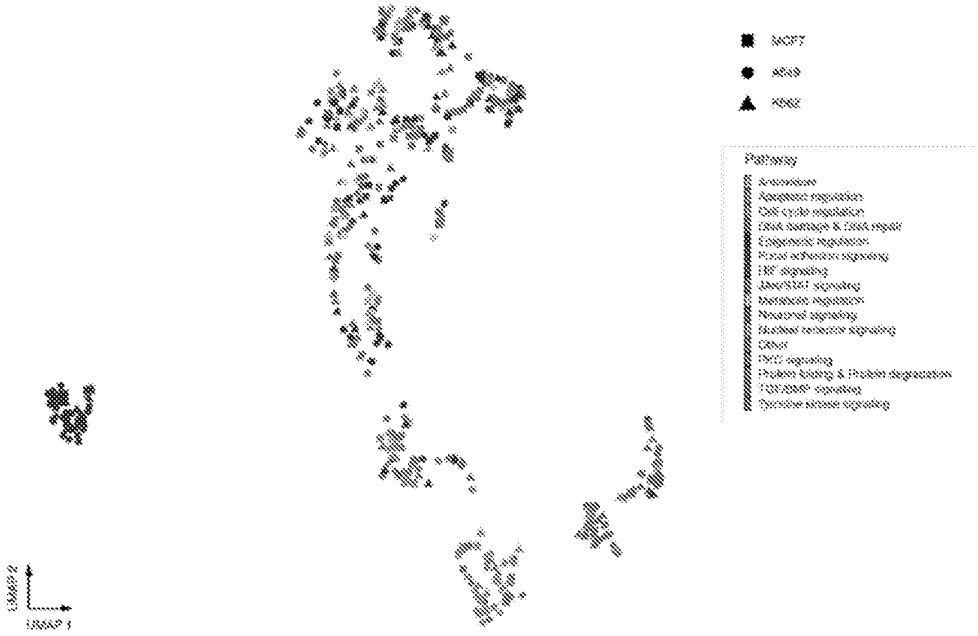


FIG. 26

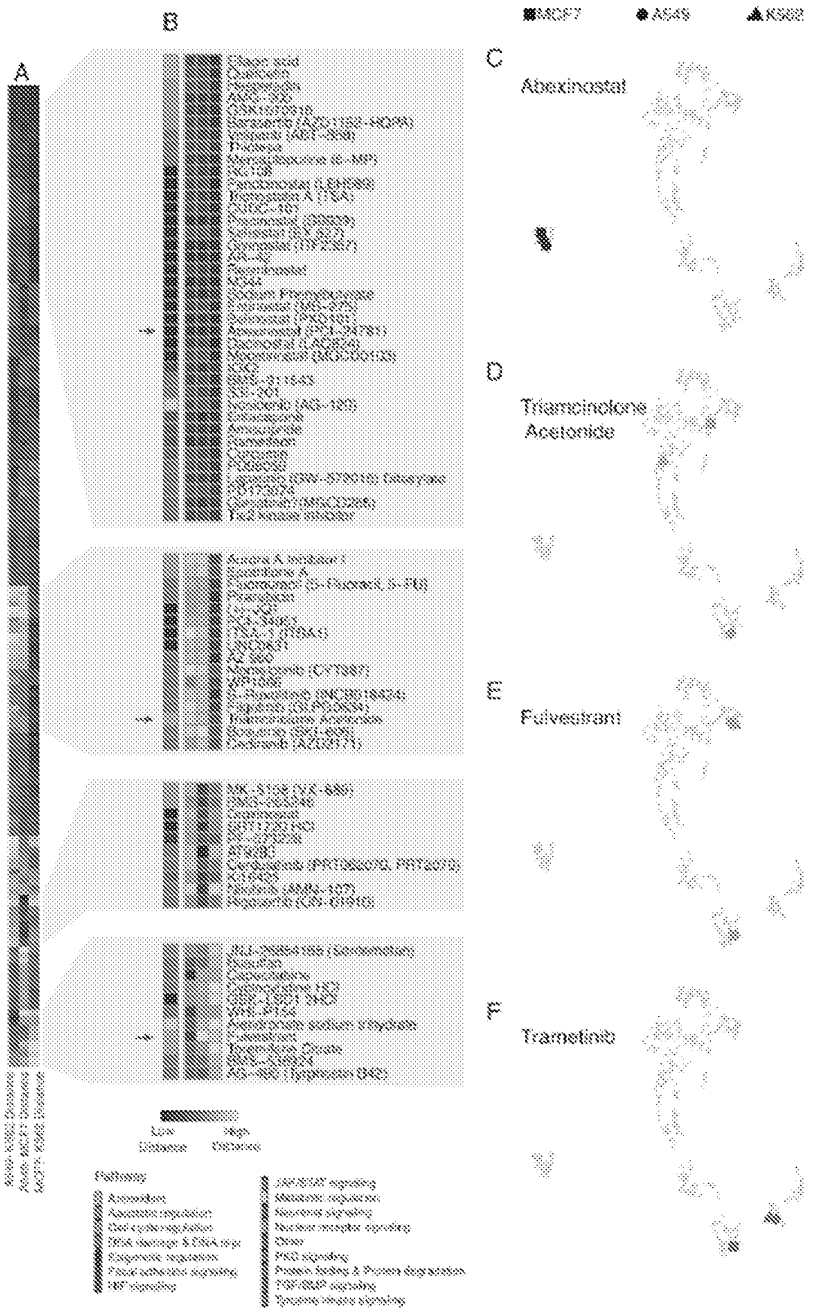

A
B
C
Abexinostat
D
Triamcinolone Acetonide
E
Fulvestrant
F
Trametinib
MCF7
A549
K562
Low
High
Pathway
Annexin
Apoptotic regulation
Cell cycle regulation
DNA damage & DNA repair
Epigenetic regulation
Focal adhesion signaling
HIF signaling
JAK/STAT signaling
Metabolic regulation
Neuronal signaling
Nuclear receptor signaling
Other
PKC signaling
Protein folding & Protein degradation
TGF/BMP signaling
Tyrosine kinase signaling

FIG. 27

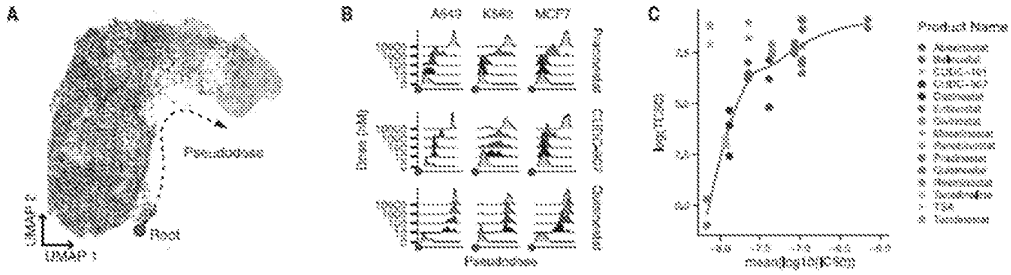

A
B
C
Pseudotime
Root
UMAP 2
UMAP 1
A549
K562
MCF7
Product Name

FIG. 28

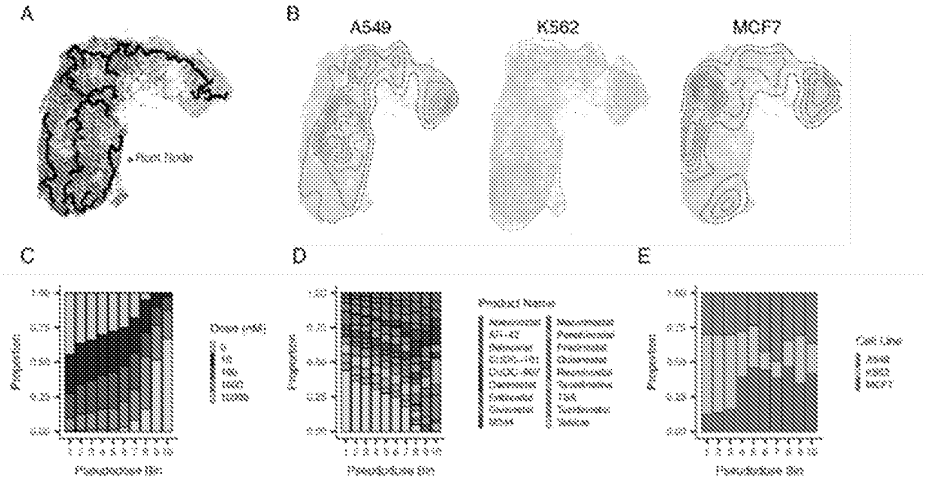

A
B
C
D
E
A549
K562
MCF7
Root Node
Proportion
Pseudotime Bin
Product Name
Cell Line

FIG. 29

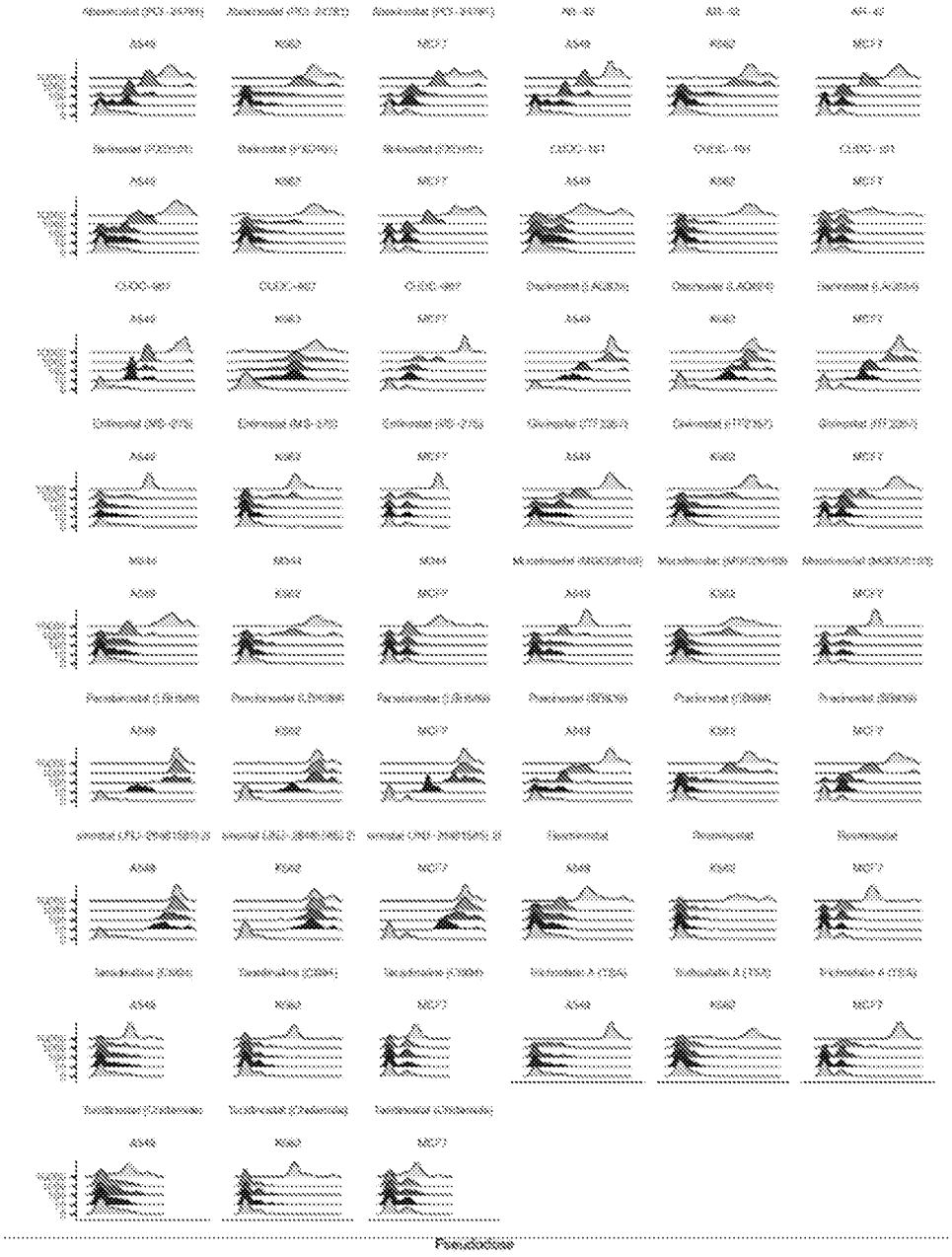


FIG. 30

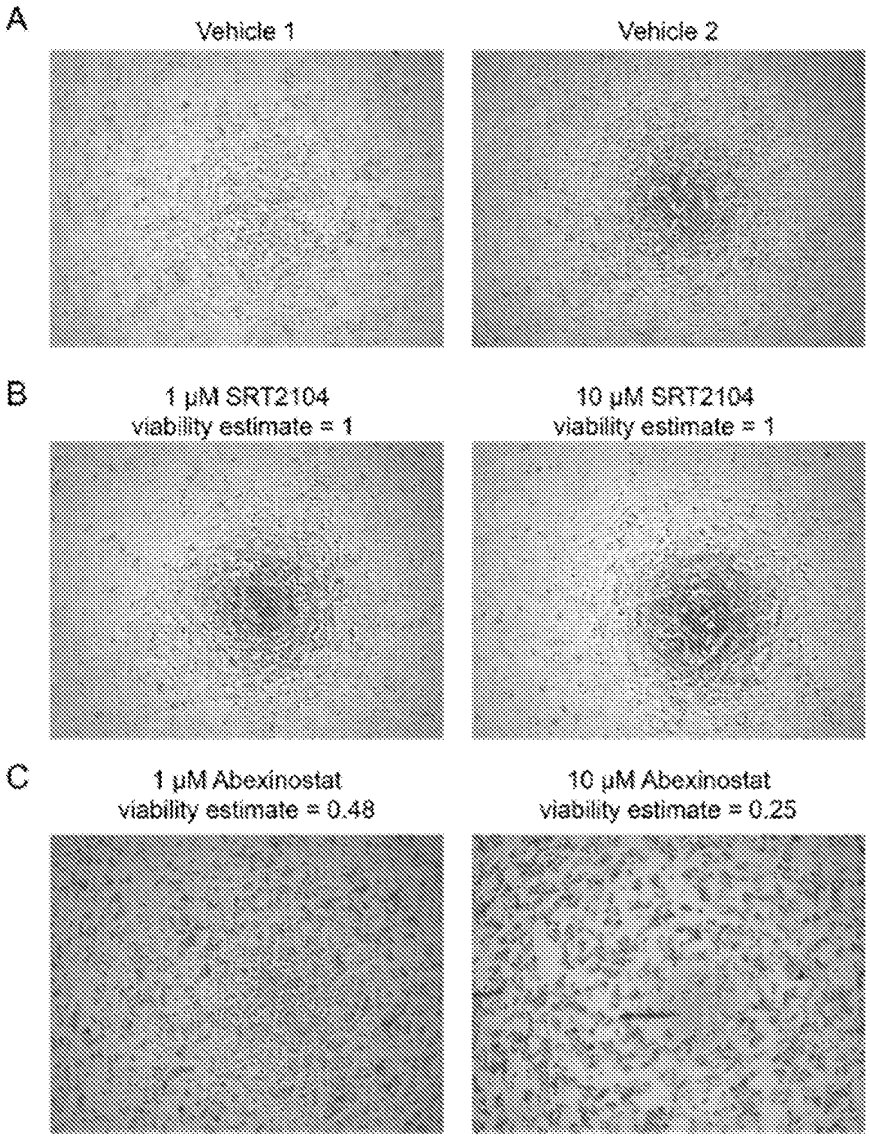

A
Vehicle 1
Vehicle 2
B
1 µM SRT2104
viability estimate = 1
10 µM SRT2104
viability estimate = 1
C
1 µM Abexinostat
viability estimate = 0.48
10 µM Abexinostat
viability estimate = 0.25

FIG. 31

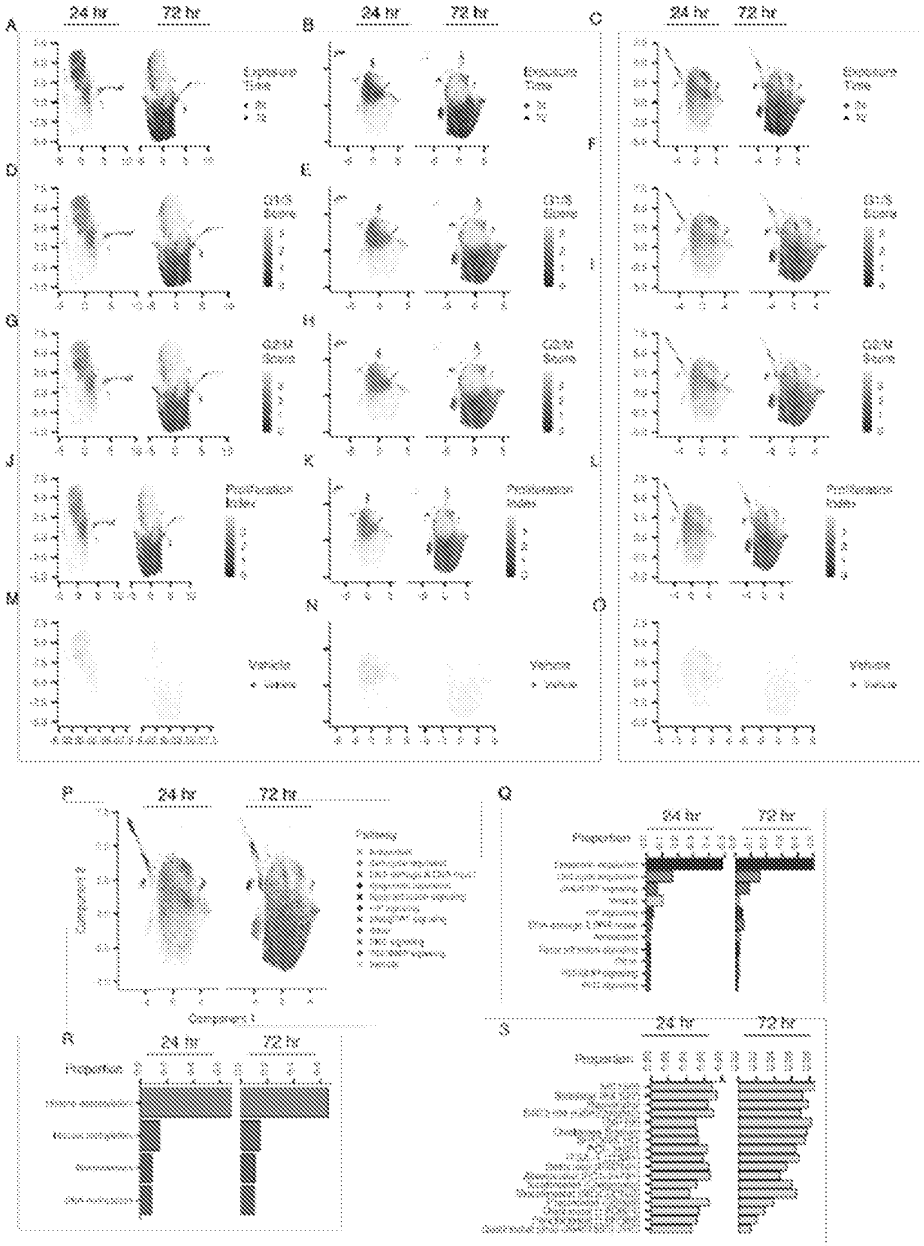


FIG. 32

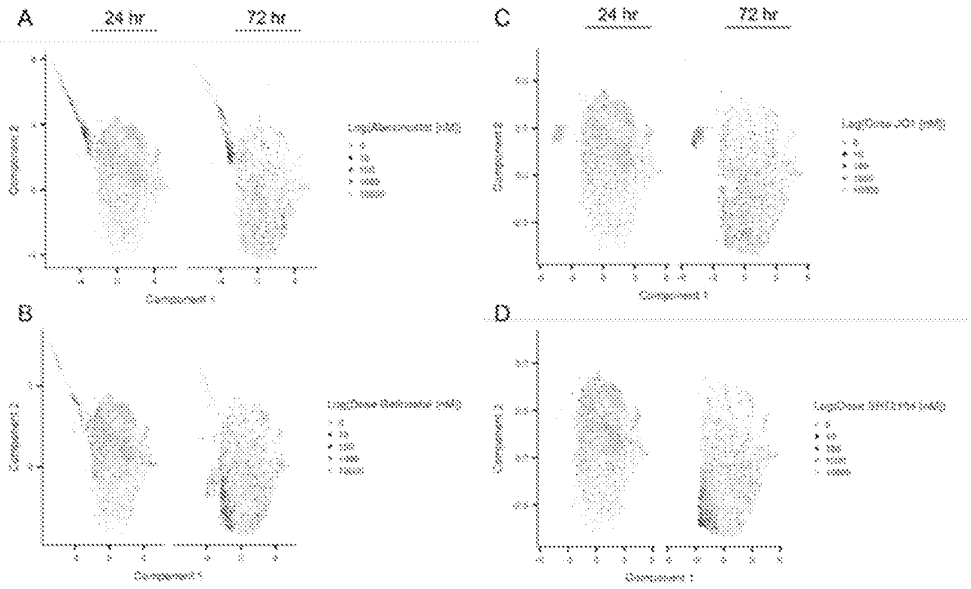


FIG. 33

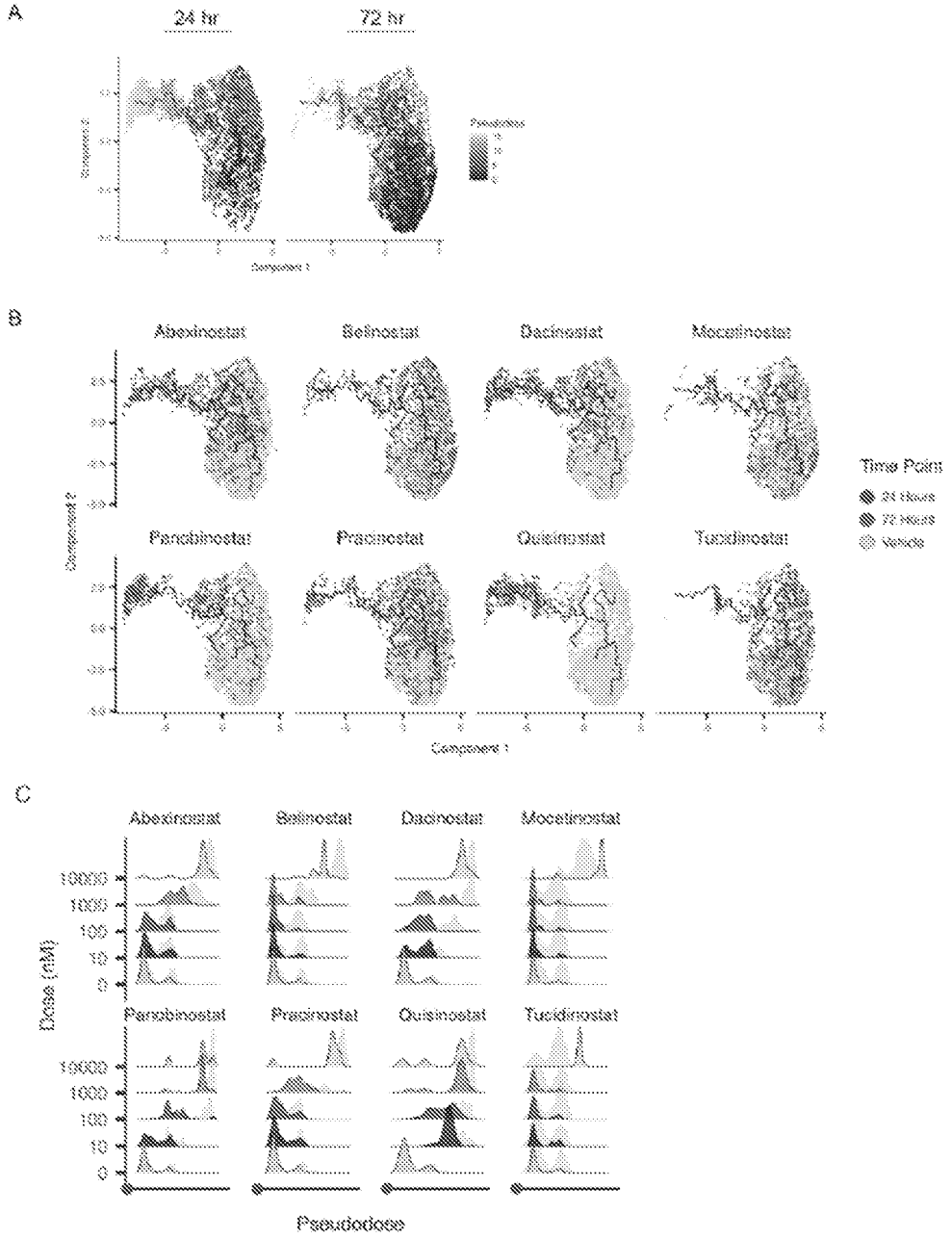

A
24 hr
72 hr
B
Abexinostat
Belinostat
Dacinostat
Mocetinostat
Panobinostat
Pracinostat
Quisinostat
Tucidinostat
Time Point
Vehicle
C
Abexinostat
Belinostat
Dacinostat
Mocetinostat
Panobinostat
Pracinostat
Quisinostat
Tucidinostat
Dose (nM)
10000
1000
100
10
0
Pseudodose

FIG. 34

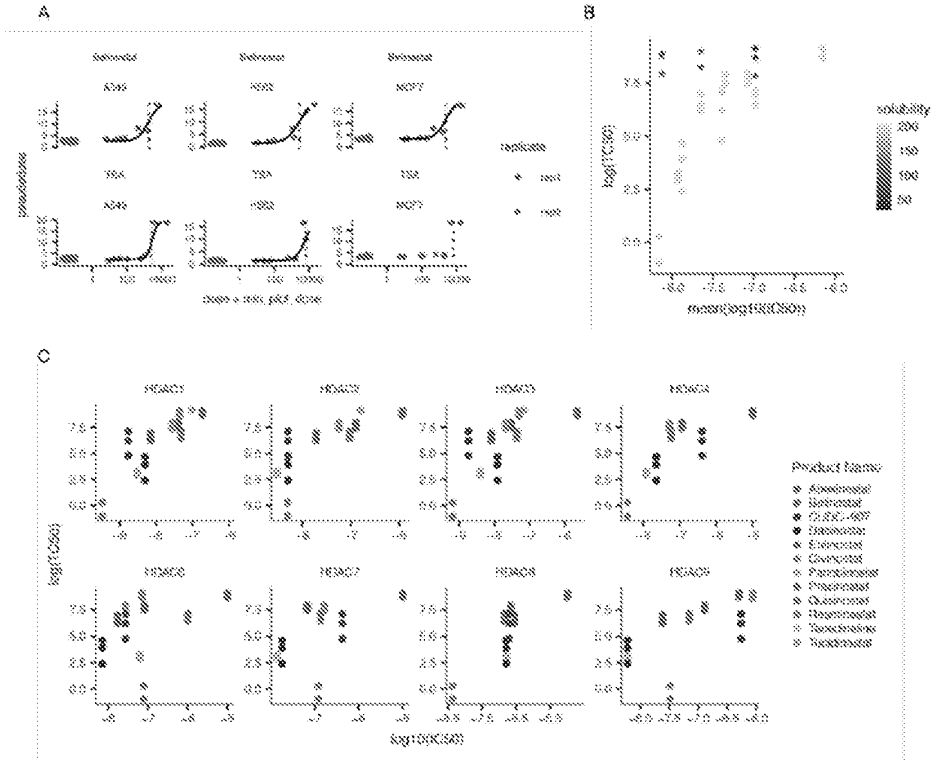


FIG. 35

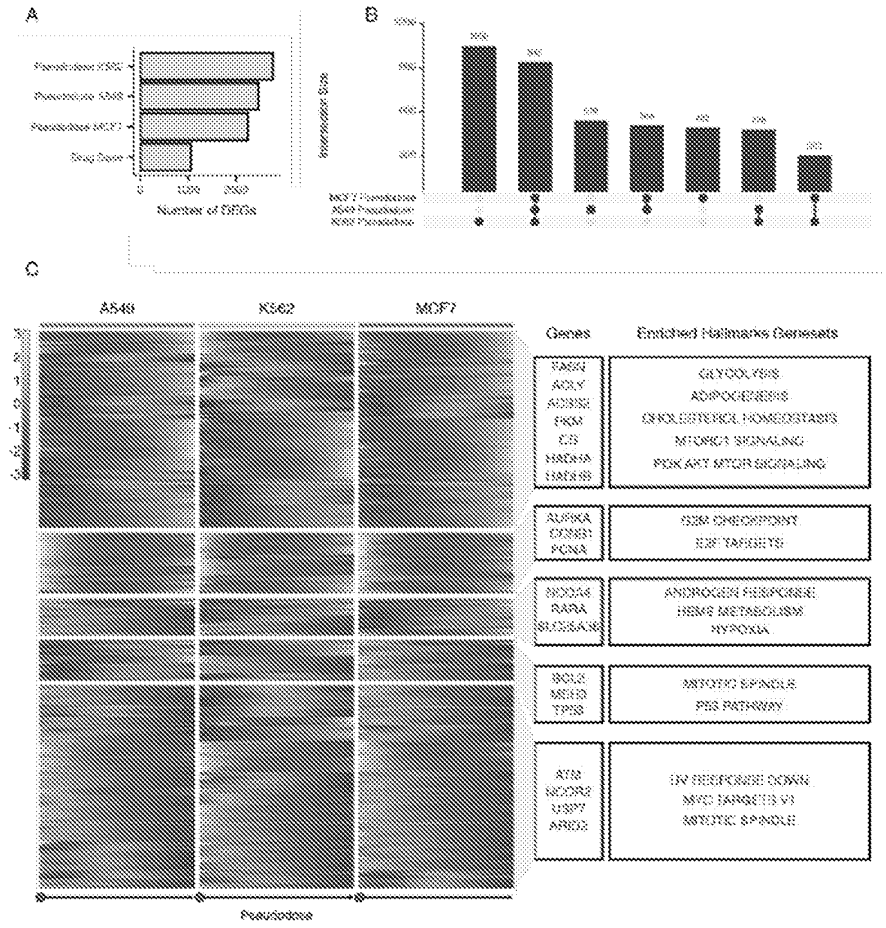

A
B
C
A549
K562
MCF7
Genes
Enriched Hallmarks Genesets
Pseudotime

FIG. 36

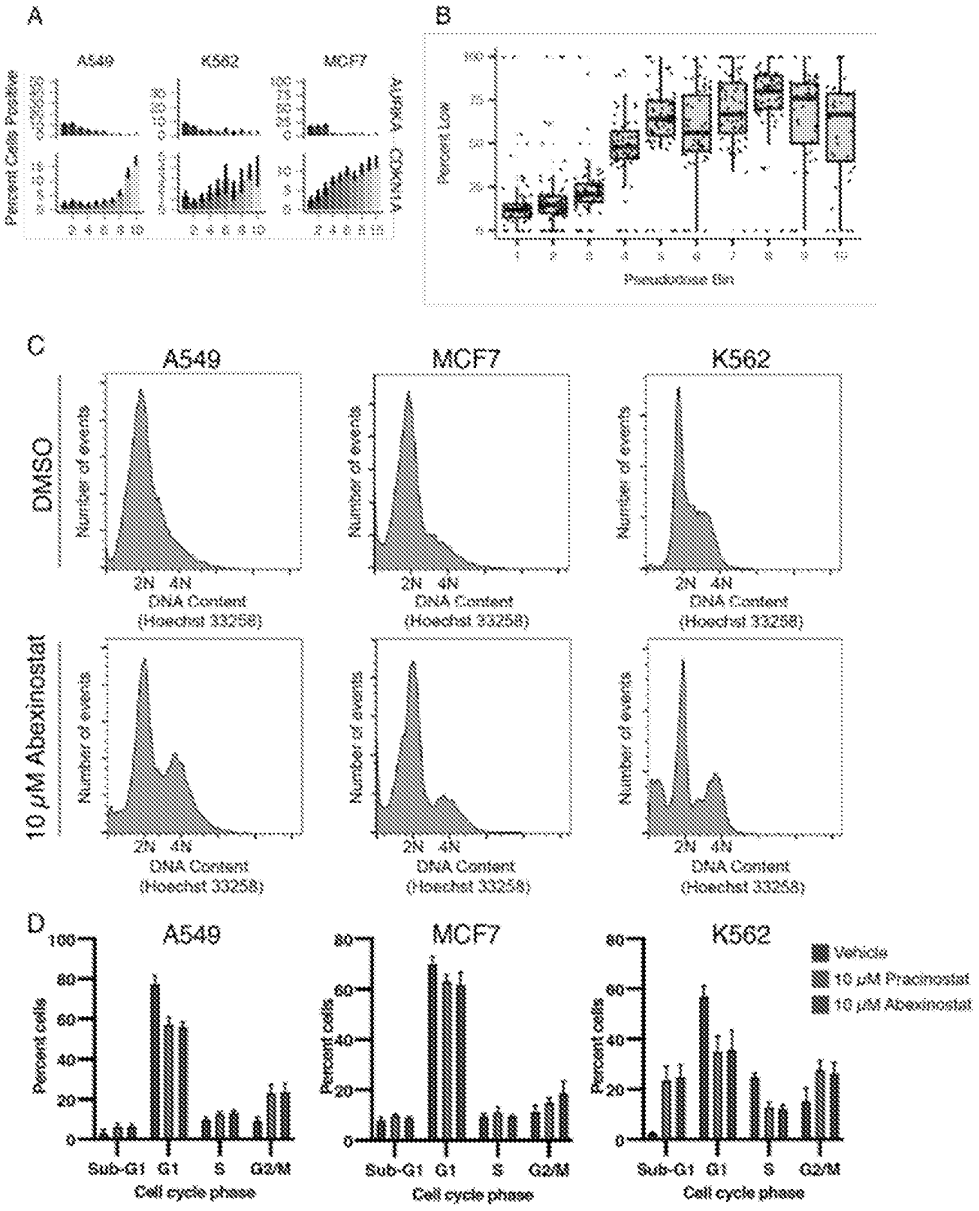

A
A549
K562
MCF7
Percent Cells Positive
Alpha-1 ConA
B
Percent Low
Pseudotime Bin
C
A549
MCF7
K562
DMSO
10 μM Abexinostat
Number of events
2N 4N
DNA Content
(Hoechst 33258)
D
A549
MCF7
K562
Percent cells
Sub-G1 G1 S G2/M
Cell cycle phase
Vehicle
10 μM Pracinostat
10 μM Abexinostat

FIG. 37

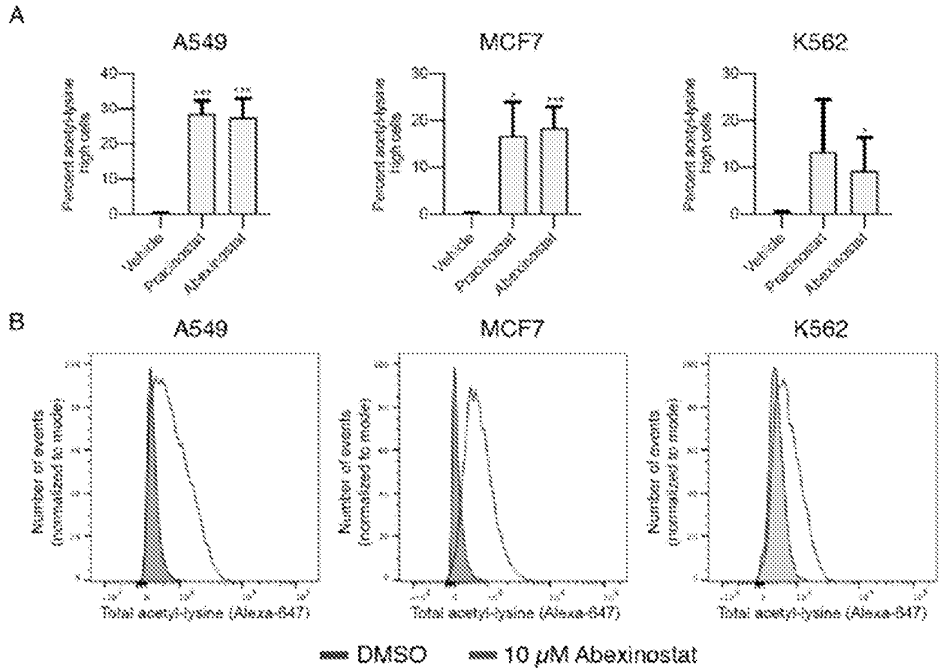

A
A549
MCF7
K562
Vehicle
Pracinostat
Abexinostat
B
A549
MCF7
K562
Total acetyl-lysine (Alexa-647)
DMSO
10 μM Abexinostat

FIG. 38

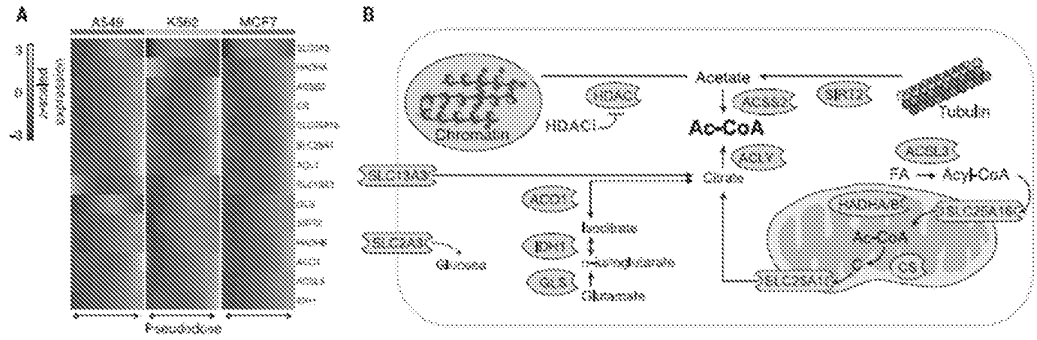

A
A549
K562
MCF7
Pseudotime
B
Acetate
HDAC
HDAC1
Chromatin
ACSS2
SIRT2
Tubulin
Ac-CoA
ACLY
ACSS1
SLC25A1
Citrate
FA → Acyl-CoA
ACO1
Isocitrate
IDH1
α-ketoglutarate
SLC2A3
Glucose
GLS
Glutamate
NADH/NP
SLC25A10
Ac-CoA
CS
SLC25A10

FIG. 39

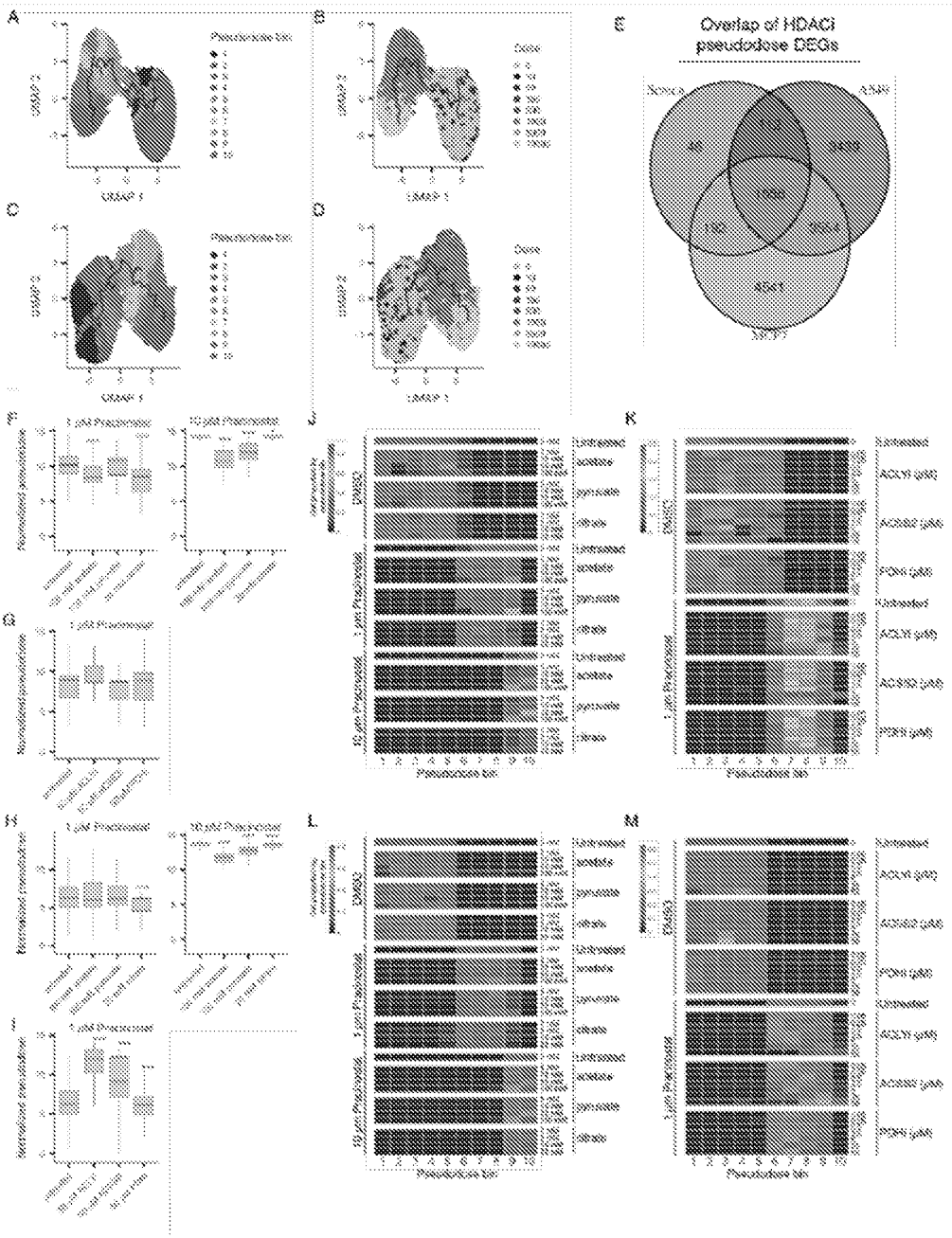


FIG. 40

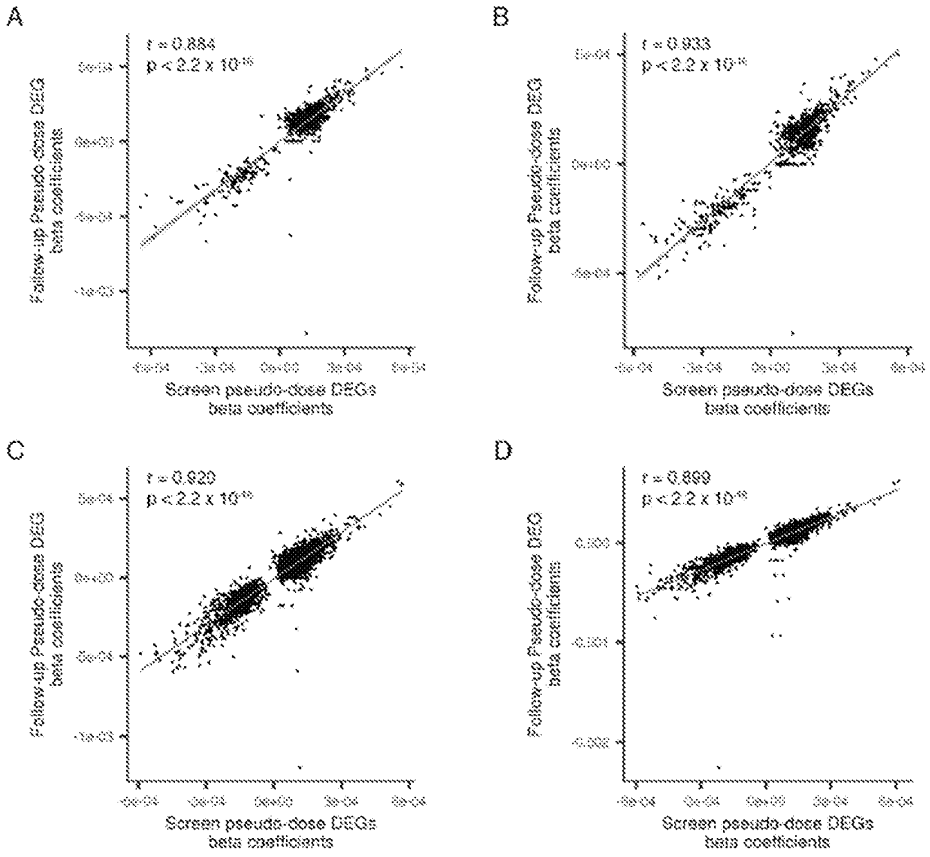

A
r = 0.884
p < 2.2 x 10^-16
Follow-up Pseudo-dose DEG beta coefficients
Screen pseudo-dose DEGs beta coefficients
B
r = 0.833
p < 2.2 x 10^-16
Follow-up Pseudo-dose DEG beta coefficients
Screen pseudo-dose DEGs beta coefficients
C
r = 0.920
p < 2.2 x 10^-16
Follow-up Pseudo-dose DEG beta coefficients
Screen pseudo-dose DEGs beta coefficients
D
r = 0.899
p < 2.2 x 10^-16
Follow-up Pseudo-dose DEG beta coefficients
Screen pseudo-dose DEGs beta coefficients

FIG. 41

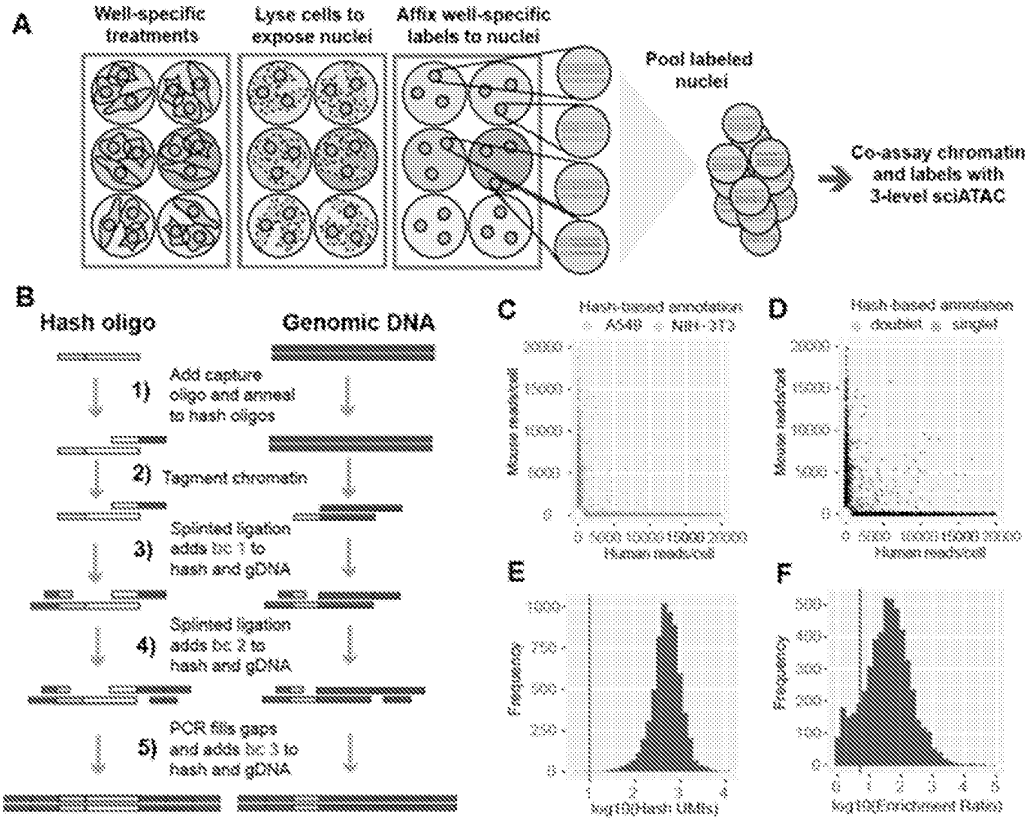

A
Well-specific treatments
Lyse cells to expose nuclei
Affix well-specific labels to nuclei
Pool labeled nuclei
Co-assay chromatin and labels with 3-level sciATAC
B
Hash oligo
Genomic DNA
1) Add capture oligo and anneal to hash oligos
2) Tagment chromatin
3) Splinted ligation adds bc 1 to hash and gDNA
4) Splinted ligation adds bc 2 to hash and gDNA
5) PCR fills gaps and adds bc 3 to hash and gDNA
C
Hash-based annotation
A549
NIH-3T3
Mouse reads/cell
Human reads/cell
D
Hash-based annotation
doublet
singlet
Mouse reads/cell
Human reads/cell
E
Frequency
log10(Hash UMIs)
F
Frequency
log10(Enrichment Ratio)

FIG. 42

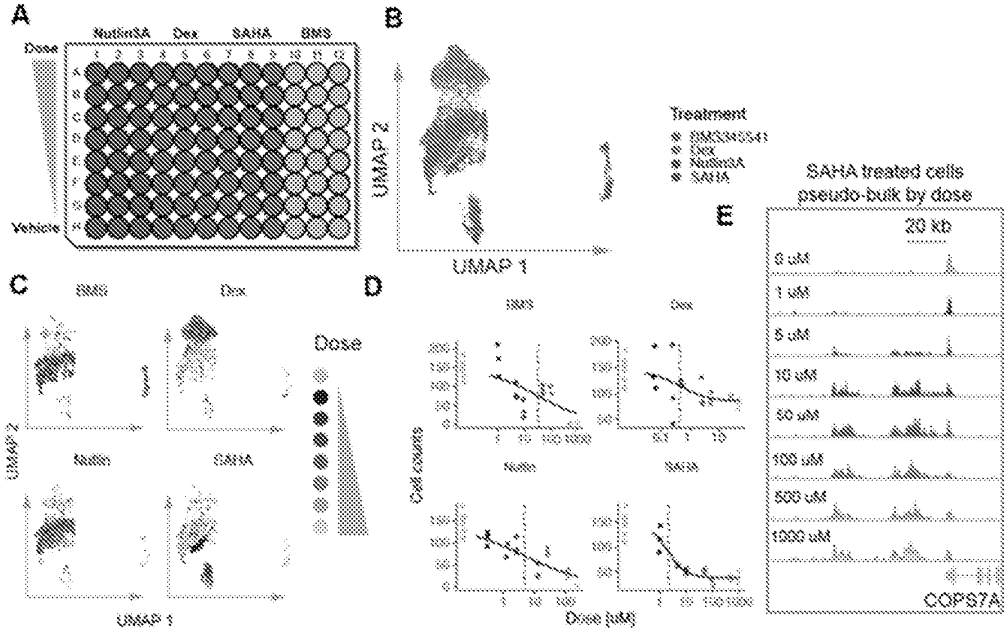

A
Nutlin3A
Dex
SAHA
BMS
Dose
Vehicle
B
UMAP 2
UMAP 1
Treatment
BMS
Dex
Nutlin3A
SAHA
C
BMS
Dex
Nutlin
SAHA
UMAP 2
UMAP 1
Dose
D
Cell counts
Dose (uM)
E
SAHA treated cells
pseudo-bulk by dose
20 kb
0 uM
1 uM
5 uM
10 uM
50 uM
100 uM
500 uM
1000 uM
COPS7A

FIG. 43

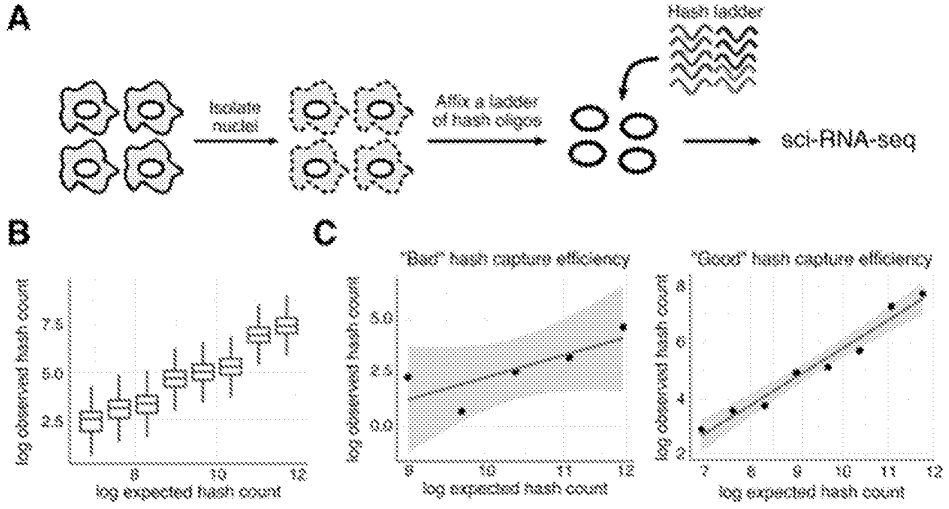

A
Isolate nuclei
Affix a ladder of hash oligos
Hash ladder
sci-RNA-seq
B
log observed hash count
log expected hash count
C
"Bad" hash capture efficiency
"Good" hash capture efficiency
log observed hash count
log expected hash count

Fig. 1

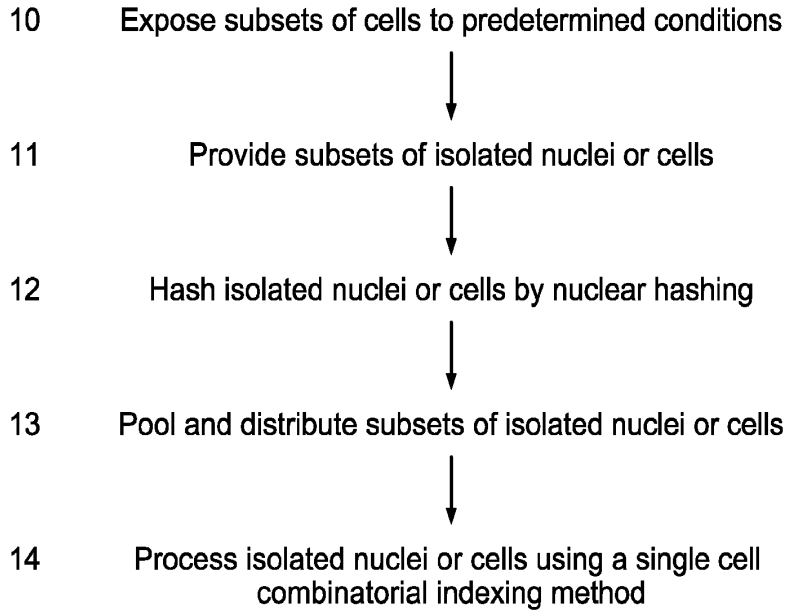

10
Expose subsets of cells to predetermined conditions
11
Provide subsets of isolated nuclei or cells
12
Hash isolated nuclei or cells by nuclear hashing
13
Pool and distribute subsets of isolated nuclei or cells
14
Process isolated nuclei or cells using a single cell combinatorial indexing method

Fig. 2

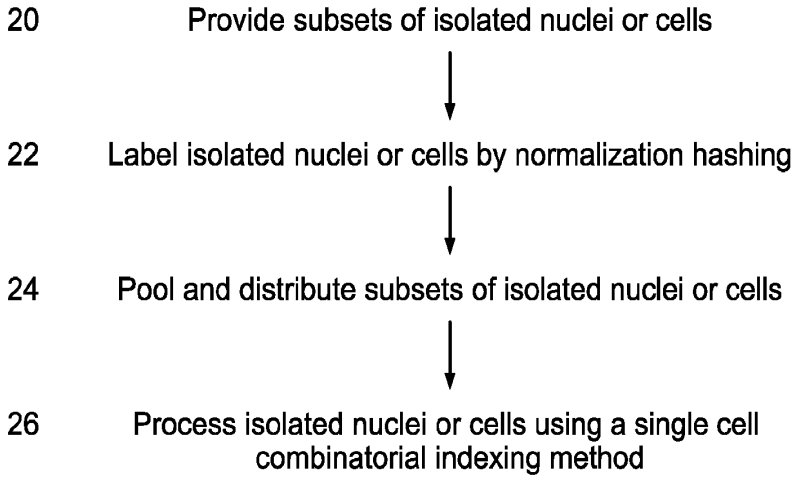

20
Provide subsets of isolated nuclei or cells
22
Label isolated nuclei or cells by normalization hashing
24
Pool and distribute subsets of isolated nuclei or cells
26
Process isolated nuclei or cells using a single cell combinatorial indexing method

Fig. 3

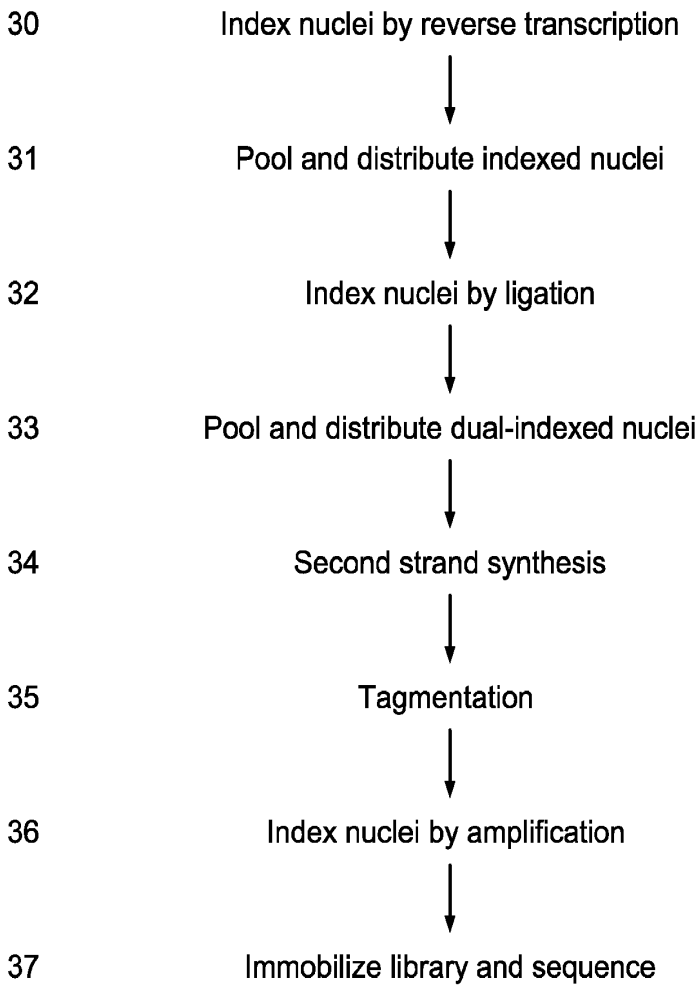
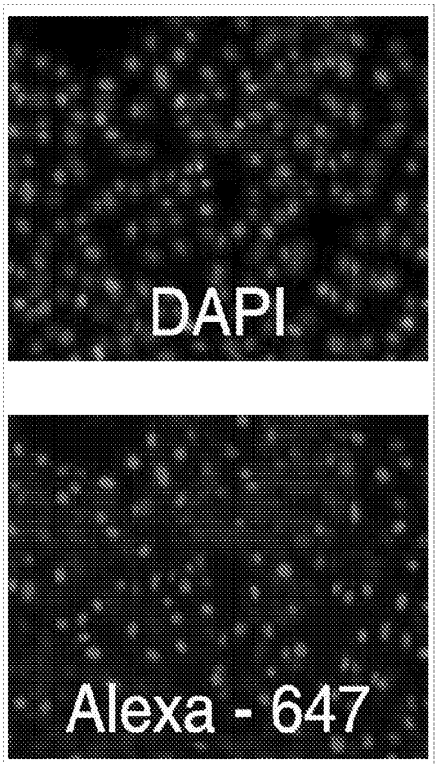

30
Index nuclei by reverse transcription
31
Pool and distribute indexed nuclei
32
Index nuclei by ligation
33
Pool and distribute dual-indexed nuclei
34
Second strand synthesis
35
Tagmentation
36
Index nuclei by amplification
37
Immobilize library and sequence

Fig. 4A

A



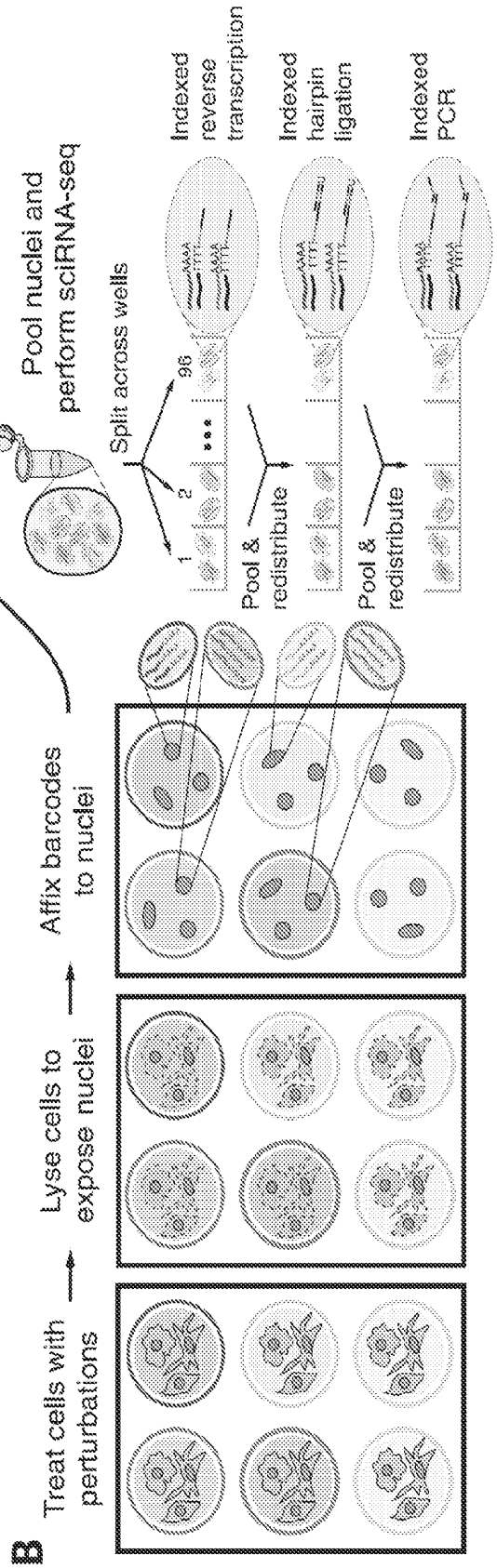

B
Treat cells with perturbations
Lyse cells to expose nuclei
Affix barcodes to nuclei
Pool nuclei and perform sciRNA-seq
Split across wells
1
2
96
Pool & redistribute
Pool & redistribute
Indexed reverse transcription
Indexed hairpin ligation
Indexed PCR

Fig. 4B

Fig. 4C

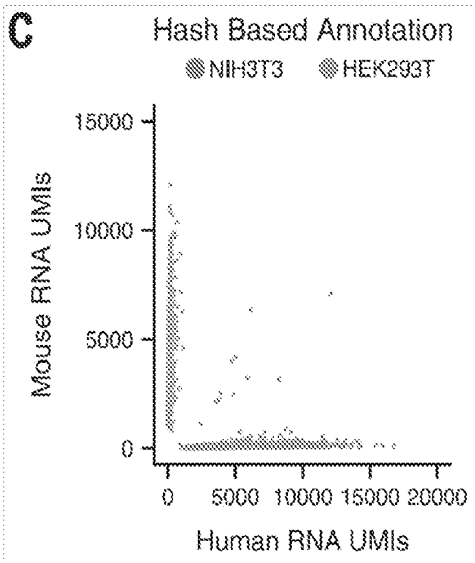


Fig. 4D

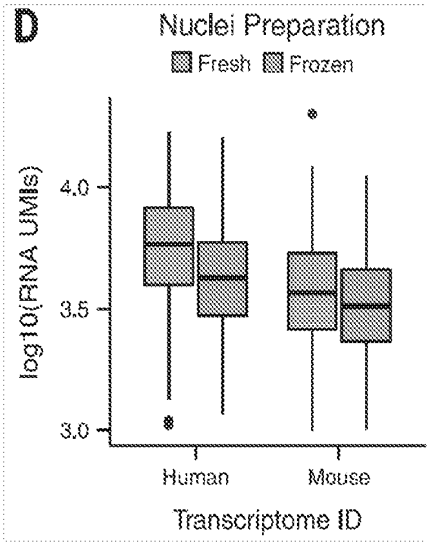


Fig. 4E

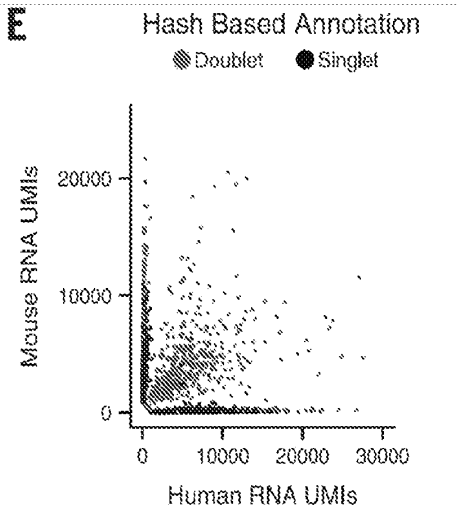


Fig. 5A

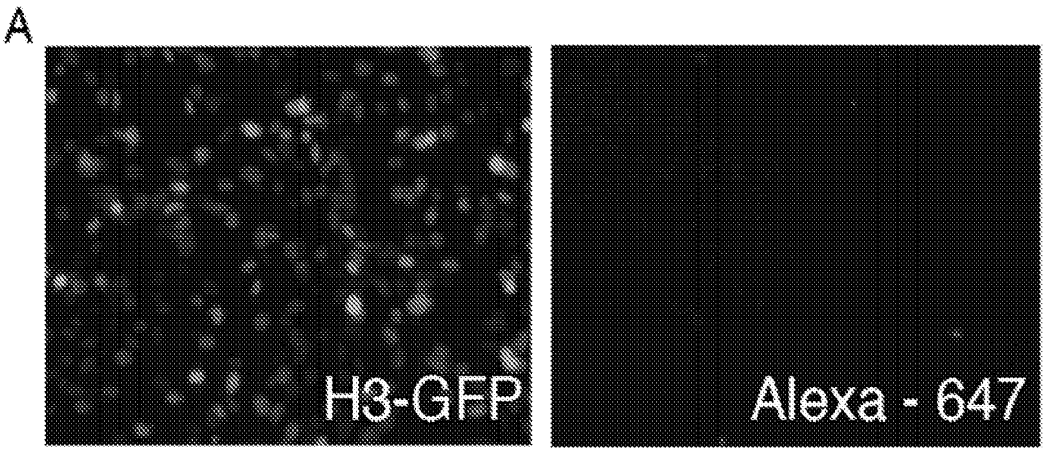


Fig. 5B

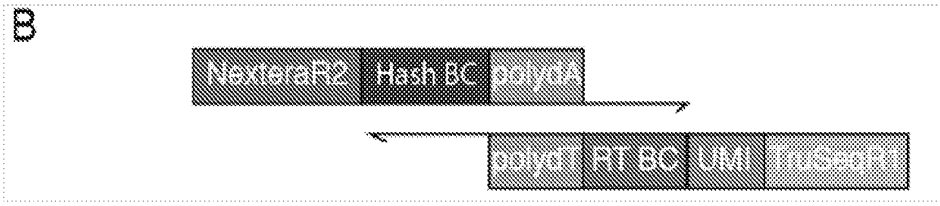


Fig. 5C

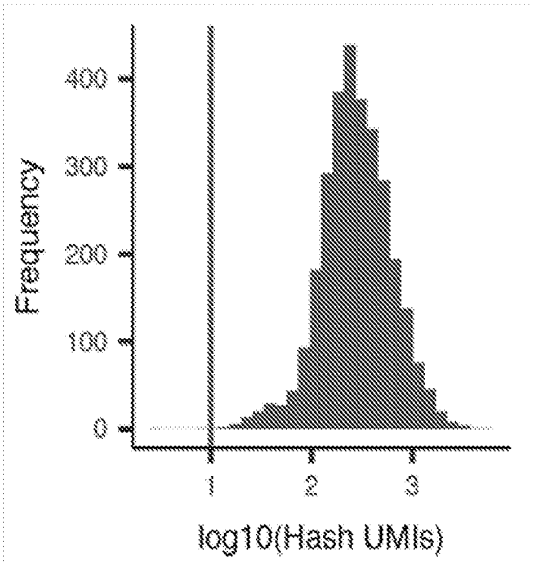


Fig. 5D

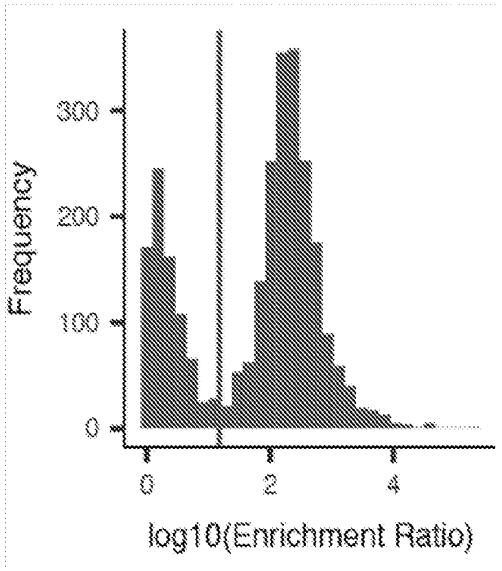


Fig. 5E

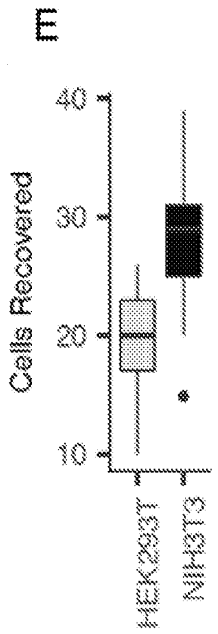


Fig. 5F

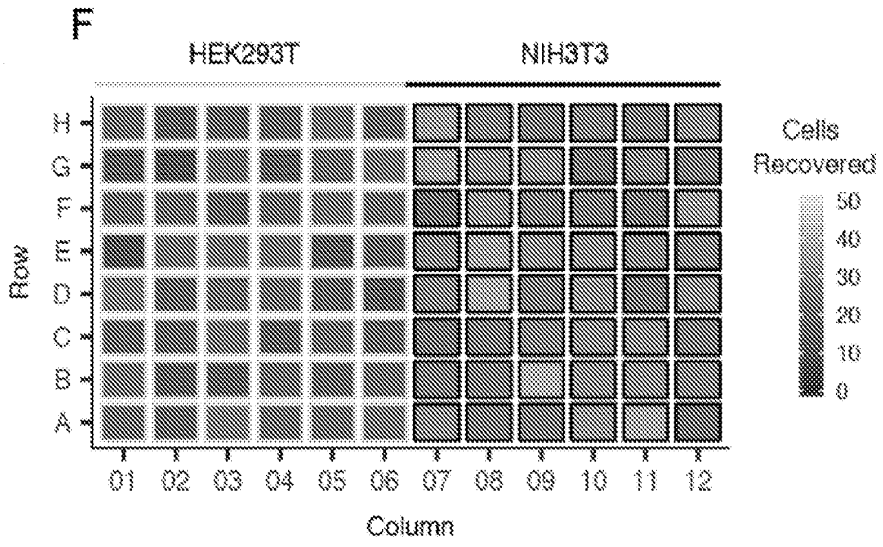


Fig. 5G

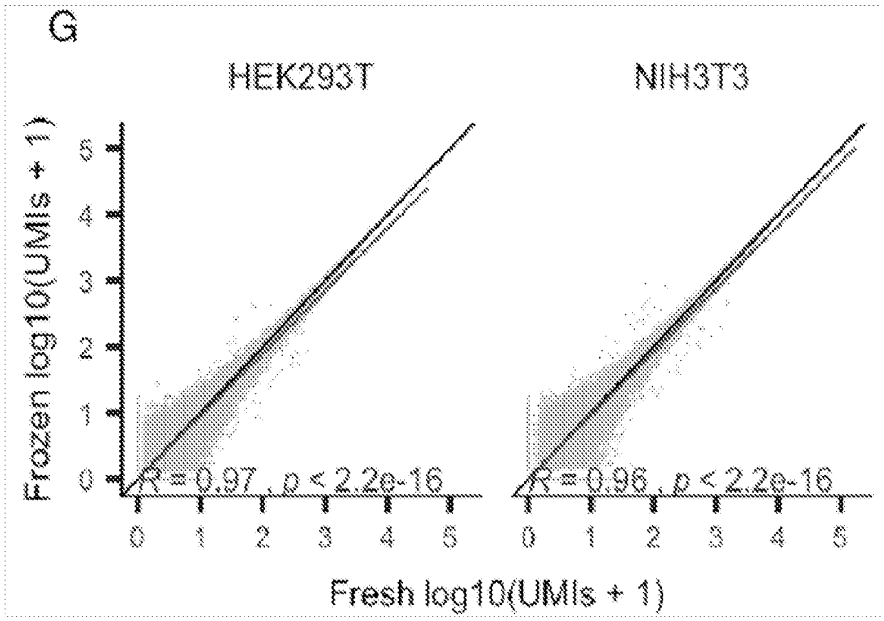


Fig. 5H

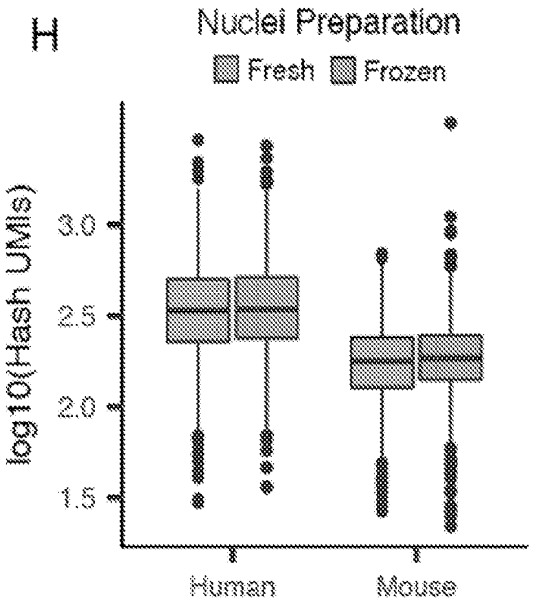


Fig. 5I

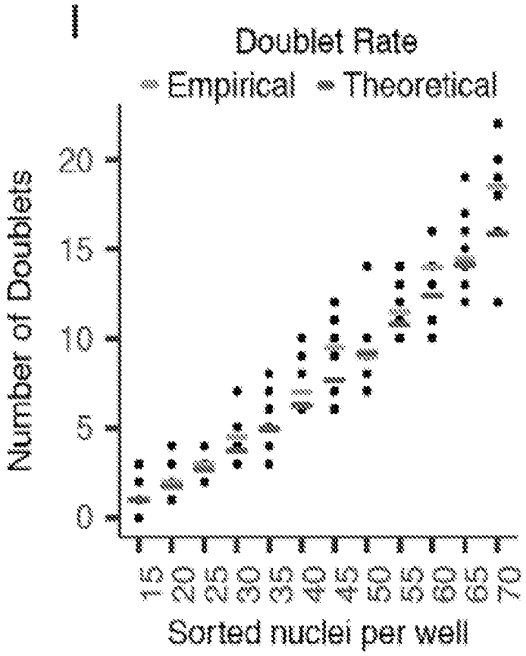


Fig. 5J

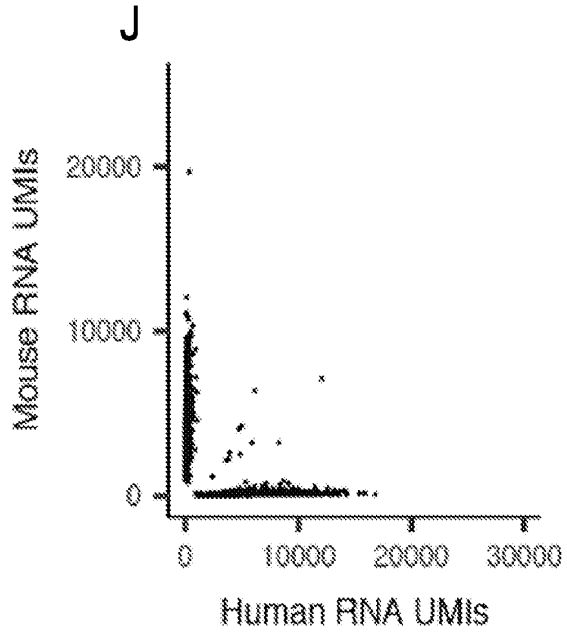


Fig. 5K

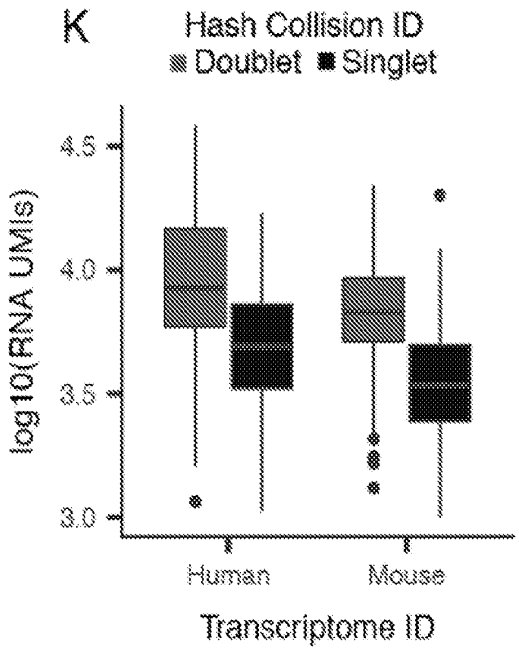


Fig. 6A

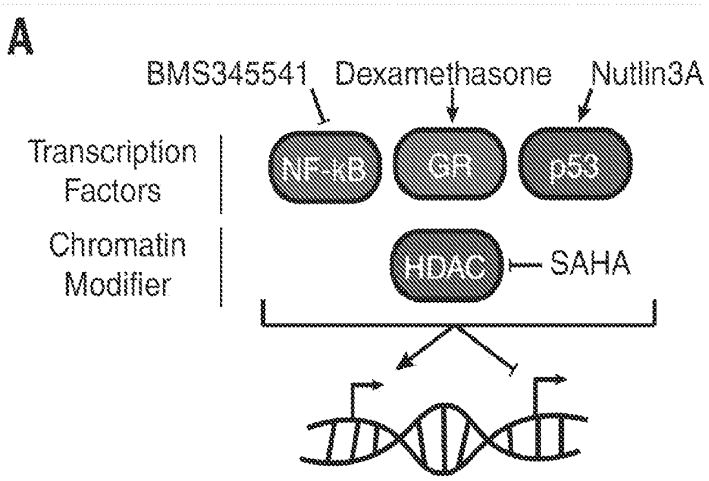


Fig. 6B

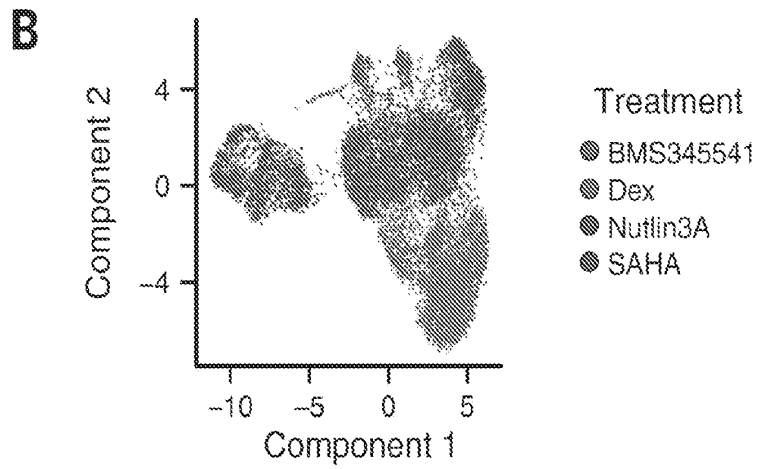


Fig. 6C

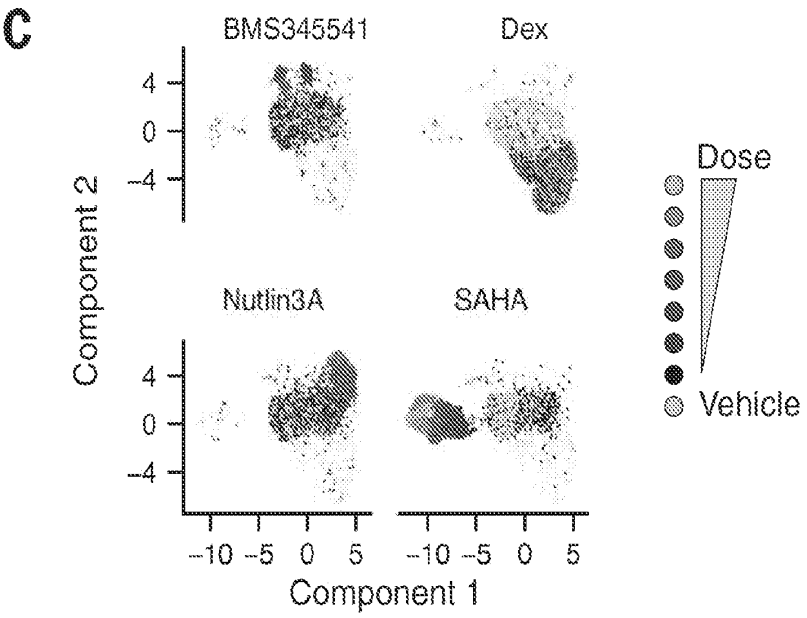


Fig. 6D

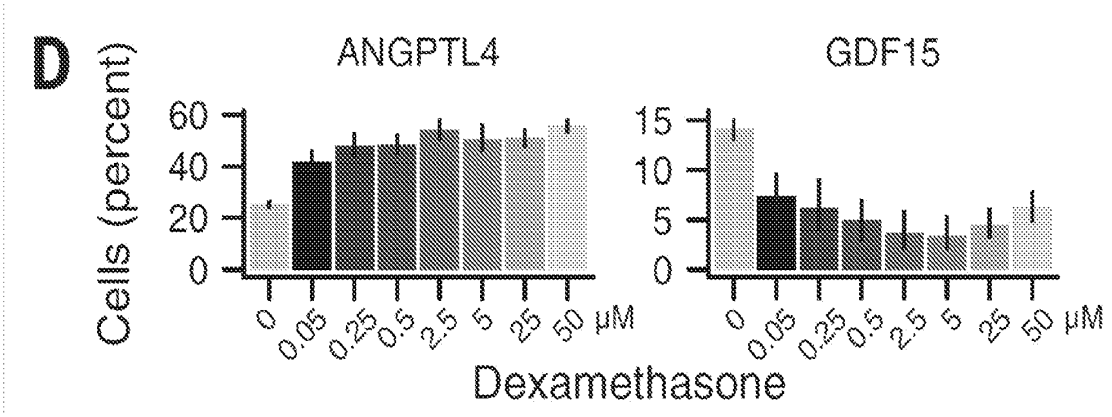

D
ANGPTL4
GDF15
Cells (percent)
60
40
20
0
15
10
5
0
0 0.05 0.25 0.5 2.5 5 25 50 μM
Dexamethasone

Fig. 6E

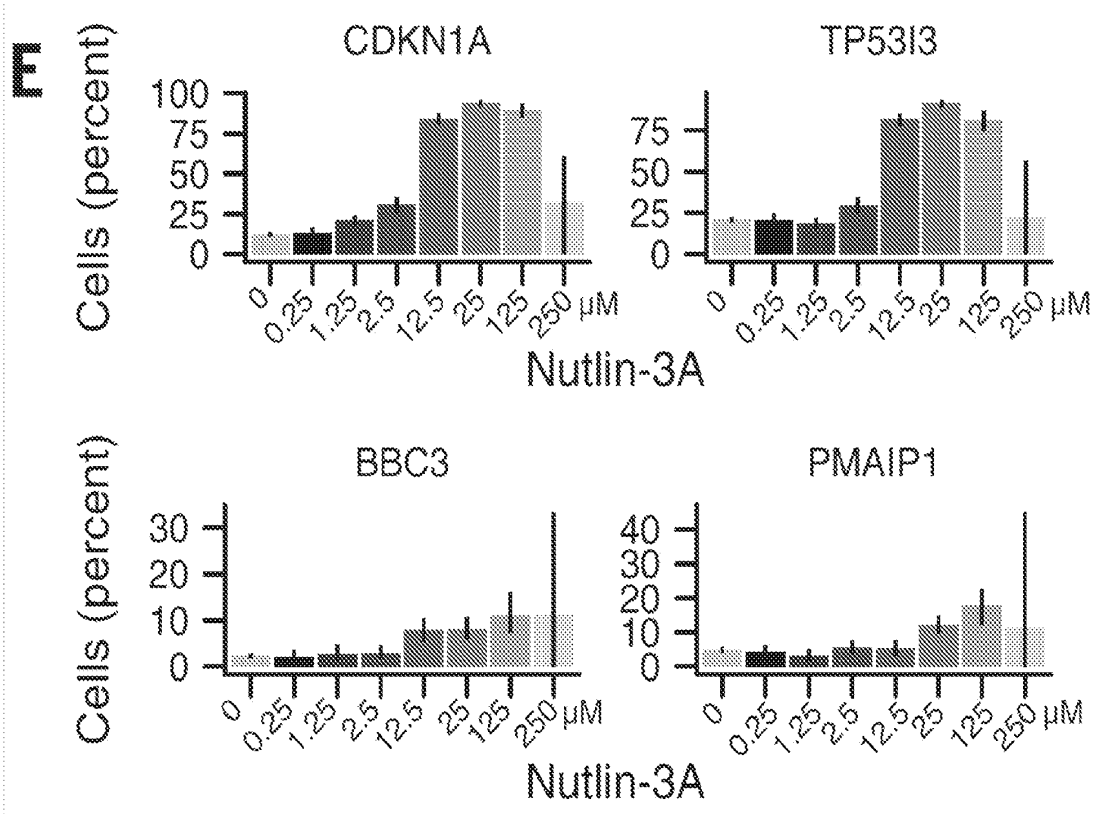

E
CDKN1A
TP53I3
Cells (percent)
100
75
50
25
0
75
50
25
0
0 0.25 1.25 2.5 12.5 25 125 250 μM
Nutlin-3A
BBC3
PMAIP1
30
20
10
0
40
30
20
10
0
Nutlin-3A

Fig. 6F

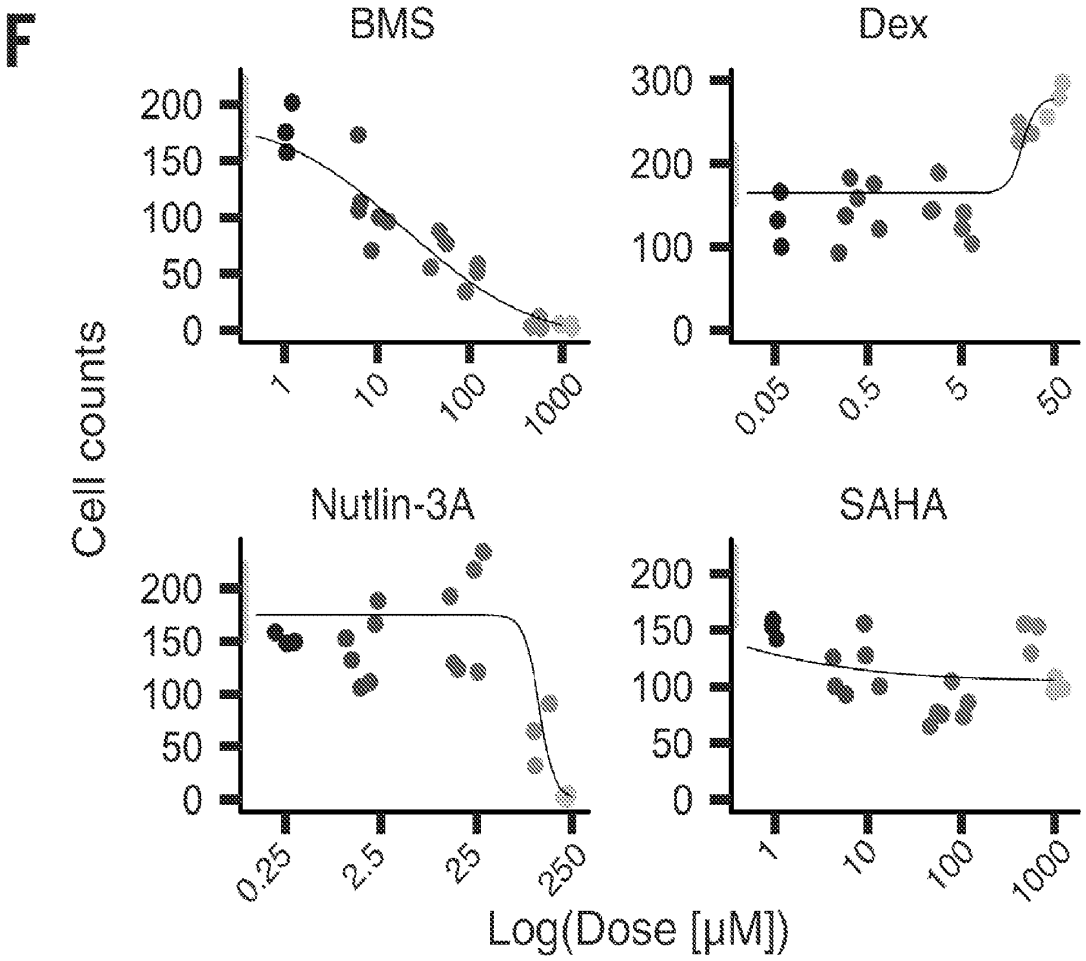

F
BMS
Dex
Nutlin-3A
SAHA
Cell counts
Log(Dose [μM])
200
150
100
50
0
300
1
10
100
1000
0.05
0.5
5
50
0.25
2.5
25
250

Fig. 7A

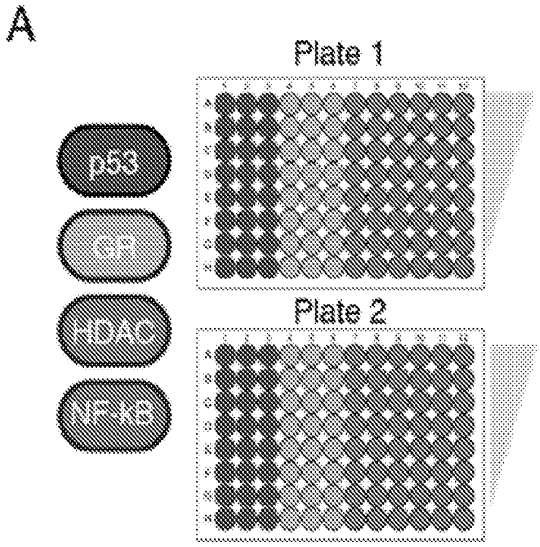


Fig. 7B

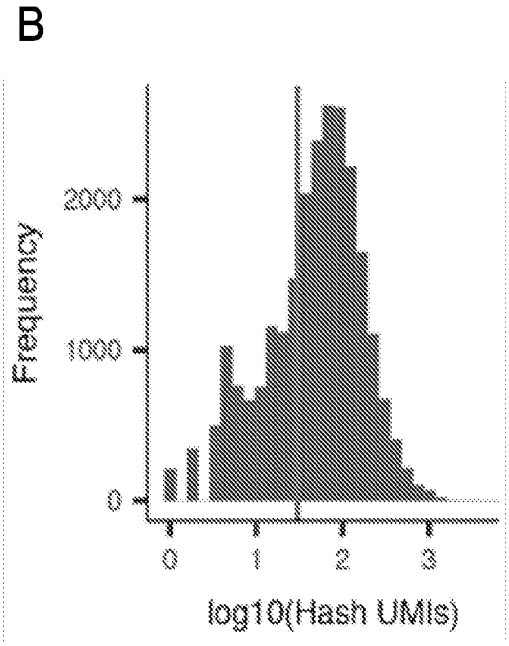


Fig. 7C

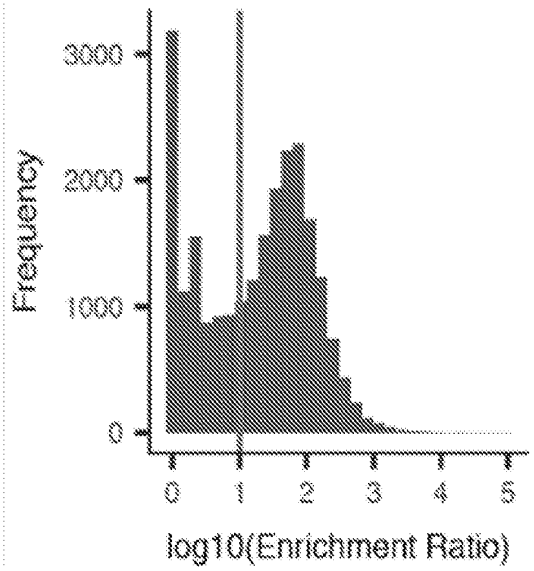


Fig. 7D

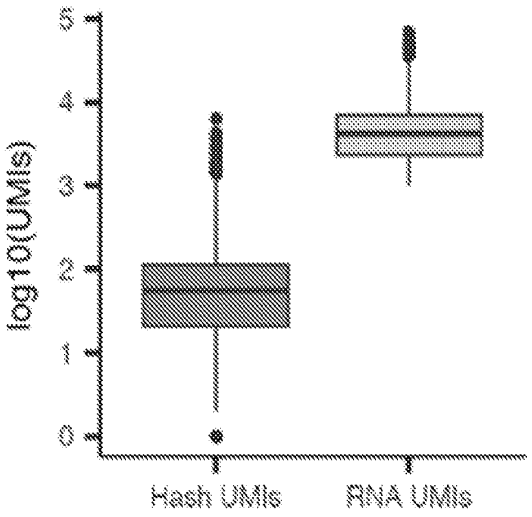


Fig. 7E

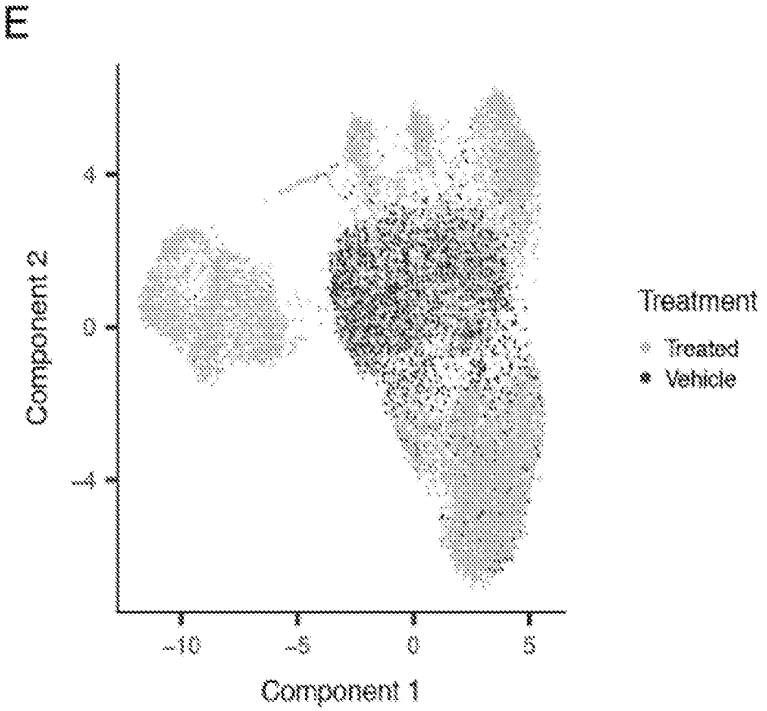

E
Component 2
4
0
−4
−10
−5
0
5
Component 1
Treatment
Treated
Vehicle

Fig. 7F

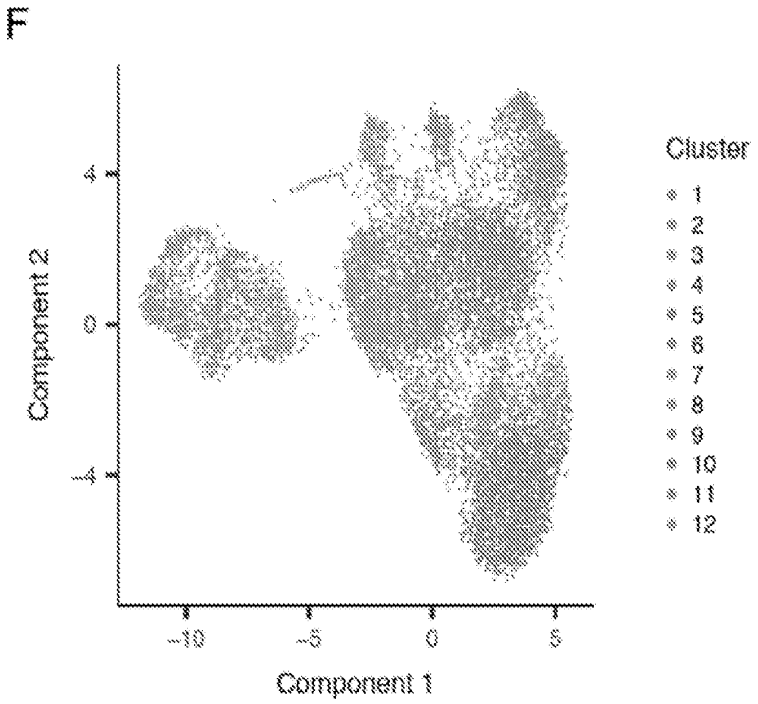

F
Component 2
4
0
−4
−10
−5
0
5
Component 1
Cluster
1
2
3
4
5
6
7
8
9
10
11
12

Fig. 7G

G

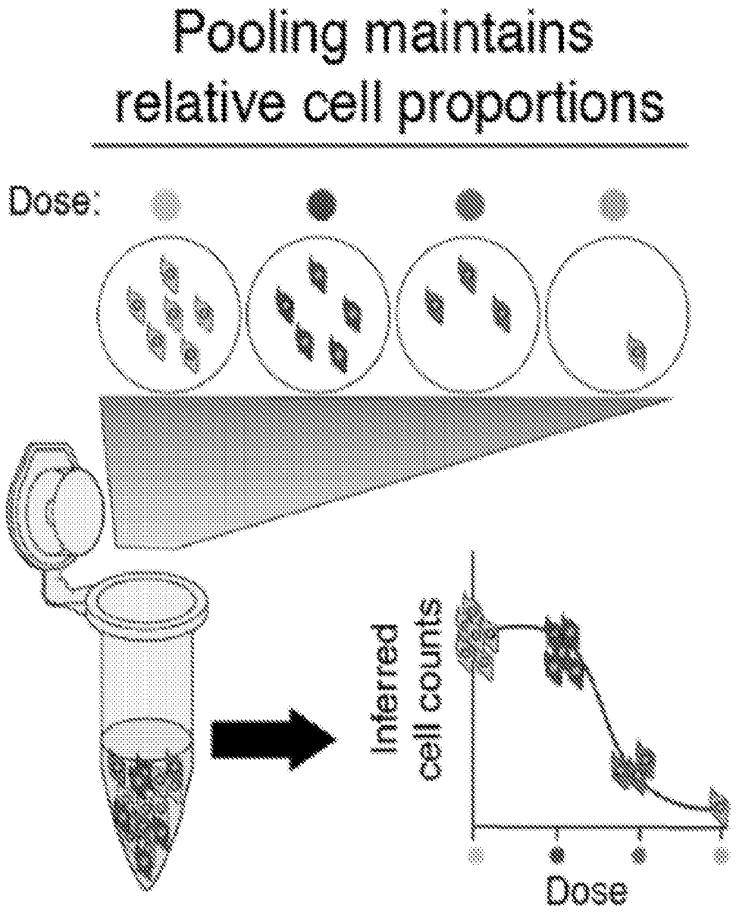

Pooling maintains
relative cell proportions
Dose:
Inferred
cell counts
Dose

Fig. 7H

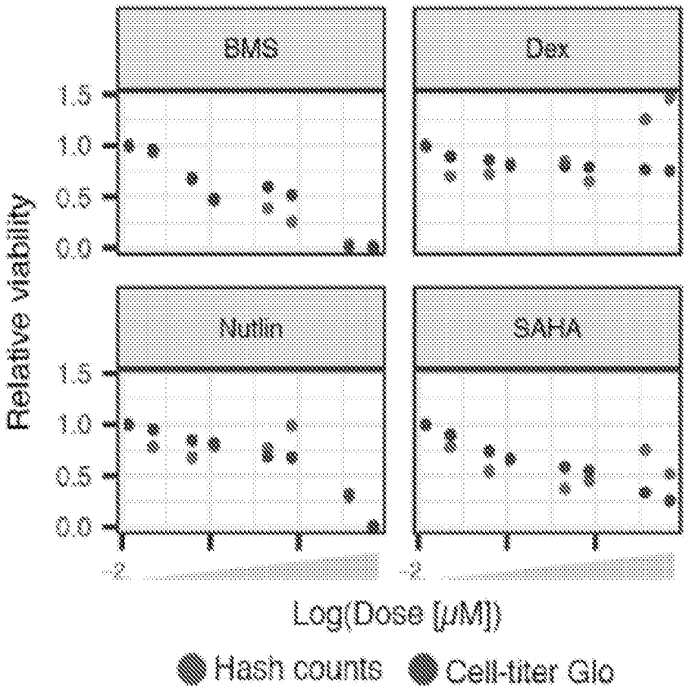
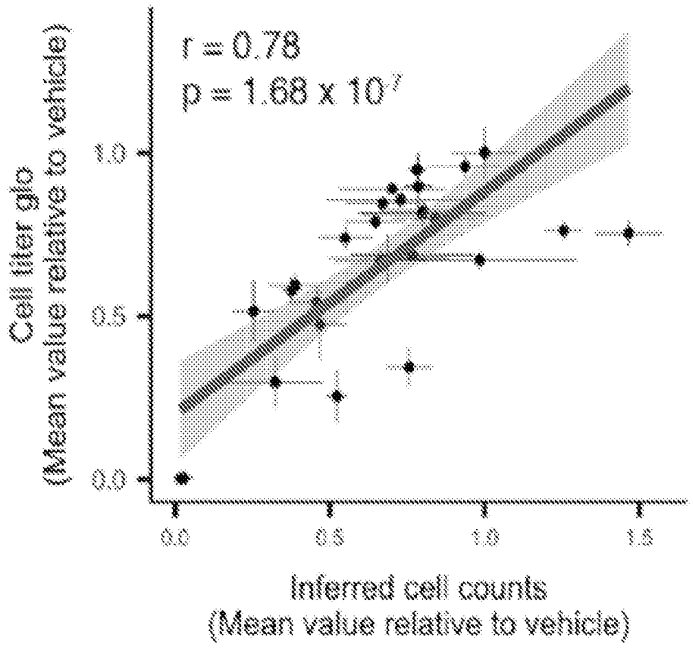

BMS
Dex
Nutlin
SAHA
Relative viability
1.5
1.0
0.5
0.0
-2
Log(Dose [μM])
Hash counts
Cell-titer Glo

Fig. 7I


r = 0.78
p = 1.68 x 10⁻⁷
Cell titer glo
(Mean value relative to vehicle)
1.0
0.5
0.0
0.0
0.5
1.0
1.5
Inferred cell counts
(Mean value relative to vehicle)

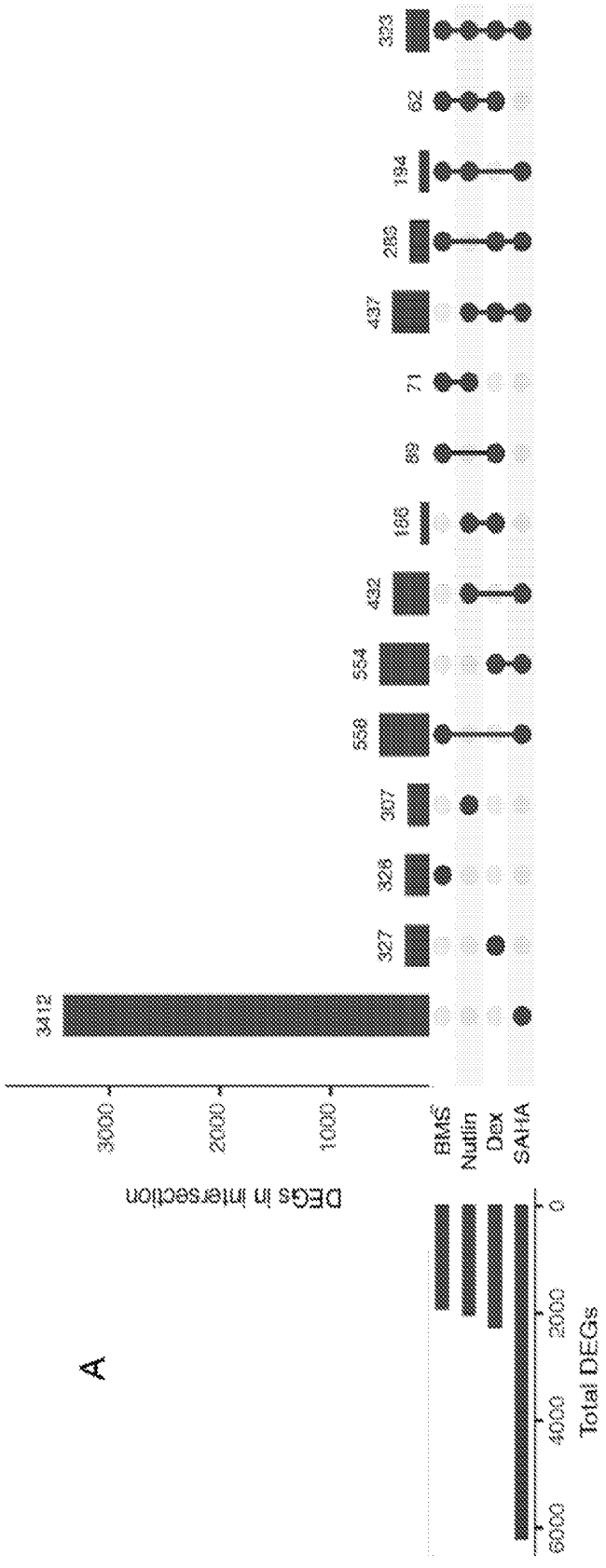

A
DEGs in intersection
3000
2000
1000
3412
327
326
307
558
554
432
166
89
71
437
285
194
62
323
BMS
Nutlin
Dex
SAHA
Total DEGs
6000
4000
2000
0

Fig. 8A

Fig. 8B

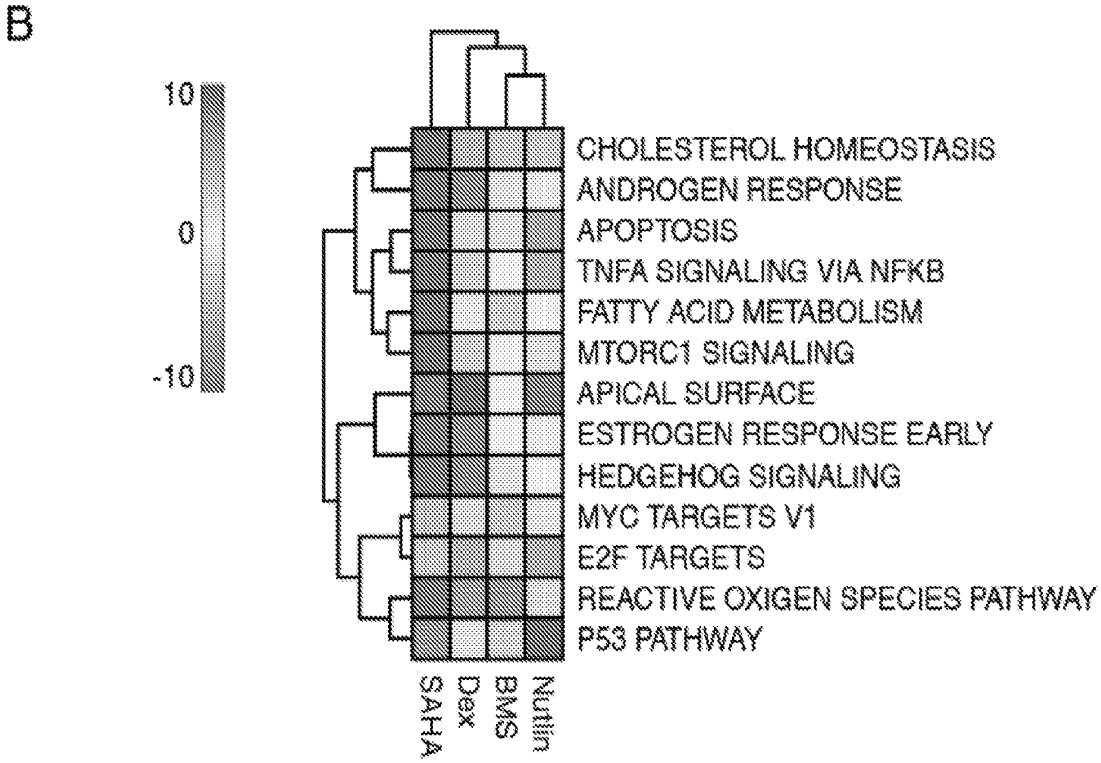

B
10
0
-10
CHOLESTEROL HOMEOSTASIS
ANDROGEN RESPONSE
APOPTOSIS
TNFA SIGNALING VIA NFKB
FATTY ACID METABOLISM
MTORC1 SIGNALING
APICAL SURFACE
ESTROGEN RESPONSE EARLY
HEDGEHOG SIGNALING
MYC TARGETS V1
E2F TARGETS
REACTIVE OXIGEN SPECIES PATHWAY
P53 PATHWAY
SAHA
Dex
BMS
Nutlin

Fig. 9A

A

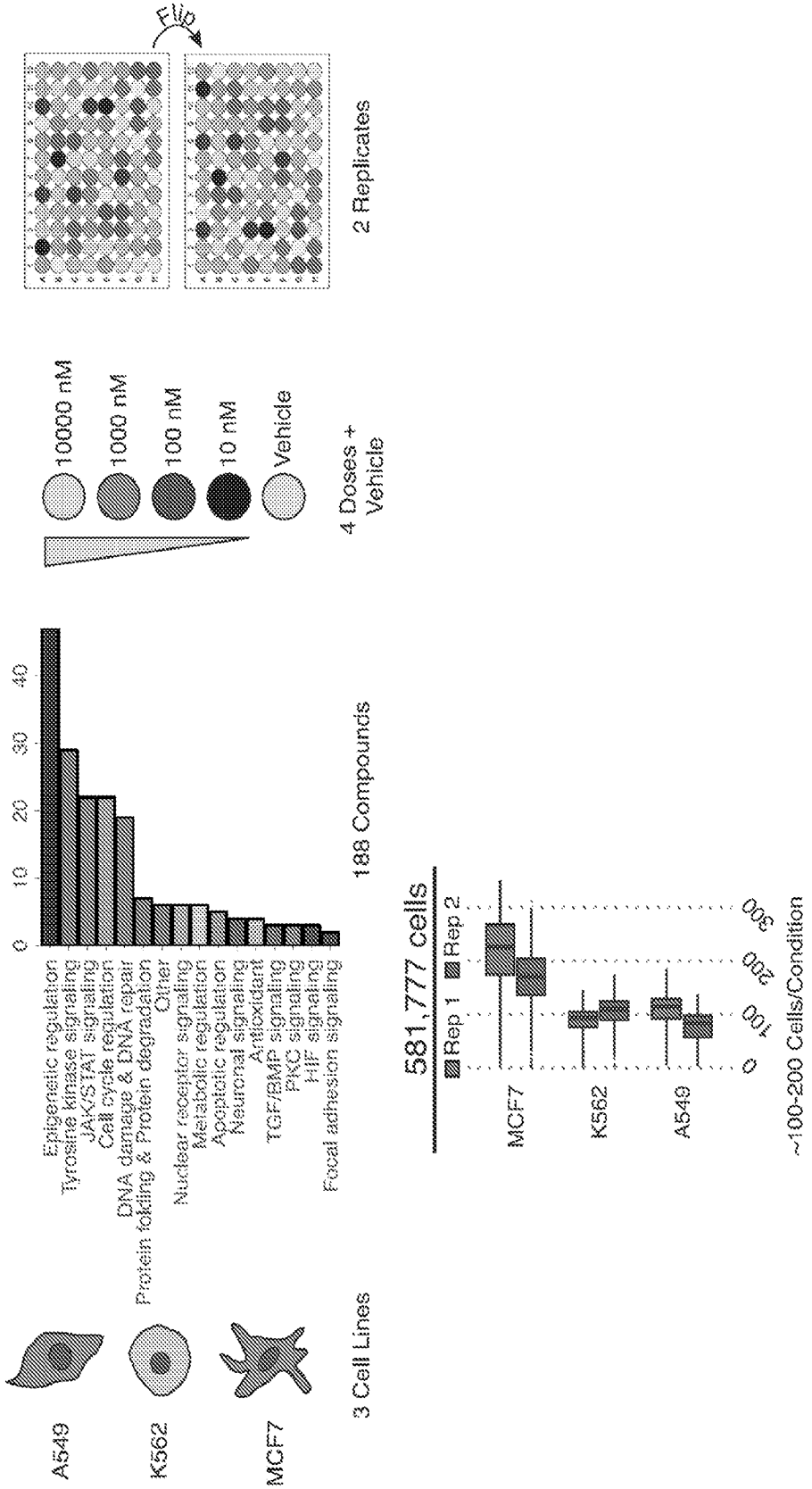
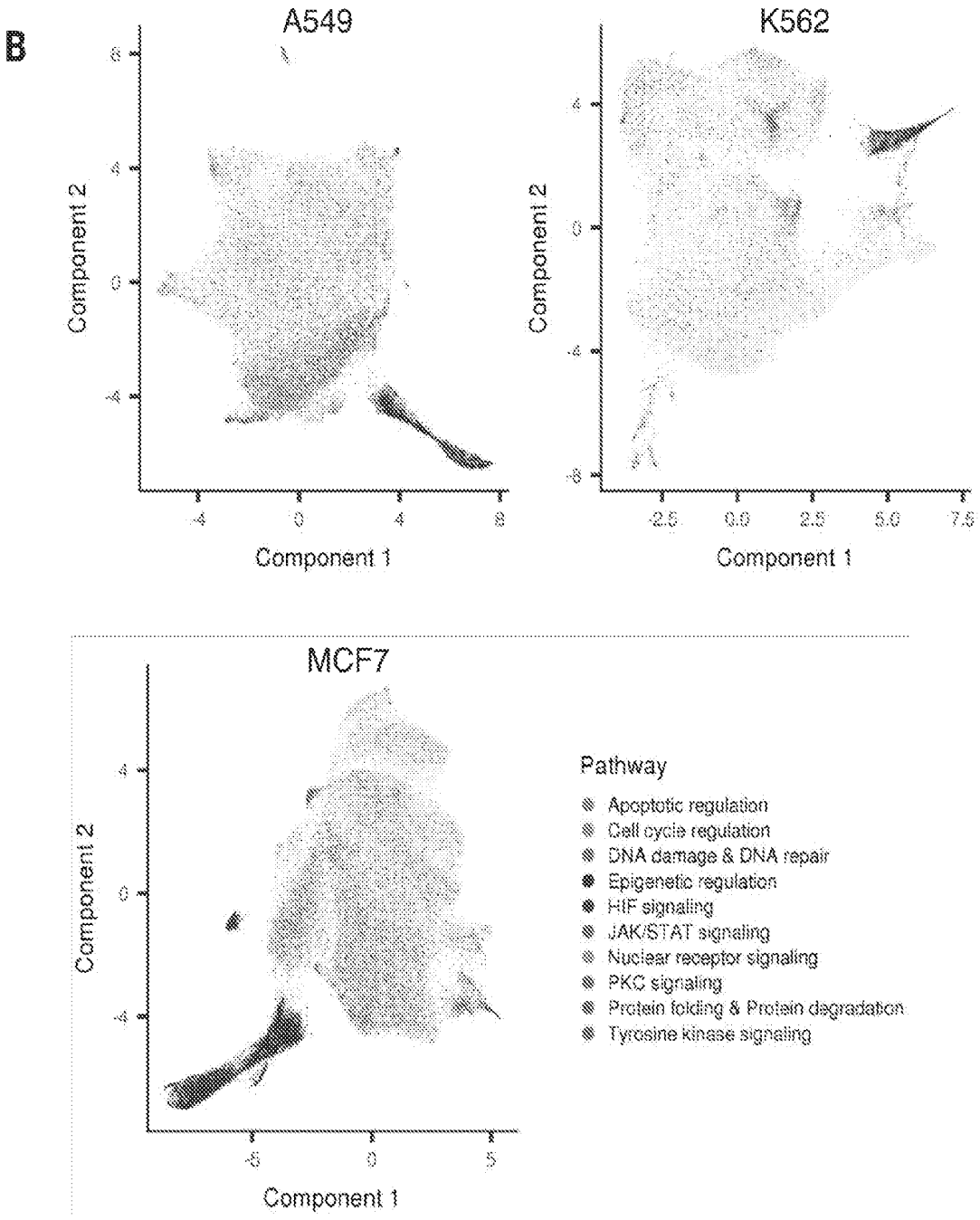

4,608 conditions - 24 hours post treatment
A549
K562
MCF7
3 Cell Lines
0
10
20
30
40
Epigenetic regulation
Tyrosine kinase signaling
JAK/STAT signaling
Cell cycle regulation
DNA damage & DNA repair
Protein folding & Protein degradation
Other
Nuclear receptor signaling
Metabolic regulation
Apoptotic regulation
Neuronal signaling
Antioxidant
TGF/BMP signaling
PKC signaling
HIF signaling
Focal adhesion signaling
188 Compounds
10000 nM
1000 nM
100 nM
10 nM
Vehicle
4 Doses + Vehicle
Flip
2 Replicates
581,777 cells
Rep 1
Rep 2
MCF7
K562
A549
0
100
200
300
~100-200 Cells/Condition

Fig. 9B


B
A549
K562
MCF7
Component 2
Component 1
Pathway
Apoptotic regulation
Cell cycle regulation
DNA damage & DNA repair
Epigenetic regulation
HIF signaling
JAK/STAT signaling
Nuclear receptor signaling
PKC signaling
Protein folding & Protein degradation
Tyrosine kinase signaling

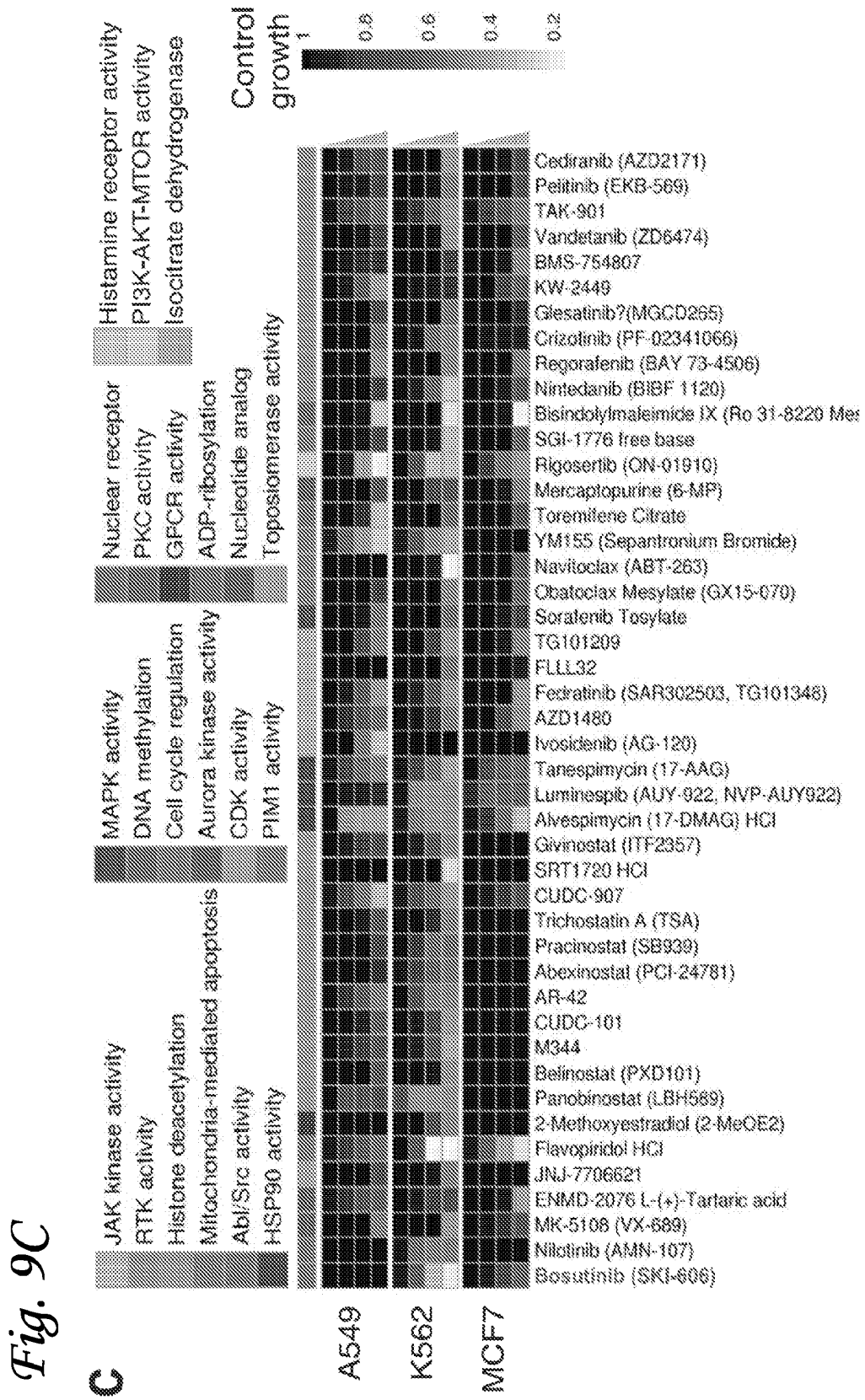

C
Control growth
1
0.8
0.6
0.4
0.2
Histamine receptor activity
PI3K-AKT-MTOR activity
Isocitrate dehydrogenase
Nuclear receptor
PKC activity
GPCR activity
ADP-ribosylation
Nucleotide analog
Topoisomerase activity
MAPK activity
DNA methylation
Cell cycle regulation
Aurora kinase activity
CDK activity
PIM1 activity
JAK kinase activity
RTK activity
Histone deacetylation
Mitochondria-mediated apoptosis
Abl/Src activity
HSP90 activity
Cediranib (AZD2171)
Peliitinib (EKB-569)
TAK-901
Vandetanib (ZD6474)
BMS-754807
KW-2449
Glesatinib?(MGCD265)
Crizotinib (PF-02341066)
Regorafenib (BAY 73-4506)
Nintedanib (BIBF 1120)
Bisindolylmaleimide IX (Ro 31-8220 Mes
SGI-1776 free base
Rigosertib (ON-01910)
Mercaptopurine (6-MP)
Toremifene Citrate
YM155 (Sepantronium Bromide)
Navitoclax (ABT-263)
Obatoclax Mesylate (GX15-070)
Sorafenib Tosylate
TG101209
FLLL32
Fedratinib (SAR302503, TG101348)
AZD1480
Ivosidenib (AG-120)
Tanespimycin (17-AAG)
Luminespib (AUY-922, NVP-AUY922)
Alvespimycin (17-DMAG) HCl
Givinostat (ITF2357)
SRT1720 HCl
CUDC-907
Trichostatin A (TSA)
Pracinostat (SB939)
Abexinostat (PCI-24781)
AR-42
CUDC-101
M344
Belinostat (PXD101)
Panobinostat (LBH589)
2-Methoxyestradiol (2-MeOE2)
Flavopiridol HCl
JNJ-7706621
ENMD-2076 L-(+)-Tartaric acid
MK-5108 (VX-689)
Nilotinib (AMN-107)
Bosutinib (SKI-606)
A549
K562
MCF7

Fig. 9C

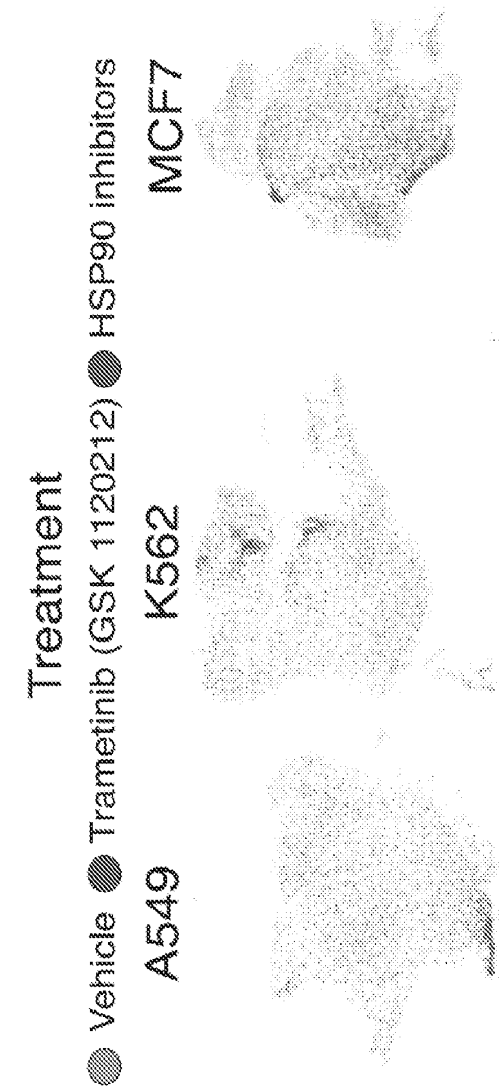

D
Treatment
Vehicle
Trametinib (GSK 1120212)
HSP90 inhibitors
A549
K562
MCF7

Fig. 9D

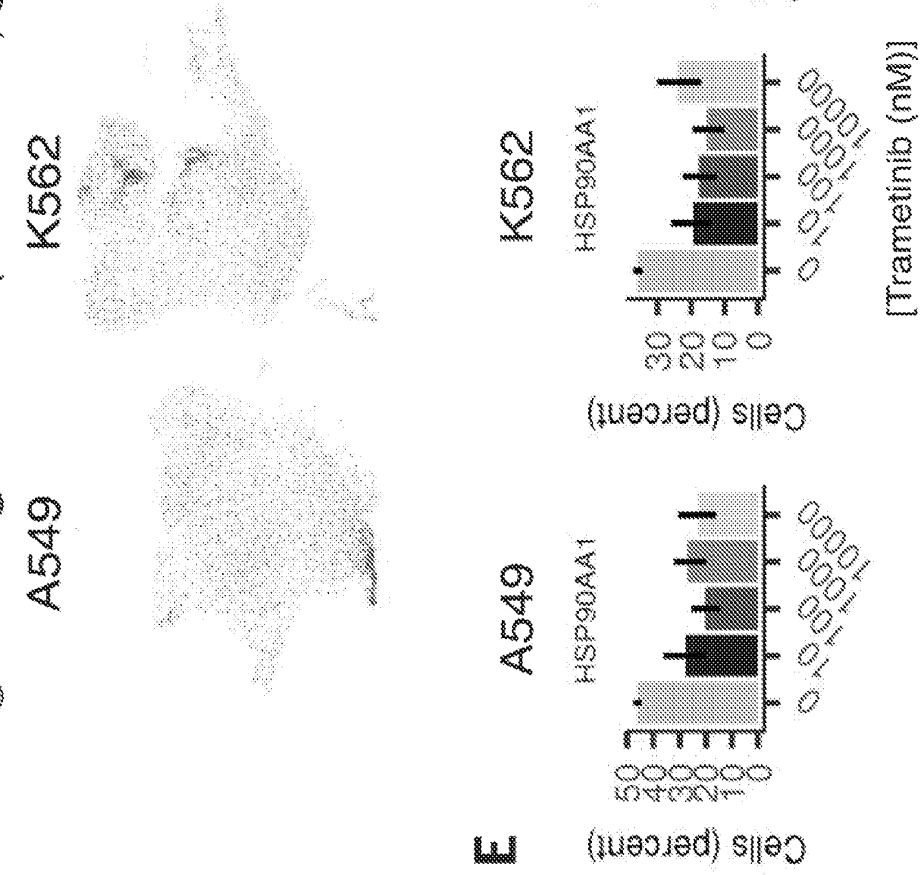

E
A549
K562
MCF7
HSP90AA1
Cells (percent)
[Trametinib (nM)]

Fig. 9E

Fig. 10A

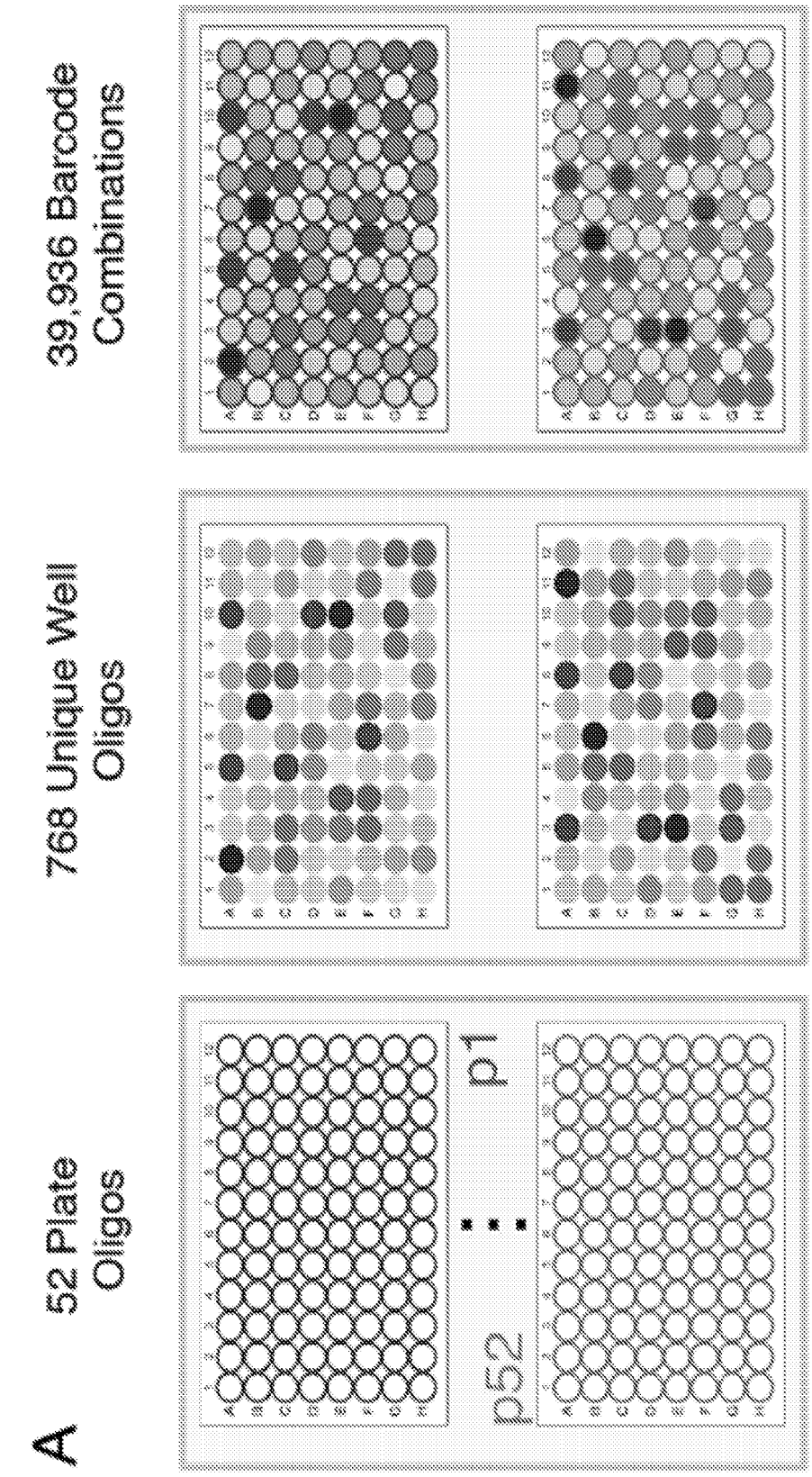

A
52 Plate Oligos
p1
p52
768 Unique Well Oligos
39,936 Barcode Combinations

Fig. 10B

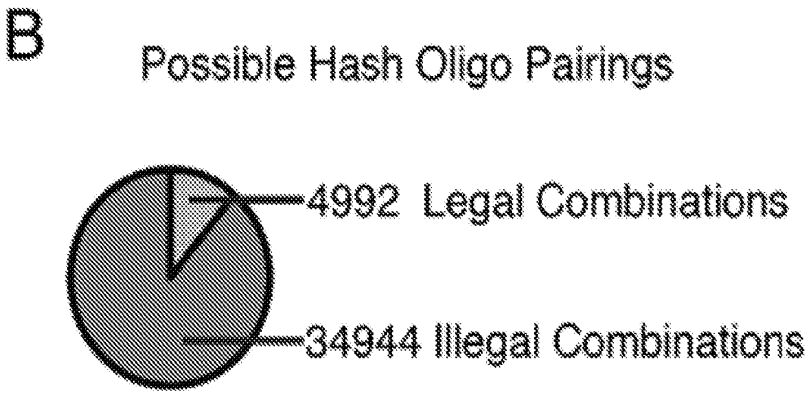


Fig. 10C

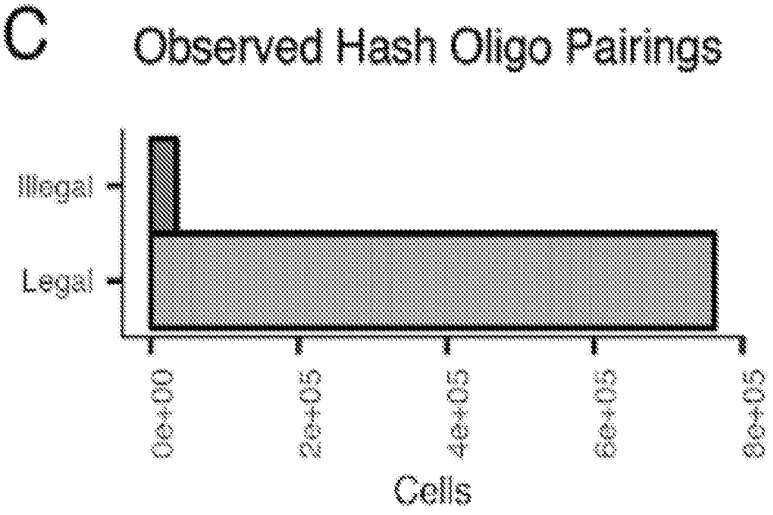


Fig. 10D

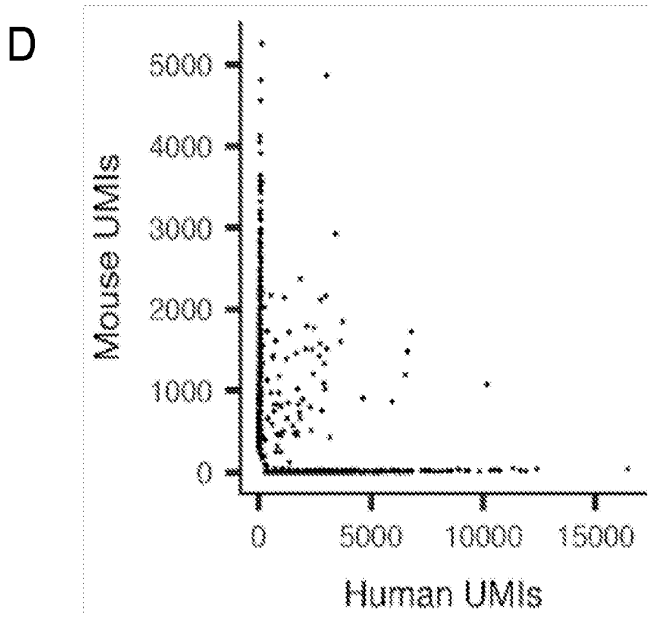


Fig. 10E

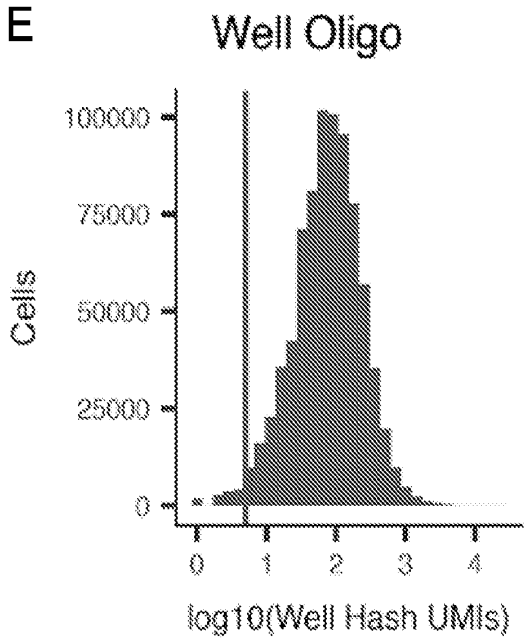


Fig. 10F

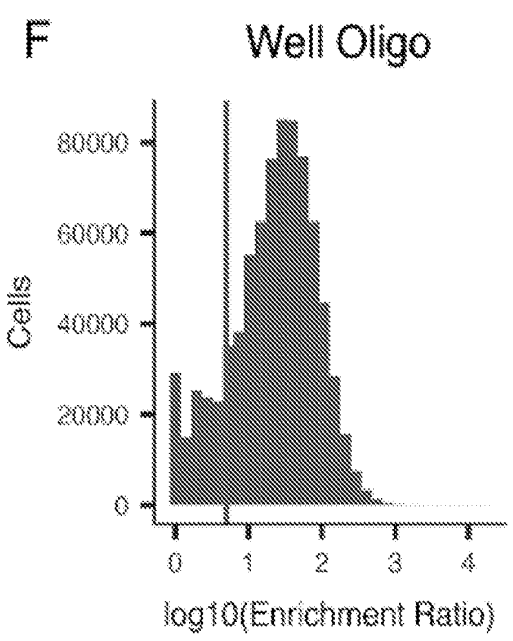


Fig. 10G

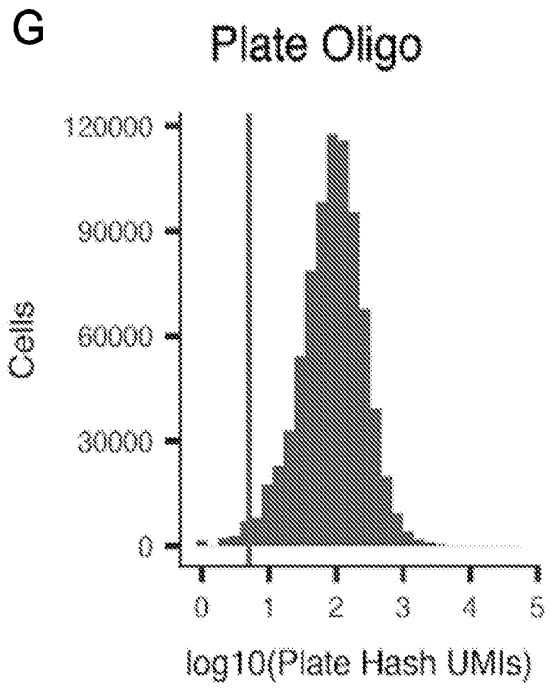
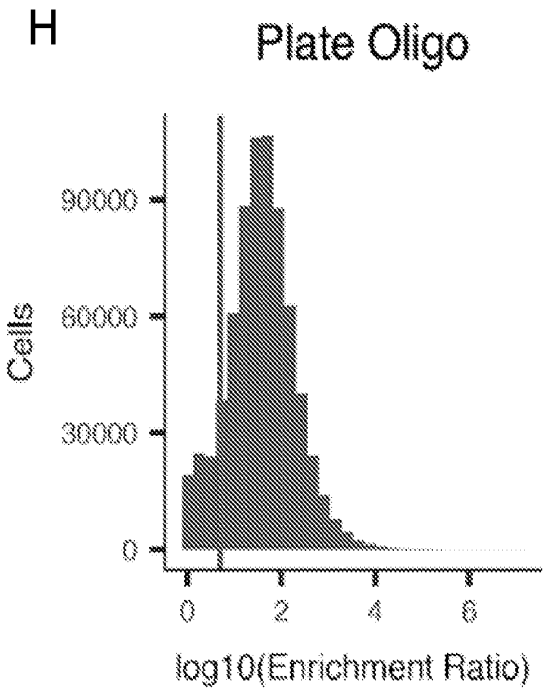


Fig. 10H



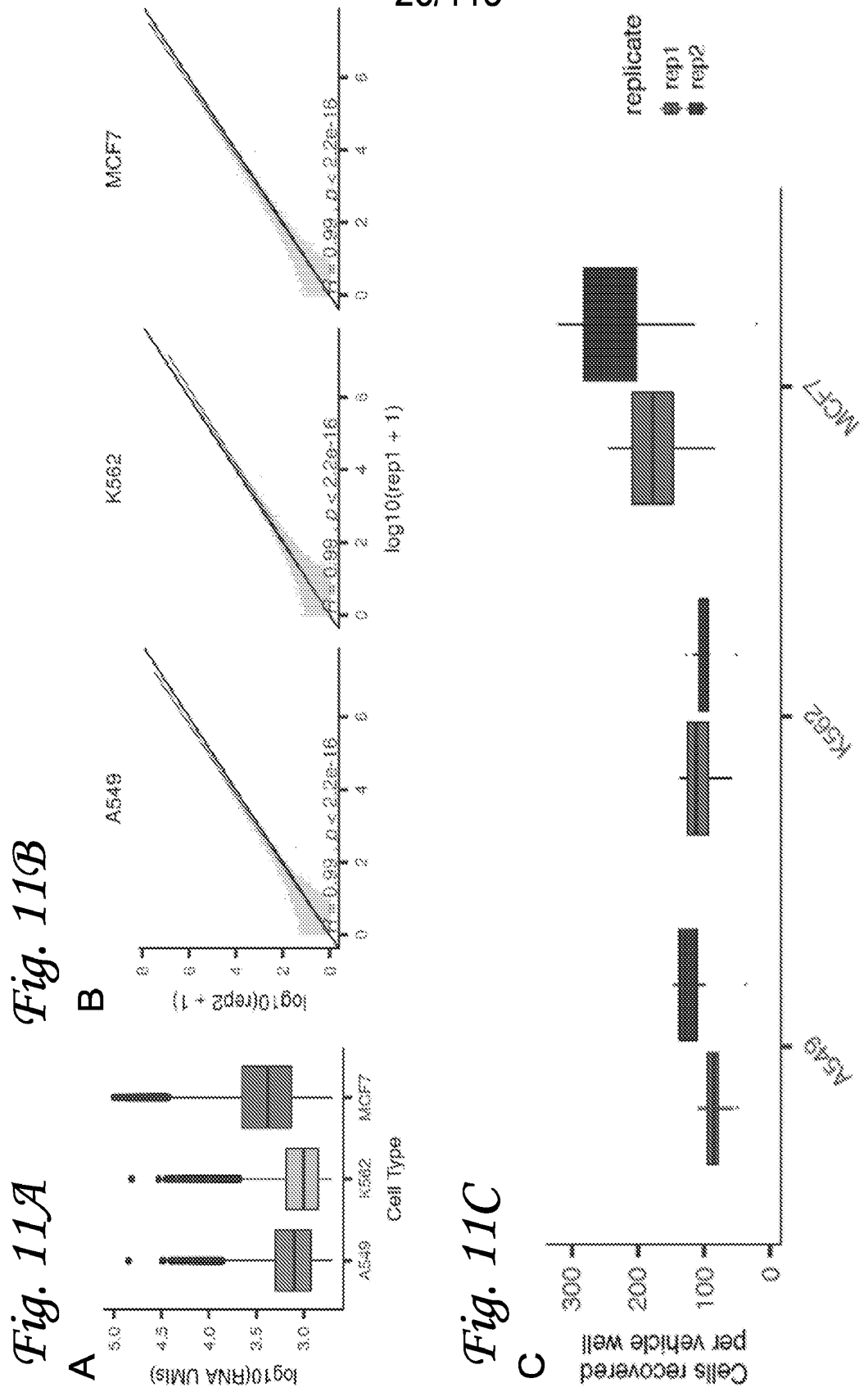


Fig. 11A

Fig. 11B

Fig. 11C

Fig. 12A

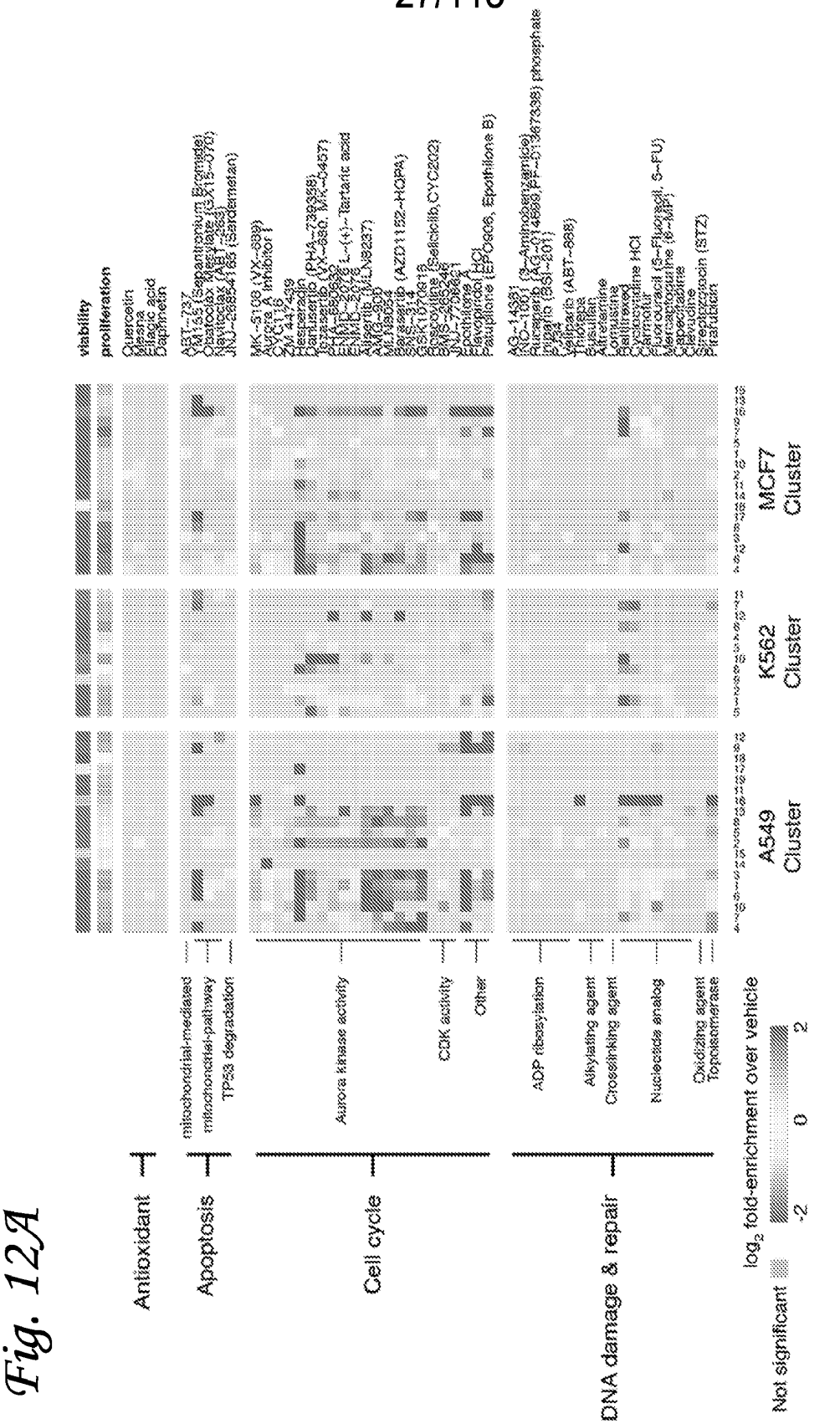

viability
proliferation
Quercetin
Mesna
Ellagic acid
Daphnetin
ABT-737
YM155 (Sepantronium Bromide)
Obatoclax Mesylate (GX15-070)
Navitoclax (ABT-263)
JNJ-26854165 (Serdemetan)
MK-5108 (VX-689)
Aurora A Inhibitor I
CYC116
ZM 447439
Hesperadin
Danusertib (PHA-739358)
Tozasertib (VX-680, MK-0457)
ENMD-2076 L-(+)-Tartaric acid
ENMD-2076
AMG-900
MLN8054
Barasertib (AZD1152-HQPA)
BMS-314
GSK1070916
Roscovitine (Seliciclib, CYC202)
BMS-265246
JNJ-7706621
Epothilone A
Flavopiridol HCl
Patupilone (EPOxxx6, Epothilone B)
AG-14361
NU-1001 (3-Aminobenzamide)
Rucaparib (AG-014699,PF-01367338) phosphate
Iniparib (BSI-201)
P-22
Veliparib (ABT-888)
Thiotepa
Elsulfan
Mitolactol
Lomustine
Carmustine
Carmofur
Fluorouracil (5-Fluoracil, 5-FU)
Mercaptopurine (6-MP)
Capecitabine
Cladribine
Streptozocin (STZ)
Pralatrexate
Antioxidant
Apoptosis
mitochondrial-mediated
mitochondrial-pathway
TP53 degradation
Cell cycle
Aurora kinase activity
CDK activity
Other
DNA damage & repair
ADP ribosylation
Alkylating agent
Crosslinking agent
Nucleotide analog
Oxidizing agent
Topoisomerase
A549 Cluster
K562 Cluster
MCF7 Cluster
log2 fold-enrichment over vehicle
Not significant
-2
0
2

Fig. 12B

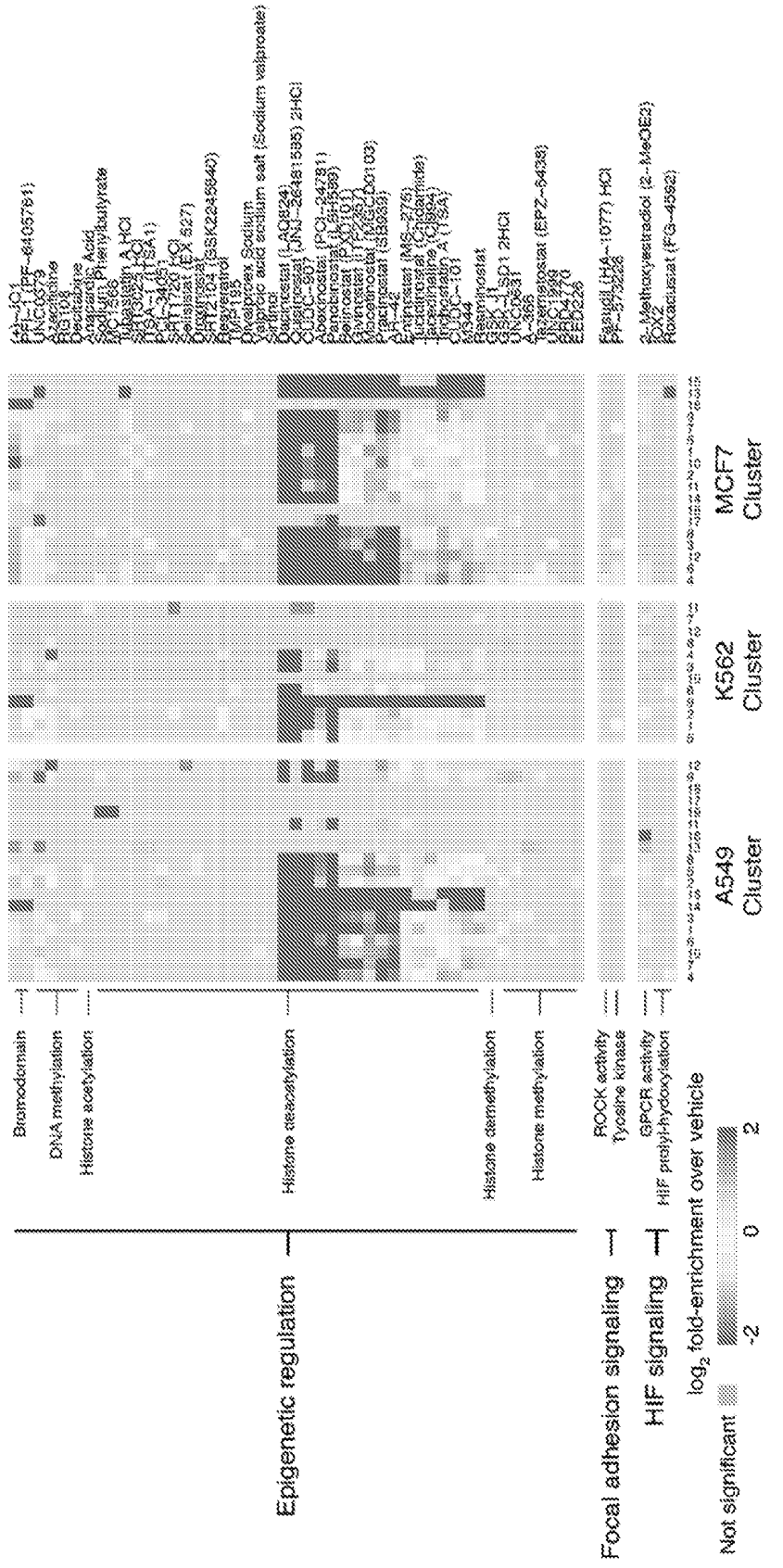

viability
proliferation
(+)-JQ1
PFI-1 (PF-6405761)
UNC0379
Azacitidine
RG108
Decitabine
Anacardic Acid
Sodium Phenylbutyrate
MC1568
Trichostatin A (TSA)
CAY10433
PCI-34051
SAHA (Vorinostat)
CAY10398 (MS-275)
Romidepsin (FK228)
Resveratrol
TMP195
Divalproex Sodium
Valproic acid sodium salt (Sodium valproate)
Entinostat (MS-275)
Givinostat
Quisinostat (JNJ-26481585) 2HCl
CUDC-907
Abexinostat (PCI-24781)
Panobinostat (LBH589)
Belinostat (PXD101)
Mocetinostat (MGCD0103)
Pracinostat (SB939)
HPOB
CAY10603 (HDAC6 Inhibitor)
Tubastatin A HCl
Tucidinostat (Chidamide)
Tacedinaline (CI994)
Trichostatin A (TSA)
CUDC-101
M344
Resminostat
GSK-J1
GSK-J1 2HCl
UNC0631
A-366
Tazemetostat (EPZ-6438)
GSK126
EPZ005687
EED226
Ezatiostat (TLK-19277) HCl
PF-573228
3-Methoxyestradiol (2-MeOE2)
COX2
Roxadustat (FG-4592)
Epigenetic regulation
Bromodomain
DNA methylation
Histone acetylation
Histone deacetylation
Histone demethylation
Histone methylation
Focal adhesion signaling
ROCK activity
Tyrosine kinase
HIF signaling
GPCR activity
HIF prolyl-hydroxylation
A549 Cluster
K562 Cluster
MCF7 Cluster
log2 fold-enrichment over vehicle
Not significant
-2
0
2

Fig. 12C

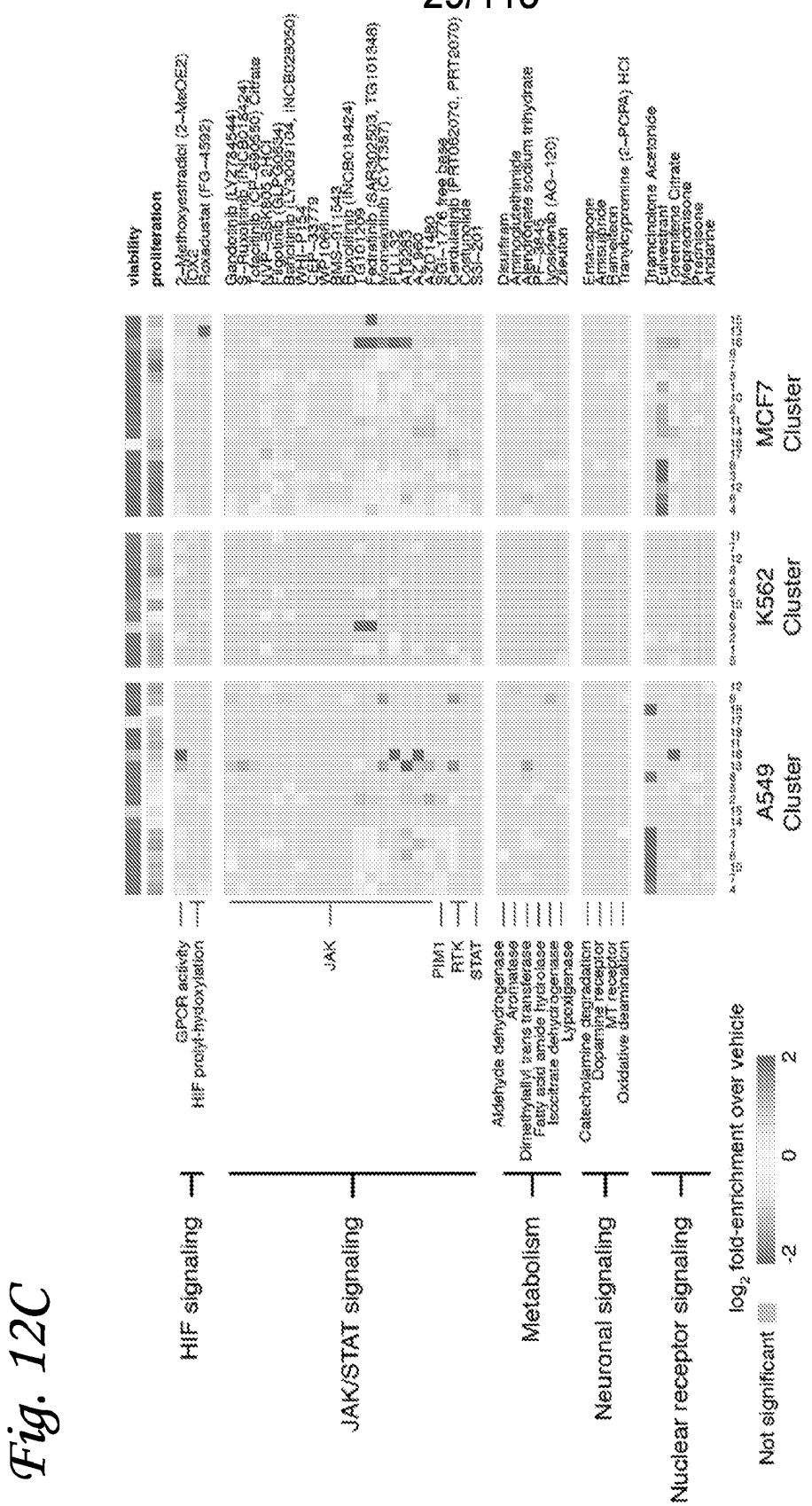

HIF signaling
JAK/STAT signaling
Metabolism
Neuronal signaling
Nuclear receptor signaling
EPOR activity
HIF prolyl-hydroxylation
JAK
PIM1
RTK
STAT
Aldehyde dehydrogenase
Aromatase
Dimethylallyl trans transferase
Fatty acid amide hydrolase
Isocitrate dehydrogenase
Lysozyme
Catecholamine degradation
Dopamine receptor
MT receptor
Oxidative deamination
viability
proliferation
A549 Cluster
K562 Cluster
MCF7 Cluster
log2 fold-enrichment over vehicle
Not significant
-2
0
2

Fig. 12D

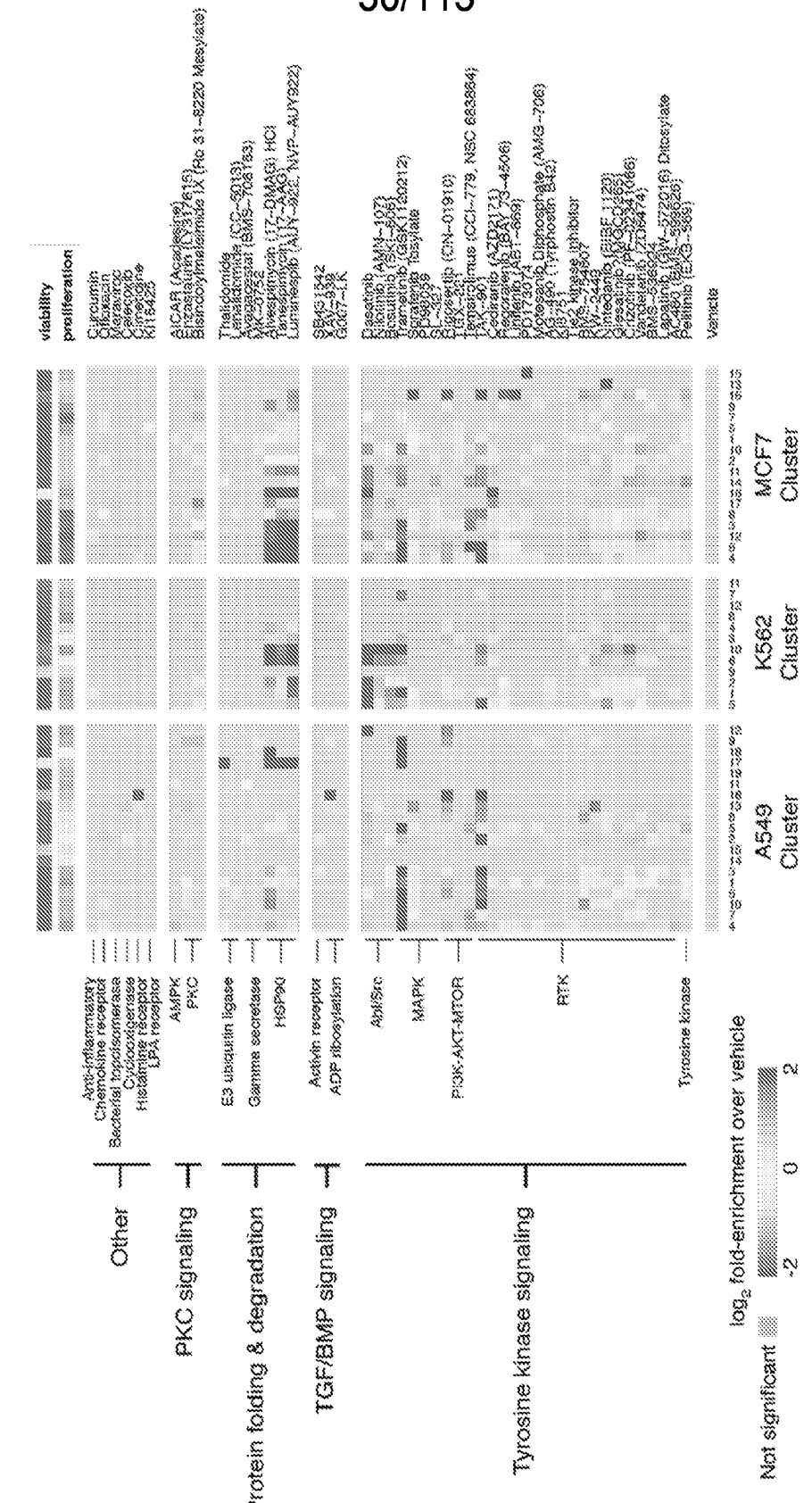

viability
proliferation
Other
Anti-inflammatory
Chemokine receptor
Bacterial topoisomerase
Cyclooxygenase
Histamine receptor
LPA receptor
PKC signaling
AMPK
PKC
Protein folding & degradation
E3 ubiquitin ligase
Gamma secretase
HSP90
TGF/BMP signaling
Activin receptor
ADP ribosylation
Tyrosine kinase signaling
Abl/Src
MAPK
PI3K-AKT-MTOR
RTK
Tyrosine kinase
Curcumin
Mifepristone
Ketanserin
Cimetidine
KI16425
AICAR (Acadesine)
Enzastaurin (LY317615)
Bisindolylmaleimide IX (Ro 31-8220 Mesylate)
Thalidomide
Lenalidomide (CC-5013)
Avagacestat (BMS-708163)
MK-0752
Alvespimycin (17-DMAG) HCl
Tanespimycin (17-AAG)
Luminespib (AUY-922; NVP-AUY922)
SB431542
A-83-01
GW627-1K
Erlotinib (AMN-107)
Erlotinib (OSI-774)
Tipifarnib (R115777)
Sorafenib Tosylate
BMS-536924
SU-14813
Ellipticine (CDN-01910)
TGX-221
Temsirolimus (CCI-779, NSC 683864)
TAK-901
Cediranib (AZD2171)
Regorafenib (BAY 73-4506)
PD173074
Motesanib Diphosphate (AMG-706)
AG-490 (Tyrphostin B42)
CI-1033
Tie2 kinase inhibitor
BMS-754807
KW-2449
Vatalanib (PTK787) 2HCl
Dasatinib (BMS-354825)
Crizotinib (PF-02341066)
PHA-665752
Foretinib (GSK1363089)
AZD6244 (ARRY-142886)
Pazopanib (GW-786034) Dihydrochloride
Axitinib (AG-013736)
Vandetanib (ZD6474)
Vatalanib (PTK787) 2HCl
Dasatinib (BMS-354825)
Erlotinib (OSI-774)
Gefitinib (ZD1839)
Lapatinib (GW-572016) Ditosylate
Pelitinib (EKB-569)
Vandetanib (ZD6474)
A549 Cluster
K562 Cluster
MCF7 Cluster
log2 fold-enrichment over vehicle
-2
0
2
Not significant

Fig. 13A

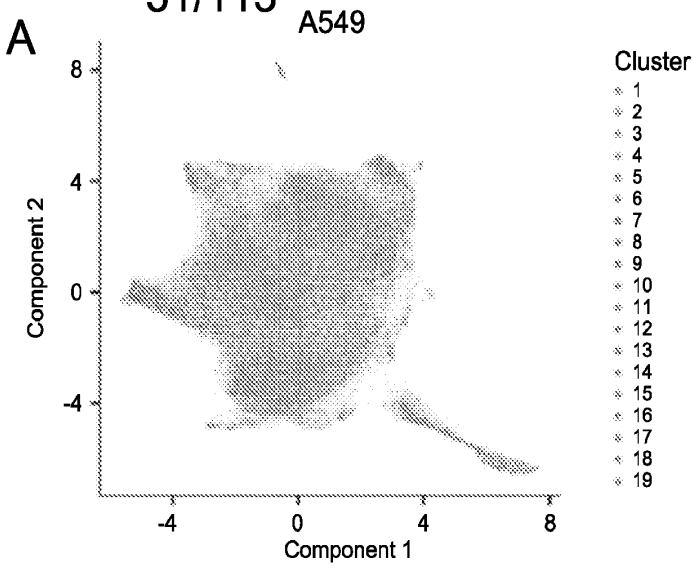


Fig. 13B

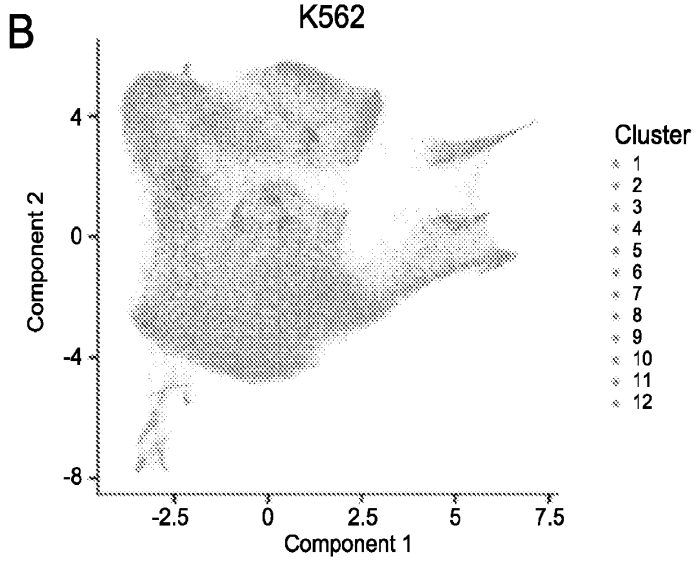


Fig. 13C

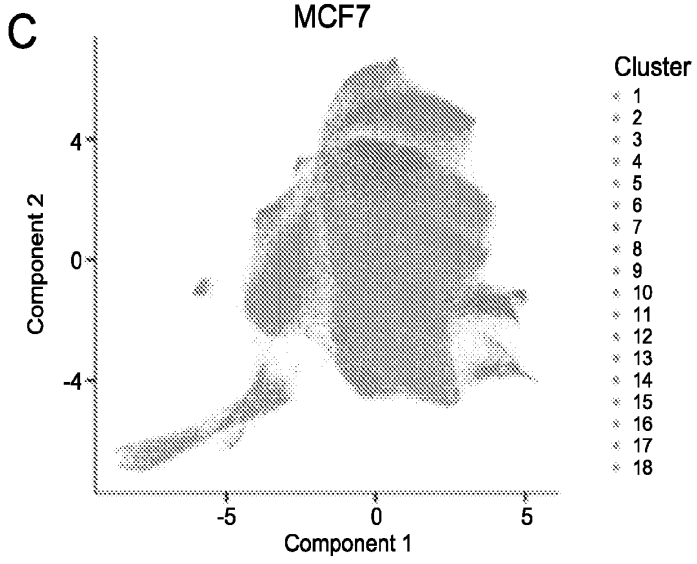


Fig. 13D

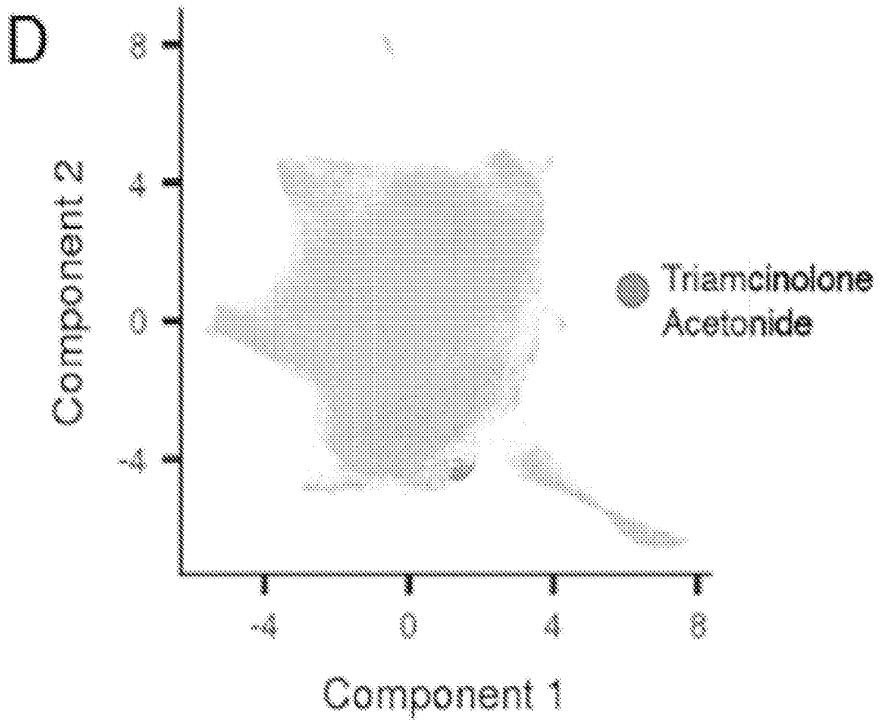


Fig. 13E

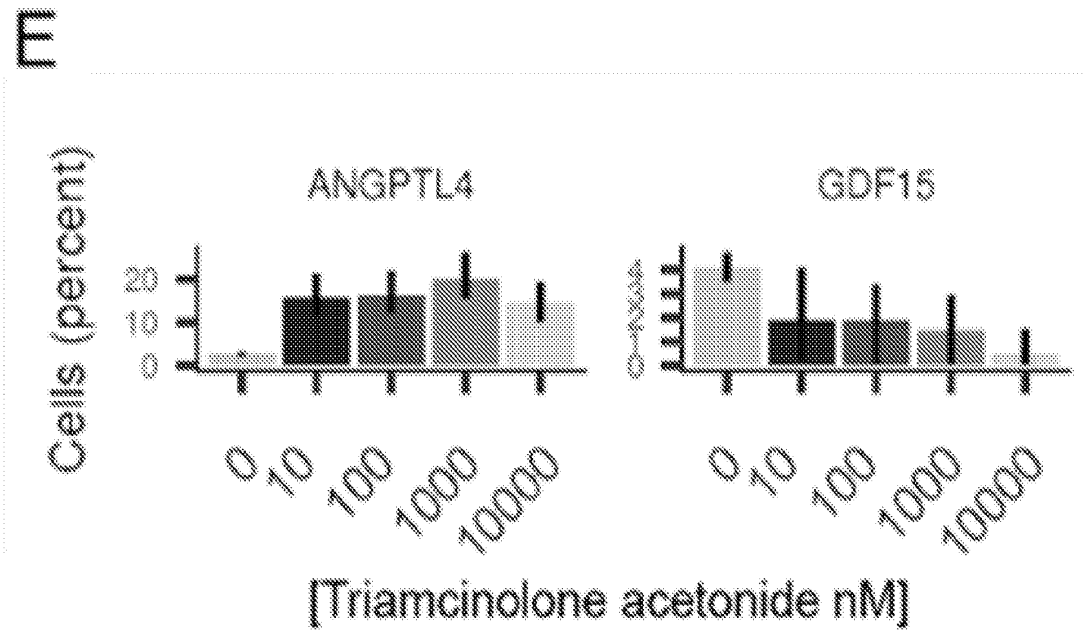


Fig. 13F

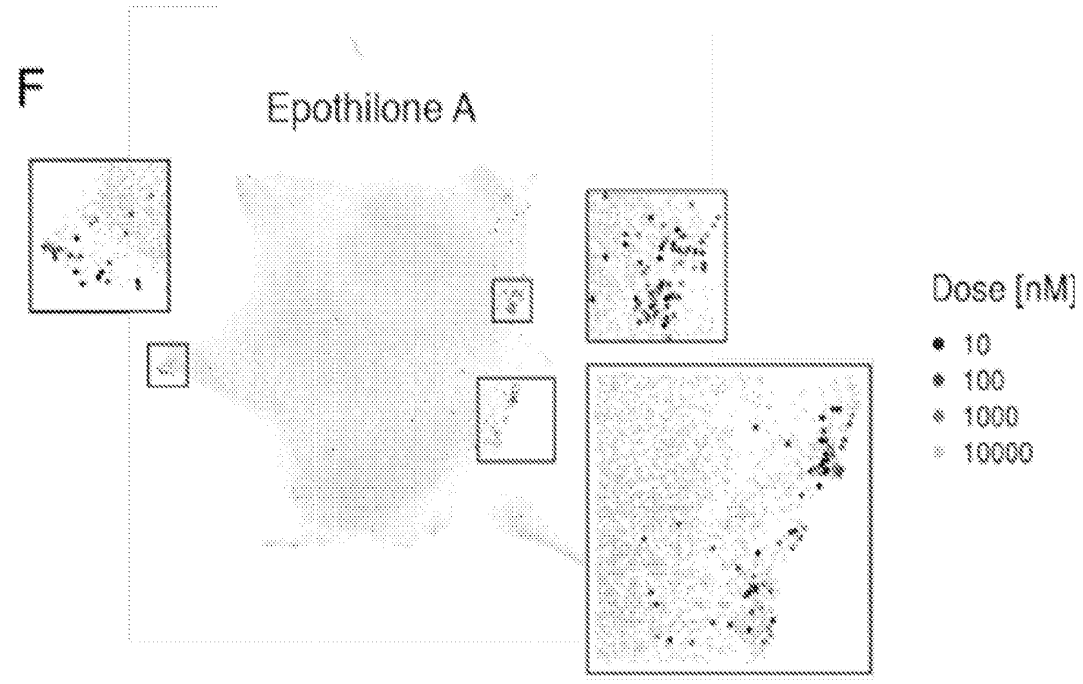
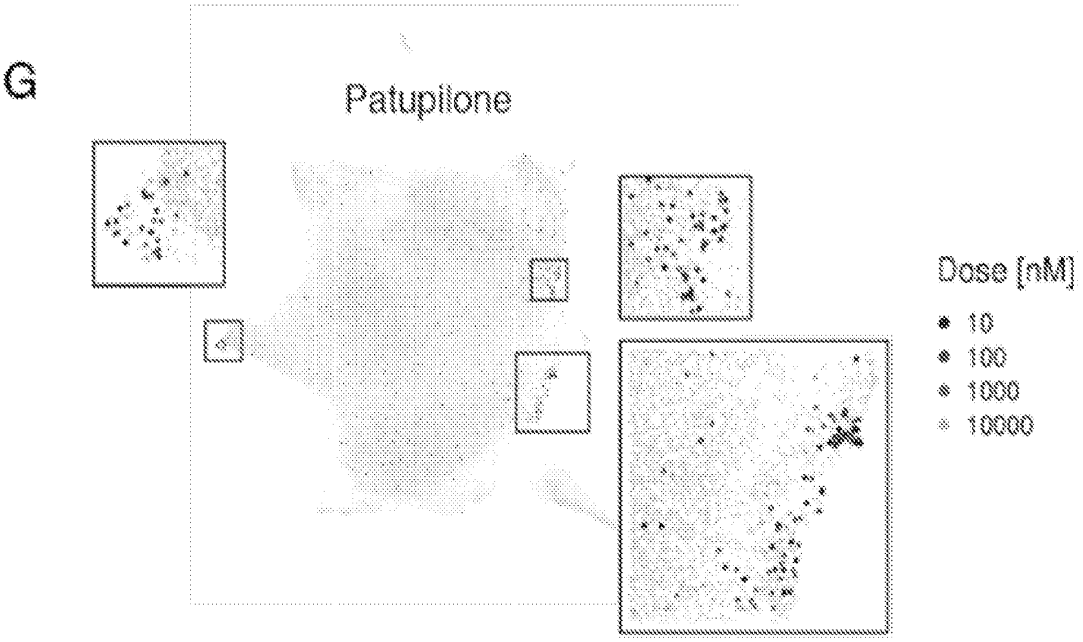


Fig. 13G



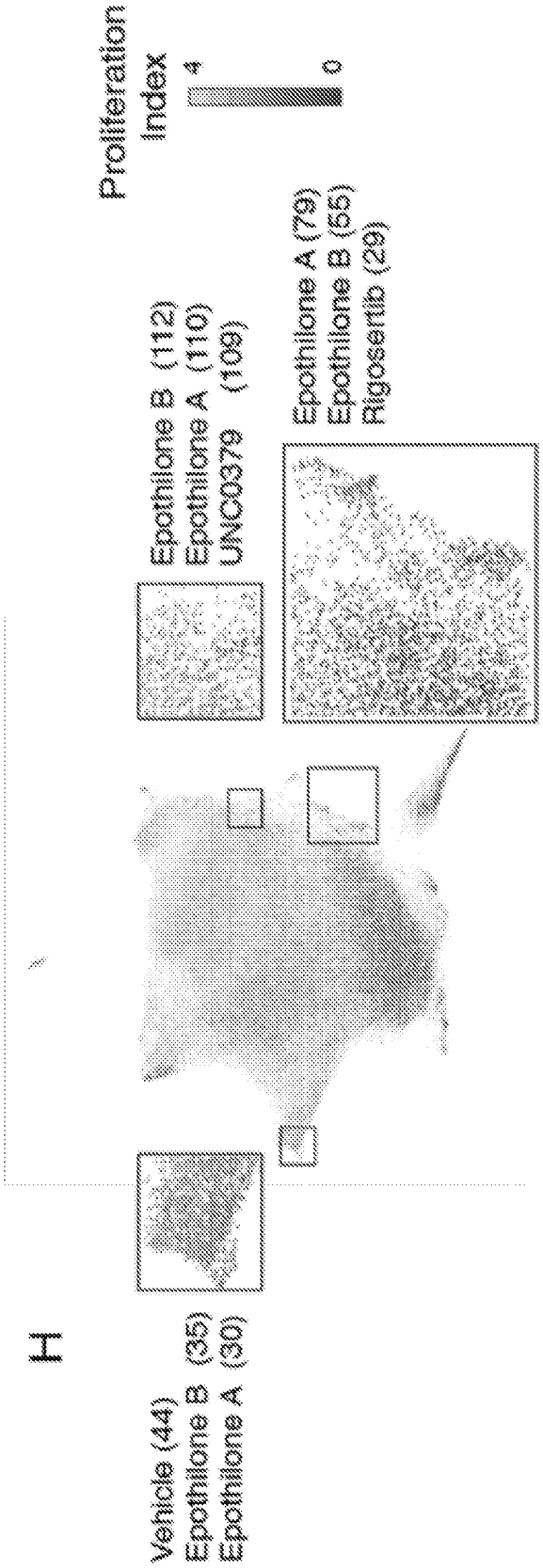

Proliferation Index
4
0
Epothilone B (112)
Epothilone A (110)
UNC0379 (109)
Epothilone A (79)
Epothilone B (55)
Rigosertib (29)
H
Vehicle (44)
Epothilone B (35)
Epothilone A (30)

Fig. 13H

Fig. 14

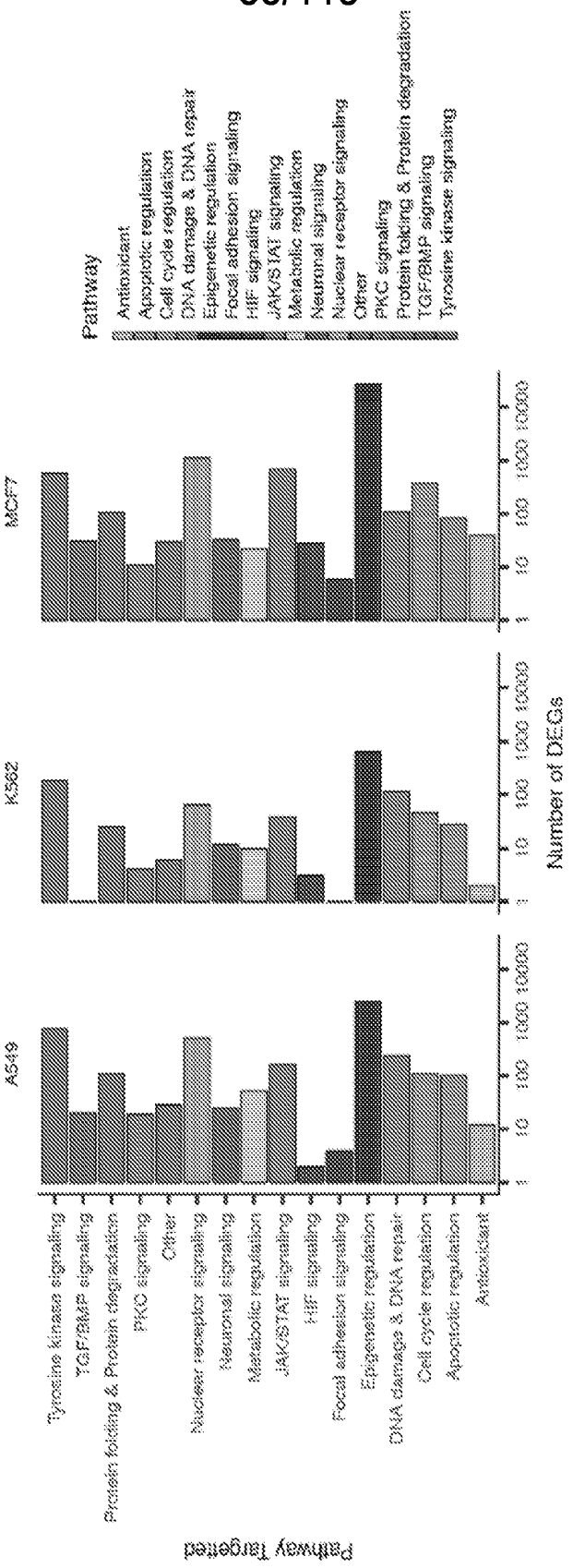

A549
K562
MCF7
Pathway
Antioxidant
Apoptotic regulation
Cell cycle regulation
DNA damage & DNA repair
Epigenetic regulation
Focal adhesion signaling
HIF signaling
JAK/STAT signaling
Metabolic regulation
Neuronal signaling
Nuclear receptor signaling
Other
PKC signaling
Protein folding & Protein degradation
TGF/BMP signaling
Tyrosine kinase signaling
Tyrosine kinase signaling
TGF/BMP signaling
Protein folding & Protein degradation
PKC signaling
Other
Nuclear receptor signaling
Neuronal signaling
Metabolic regulation
JAK/STAT signaling
HIF signaling
Focal adhesion signaling
Epigenetic regulation
DNA damage & DNA repair
Cell cycle regulation
Apoptotic regulation
Antioxidant
1
10
100
1000
10000
Number of DEGs
Pathway Targeted

Fig. 15A

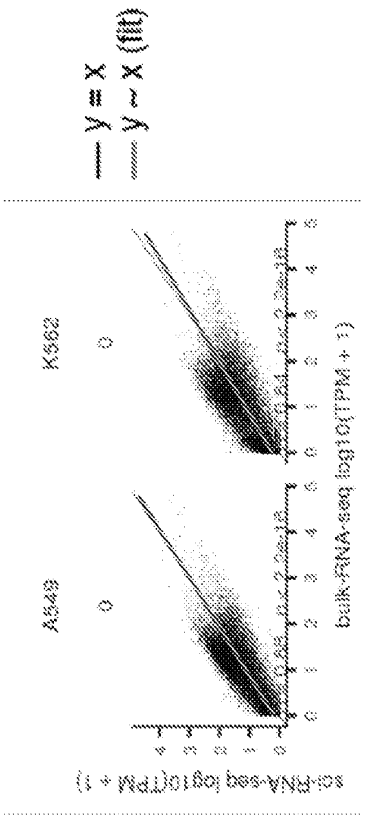


Fig. 15B

Fig. 16A

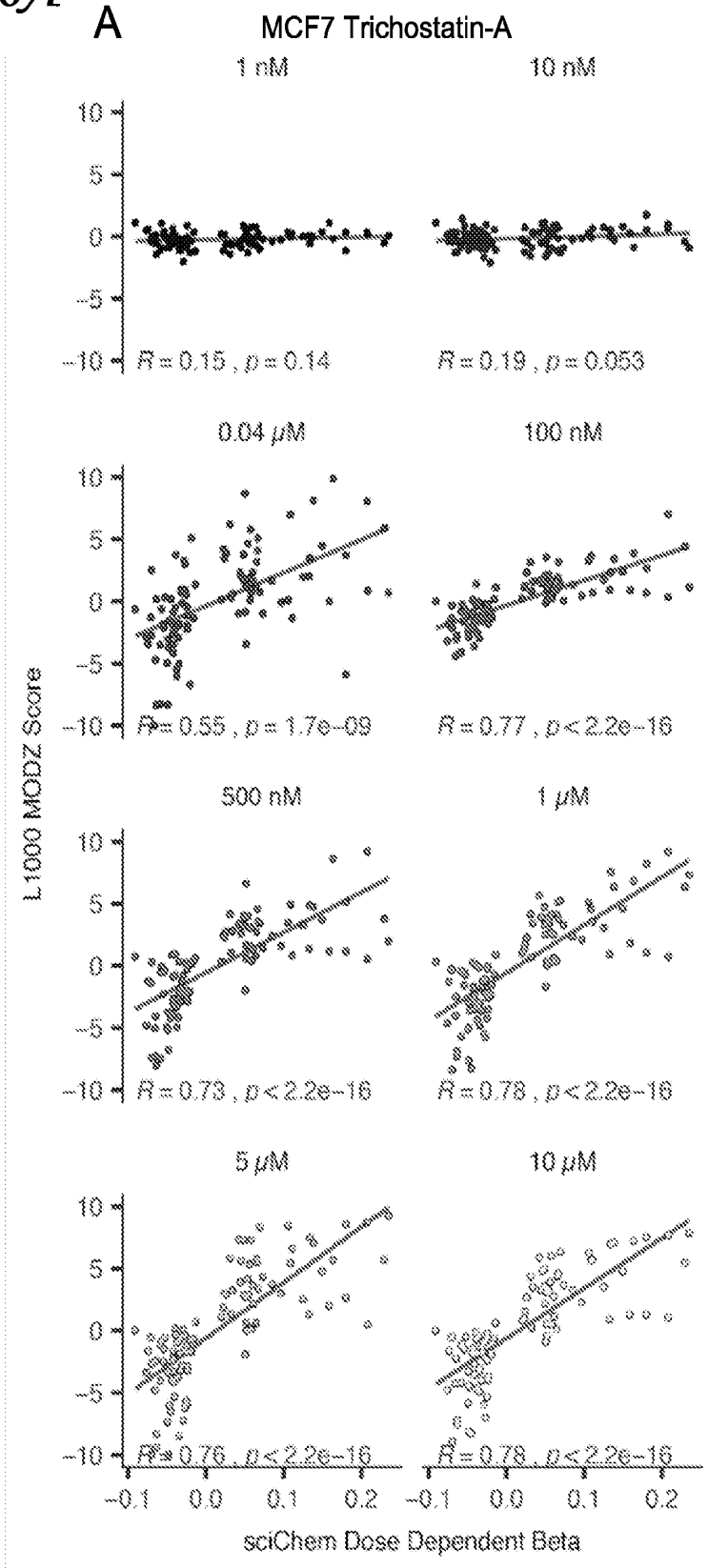

A
MCF7 Trichostatin-A
1 nM
10 nM
0.04 μM
100 nM
500 nM
1 μM
5 μM
10 μM
R = 0.15 , p = 0.14
R = 0.19 , p = 0.053
R = 0.55 , p = 1.7e−09
R = 0.77 , p < 2.2e−16
R = 0.73 , p < 2.2e−16
R = 0.78 , p < 2.2e−16
R = 0.76 , p < 2.2e−16
R = 0.78 , p < 2.2e−16
L1000 MODZ Score
sciChem Dose Dependent Beta

Fig. 16B

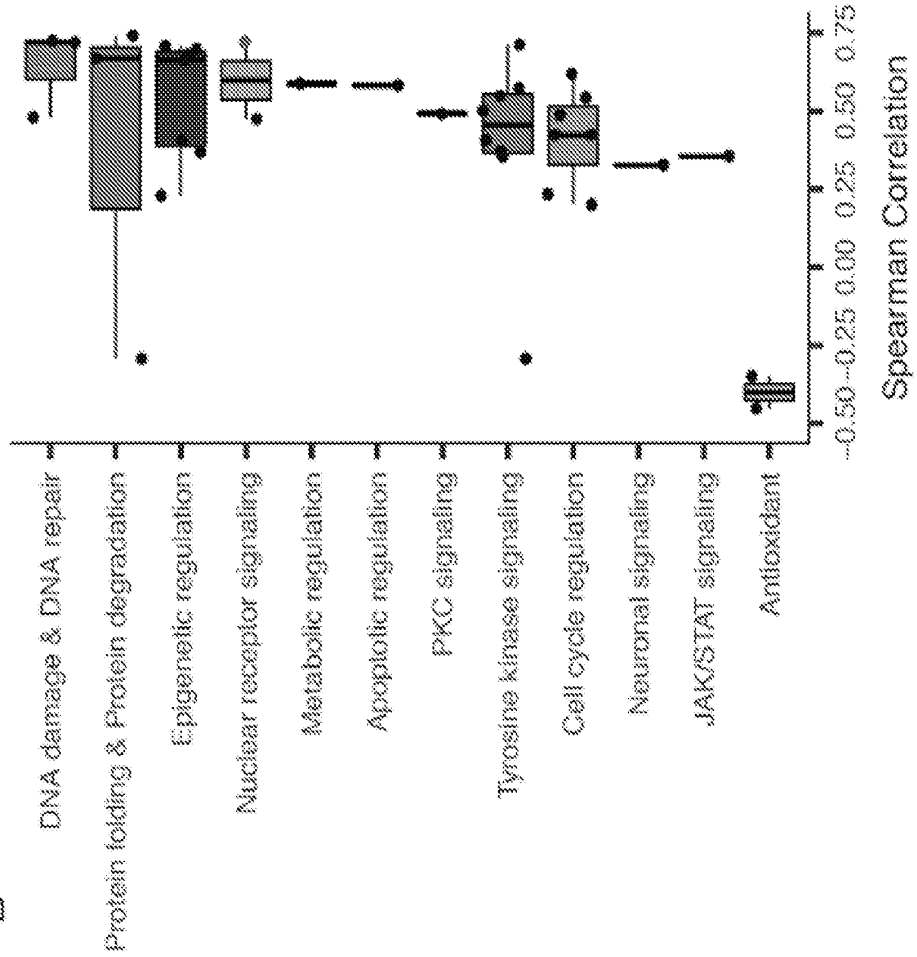
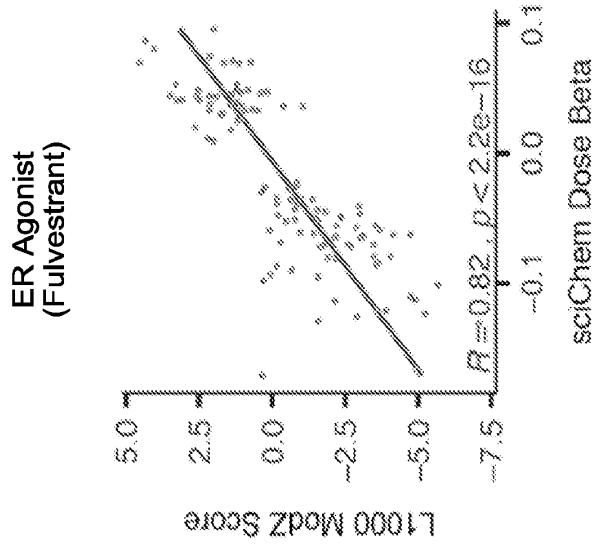


Fig. 16C



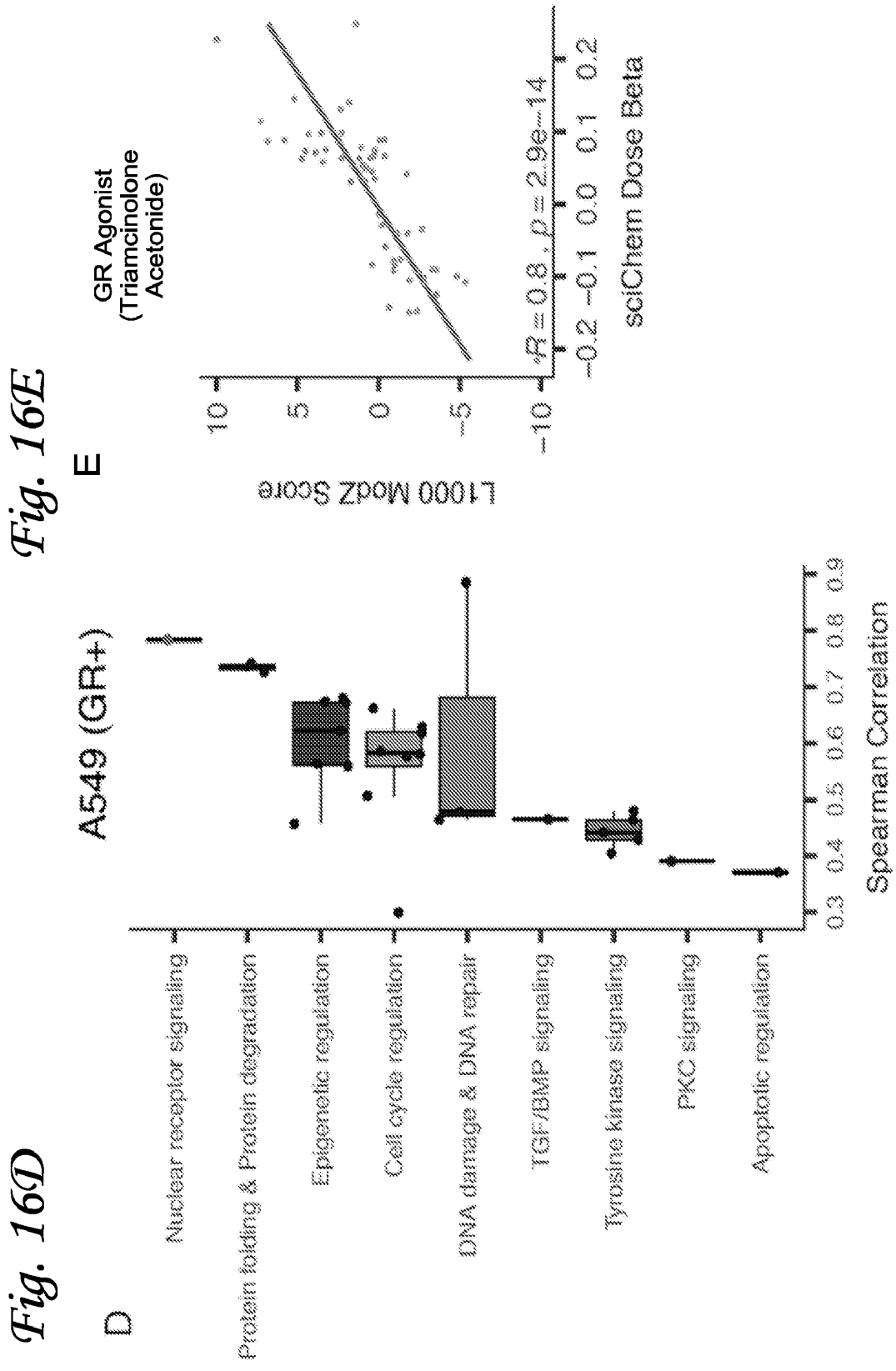


Fig. 16D

Fig. 16E

Fig. 17A

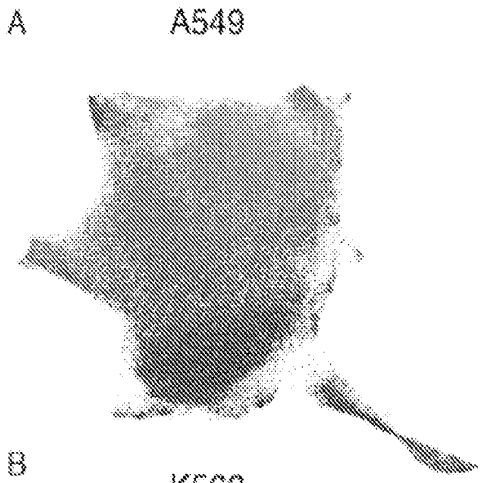


Fig. 17B



Fig. 17C

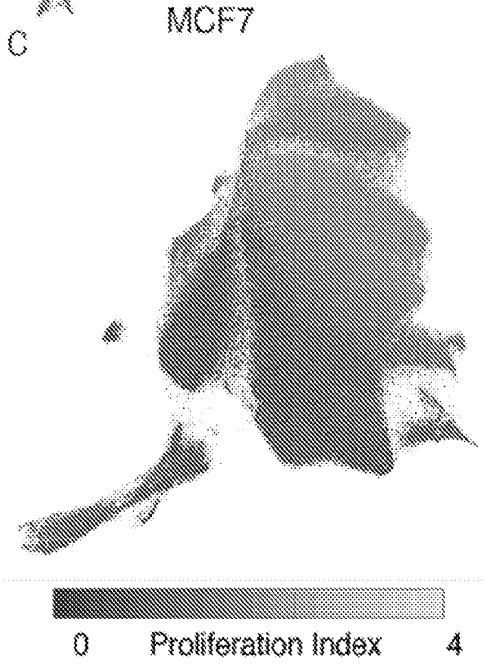


Fig. 17D

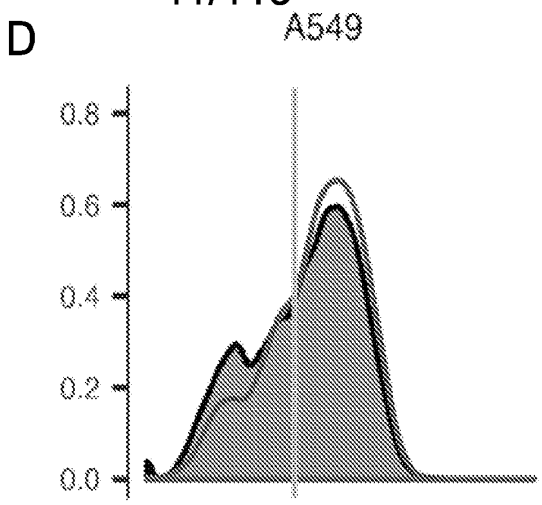


Fig. 17E

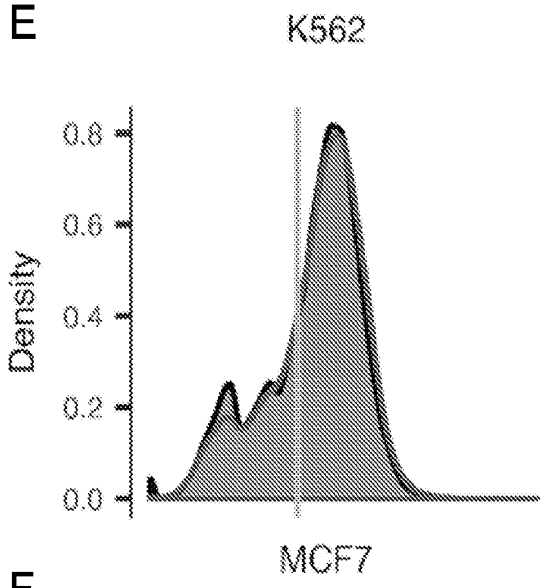


Fig. 17F

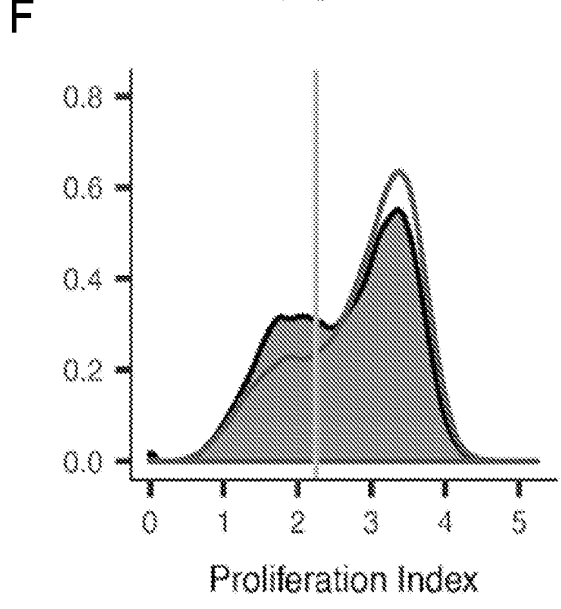


Fig. 17G



Fig. 17H

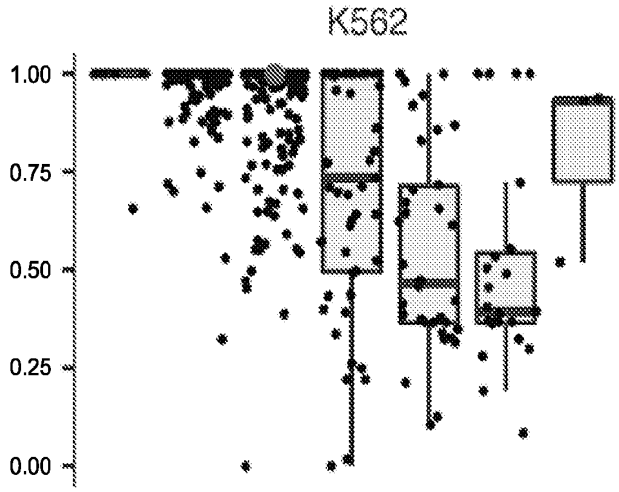
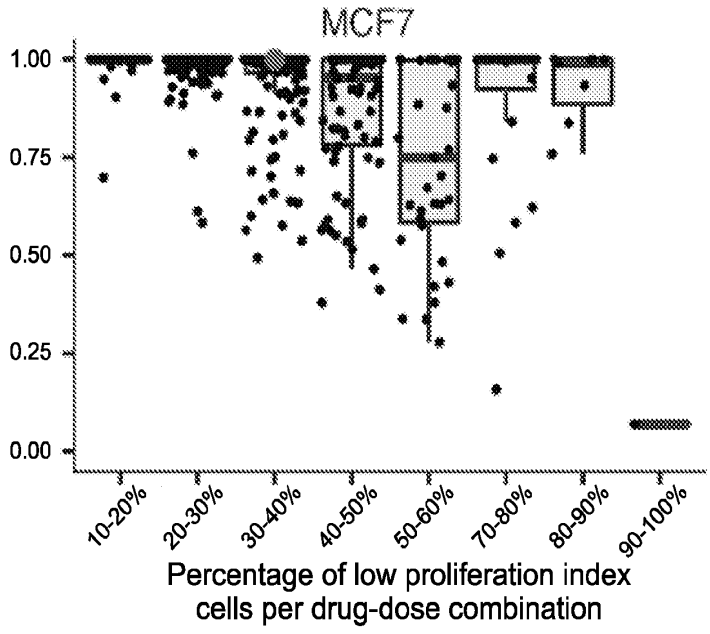


Fig. 17I



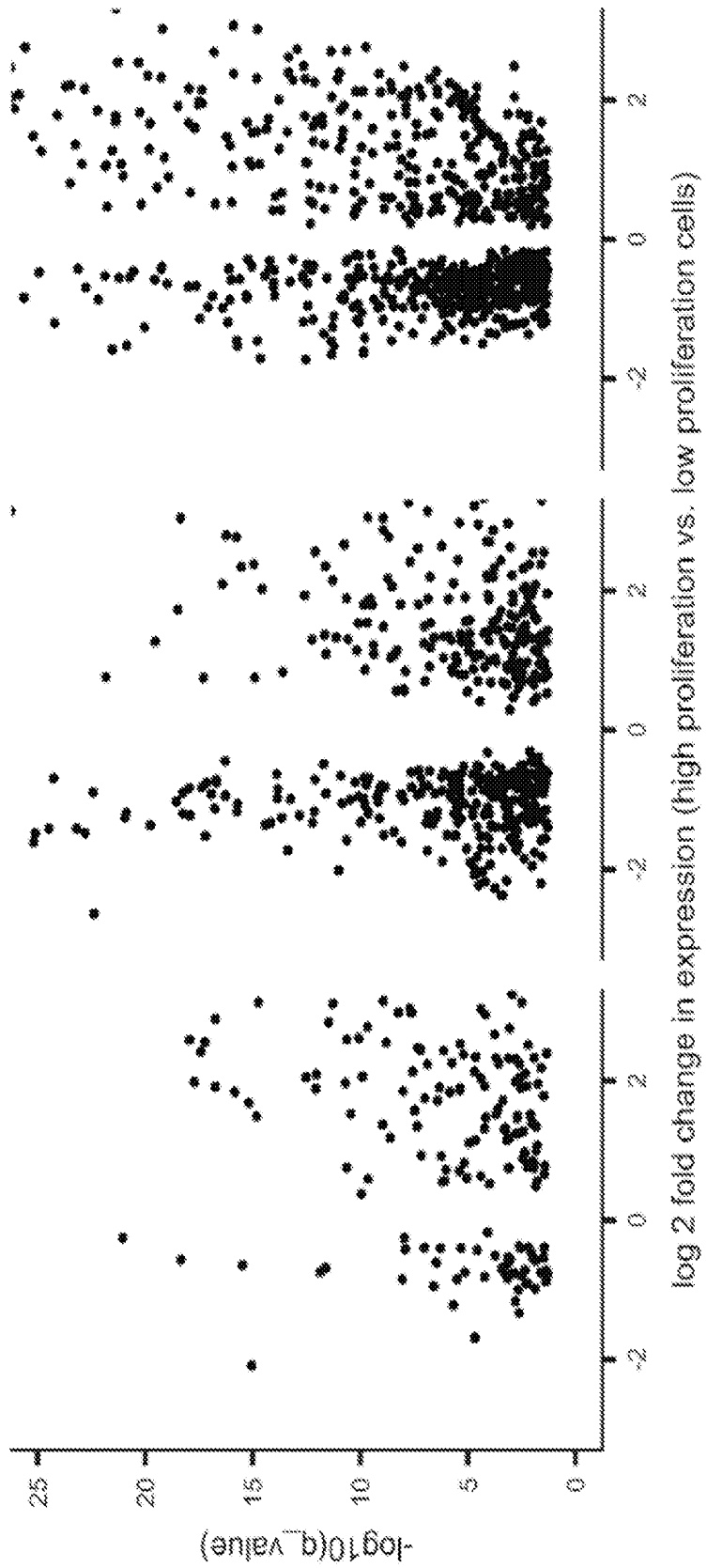

MCF7
K562
A549
-log10(q_value)
25
20
15
10
5
0
-2
0
2
log 2 fold change in expression (high proliferation vs. low proliferation cells)

Fig. 17J

Fig. 18A

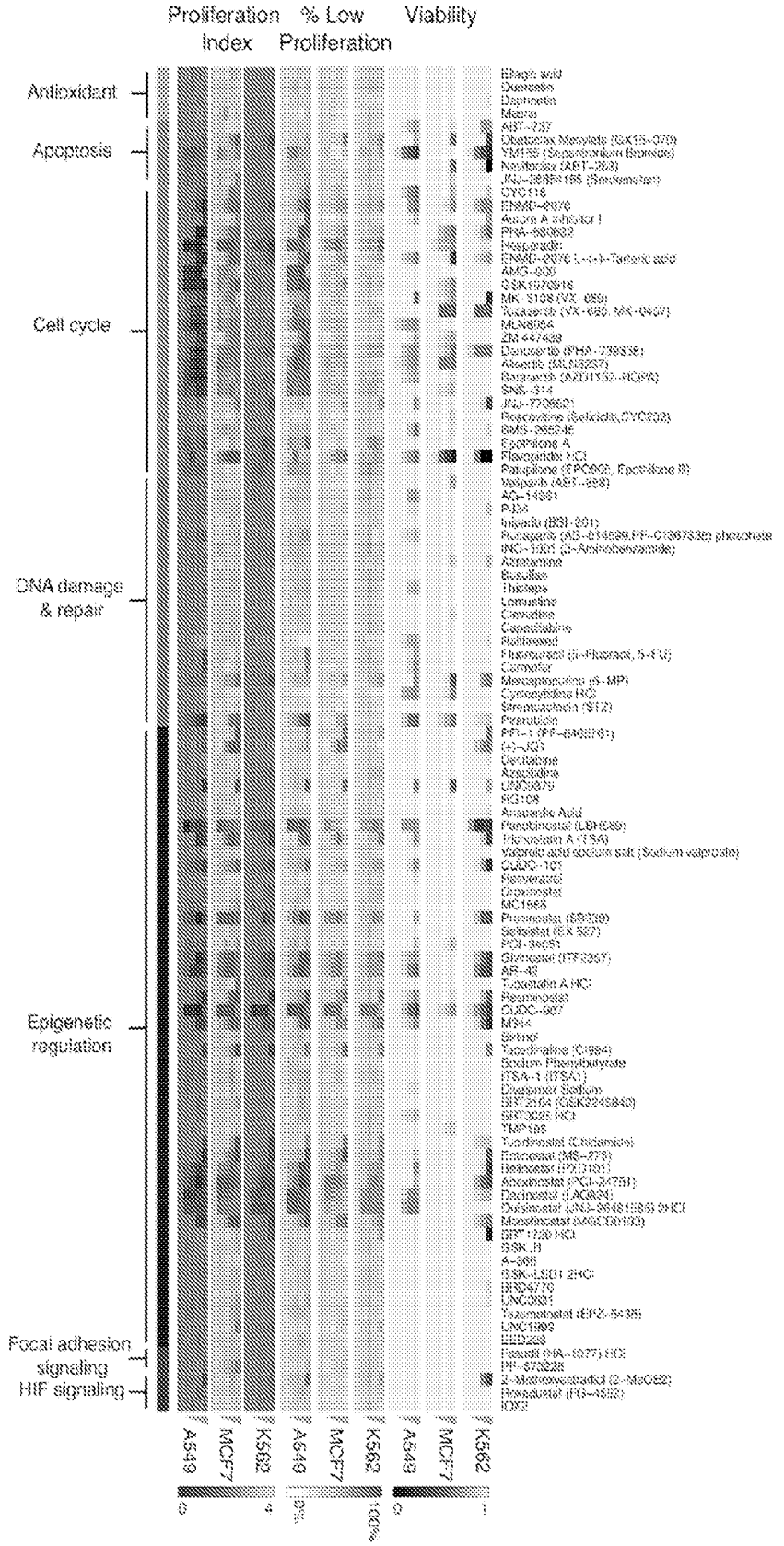

Proliferation Index
% Low Proliferation
Viability
Antioxidant
Apoptosis
Cell cycle
DNA damage & repair
Epigenetic regulation
Focal adhesion signaling
HIF signaling
A549
MCF7
K562
A549
MCF7
K562
A549
MCF7
K562
0
1
0%
100%
0
1

Fig. 18B

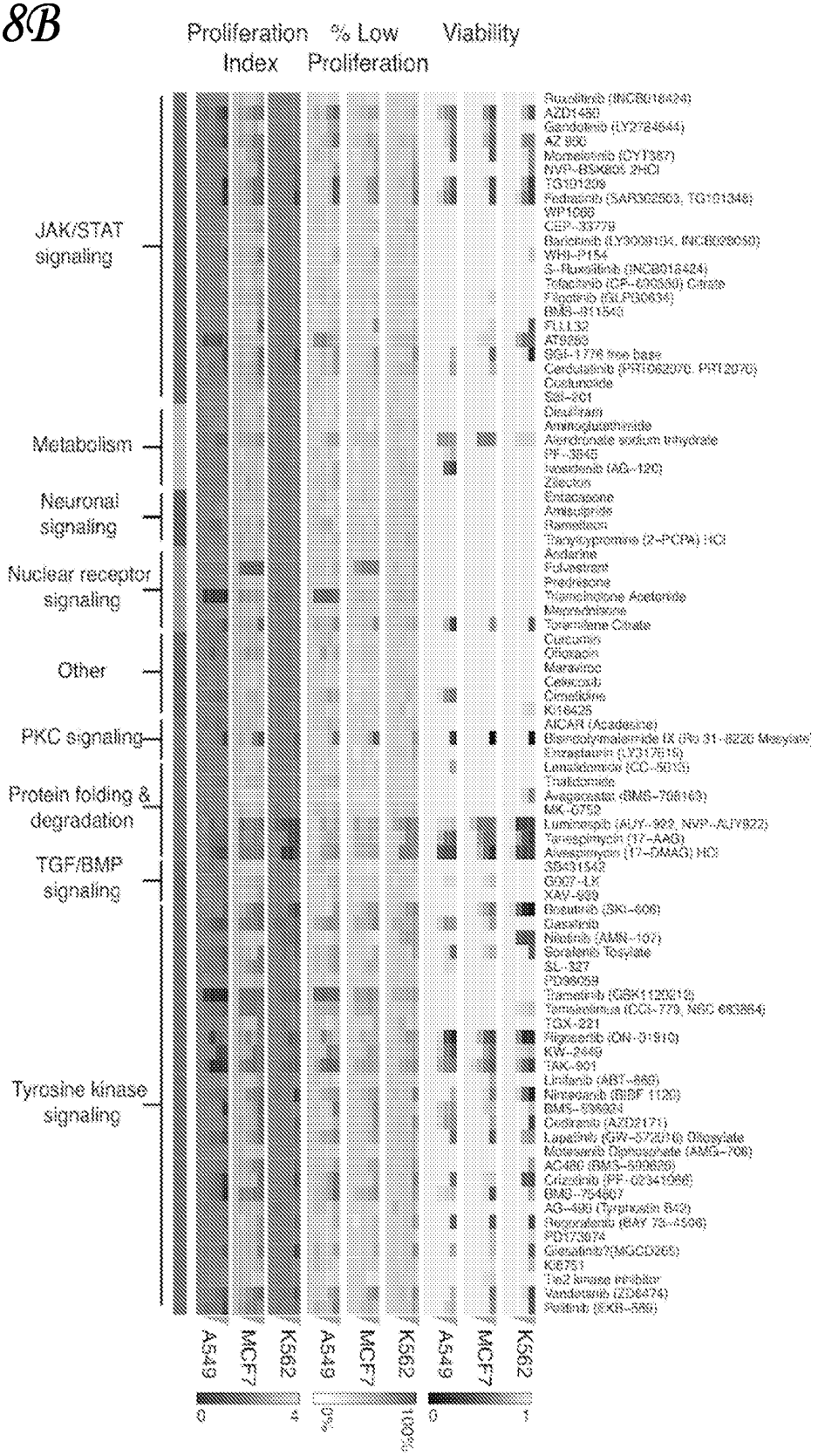

Proliferation Index
% Low Proliferation
Viability
JAK/STAT signaling
Metabolism
Neuronal signaling
Nuclear receptor signaling
Other
PKC signaling
Protein folding & degradation
TGF/BMP signaling
Tyrosine kinase signaling
Ruxolitinib (INCB018424)
AZD1480
Gandotinib (LY2784544)
AZ 960
Momelotinib (CYT387)
NVP-BSK805 2HCl
TG101209
Fedratinib (SAR302503, TG101348)
WP1066
CEP-33779
Baricitinib (LY3009104, INCB028050)
WHI-P154
S-Ruxolitinib (INCB018424)
Tofacitinib (CP-690550) Citrate
Filgotinib (GLPG0634)
BMS-911543
FLLI32
AT9283
BGB-1776 free base
Cerdulatinib (PRT062070, PRT2070)
Cucurbitacin
Sal-003
Disulfiram
Ammoglutethimide
Alendronate sodium trihydrate
PF-3845
Ivosidenib (AG-120)
Zileuton
Entacapone
Amisulpride
Ramelteon
Tranylcypromine (2-PCPA) HCl
Acidarine
Fulvestrant
Prednisone
Triamcinolone Acetonide
Megestrol acetate
Toremifene Citrate
Curcumin
Ofloxacin
Maraviroc
Celecoxib
Cimetidine
K-16425
AICAR (Acadesine)
Bisindolylmaleimide IX (Ro 31-8220 Mesylate)
Entrectinib (LY3176116)
Lenalidomide (CC-5013)
Thalidomide
Avagacestat (BMS-708163)
MK-0752
Luminespib (AUY-922, NVP-AUY922)
Tanespimycin (17-AAG)
Alvespimycin (17-DMAG) HCl
SB431542
GSK-3 IX
XAV-939
Dasatinib (BMS-354825)
Gefitinib
Nilotinib (AMN-107)
Sorafenib Tosylate
SL-327
PD98059
Trametinib (GSK1120212)
Temsirolimus (CCI-779, NSC 683864)
TGX-221
Pilaralisib (XL-147)
KW-2449
TAK-901
Linifanib (ABT-869)
Nintedanib (BIBF 1120)
BMS-599626
Crizotinib (PF-02341066)
Lapatinib (GW-572016) Ditosylate
Motesanib Diphosphate (AMG-706)
AC480 (BMS-599626)
Crizotinib (PF-02341066)
BMS-754807
AG-490 (Tyrphostin B42)
Regorafenib (BAY 73-4506)
PD173074
Glesatinib (MGCD265)
KB751
Tie2 kinase inhibitor
Vandetanib (ZD6474)
Foretinib (GSK-1363089)
A549
MCF7
K562
A549
MCF7
K562
A549
MCF7
K562
0
1
0%
100%
0
1

Fig. 19A

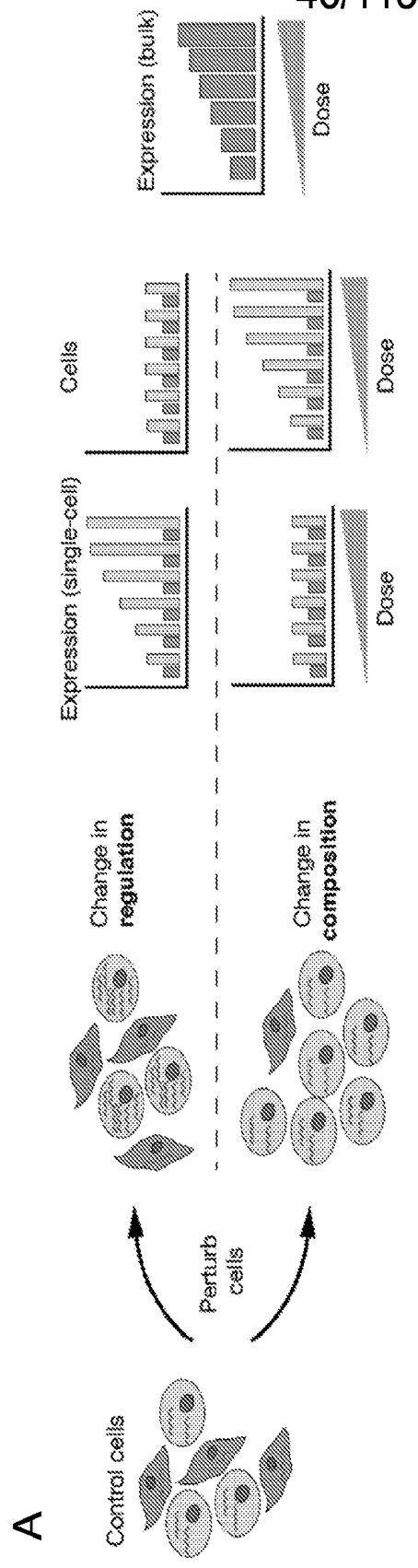

A
Control cells
Perturb cells
Change in regulation
Change in composition
Expression (single-cell)
Cells
Dose
Dose
Dose
Expression (bulk)
Dose

Fig. 19B

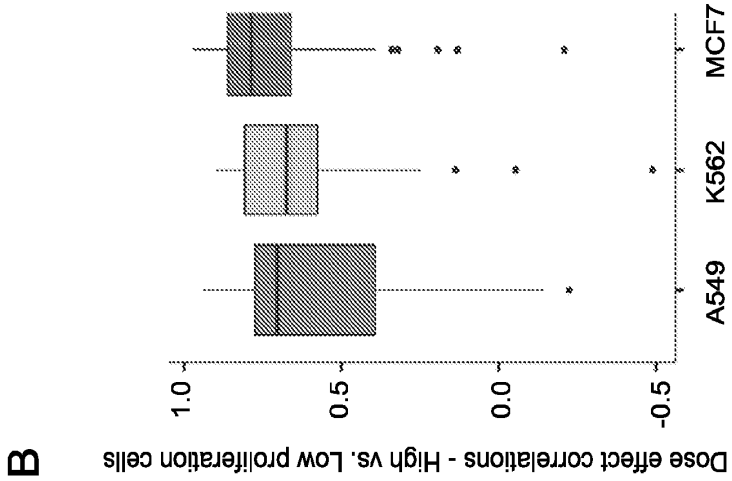


Fig. 19C

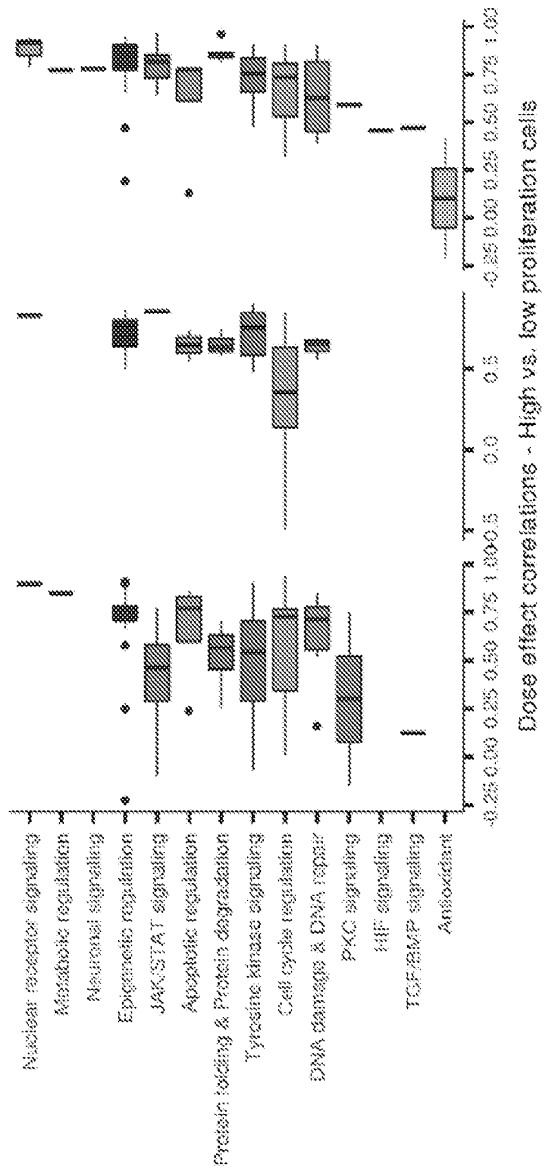
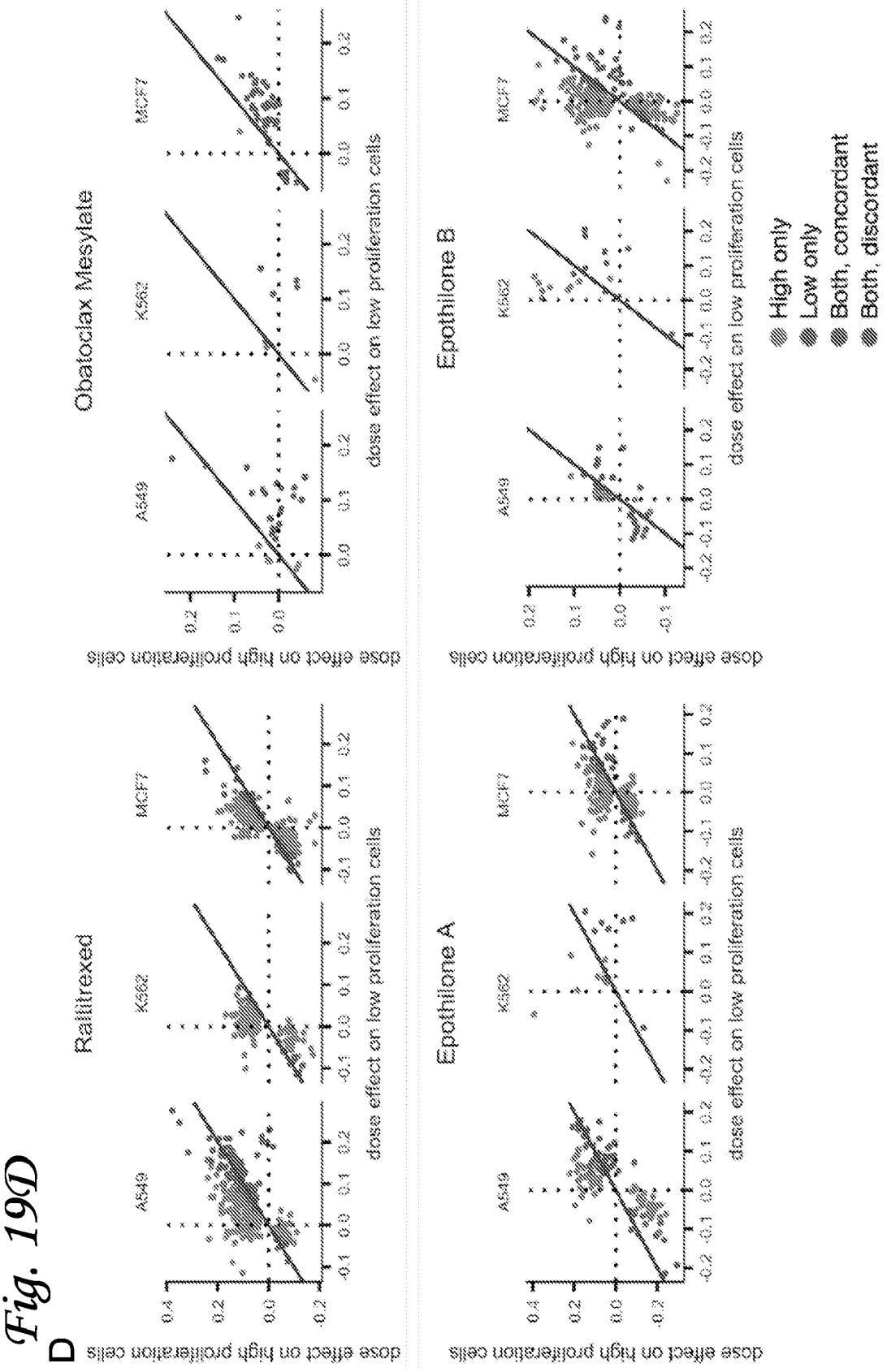


Fig. 19D


D
Ralitrexed
Obatoclax Mesylate
Epothilone A
Epothilone B
A549
K562
MCF7
dose effect on high proliferation cells
dose effect on low proliferation cells
High only
Low only
Both, concordant
Both, discordant

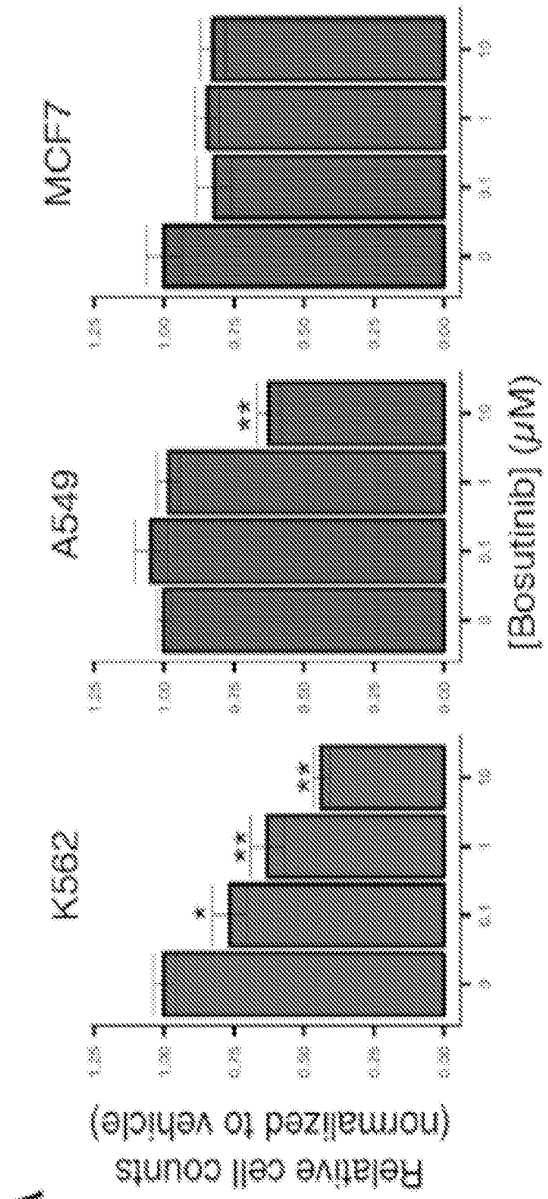


Fig. 20A

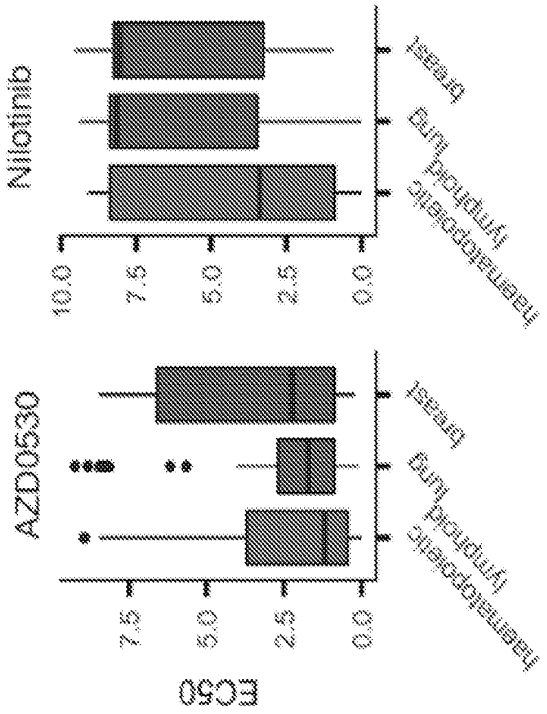


Fig. 20B

Fig. 20C

C

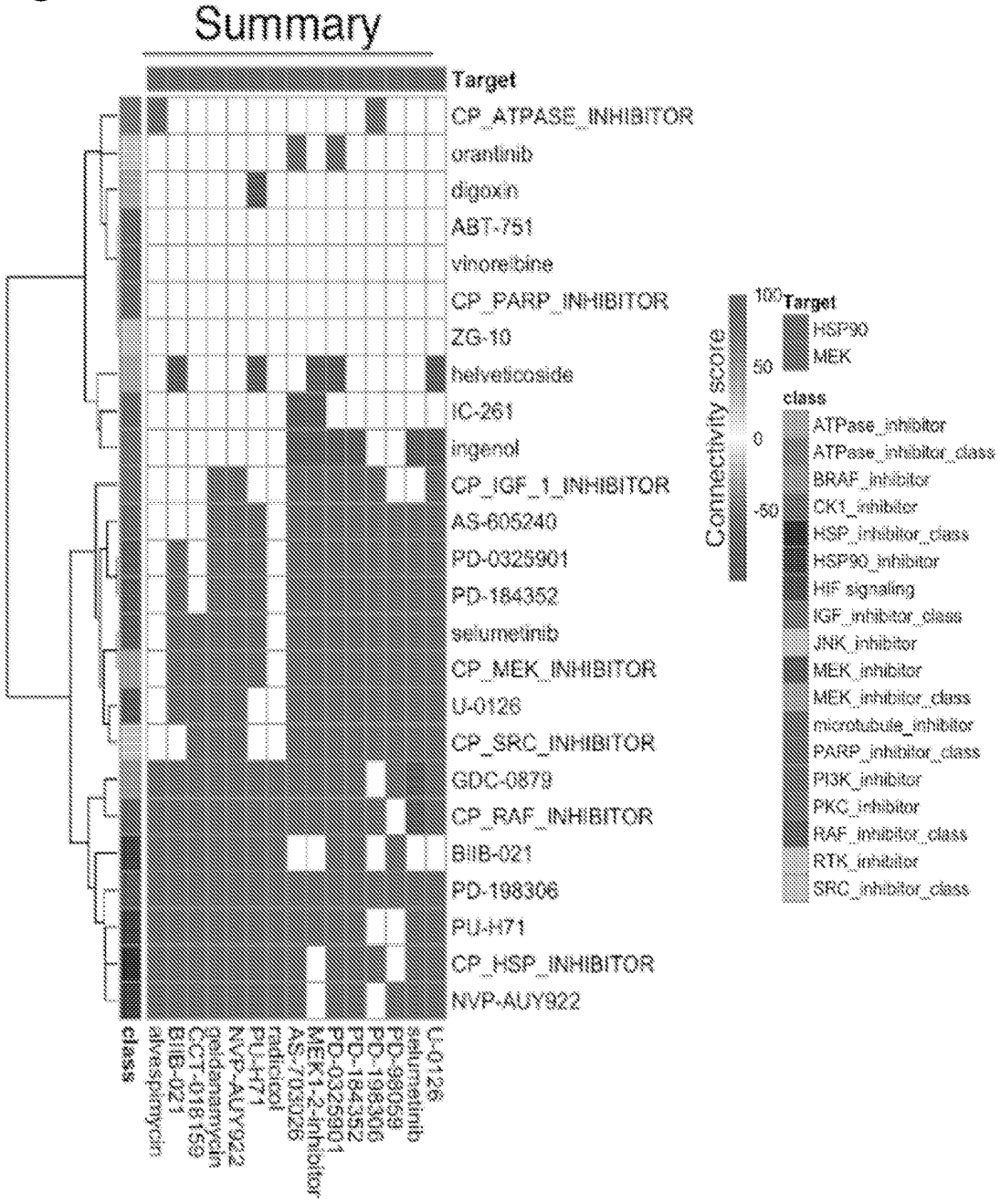

Summary
Target
CP_ATPASE_INHIBITOR
oranlinib
digoxin
ABT-751
vinorelbine
CP_PARP_INHIBITOR
ZG-10
helveticoside
IC-261
ingenol
CP_IGF_1_INHIBITOR
AS-605240
PD-0325901
PD-184352
selumetinib
CP_MEK_INHIBITOR
U-0126
CP_SRC_INHIBITOR
GDC-0879
CP_RAF_INHIBITOR
BIIB-021
PD-198306
PU-H71
CP_HSP_INHIBITOR
NVP-AUY922
class
alvespimycin
BIIB-021
CCT-018159
geldanamycin
NVP-AUY922
PU-H71
radicicol
AS-703026
MEK1-2-inhibitor
PD-0325901
PD-184352
PD-198306
PD-98059
selumetinib
U-0126
Connectivity score
100
50
0
-50
Target
HSP90
MEK
class
ATPase_inhibitor
ATPase_inhibitor_class
BRAF_inhibitor
CK1_inhibitor
HSP_inhibitor_class
HSP90_inhibitor
HIF signaling
IGF_inhibitor_class
JNK_inhibitor
MEK_inhibitor
MEK_inhibitor_class
microtubule_inhibitor
PARP_inhibitor_class
PI3K_inhibitor
PKC_inhibitor
RAF_inhibitor_class
RTK_inhibitor
SRC_inhibitor_class

Fig. 20D

D

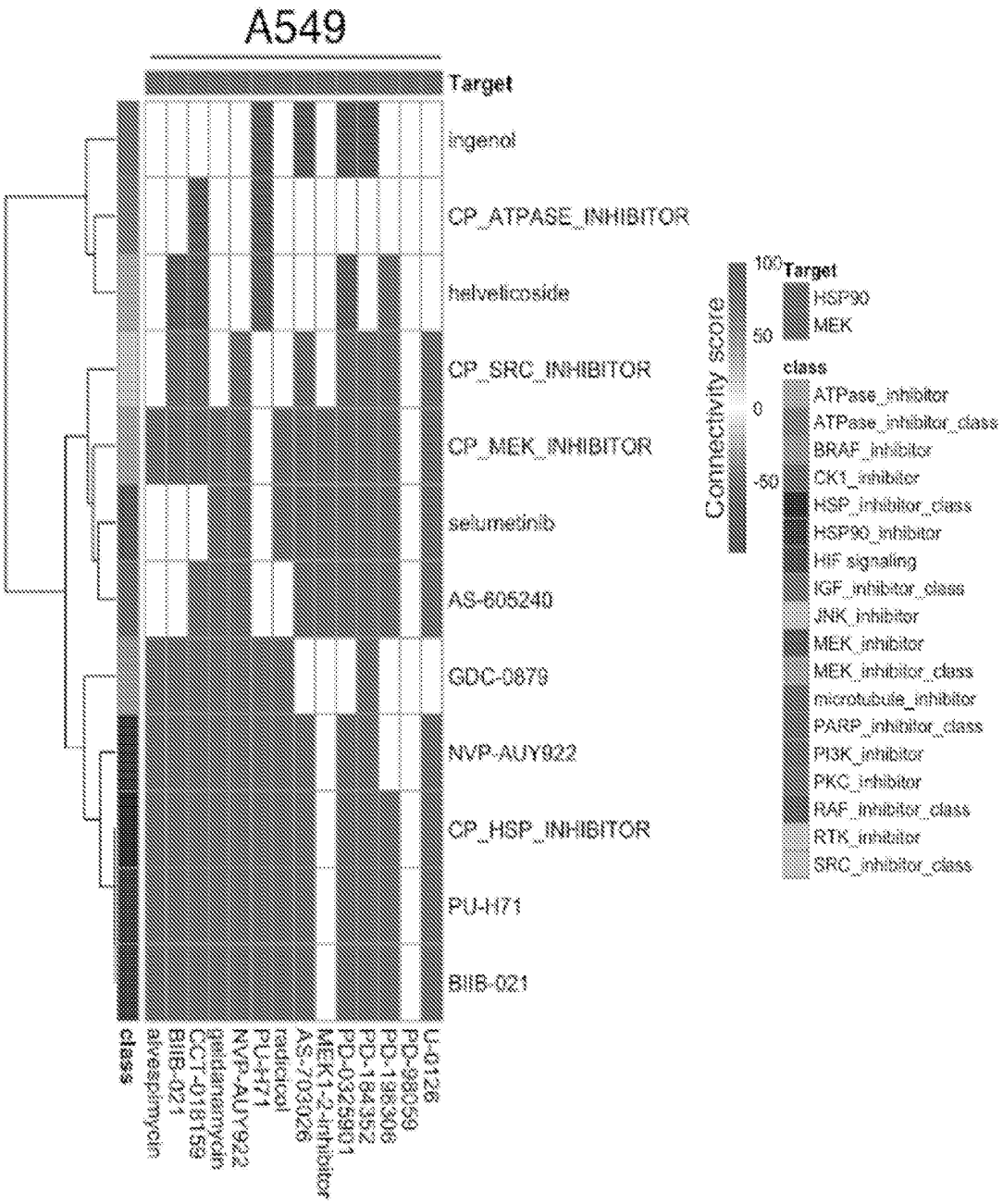

A549
Target
ingenol
CP_ATPASE_INHIBITOR
helveticoside
CP_SRC_INHIBITOR
CP_MEK_INHIBITOR
selumetinib
AS-605240
GDC-0879
NVP-AUY922
CP_HSP_INHIBITOR
PU-H71
BIIB-021
class
alvespimycin
BIIB-021
CCT-018159
geldanamycin
NVP-AUY922
PU-H71
radicicol
AS-703026
MEK1-2-inhibitor
PD-0325901
PD-184352
PD-198306
PD-98059
U-0126
Connectivity score
100
50
0
-50
Target
HSP90
MEK
class
ATPase_inhibitor
ATPase_inhibitor_class
BRAF_inhibitor
CK1_inhibitor
HSP_inhibitor_class
HSP90_inhibitor
HIF signaling
IGF_inhibitor_class
JNK_inhibitor
MEK_inhibitor
MEK_inhibitor_class
microtubule_inhibitor
PARP_inhibitor_class
PI3K_inhibitor
PKC_inhibitor
RAF_inhibitor_class
RTK_inhibitor
SRC_inhibitor_class

Fig. 20E

E

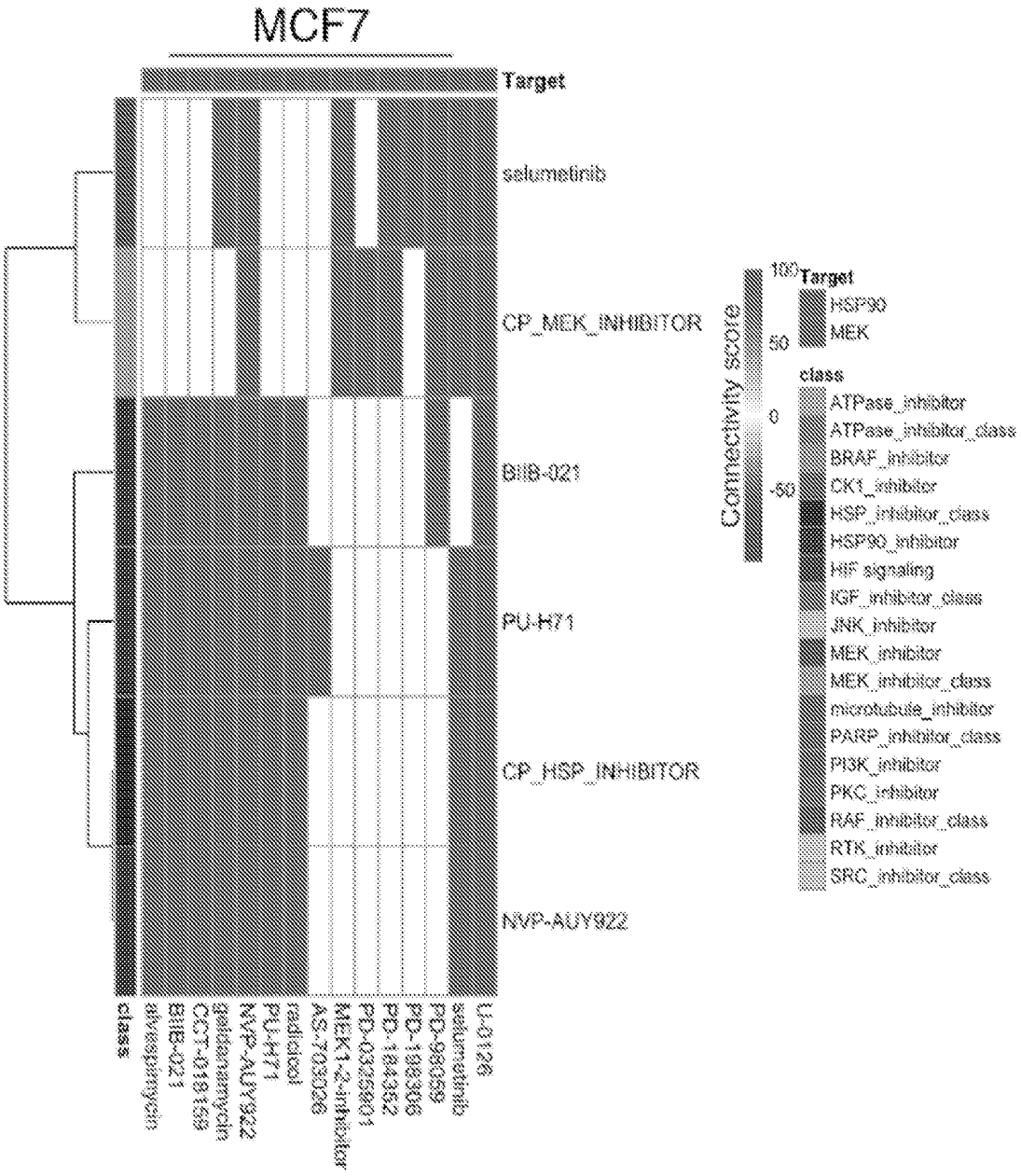

MCF7
Target
selumetinib
CP_MEK_INHIBITOR
BIIB-021
PU-H71
CP_HSP_INHIBITOR
NVP-AUY922
class
alvespimycin
BIIB-021
CGT-018159
geldanamycin
NVP-AUY922
PU-H71
radicicol
AS-703026
MEK1-2-inhibitor
PD-0325901
PD-184352
PD-198306
PD-98059
selumetinib
U-0126
Connectivity score
100
50
0
-50
Target
HSP90
MEK
class
ATPase_inhibitor
ATPase_inhibitor_class
BRAF_inhibitor
CK1_inhibitor
HSP_inhibitor_class
HSP90_inhibitor
HIF signaling
IGF_inhibitor_class
JNK_inhibitor
MEK_inhibitor
MEK_inhibitor_class
microtubule_inhibitor
PARP_inhibitor_class
PI3K_inhibitor
PKC_inhibitor
RAF_inhibitor_class
RTK_inhibitor
SRC_inhibitor_class

Fig. 21

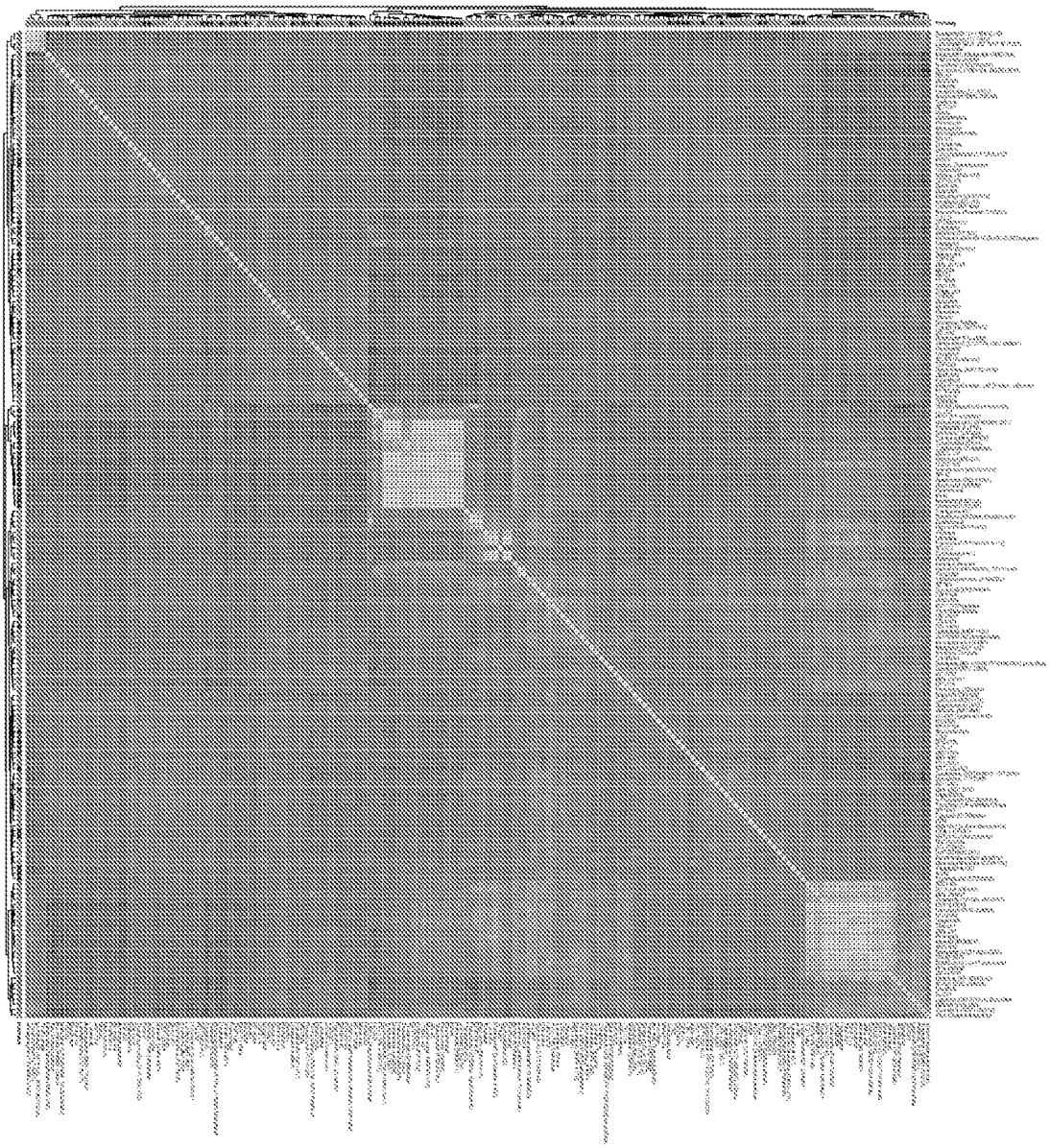


Fig. 22

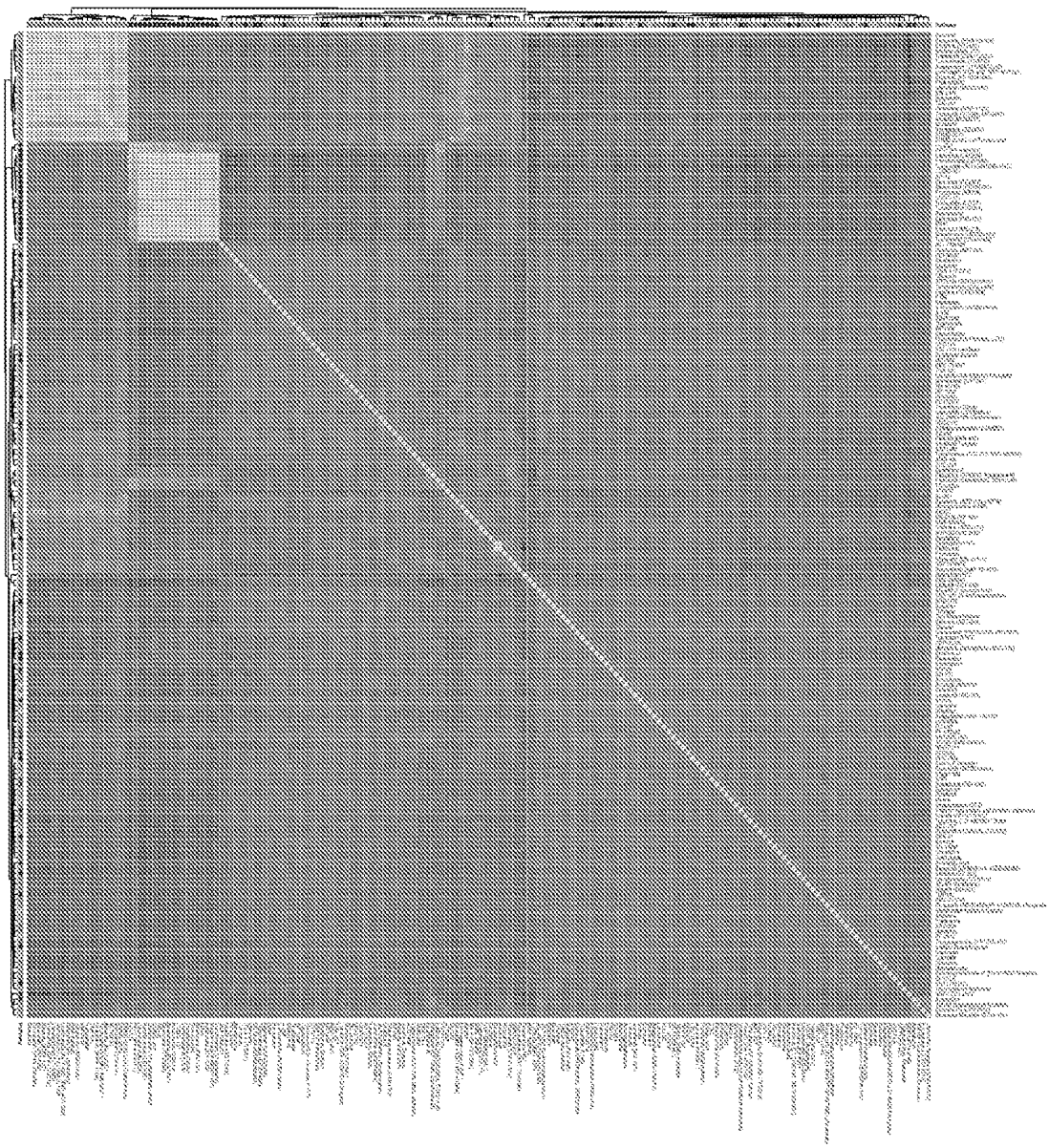


Fig. 23

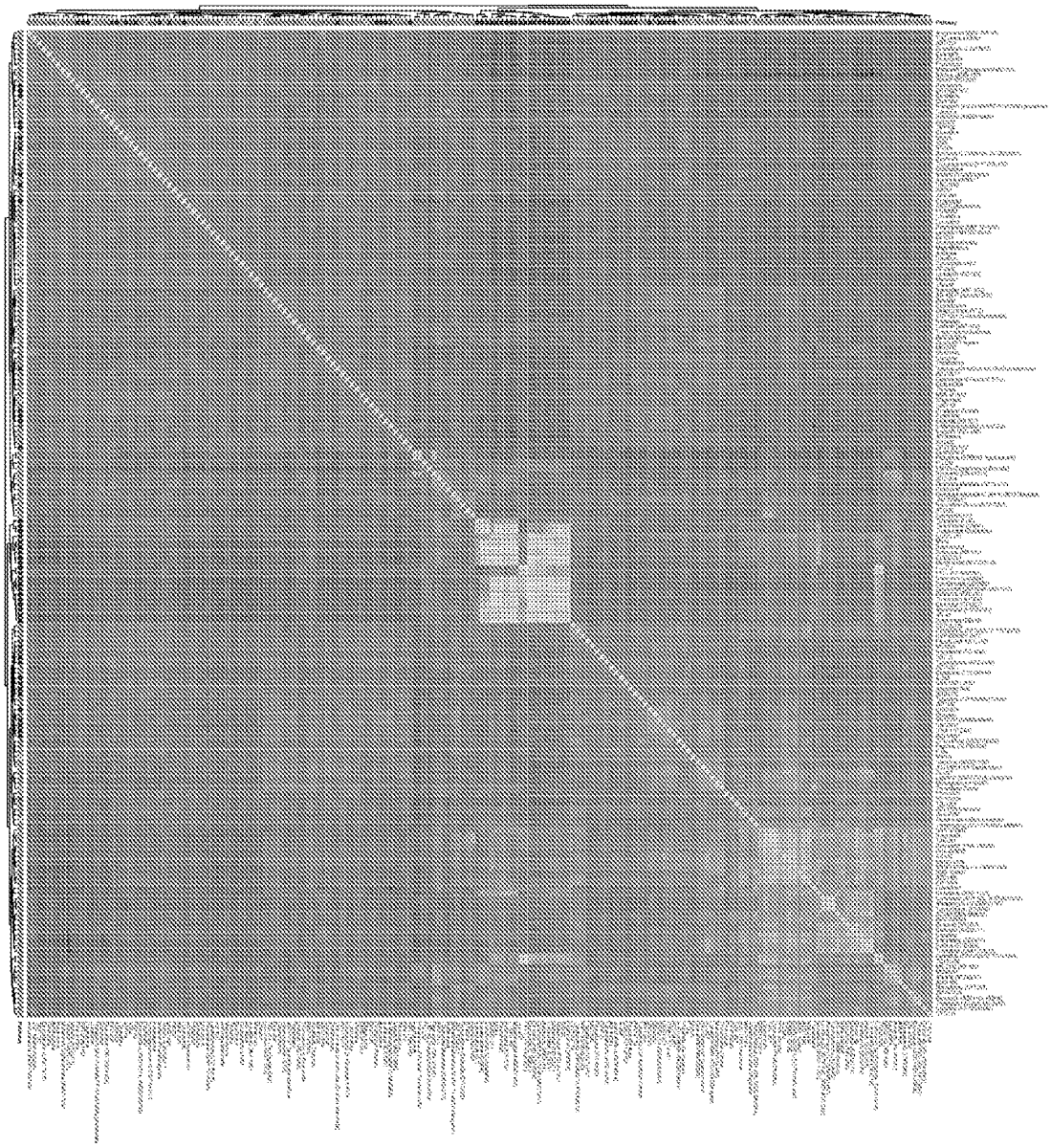


Fig. 24A

A

A549

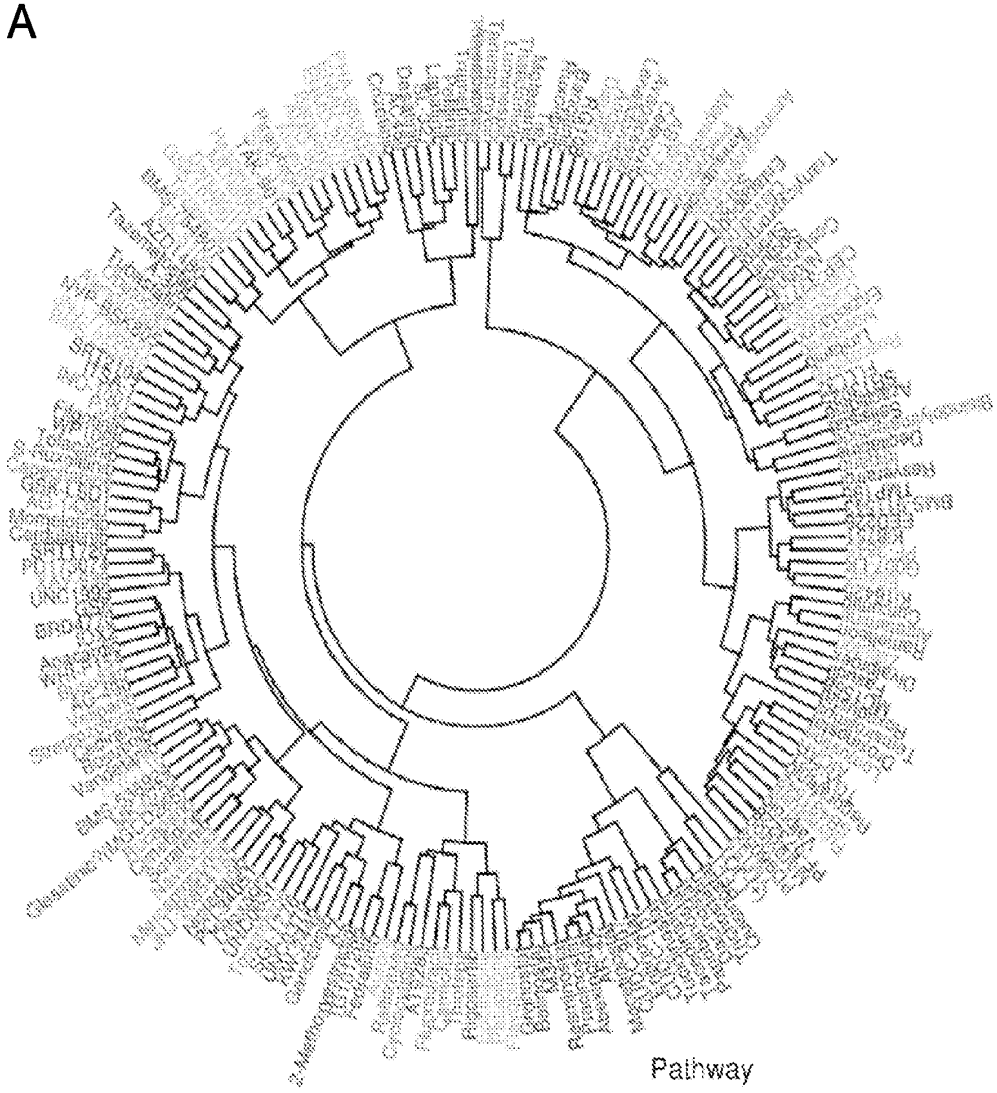


Fig. 24B

B

K562

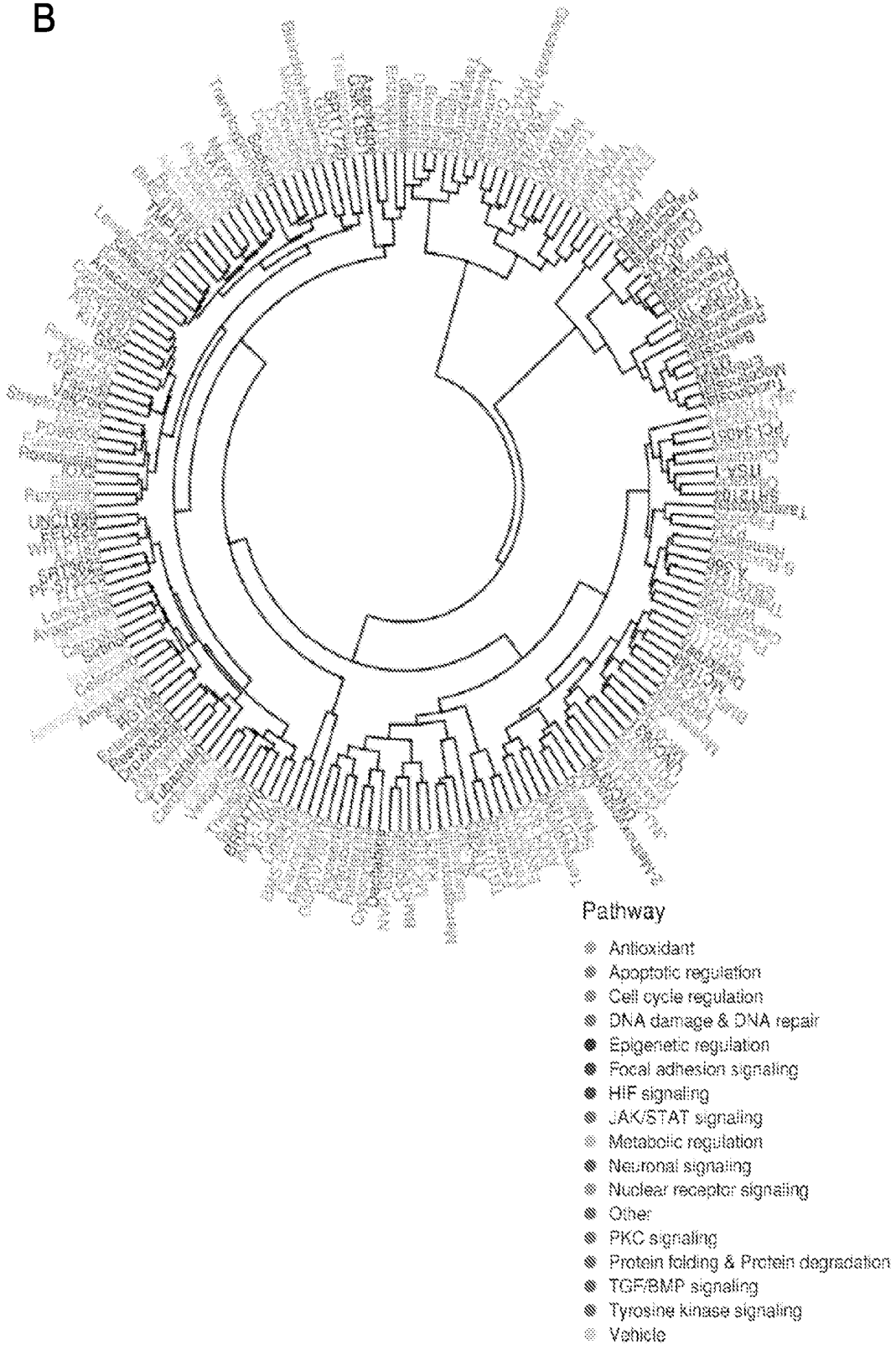


Fig. 24C

C

MCF7

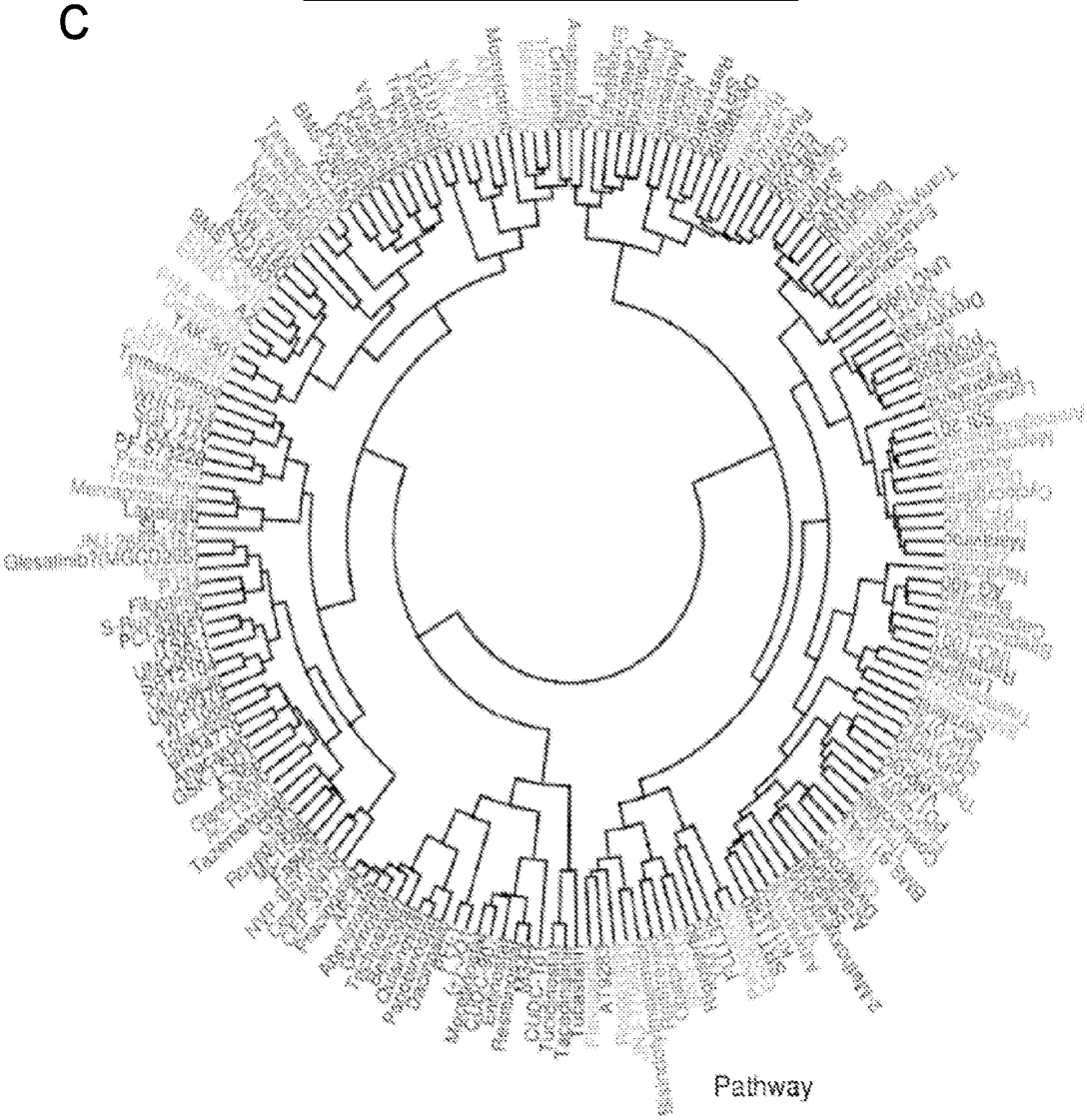
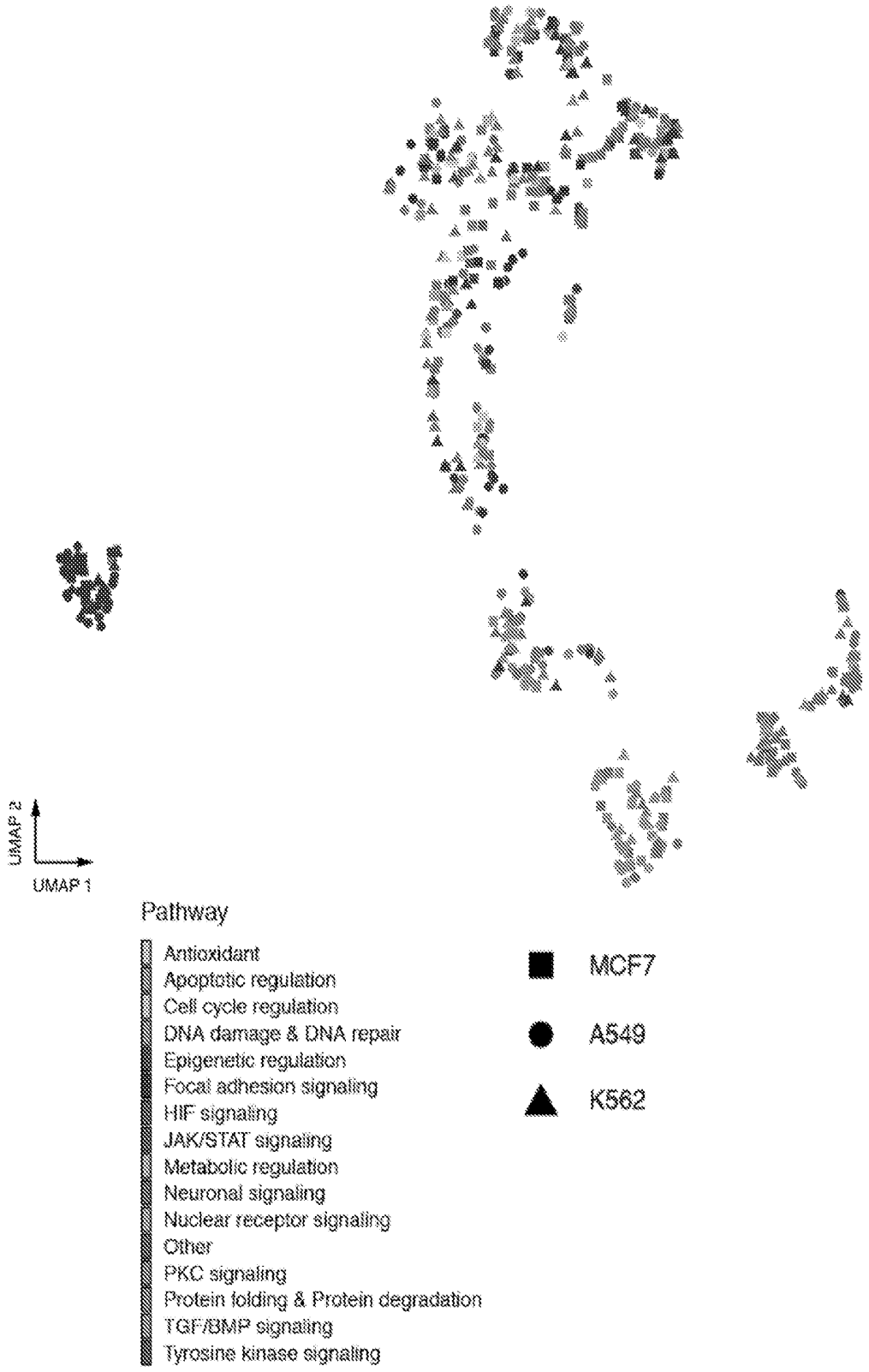


Fig. 25


UMAP 2
UMAP 1
Pathway
Antioxidant
Apoptotic regulation
Cell cycle regulation
DNA damage & DNA repair
Epigenetic regulation
Focal adhesion signaling
HIF signaling
JAK/STAT signaling
Metabolic regulation
Neuronal signaling
Nuclear receptor signaling
Other
PKC signaling
Protein folding & Protein degradation
TGF/BMP signaling
Tyrosine kinase signaling
MCF7
A549
K562

Figs. 26A, 26B

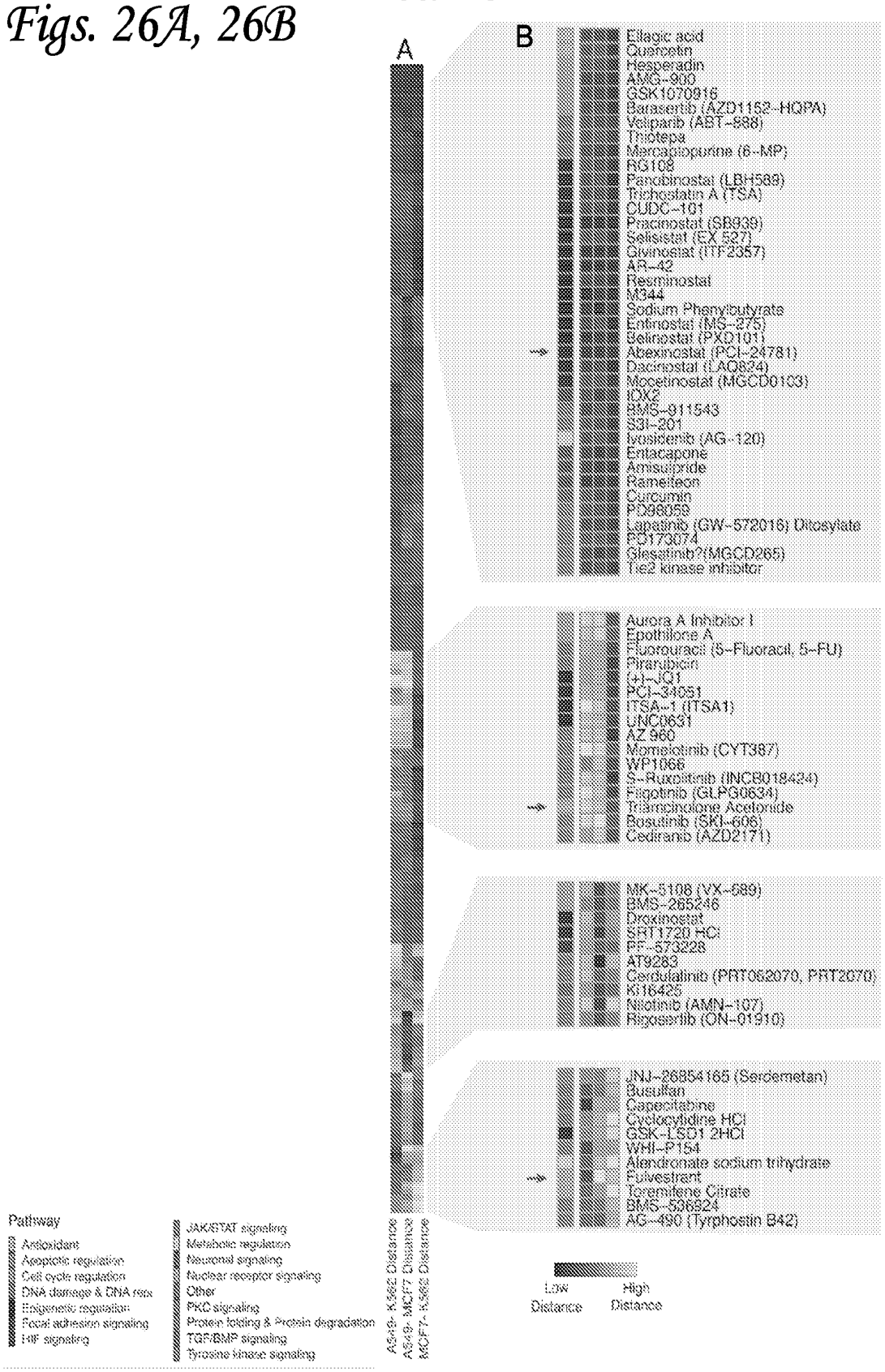

A
B
Ellagic acid
Quercetin
Hesperadin
AMG-900
GSK1070916
Barasertib (AZD1152-HQPA)
Veliparib (ABT-888)
Triciribine
Mercaptopurine (6-MP)
RG108
Panobinostat (LBH589)
Trichostatin A (TSA)
CUDC-101
Pracinostat (SB939)
Selisistat (EX 527)
Givinostat (ITF2357)
AR-42
Resminostat
M344
Sodium Phenylbutyrate
Entinostat (MS-275)
Belinostat (PXD101)
Abexinostat (PCI-24781)
Dacinostat (LAQ824)
Mocetinostat (MGCD0103)
IOX2
BMS-911543
S3I-201
Ivosidenib (AG-120)
Entacapone
Amisulpride
Ramelteon
Curcumin
PD98059
Lapatinib (GW-572016) Ditosylate
PD173074
Glesatinib?(MGCD265)
Tie2 kinase inhibitor
Aurora A Inhibitor I
Epothilone A
Fluorouracil (5-Fluoracil, 5-FU)
Piranubicin
(+)-JQ1
PCI-34051
ITSA-1 (ITSA1)
UNC0631
AZ 960
Momelotinib (CYT387)
WP1066
S-Ruxolitinib (INCB018424)
Filgotinib (GLPG0634)
Triamcinolone Acetonide
Bosutinib (SKI-606)
Cediranib (AZD2171)
MK-5108 (VX-689)
BMS-265246
Droxinostat
SRT1720 HCl
PF-573228
AT9283
Cerdulatinib (PRT062070, PRT2070)
KI16425
Nilotinib (AMN-107)
Rigosertib (ON-01910)
JNJ-26854165 (Serdemetan)
Busulfan
Capecitabine
Cyclocytidine HCl
GSK-LSD1 2HCl
WHI-P154
Alendronate sodium trihydrate
Fulvestrant
Toremifene Citrate
BMS-536924
AG-490 (Tyrphostin B42)
A549- K562 Distance
A549- MCF7 Distance
MCF7- K562 Distance
Low Distance
High Distance
Pathway
Antioxidant
Apoptotic regulation
Cell cycle regulation
DNA damage & DNA rep
Epigenetic regulation
Focal adhesion signaling
HIF signaling
JAK/STAT signaling
Metabolic regulation
Neuronal signaling
Nuclear receptor signaling
Other
PKC signaling
Protein folding & Protein degradation
TGF/BMP signaling
Tyrosine kinase signaling

Fig. 26C

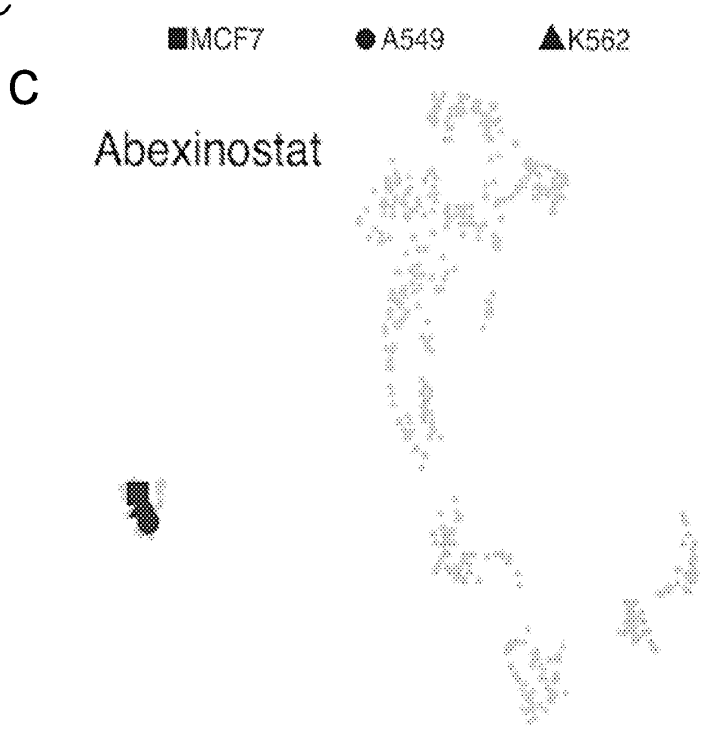


Fig. 26D

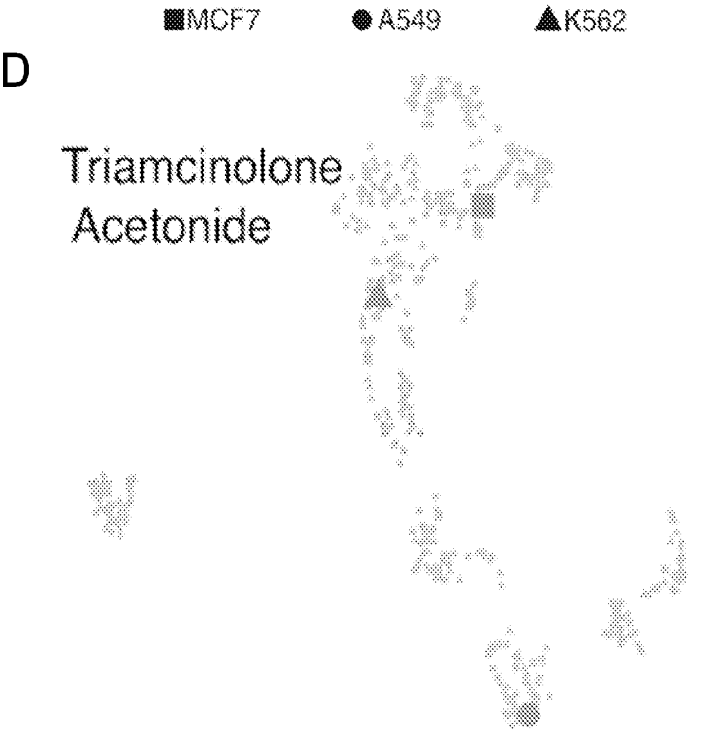


Fig. 26E

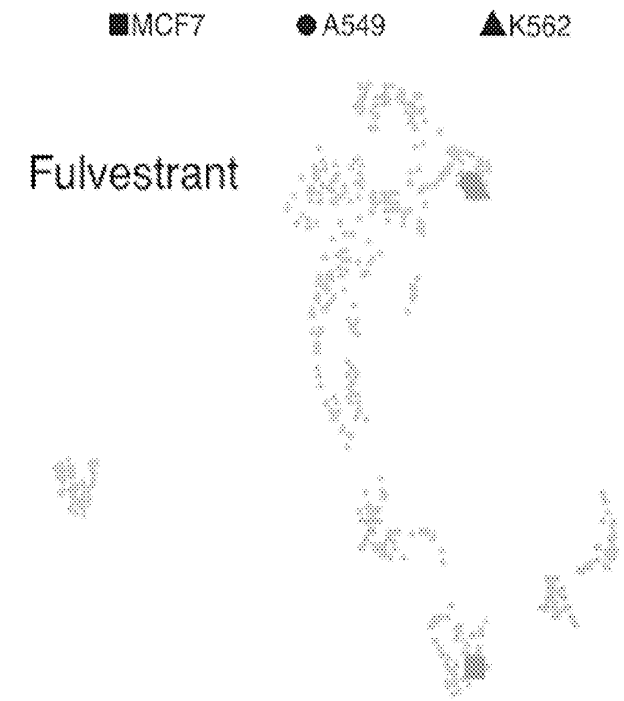


Fig. 26F

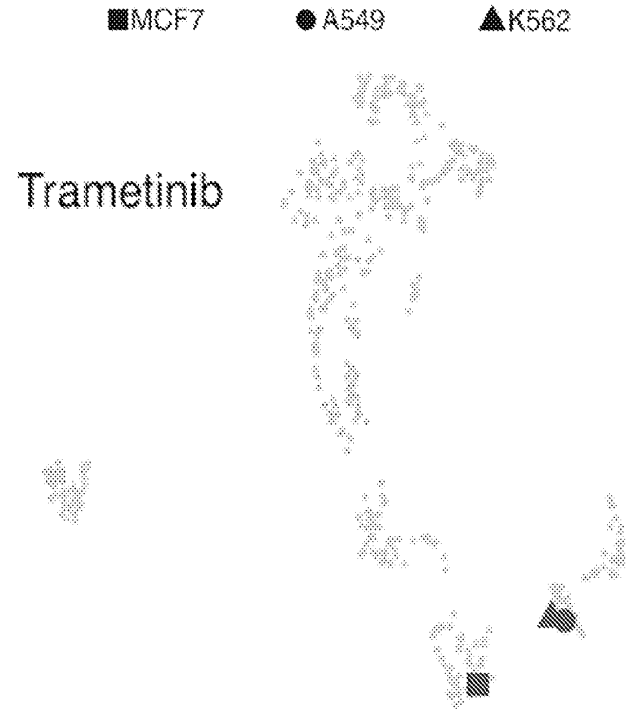


Fig. 27A

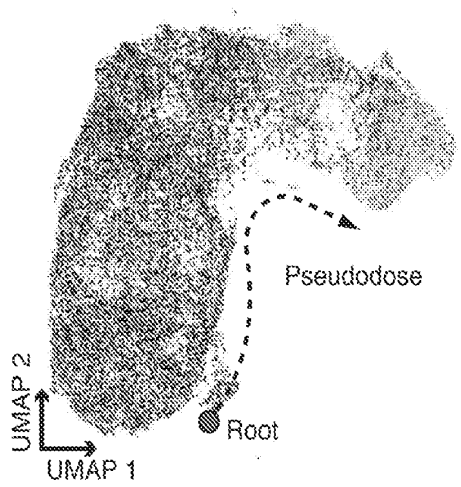


Fig. 27B

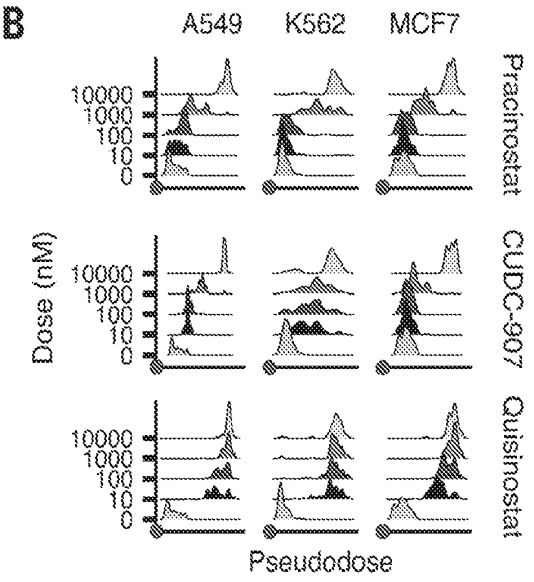


Fig. 27C

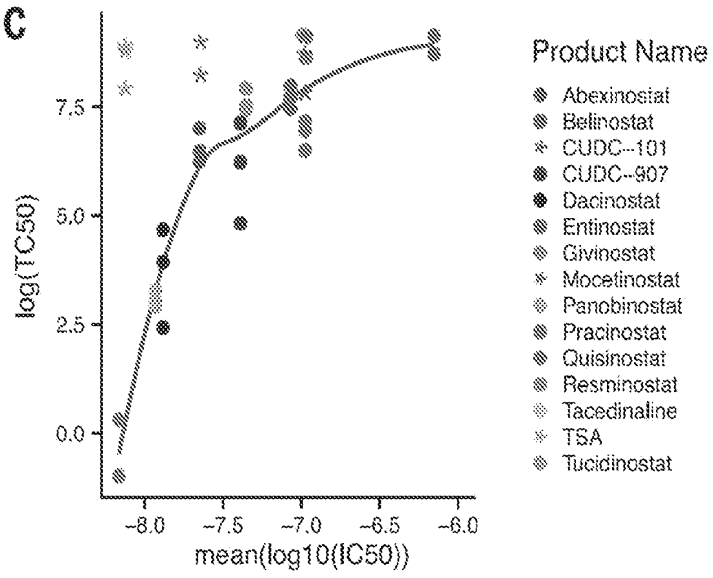


Fig. 28A

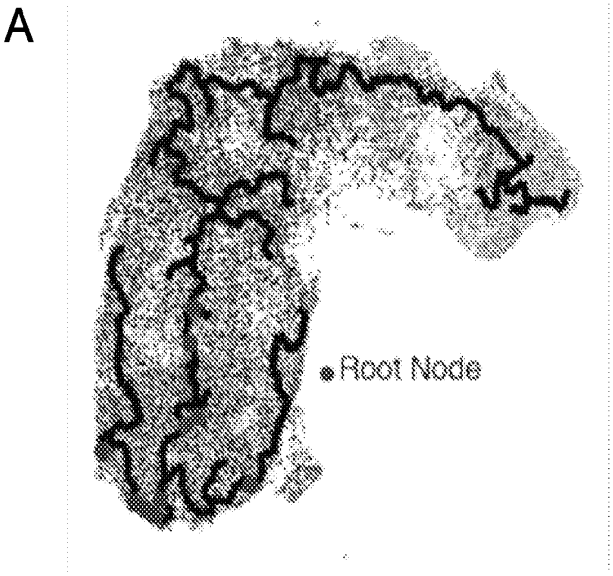


Fig. 28B



Fig. 28C

C

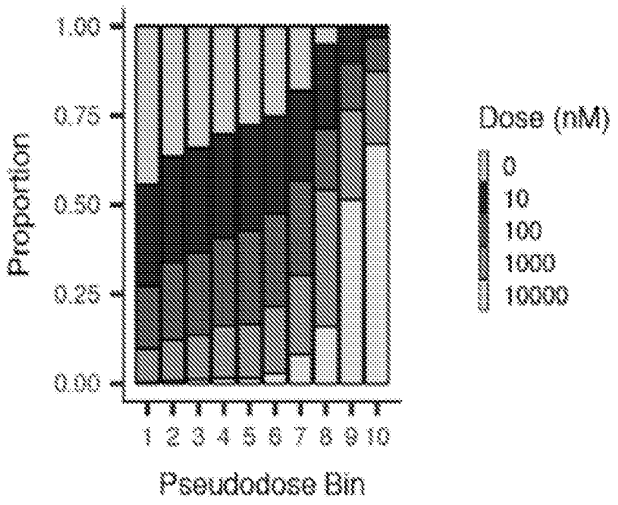


Fig. 28D

D

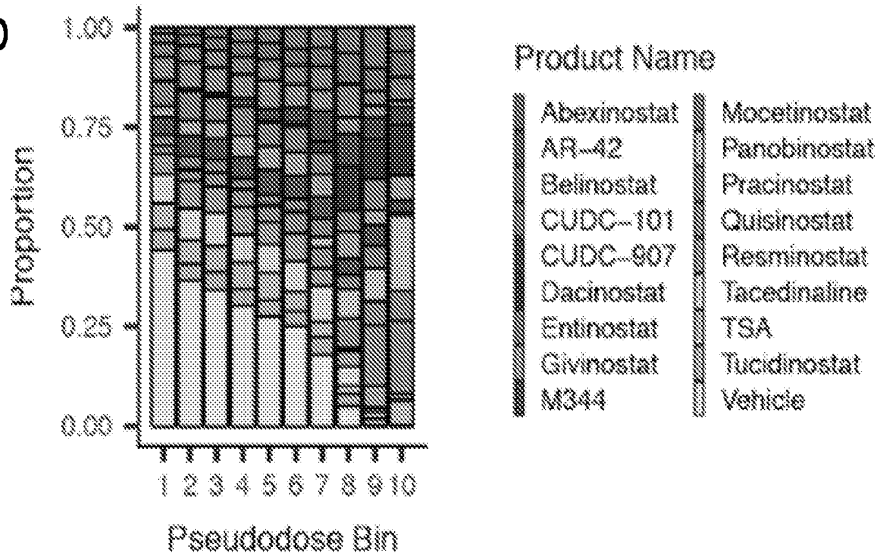


Fig. 28E

E

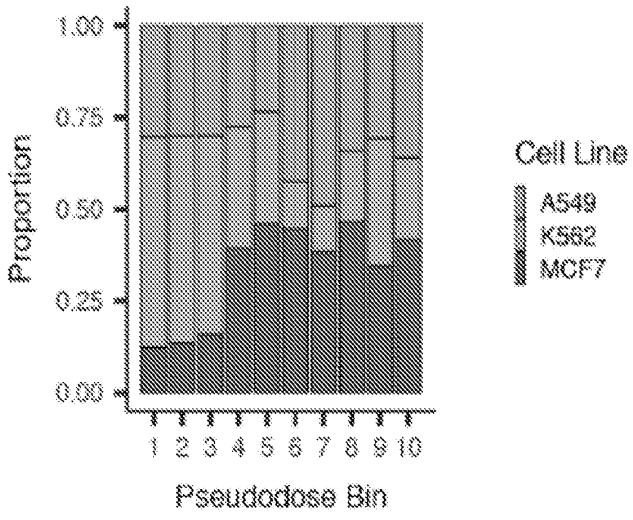


Fig. 29A

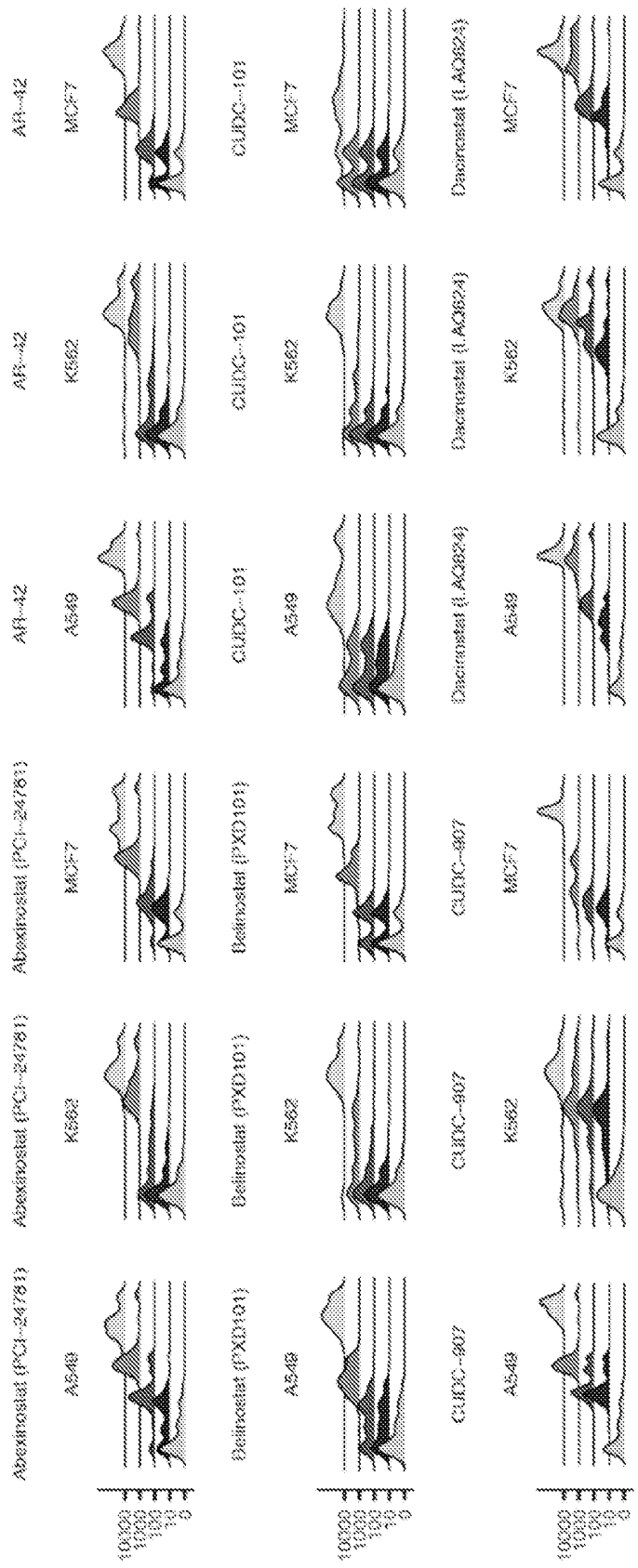

Abexinostat (PCI-24781)
A549
Abexinostat (PCI-24781)
K562
Abexinostat (PCI-24781)
MCF7
AR-42
A549
AR-42
K562
AR-42
MCF7
Entinostat (MS-275)
A549
Entinostat (MS-275)
K562
Entinostat (MS-275)
MCF7
CUDC-907
A549
CUDC-907
K562
CUDC-907
MCF7
CUDC-101
A549
CUDC-101
K562
CUDC-101
MCF7
Panobinostat (LBH589)
A549
Panobinostat (LBH589)
K562
Panobinostat (LBH589)
MCF7
10000
1000
100
10
1
0

Fig. 29B

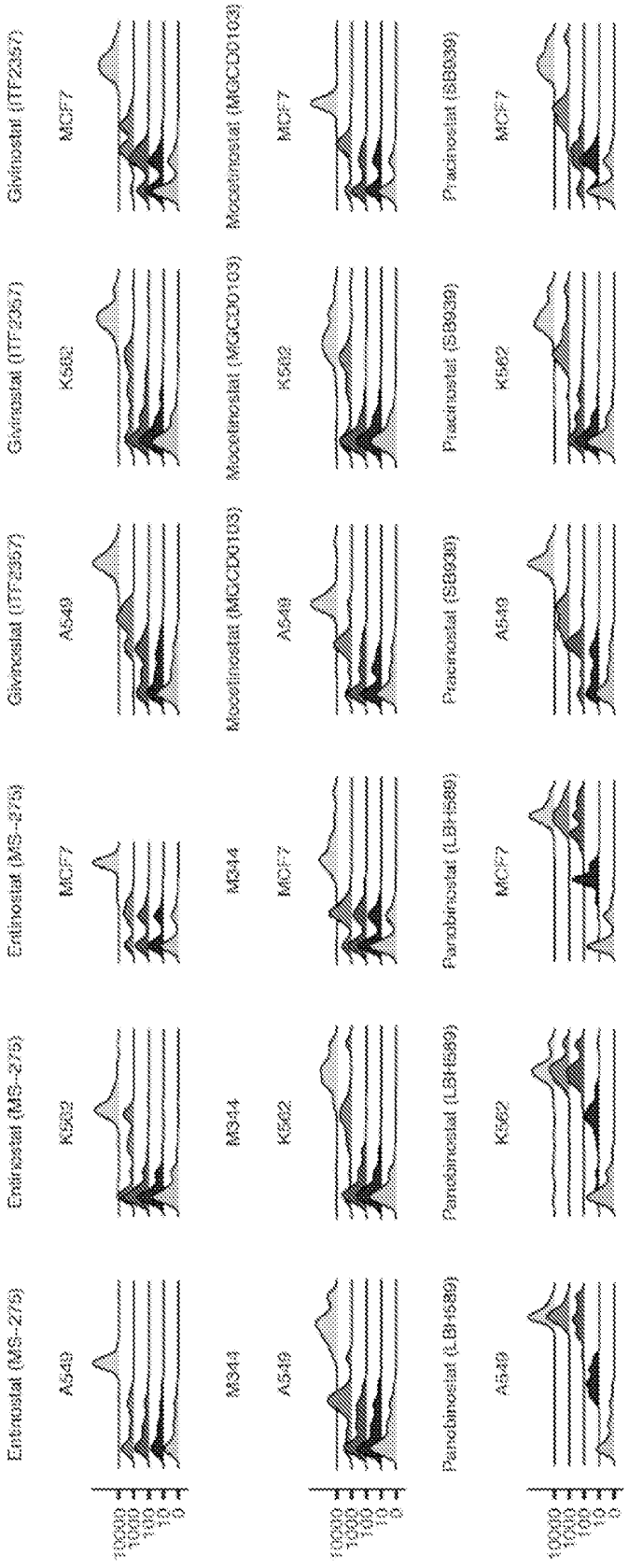

Entinostat (MS-275)
A549
Entinostat (MS-275)
K562
Entinostat (MS-275)
MCF7
Givinostat (ITF2357)
A549
Givinostat (ITF2357)
K562
Givinostat (ITF2357)
MCF7
10000
1000
100
10
0
M344
M344
M344
Mocetinostat (MGCD0103)
Mocetinostat (MGCD0103)
Mocetinostat (MGCD0103)
A549
K562
MCF7
Panobinostat (LBH589)
Panobinostat (LBH589)
Panobinostat (LBH589)
Pracinostat (SB939)
Pracinostat (SB939)
Pracinostat (SB939)
A549
K562
MCF7

Fig. 29C

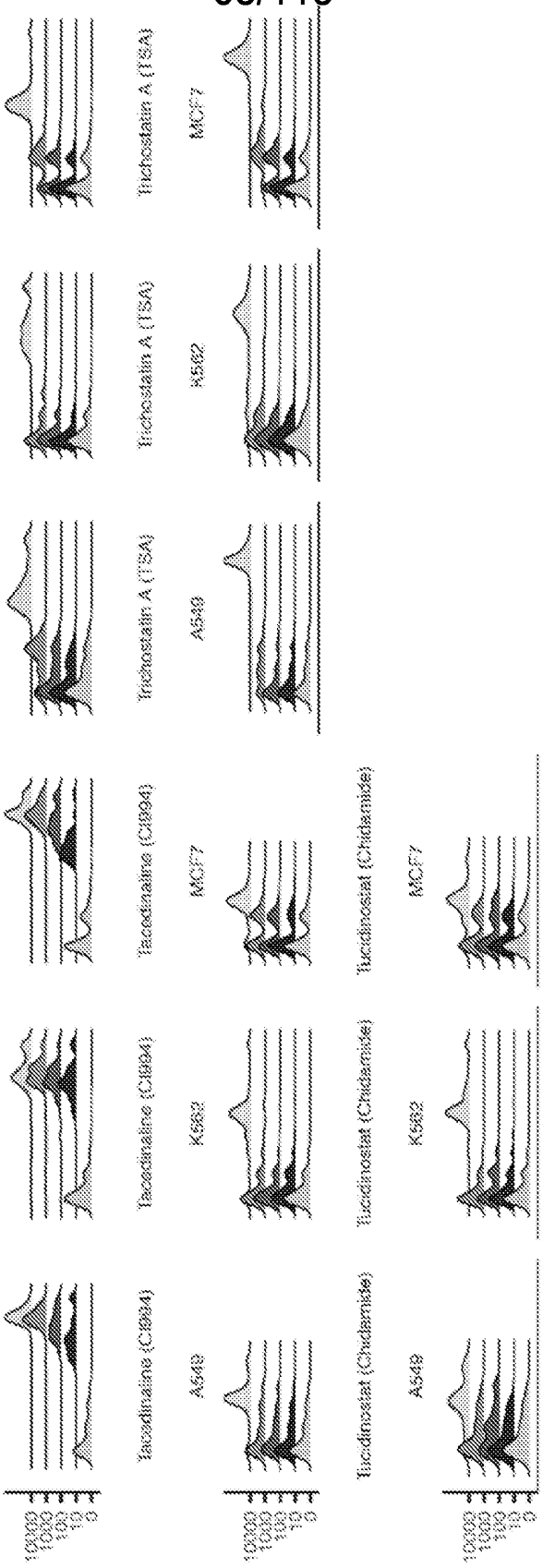

sinostat (JNJ-26481585) 2I
A549
Tacedinaline (CI994)
Tucidinostat (Chidamide)
sinostat (JNJ-26481585) 2I
K562
Tacedinaline (CI994)
Tucidinostat (Chidamide)
sinostat (JNJ-26481585) 2I
MCF7
Tacedinaline (CI994)
Tucidinostat (Chidamide)
Resminostat
A549
Trichostatin A (TSA)
Resminostat
K562
Trichostatin A (TSA)
Resminostat
MCF7
Trichostatin A (TSA)
10000
1000
100
10
0

Fig. 30A

A

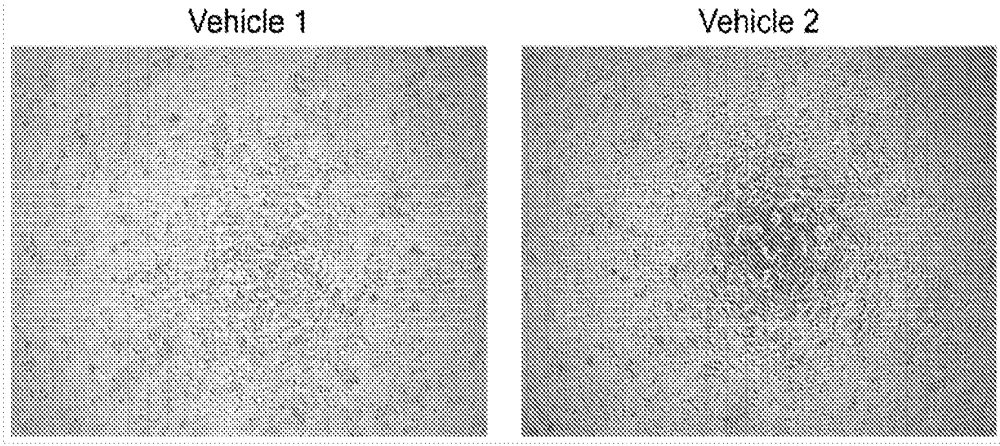


Fig. 30B

B

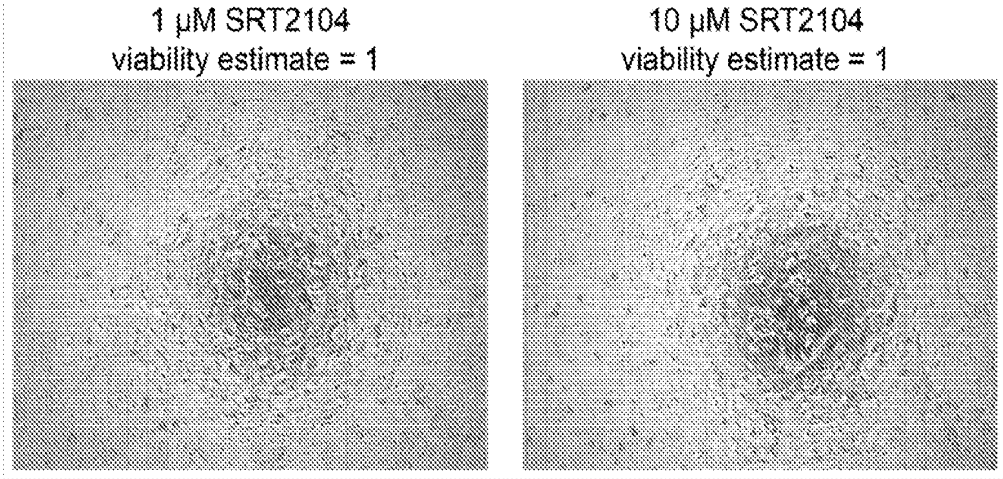


Fig. 30C

C

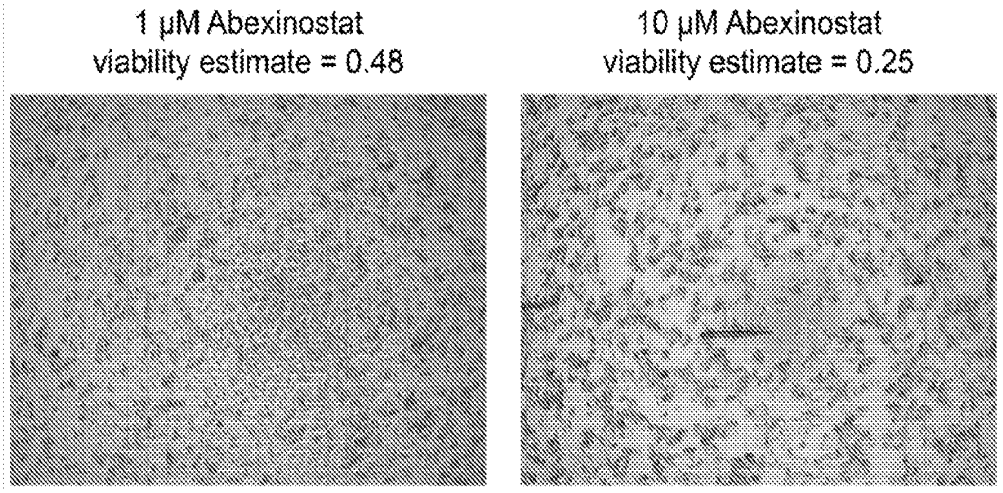


Fig. 31A

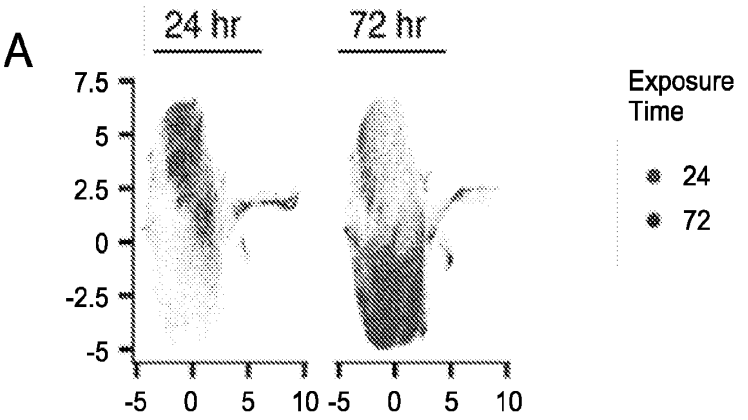


Fig. 31B

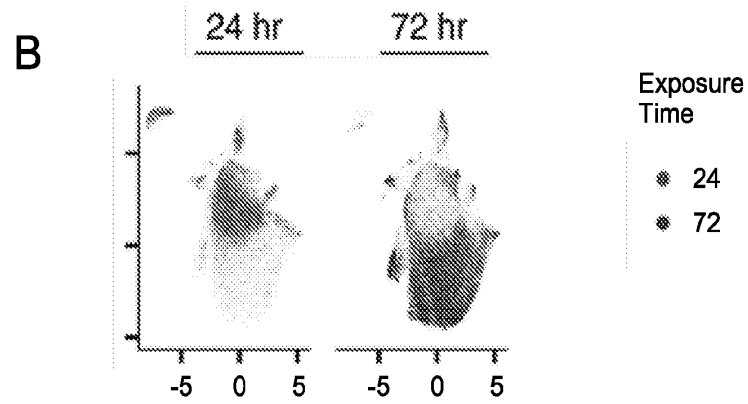


Fig. 31C

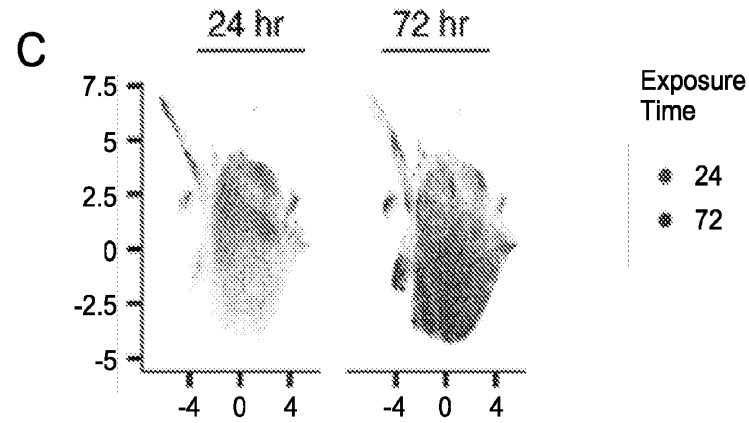


Fig. 31D

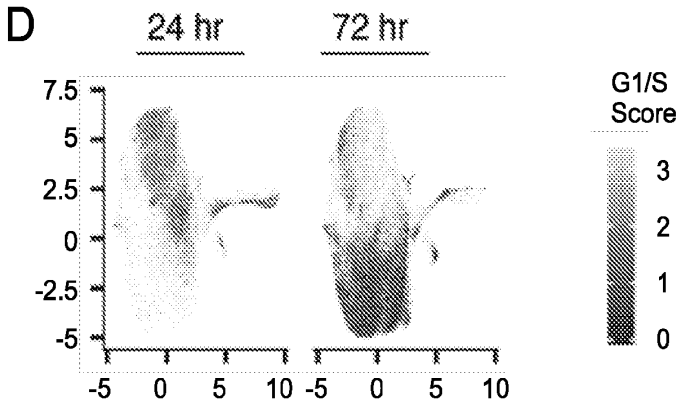


Fig. 31E

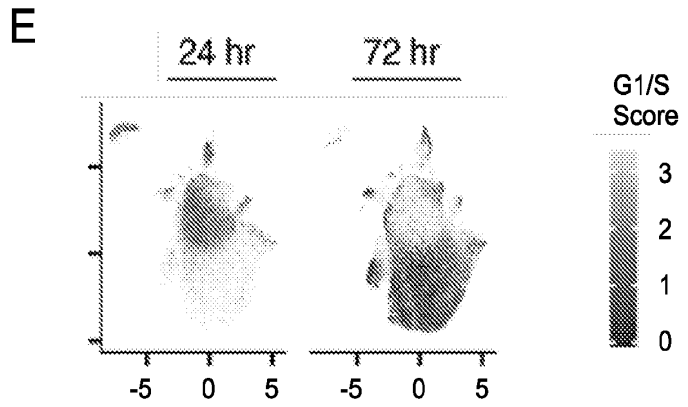


Fig. 31F

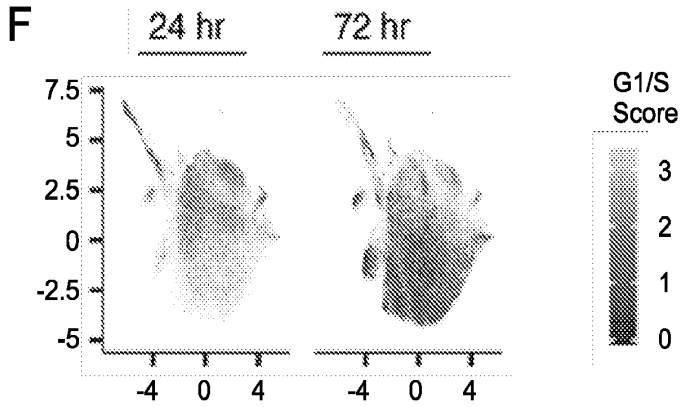


Fig. 31G

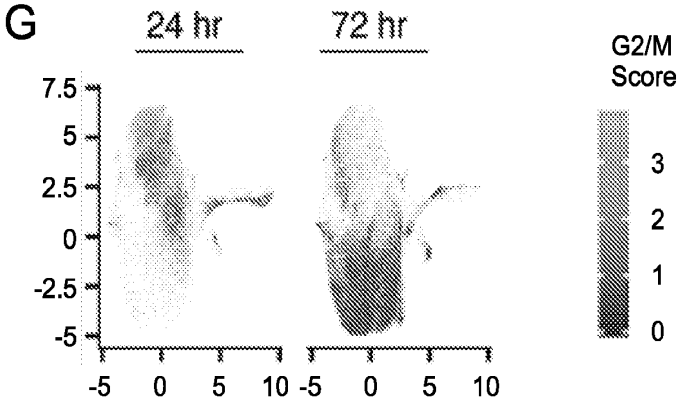


Fig. 31H

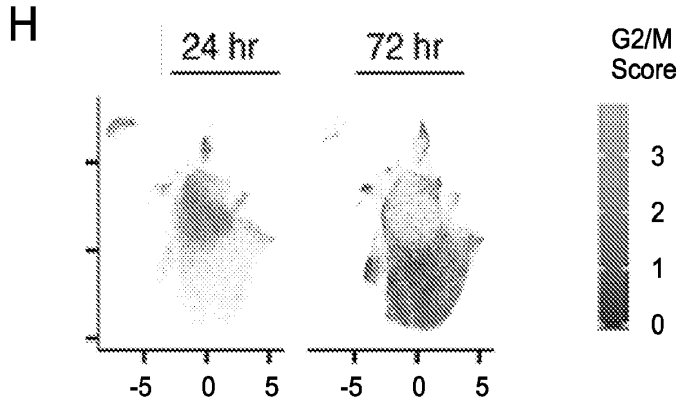


Fig. 31I

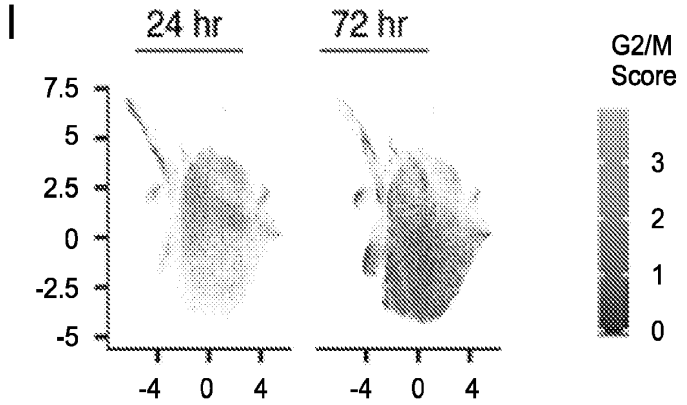


Fig. 31J

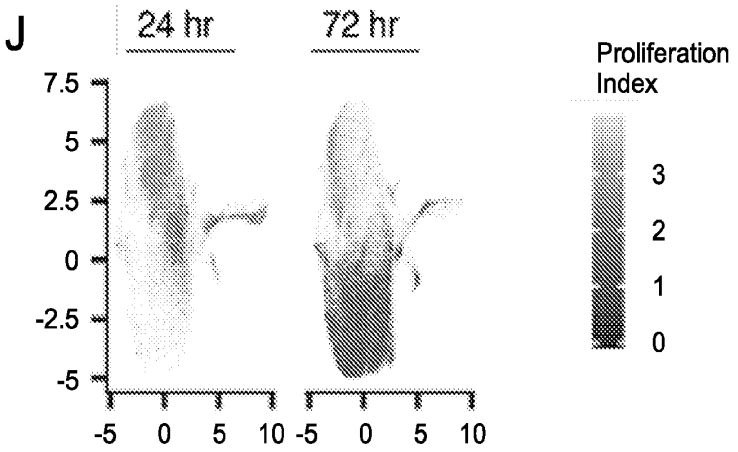


Fig. 31K

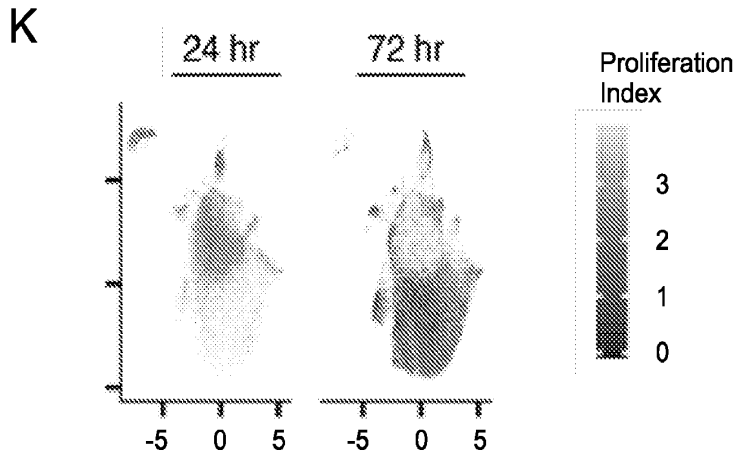


Fig. 31L

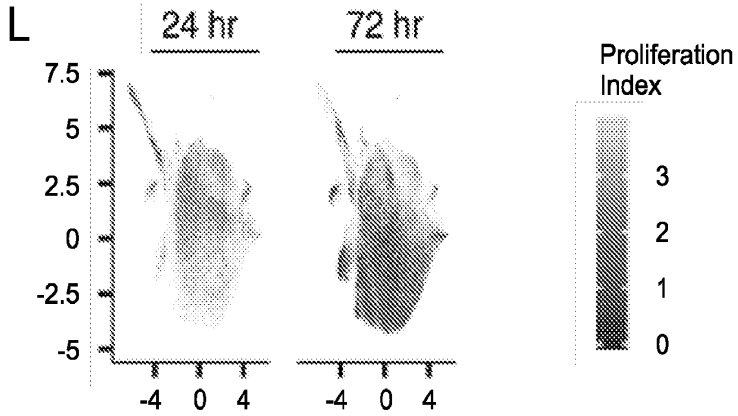


Fig. 31M

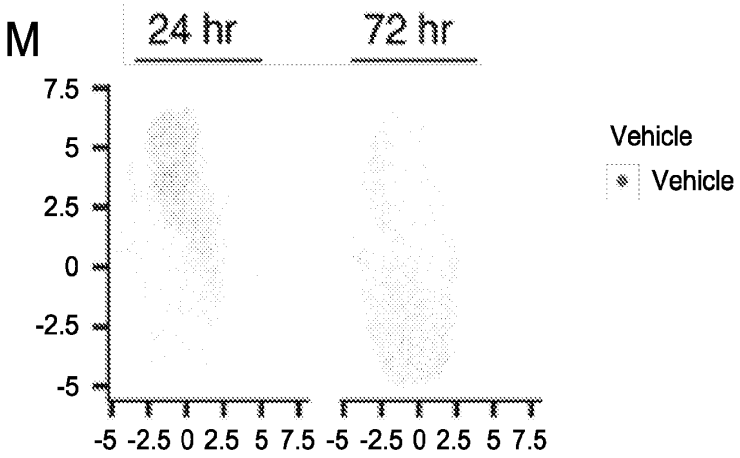


Fig. 31N

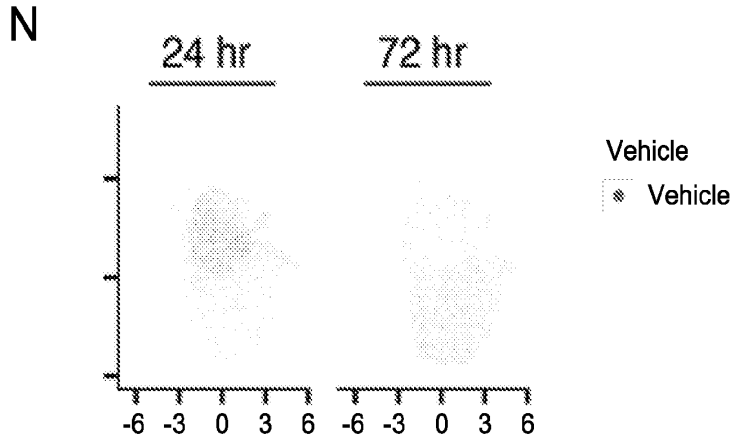


Fig. 31O

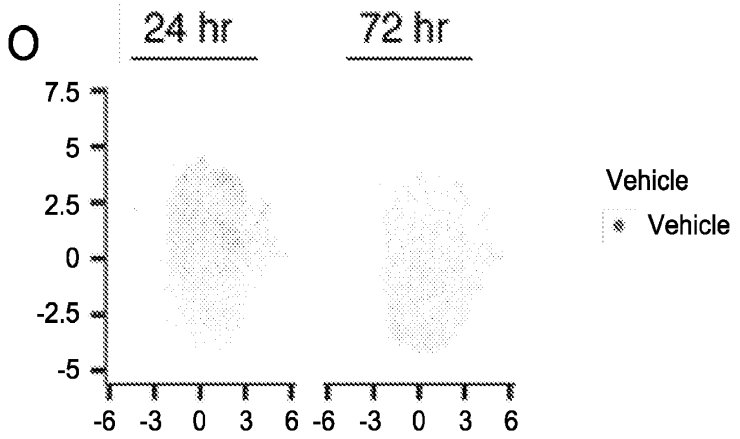


Fig. 31P

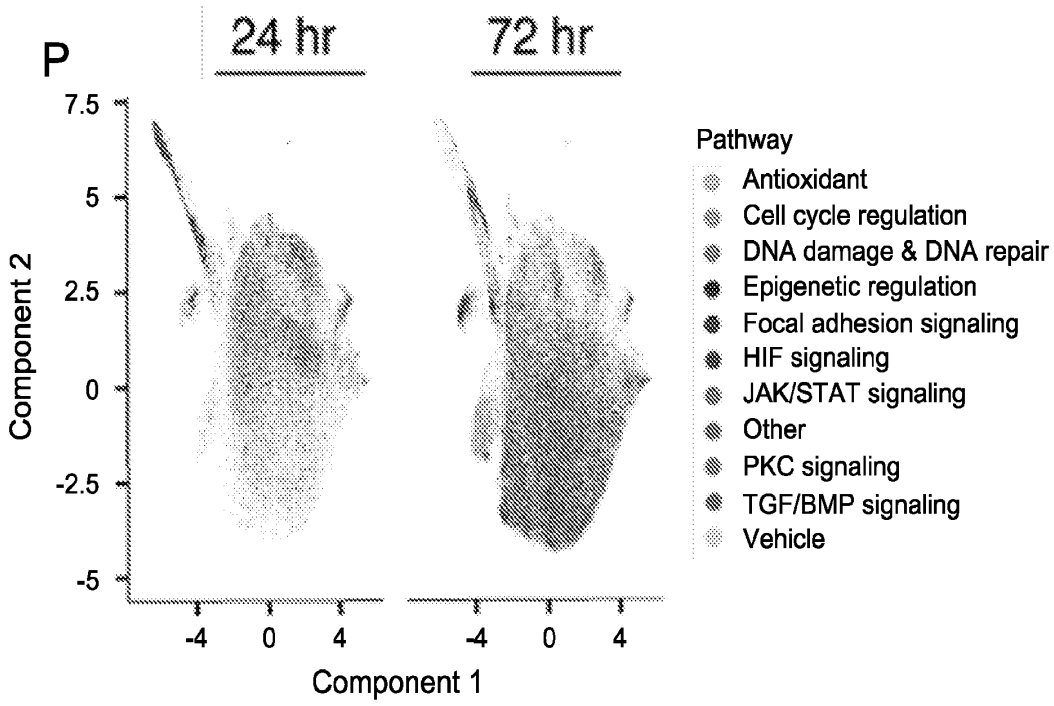


Fig. 31Q

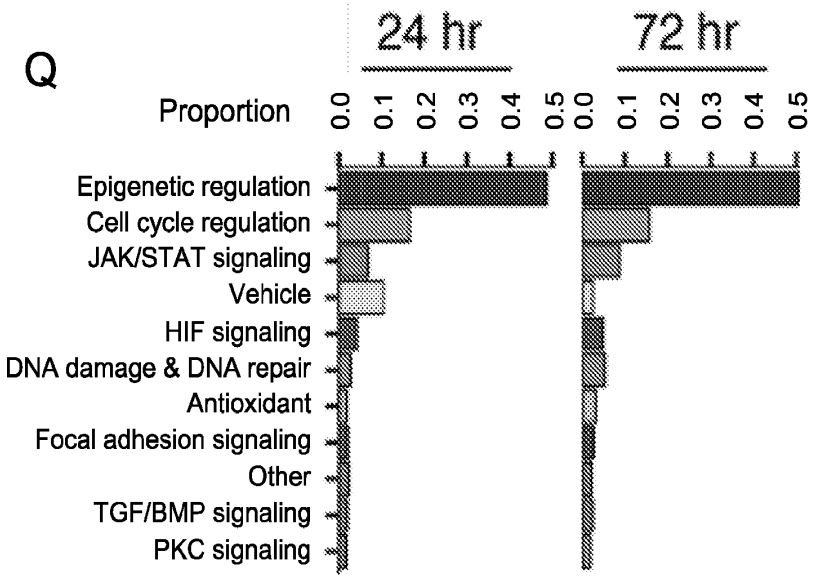


Fig. 31R

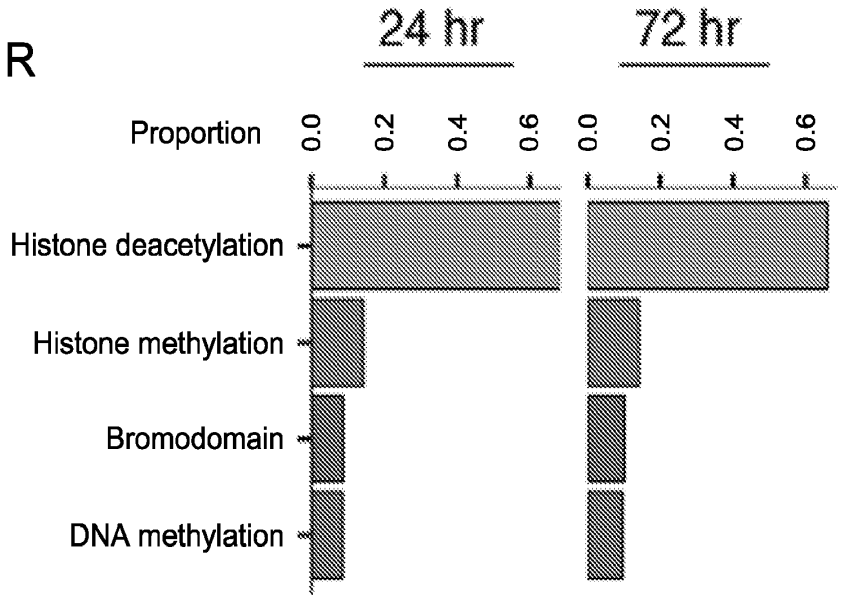


Fig. 31S

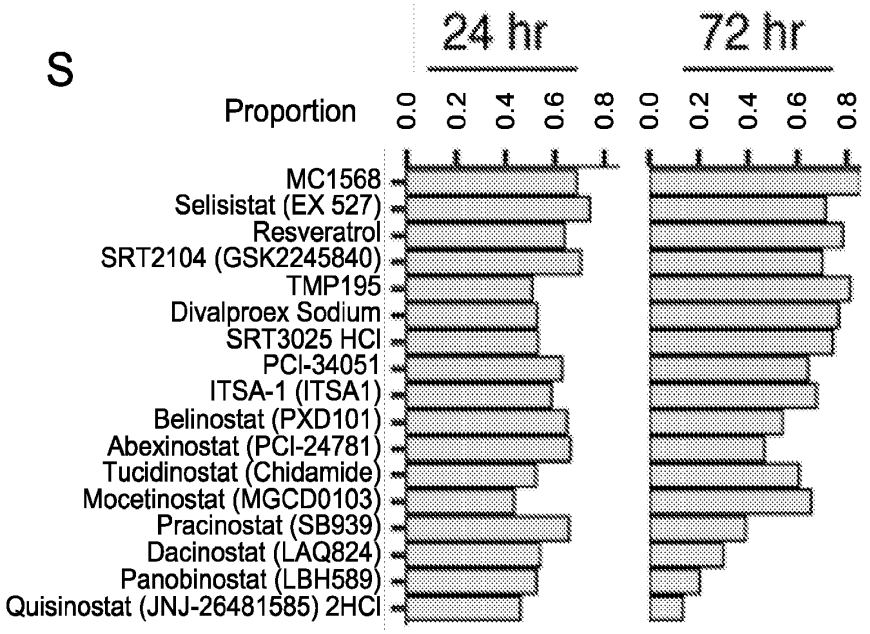


Fig. 32A

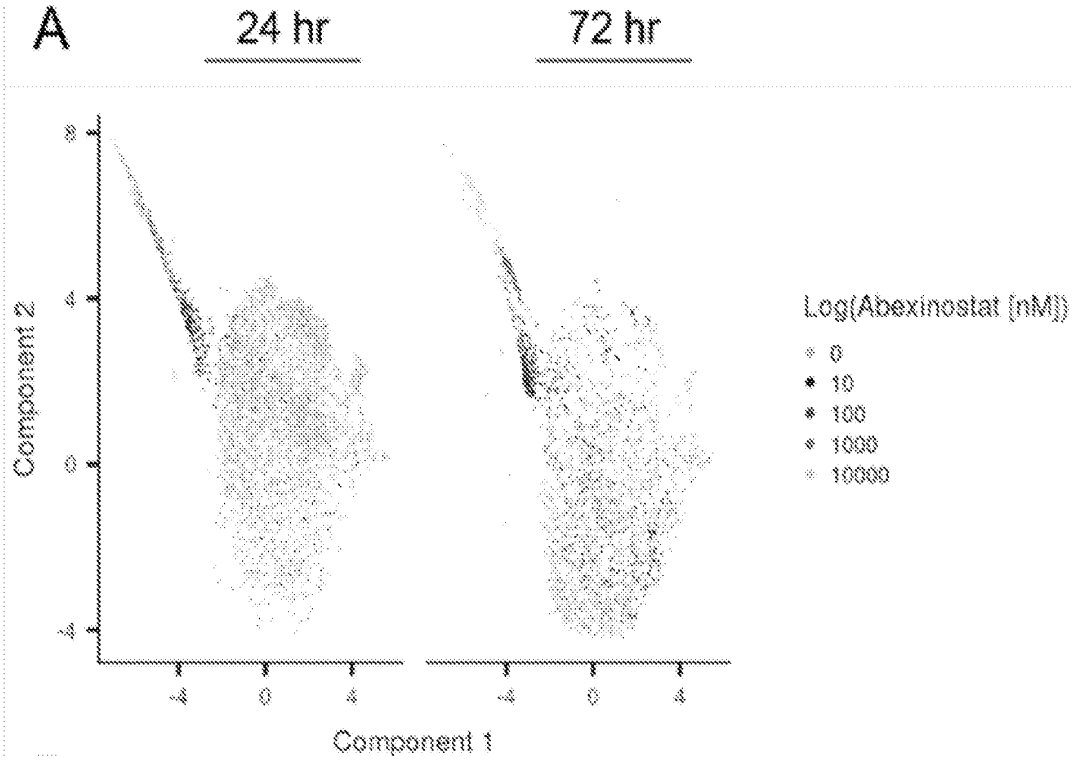


Fig. 32B

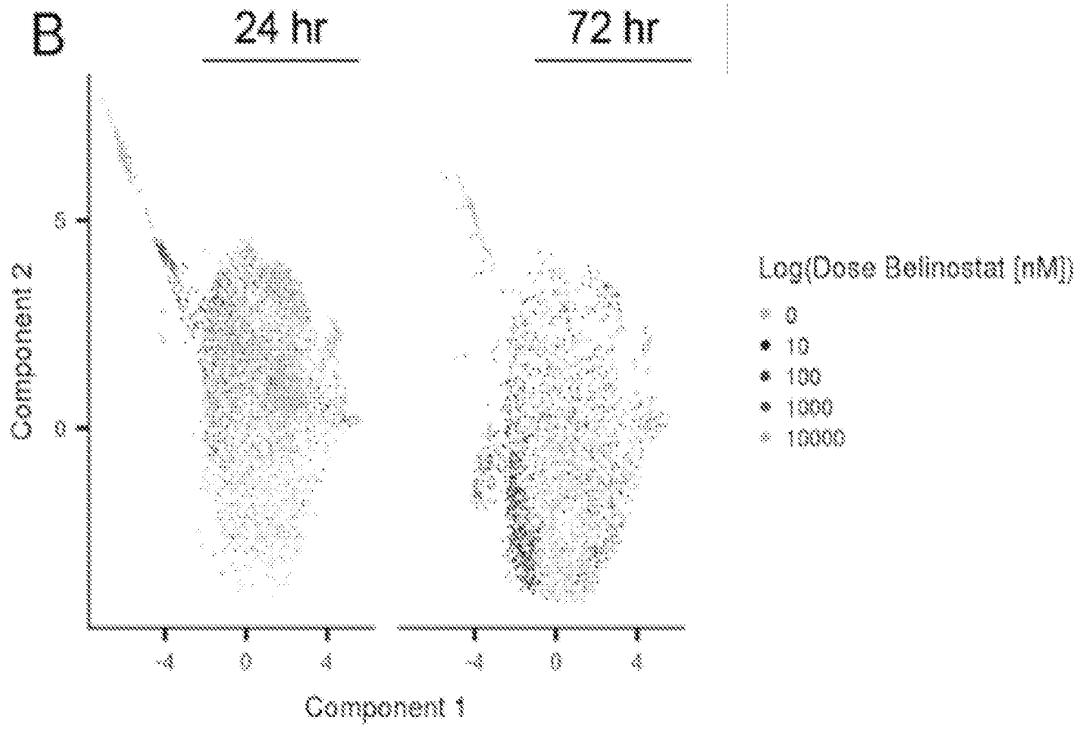


Fig. 32C

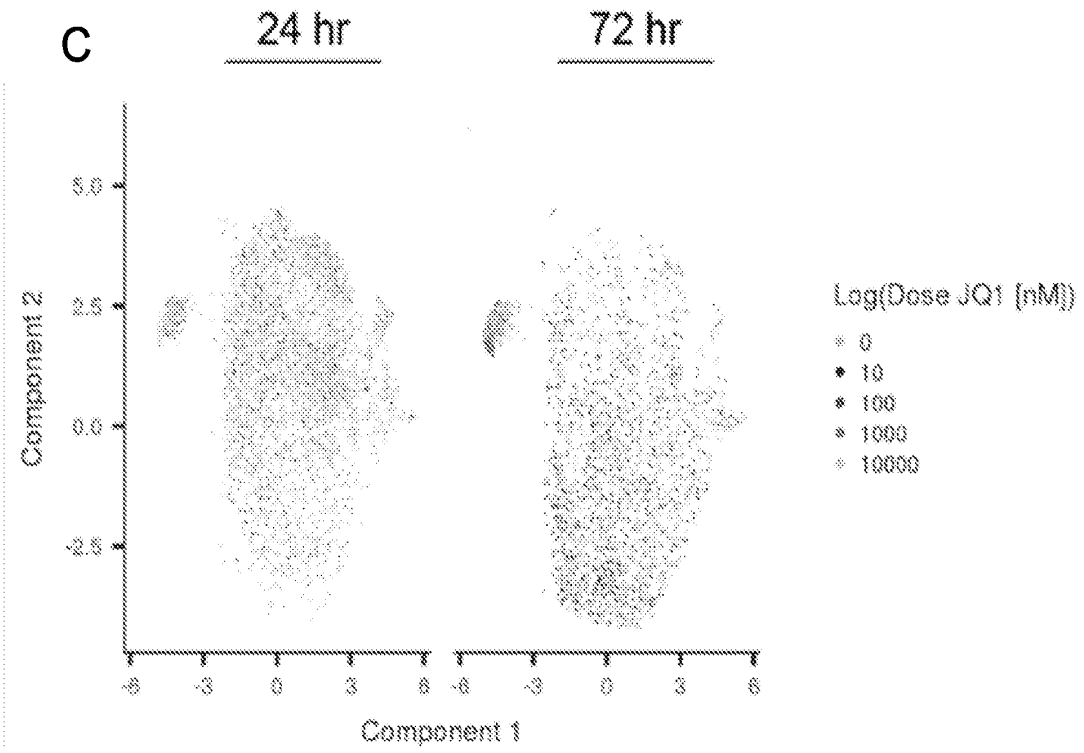
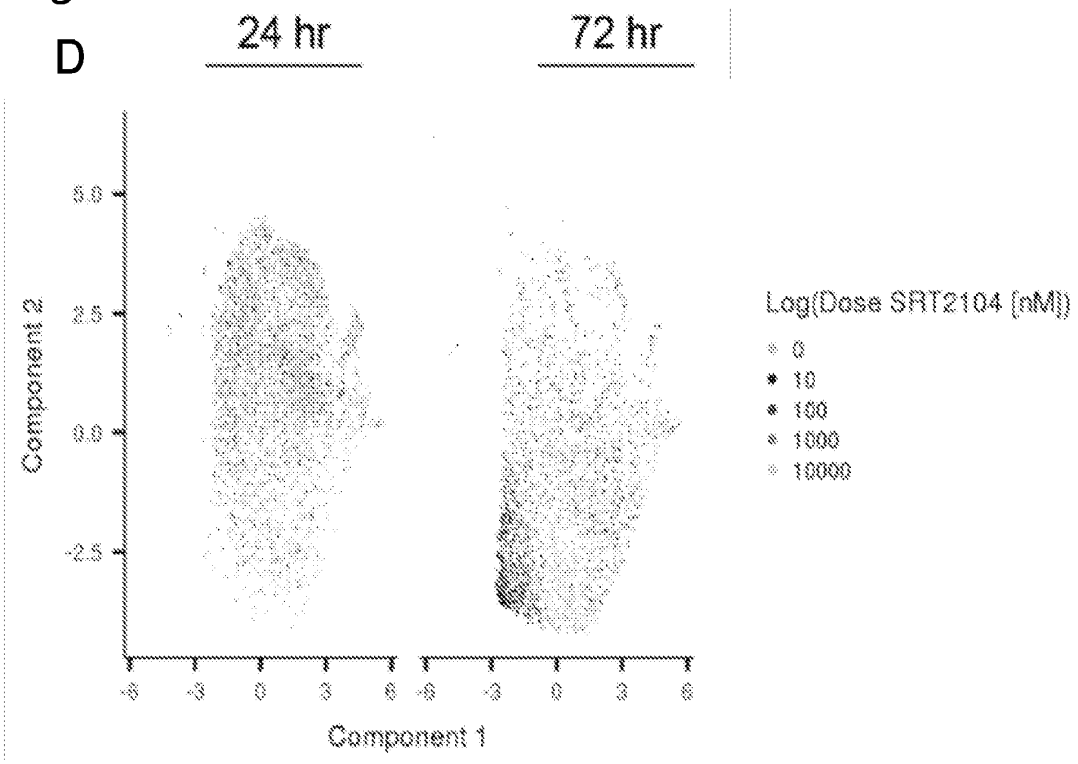
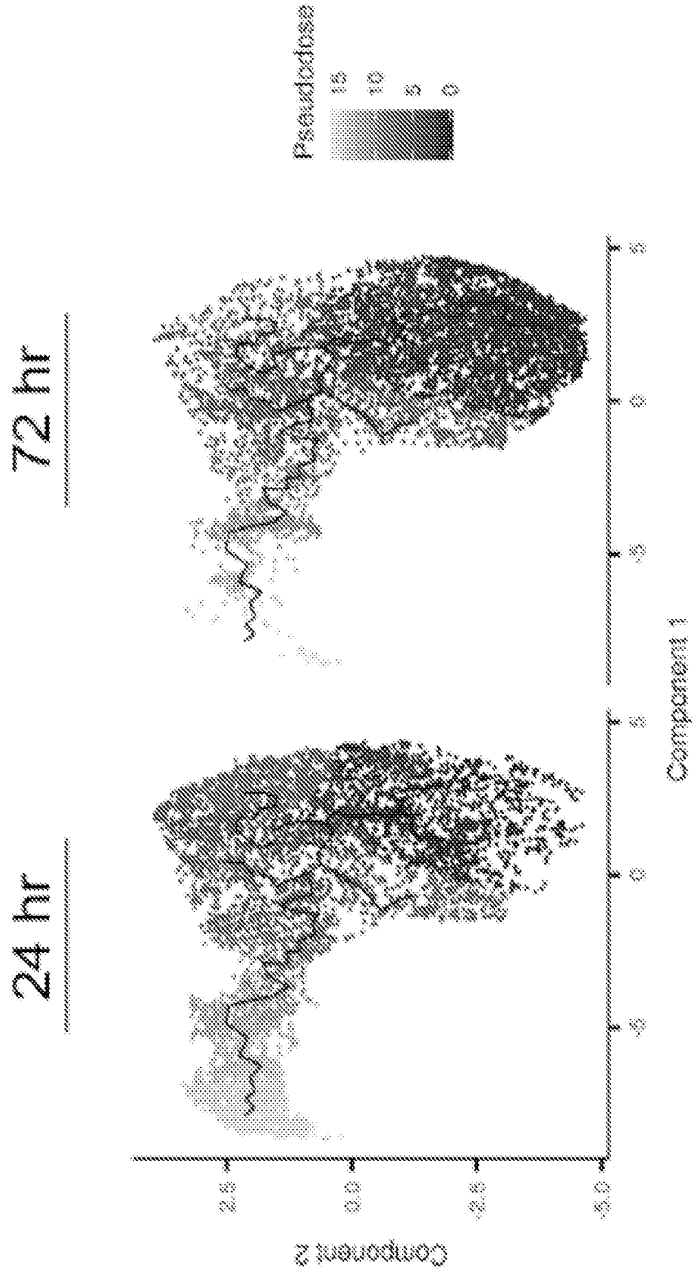


Fig. 32D

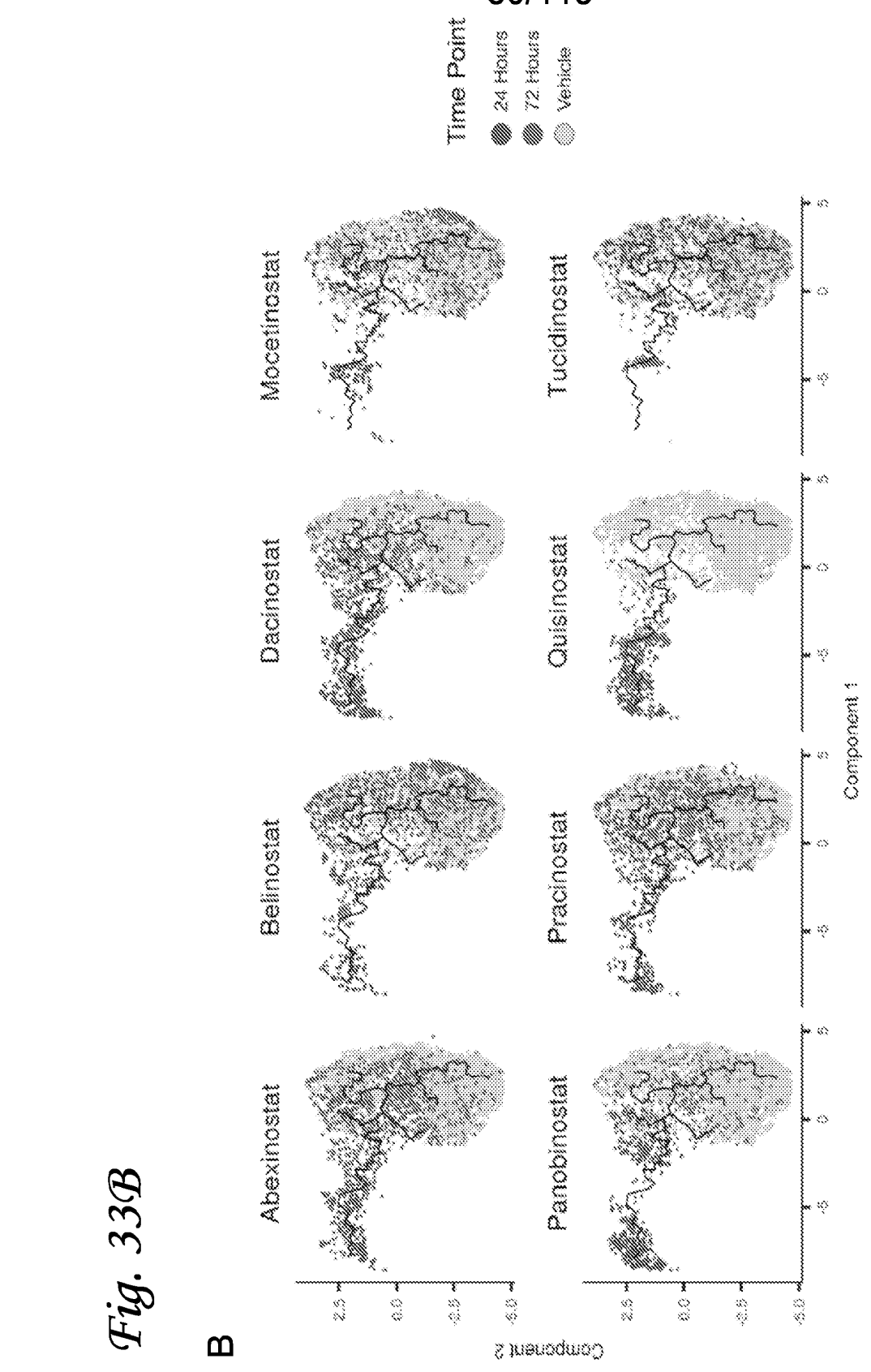



Pseudotase
15
10
5
0
72 hr
24 hr
Component 1
Component 2
2.5
0.0
-2.5
-5.0

A

Fig. 33A

Fig. 33B


B
Time Point
24 Hours
72 Hours
Vehicle
Abexinostat
Belinostat
Dacinostat
Mocetinostat
Panobinostat
Pracinostat
Quisinostat
Tucidinostat
Component 1
Component 2

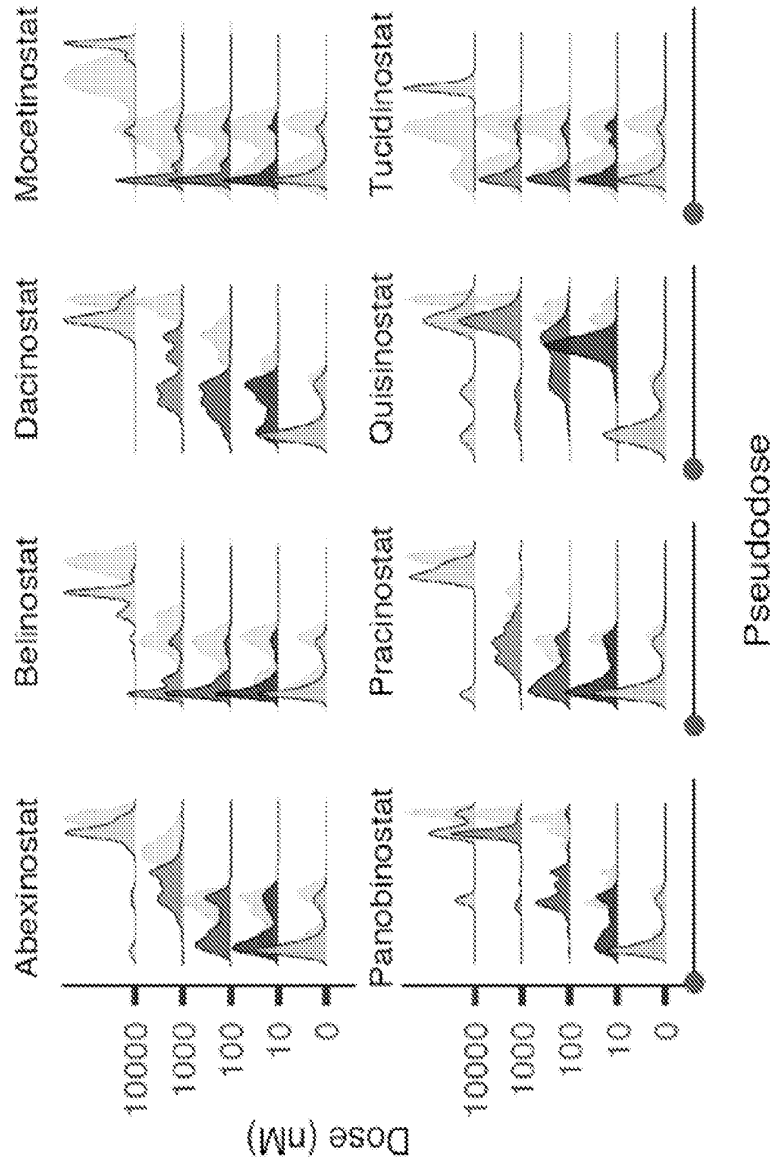
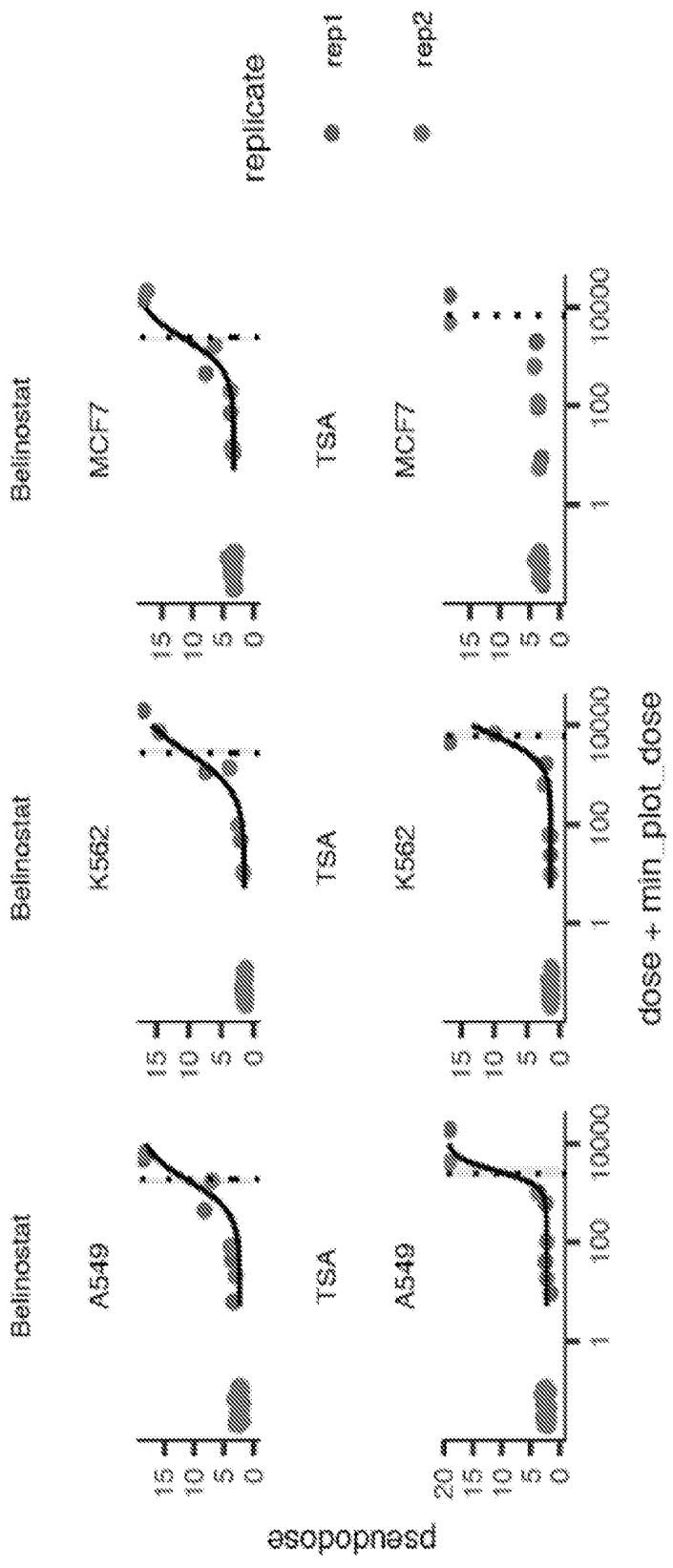

C
Abexinostat
Belinostat
Dacinostat
Mocetinostat
Panobinostat
Pracinostat
Quisinostat
Tucidinostat
Dose (nM)
10000
1000
100
10
0
Pseudodose

Fig. 33C

Fig. 34A


A
Belinostat
TSA
A549
K562
MCF7
psenopose
dose + min_plot_dose
replicate
rep1
rep2

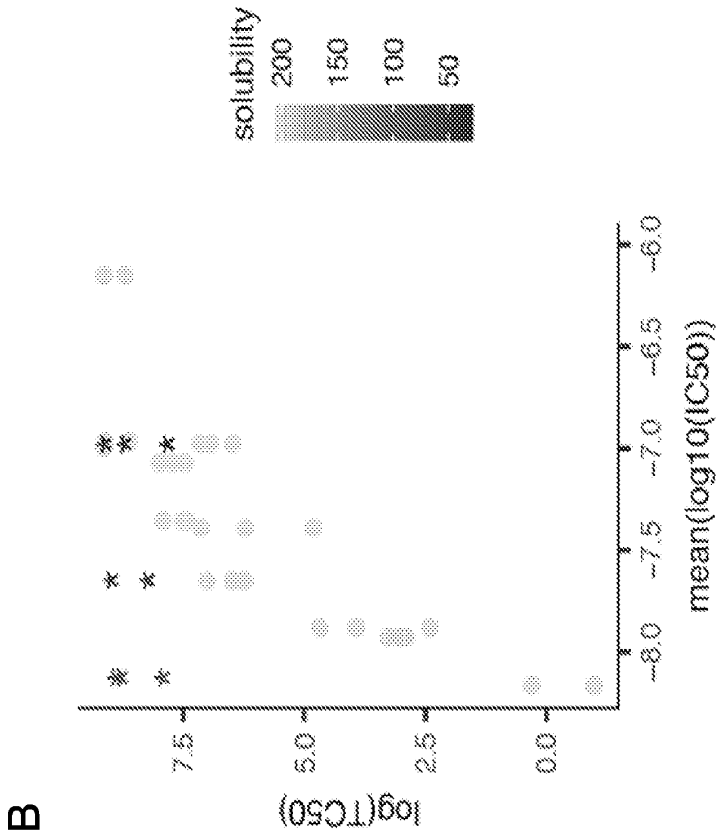

B
solubility
200
150
100
50
log(TC50)
7.5
5.0
2.5
0.0
mean(log10(IC50))
−8.0
−7.5
−7.0
−6.5
−6.0

Fig. 34B

Fig. 34C

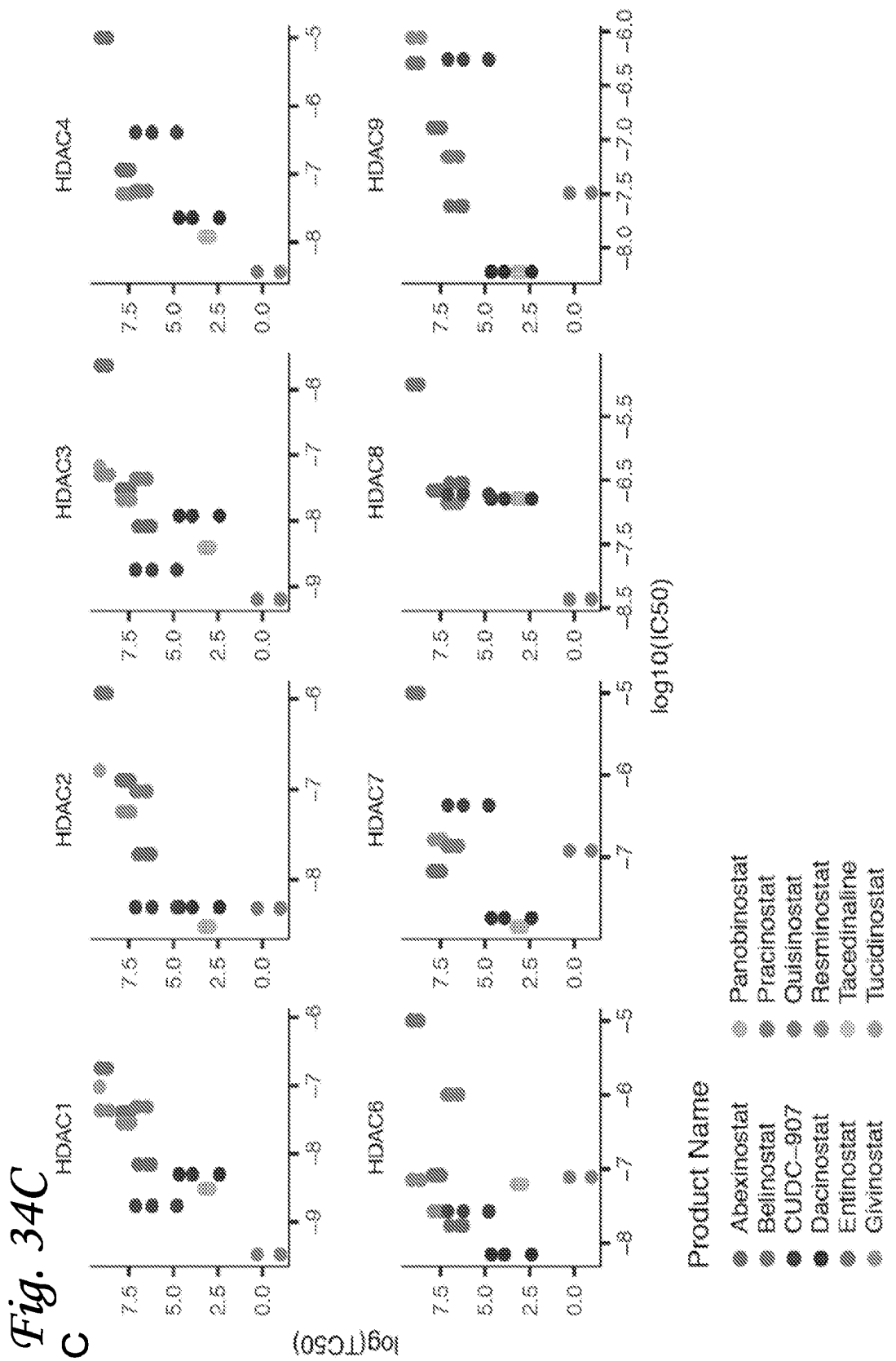

HDAC1
HDAC2
HDAC3
HDAC4
HDAC6
HDAC7
HDAC8
HDAC9
log(TC50)
log10(IC50)
Product Name
Abexinostat
Belinostat
CUDC−907
Dacinostat
Entinostat
Givinostat
Panobinostat
Pracinostat
Quisinostat
Resminostat
Tacedinaline
Tucidinostat

Fig. 35A

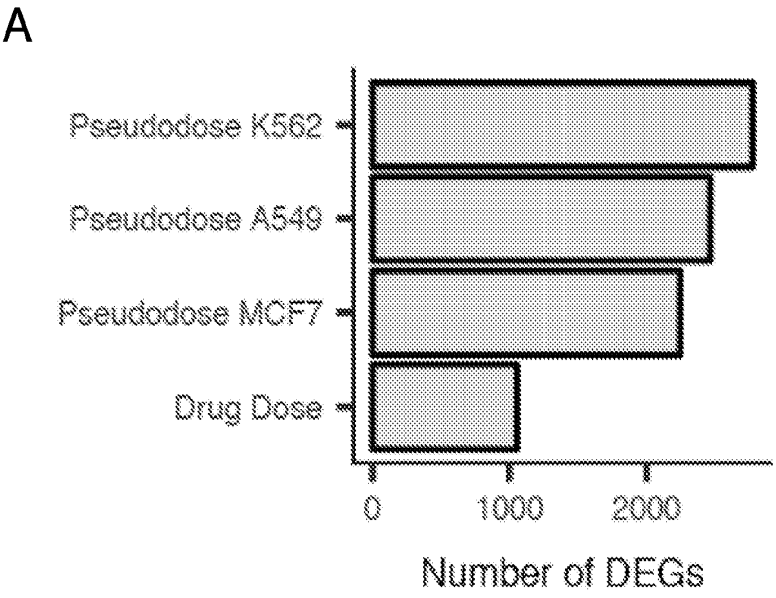
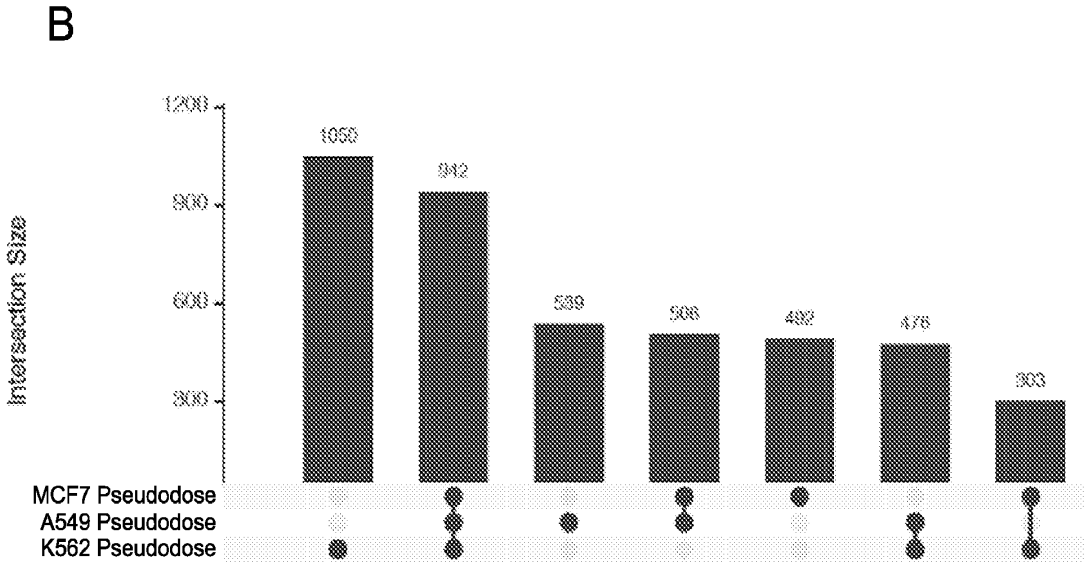


Fig. 35B



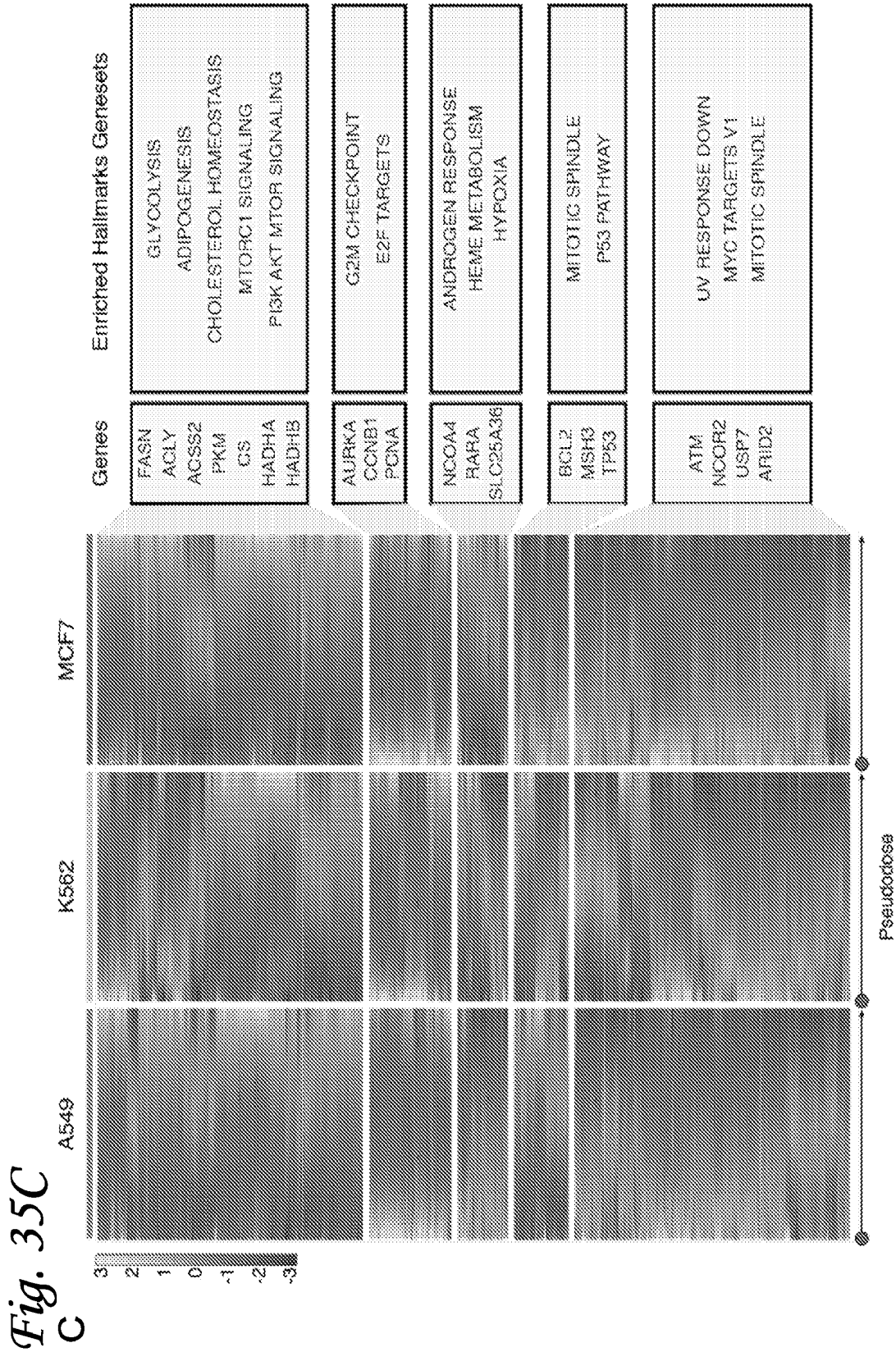

Enriched Hallmarks Genesets
Genes
GLYCOLYSIS
ADIPOGENESIS
CHOLESTEROL HOMEOSTASIS
MTORC1 SIGNALING
PI3K AKT MTOR SIGNALING
FASN
ACLY
ACSS2
PKM
CS
HADHA
HADHB
G2M CHECKPOINT
E2F TARGETS
AURKA
CCNB1
PCNA
ANDROGEN RESPONSE
HEME METABOLISM
HYPOXIA
NCOA4
RARA
SLC25A36
MITOTIC SPINDLE
P53 PATHWAY
BCL2
MSH3
TP53
UV RESPONSE DOWN
MYC TARGETS V1
MITOTIC SPINDLE
ATM
NCOR2
USP7
ARID2
A549
K562
MCF7
Pseudodose
3
2
1
0
-1
-2
-3

Fig. 35C

Fig. 36A

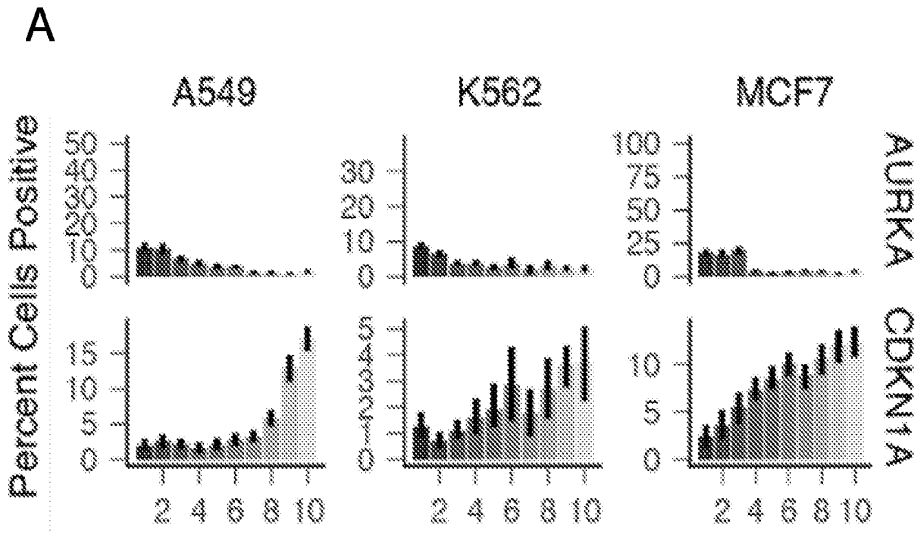
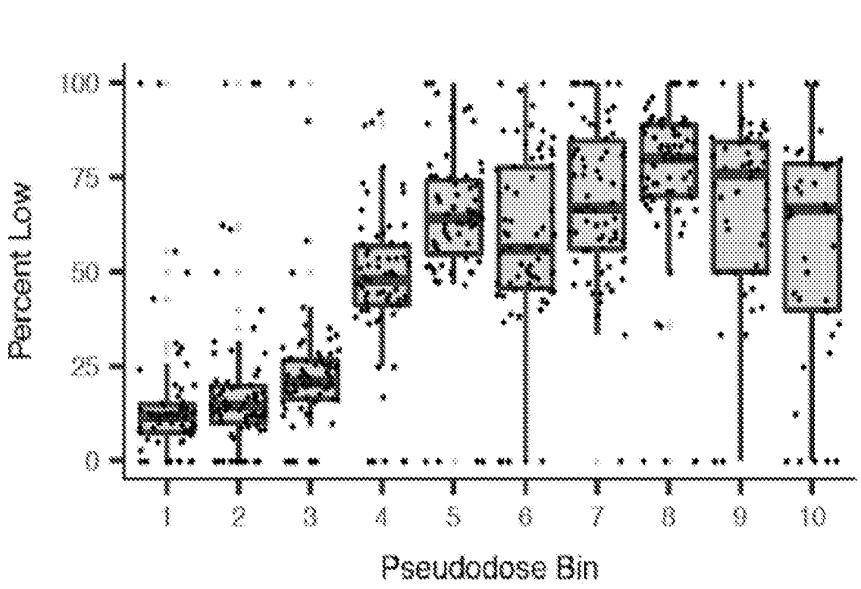


Fig. 36B



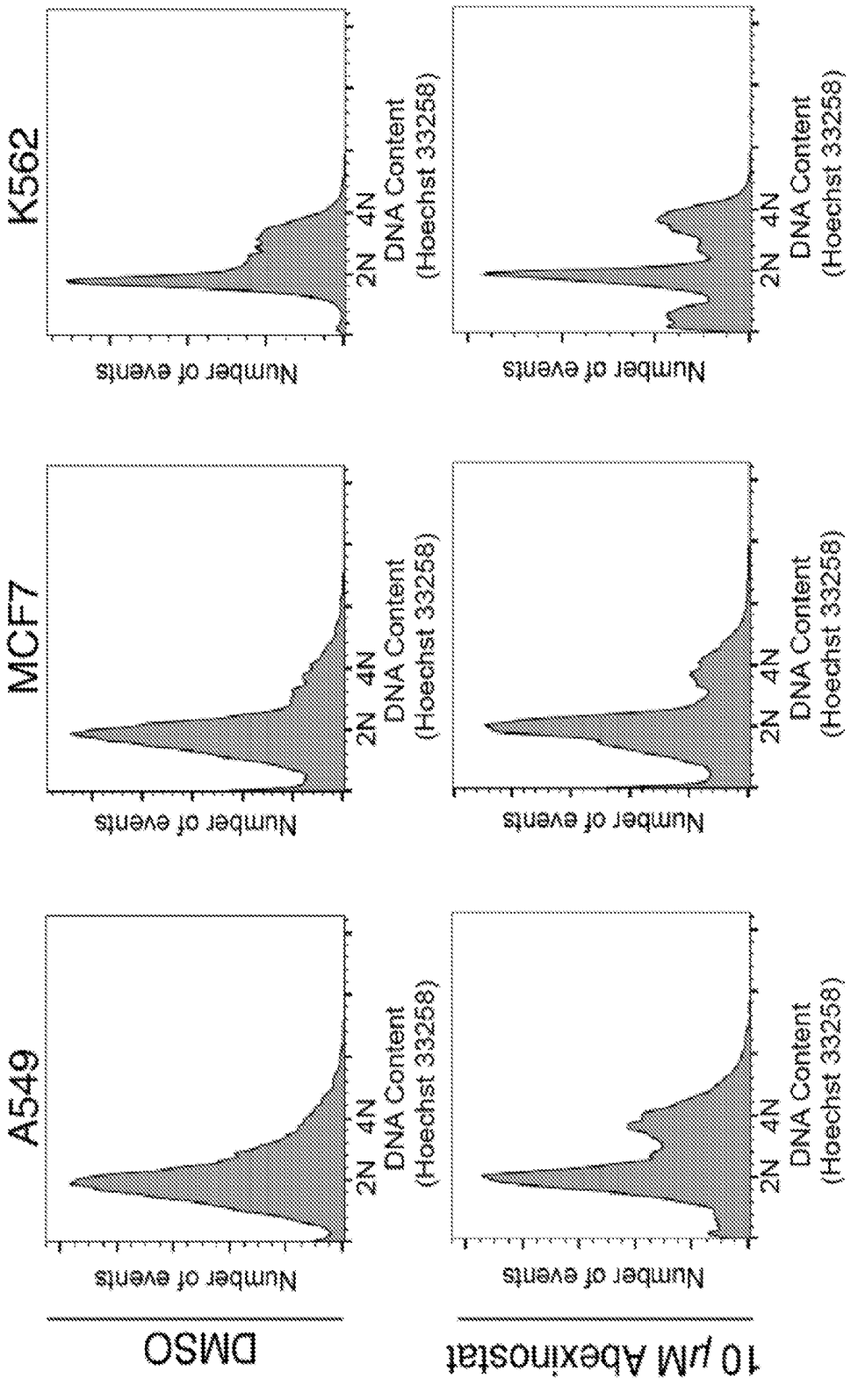
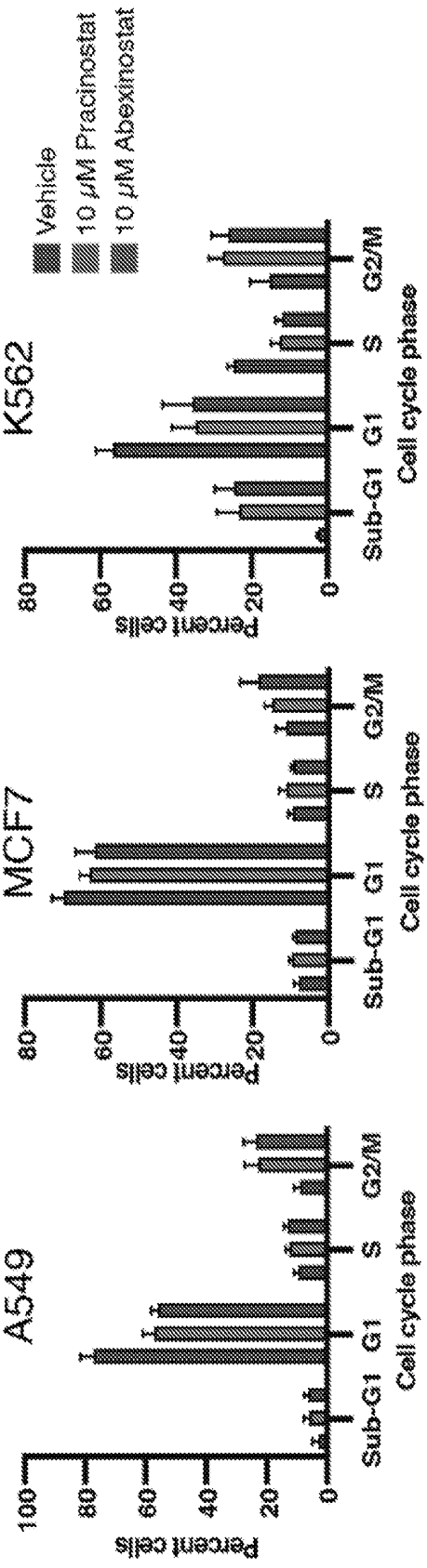

A549
MCF7
K562
DMSO
10 μM Abexinostat
Number of events
2N 4N
DNA Content
(Hoechst 33258)

Fig. 36C
C

Fig. 36D

D


A549
MCF7
K562
Vehicle
10 μM Pracinostat
10 μM Abeximostat
Percent cells
0
20
40
60
80
100
Sub-G1
G1
S
G2/M
Cell cycle phase

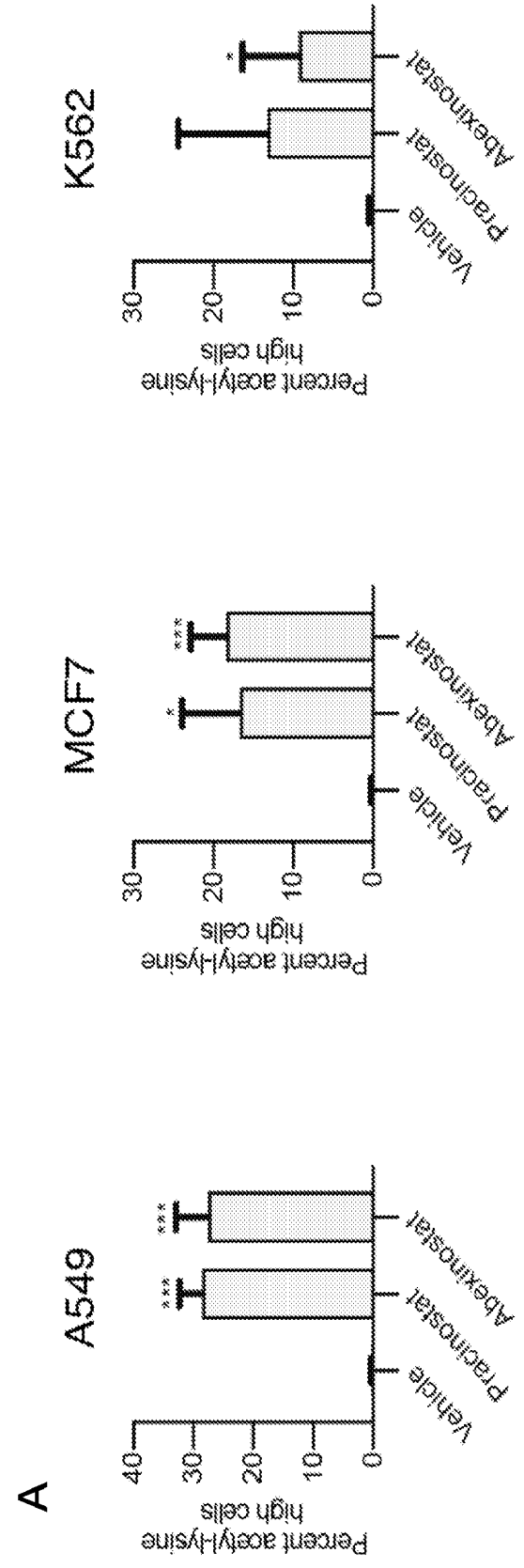

A
A549
K562
MCF7
Percent acetyl-lysine high cells
0
10
20
30
40
Vehicle
Panobinostat
Abexinostat
***
*

Fig. 37A

Fig. 37B

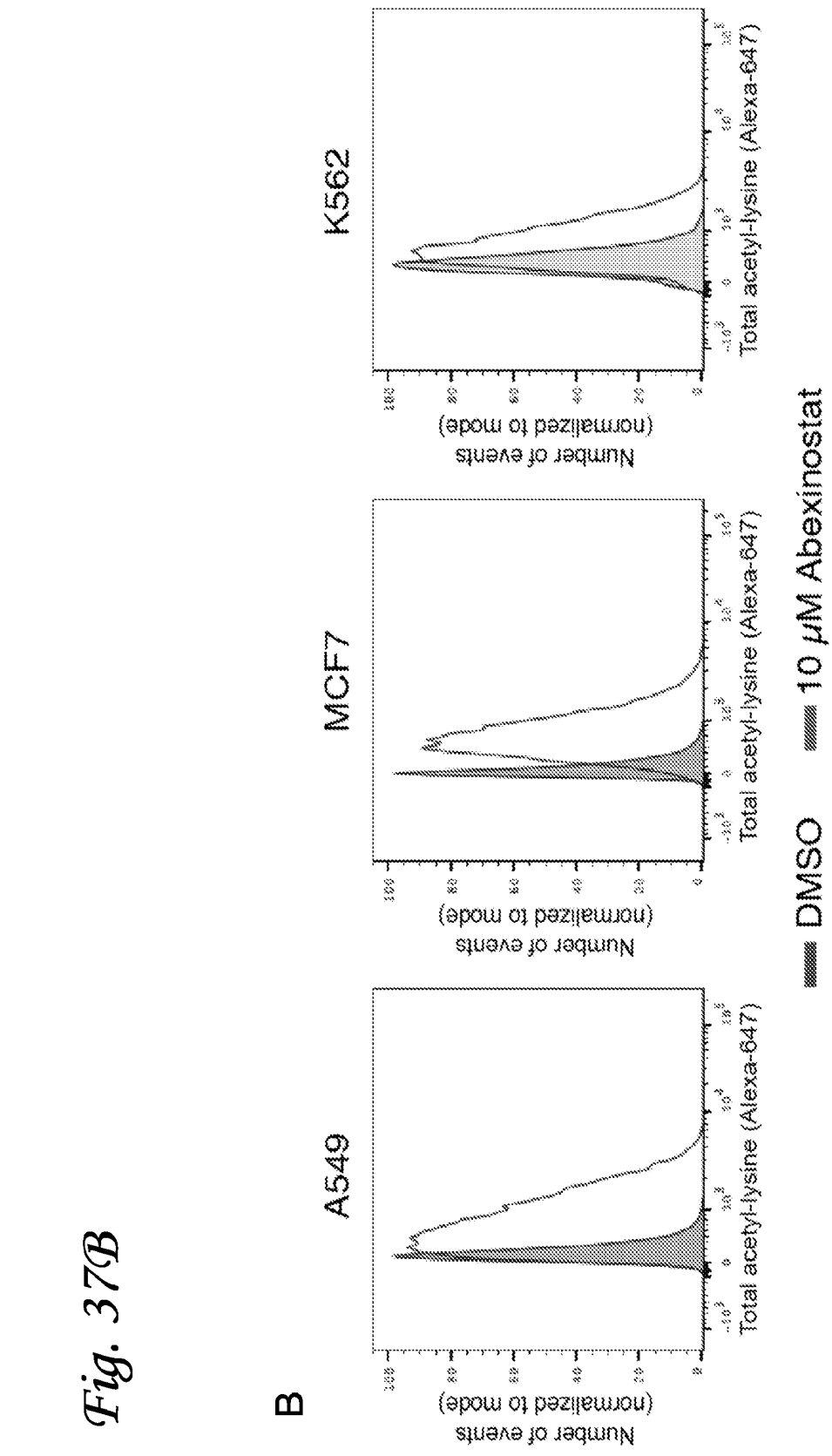

B
A549
MCF7
K562
Number of events (normalized to mode)
Total acetyl-lysine (Alexa-647)
DMSO
10 μM Abexinostat

Fig. 38A

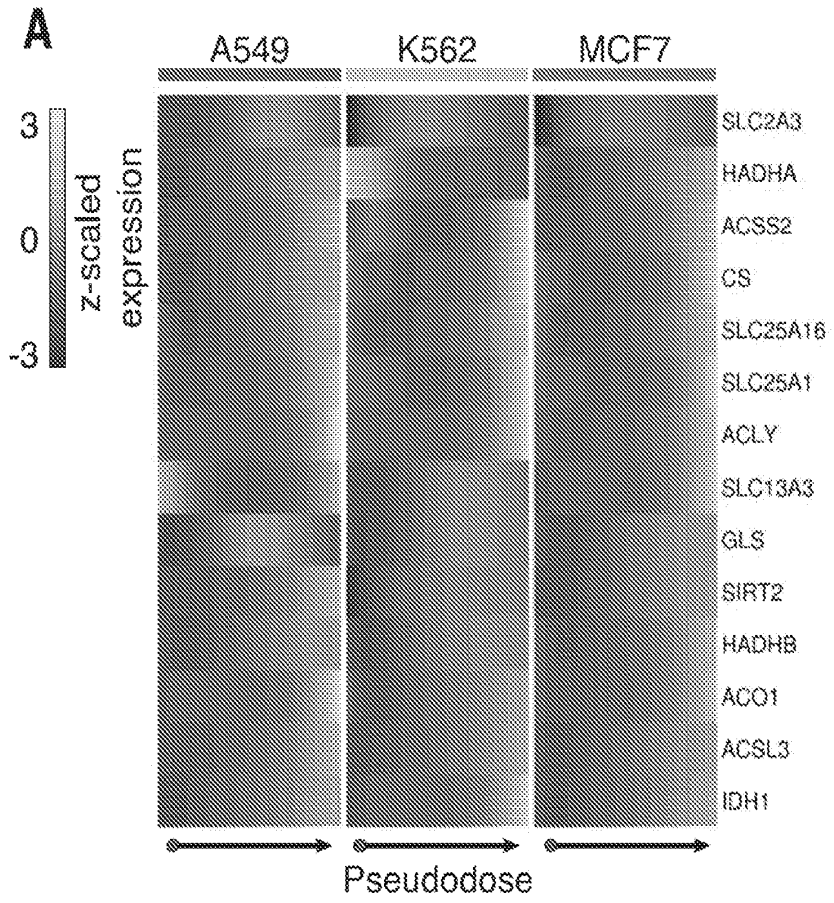
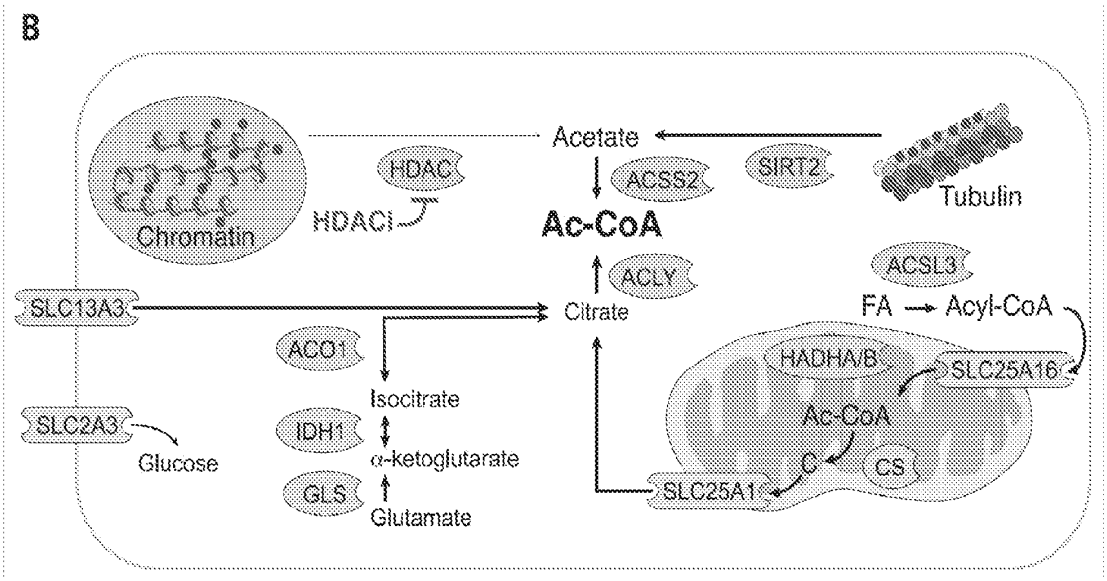


Fig. 38B



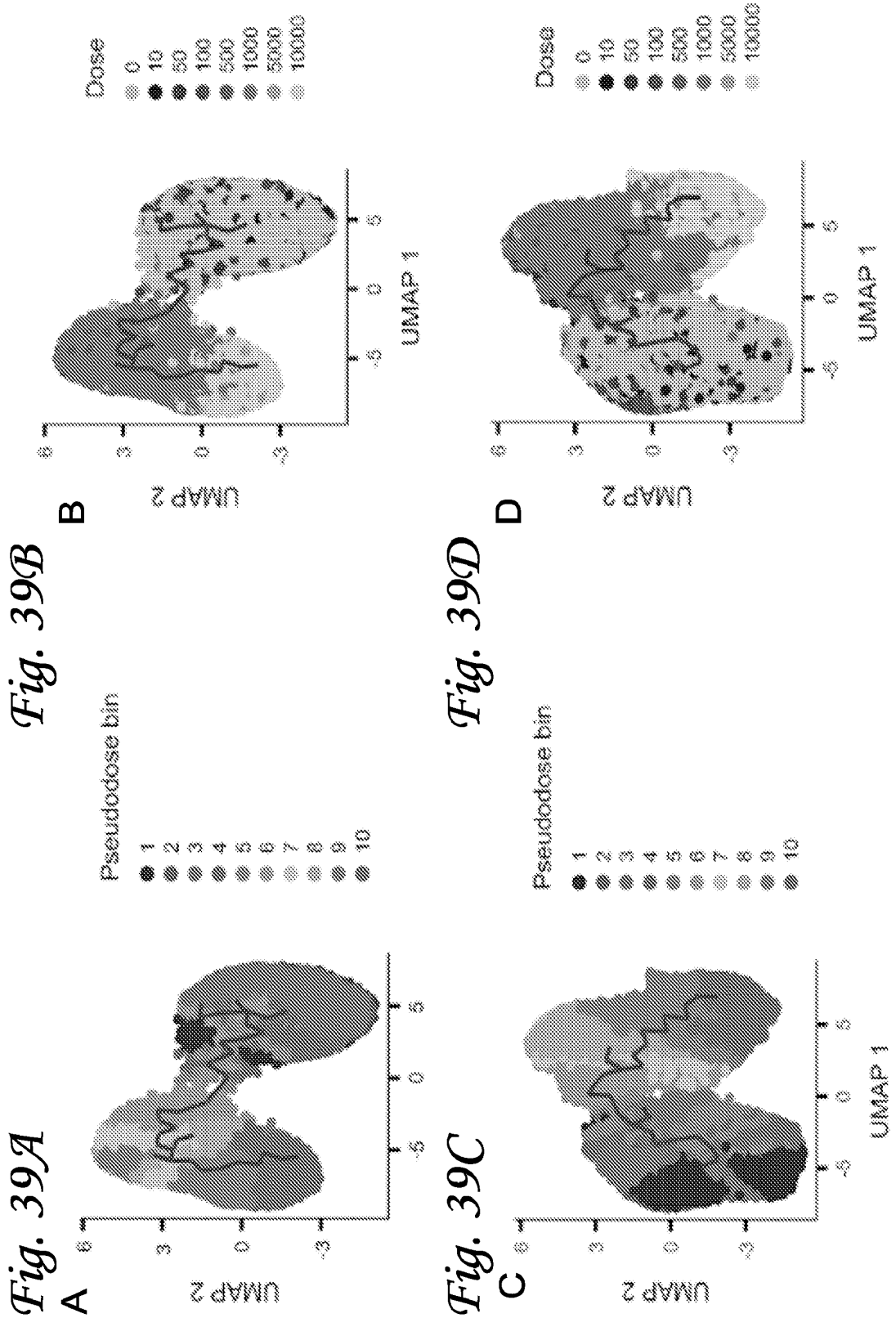


Fig. 39A

Fig. 39B

Fig. 39C

Fig. 39D

Fig. 39E

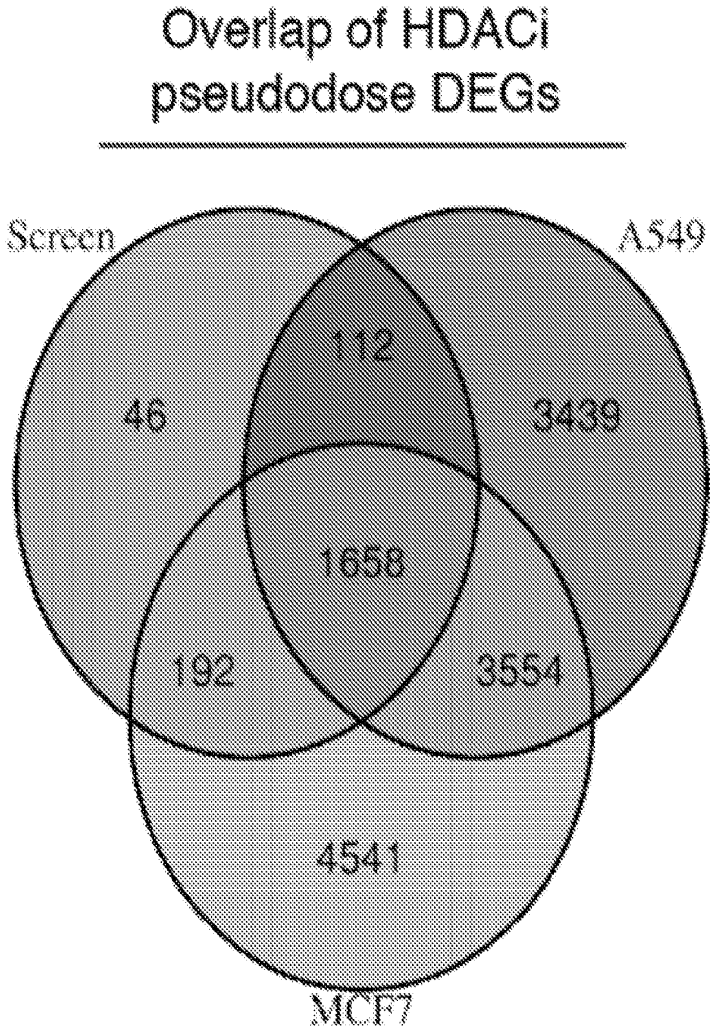

Overlap of HDACi pseudodose DEGs
Screen
A549
MCF7
46
112
3439
1658
192
3554
4541

Fig. 39F

F

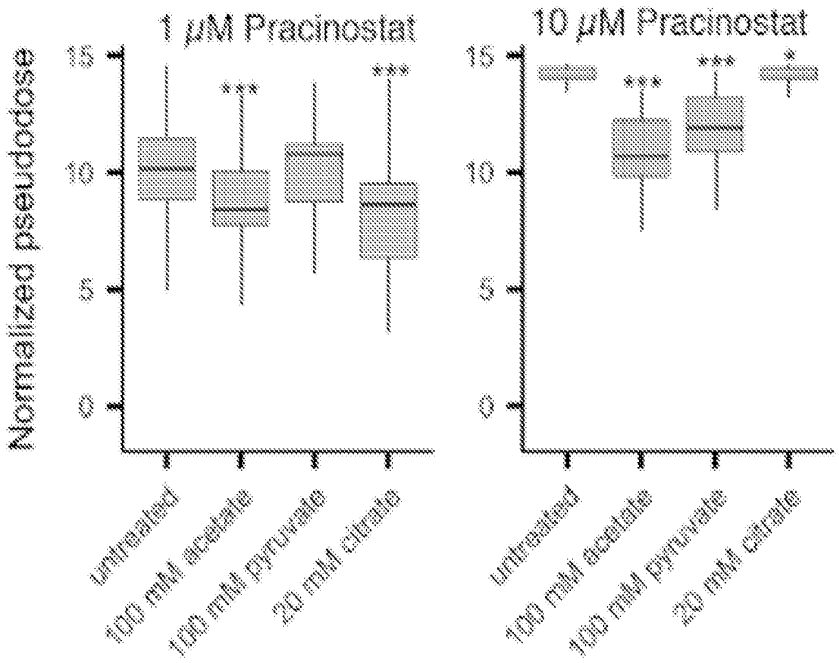


Fig. 39G

G

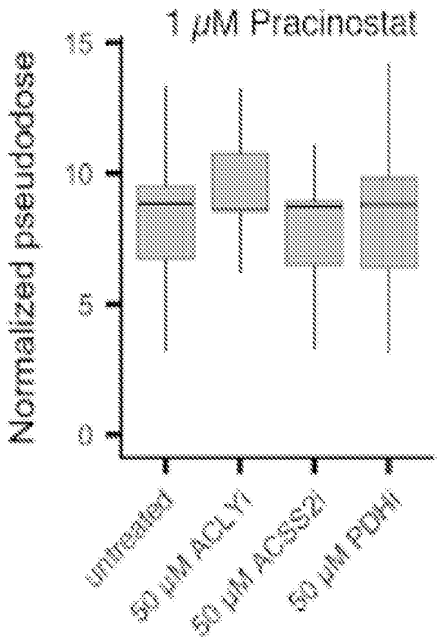


Fig. 39H

H

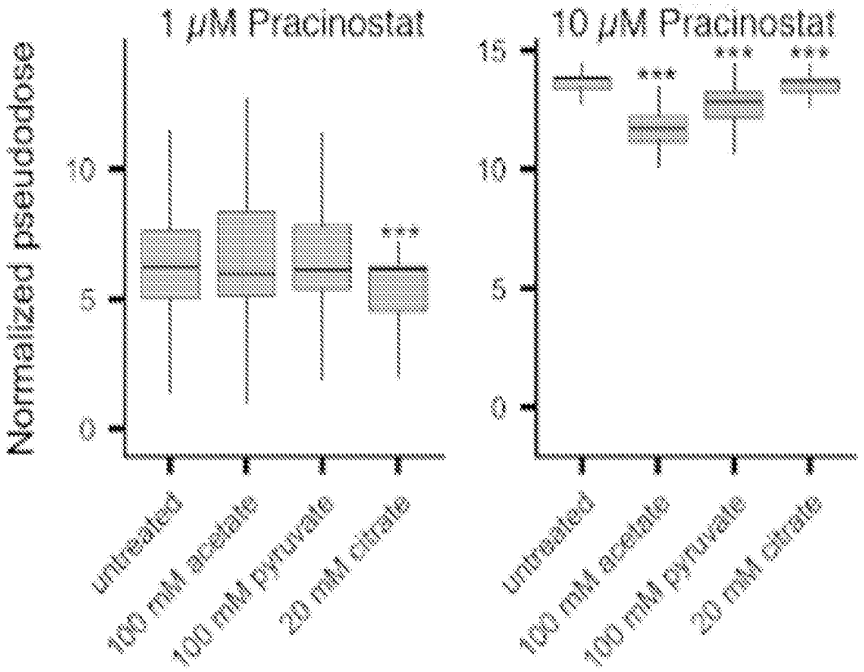


Fig. 39I

I

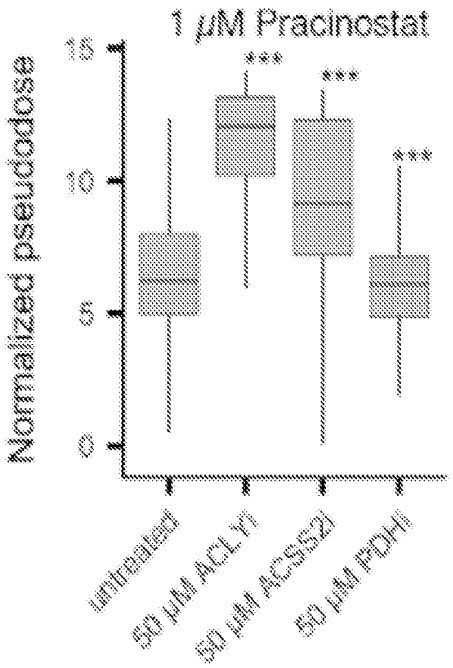


Fig. 39J

J

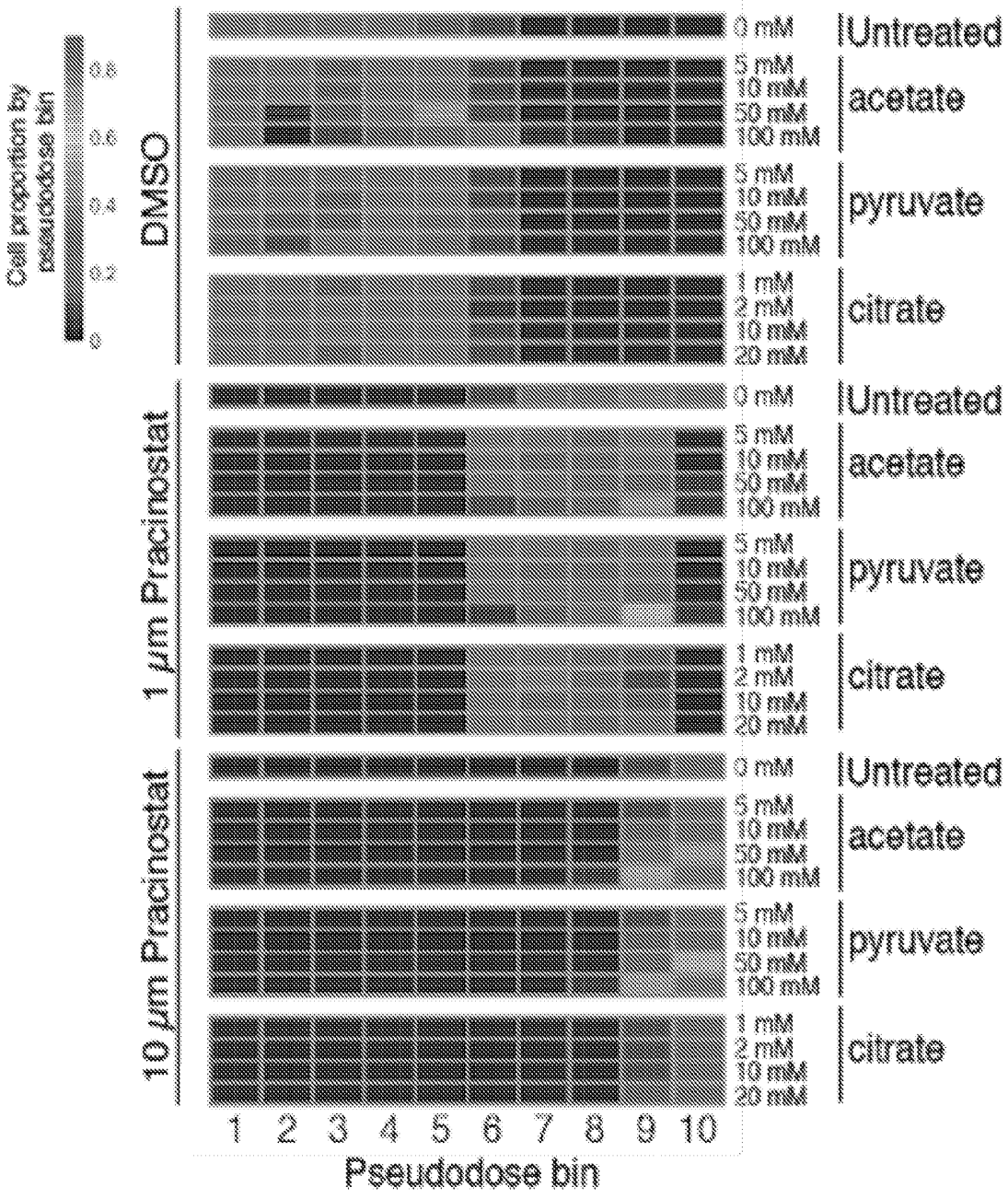

Cell proportion by pseudodose bin
0.8
0.6
0.4
0.2
0
DMSO
1 μm Pracinostat
10 μm Pracinostat
0 mM
5 mM
10 mM
50 mM
100 mM
1 mM
2 mM
10 mM
20 mM
Untreated
acetate
pyruvate
citrate
1 2 3 4 5 6 7 8 9 10
Pseudodose bin

Fig. 39K

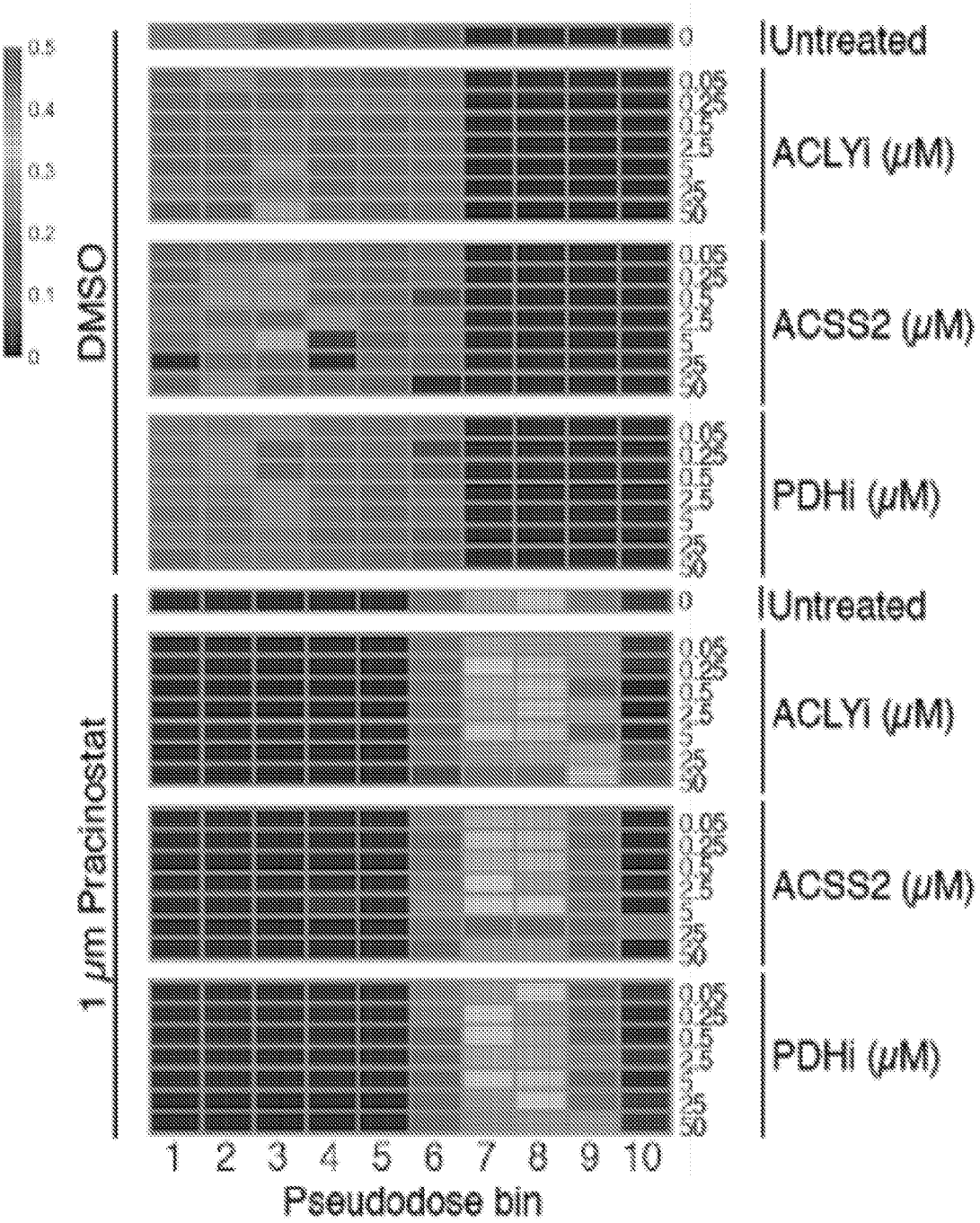

K
0.5
0.4
0.3
0.2
0.1
0
DMSO
1 μm Pracinostat
Untreated
ACLYi (μM)
ACSS2 (μM)
PDHi (μM)
Untreated
ACLYi (μM)
ACSS2 (μM)
PDHi (μM)
1 2 3 4 5 6 7 8 9 10
Pseudodose bin

Fig. 39L

L

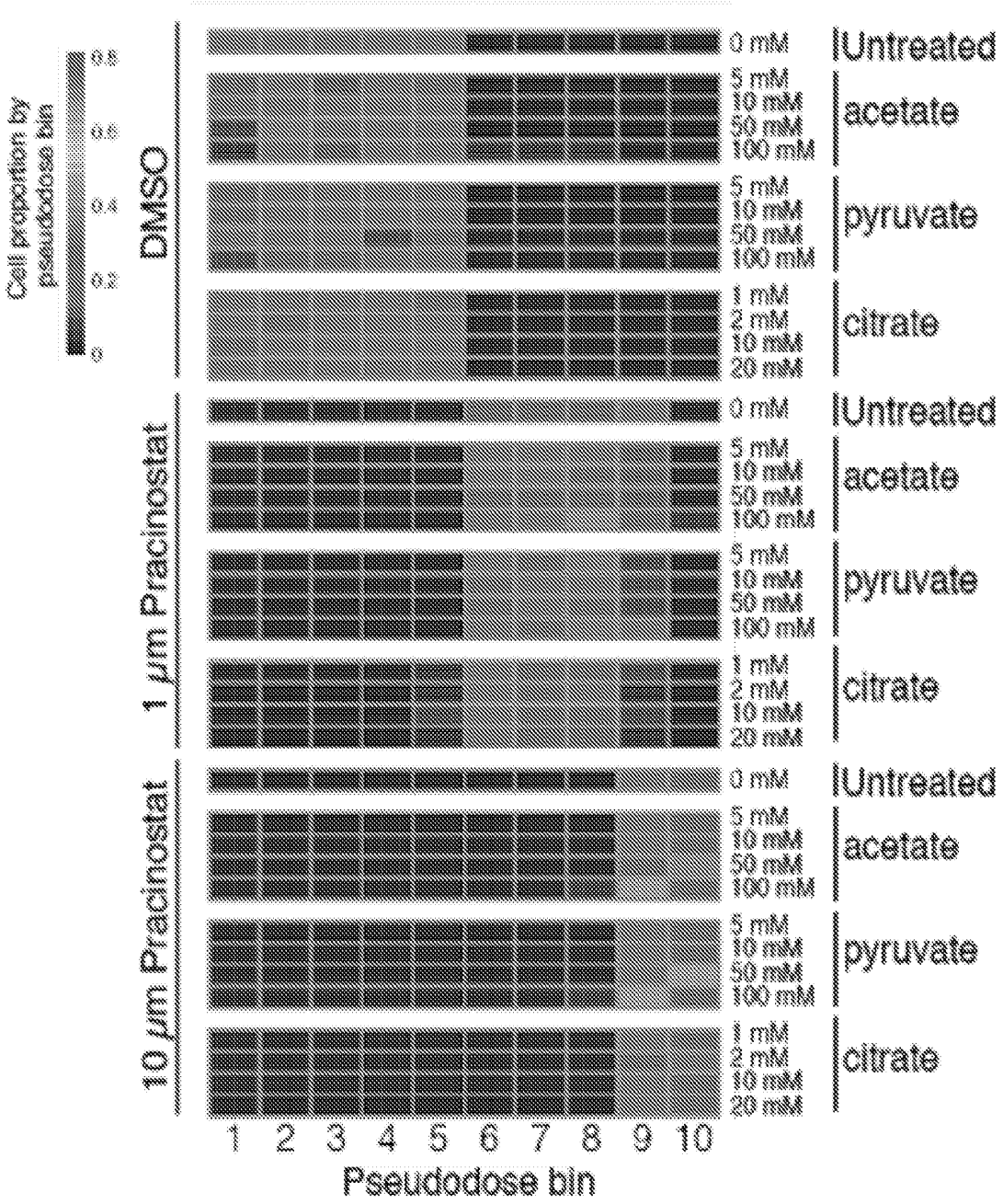

Call proportion by pseudodose bin
0.8
0.6
0.4
0.2
0
DMSO
1 μm Pracinostat
10 μm Pracinostat
0 mM
5 mM
10 mM
50 mM
100 mM
1 mM
2 mM
10 mM
20 mM
Untreated
acetate
pyruvate
citrate
1 2 3 4 5 6 7 8 9 10
Pseudodose bin

Fig. 39M

M

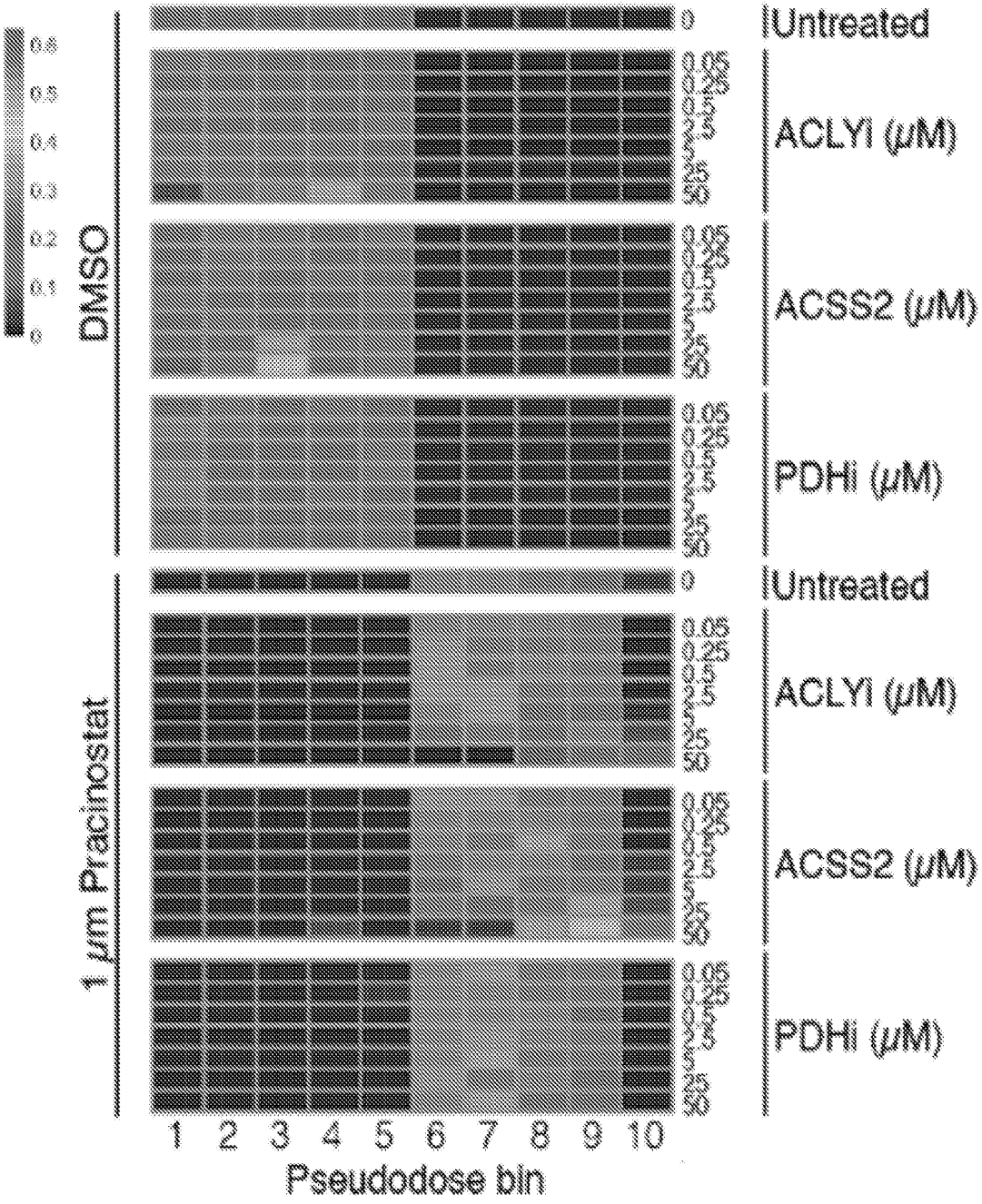

DMSO
1 μm Pracinostat
Untreated
ACLYi (μM)
ACSS2 (μM)
PDHi (μM)
0
0.05
0.25
0.5
2.5
5
25
50
1 2 3 4 5 6 7 8 9 10
Pseudodose bin

Fig. 40A

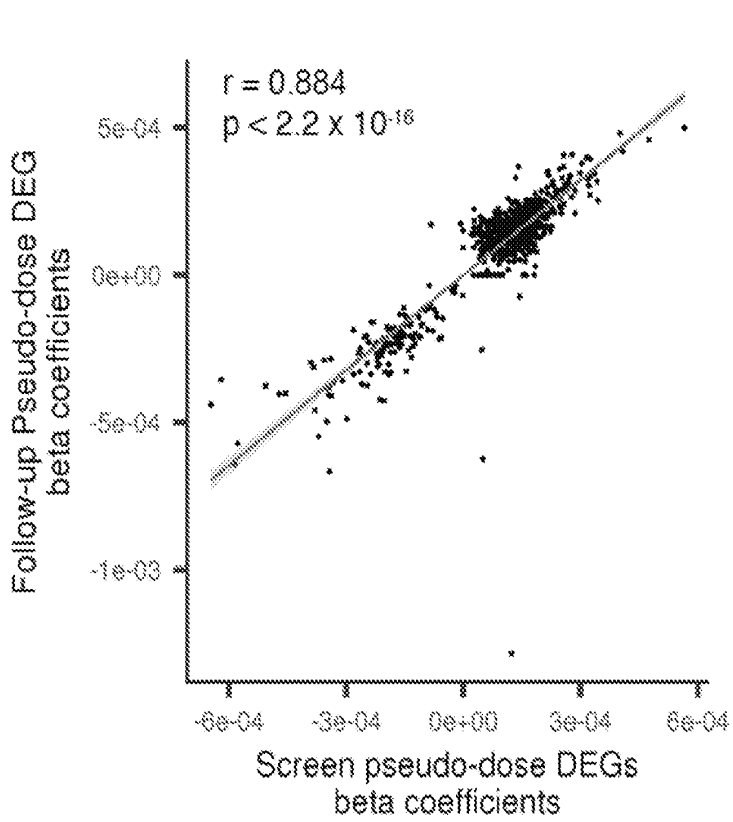


Fig. 40B

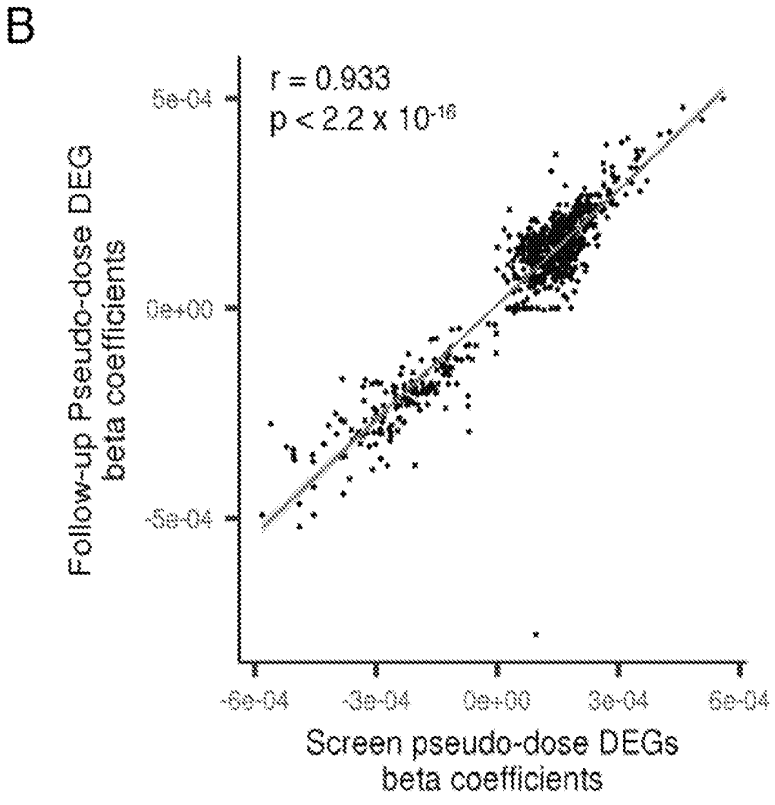


Fig. 40C

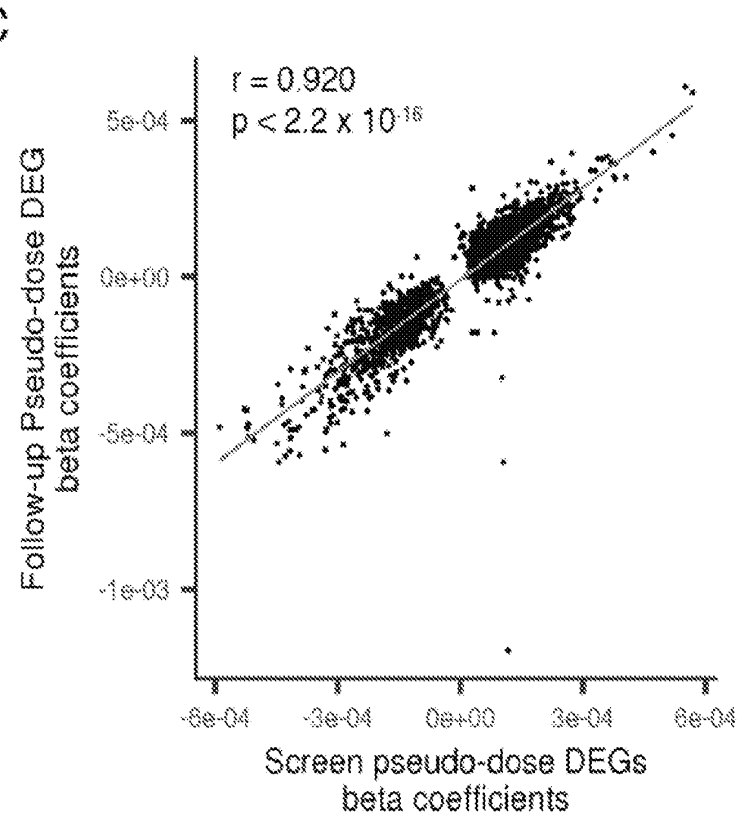
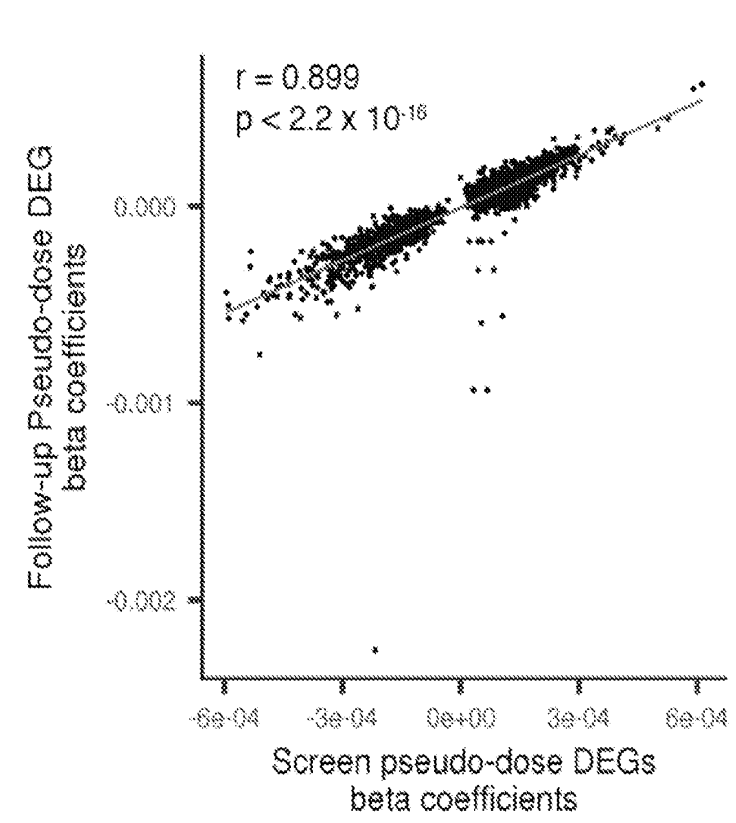


Fig. 40D



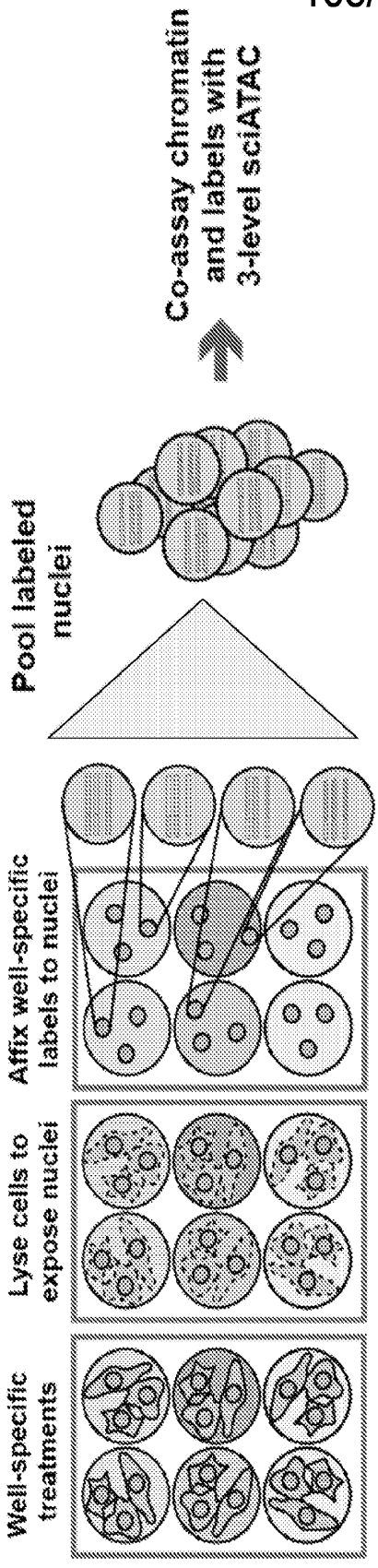
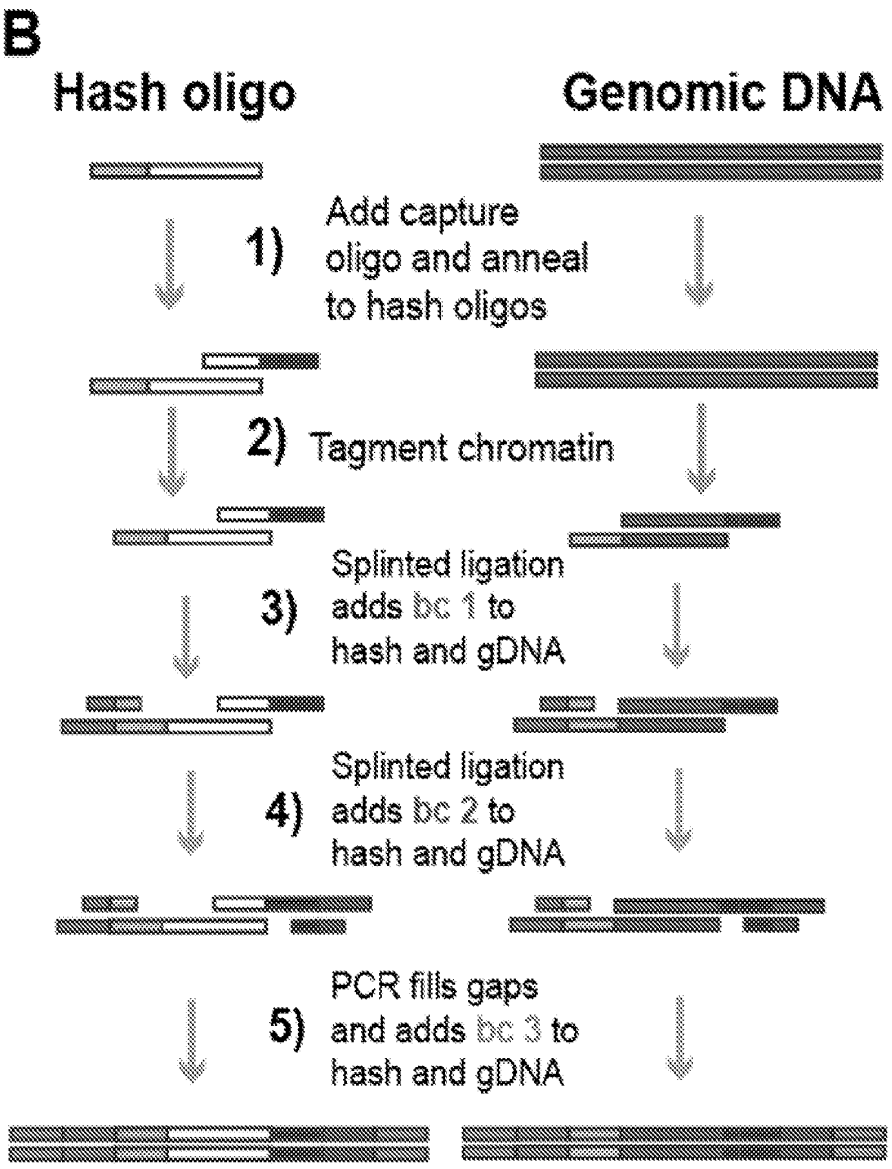

Co-assay chromatin and labels with 3-level sciATAC
Pool labeled nuclei
Affix well-specific labels to nuclei
Lyse cells to expose nuclei
Well-specific treatments

Fig. 41A
A

Fig. 41B


B
Hash oligo
Genomic DNA
1) Add capture oligo and anneal to hash oligos
2) Tagment chromatin
3) Splinted ligation adds bc 1 to hash and gDNA
4) Splinted ligation adds bc 2 to hash and gDNA
5) PCR fills gaps and adds bc 3 to hash and gDNA

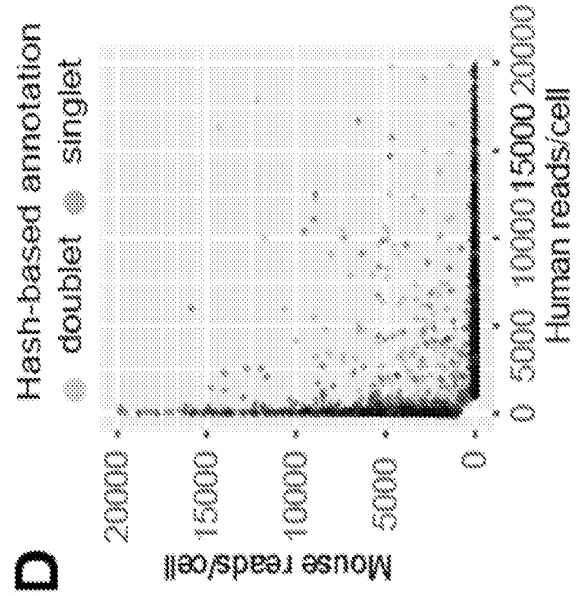


Fig. 41D

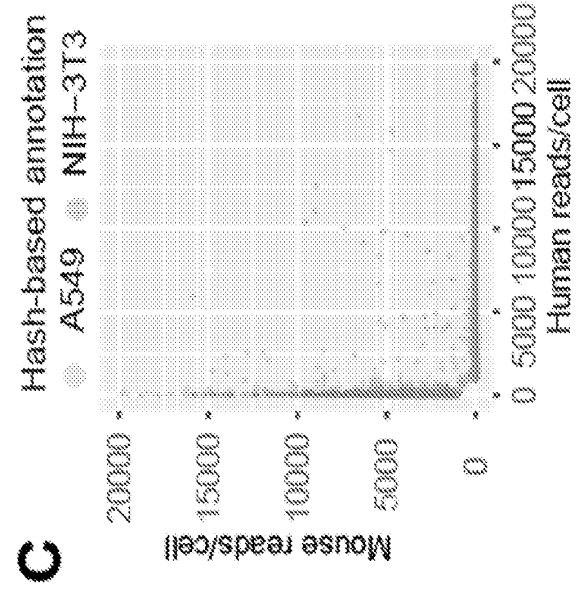


Fig. 41C

Fig. 41F

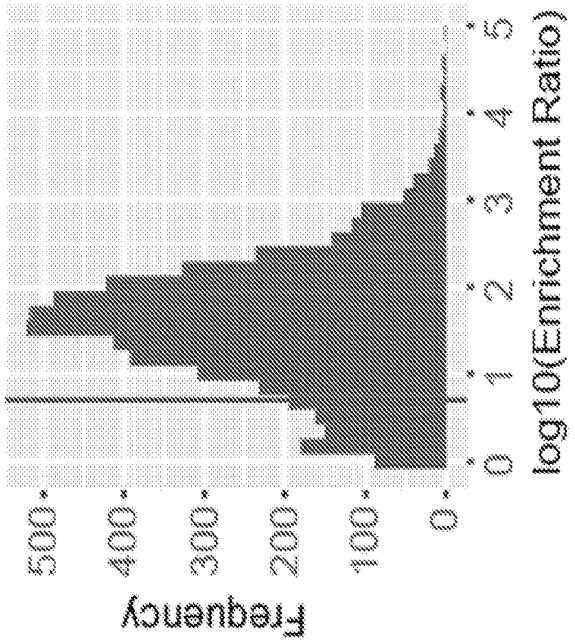


Fig. 41E

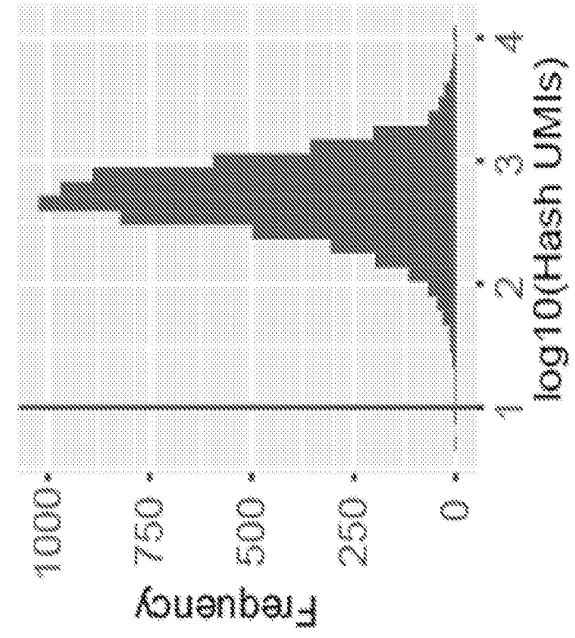
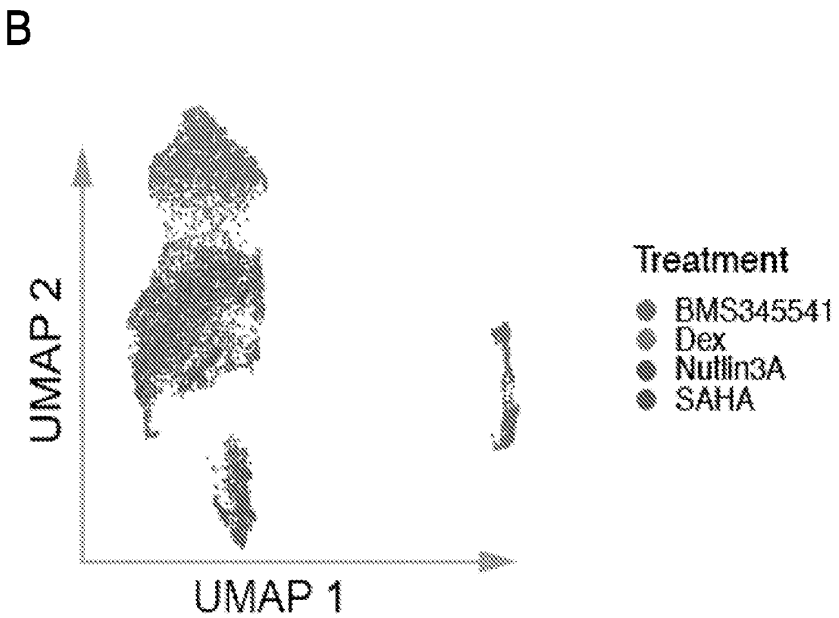


Fig. 42A



Fig. 42B



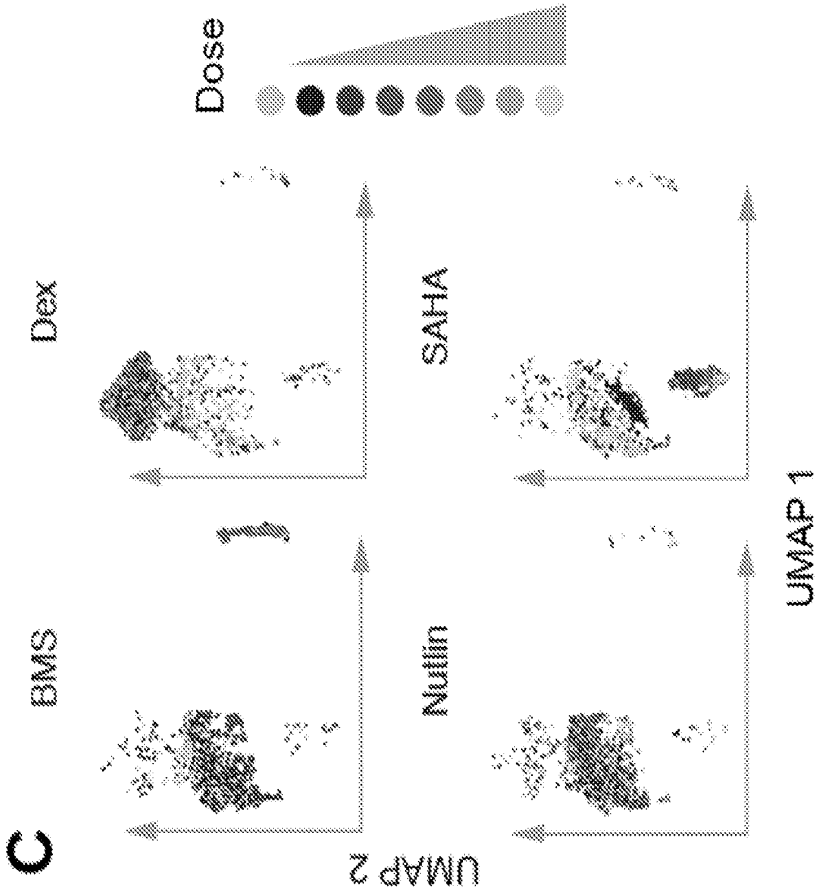


Fig. 42C

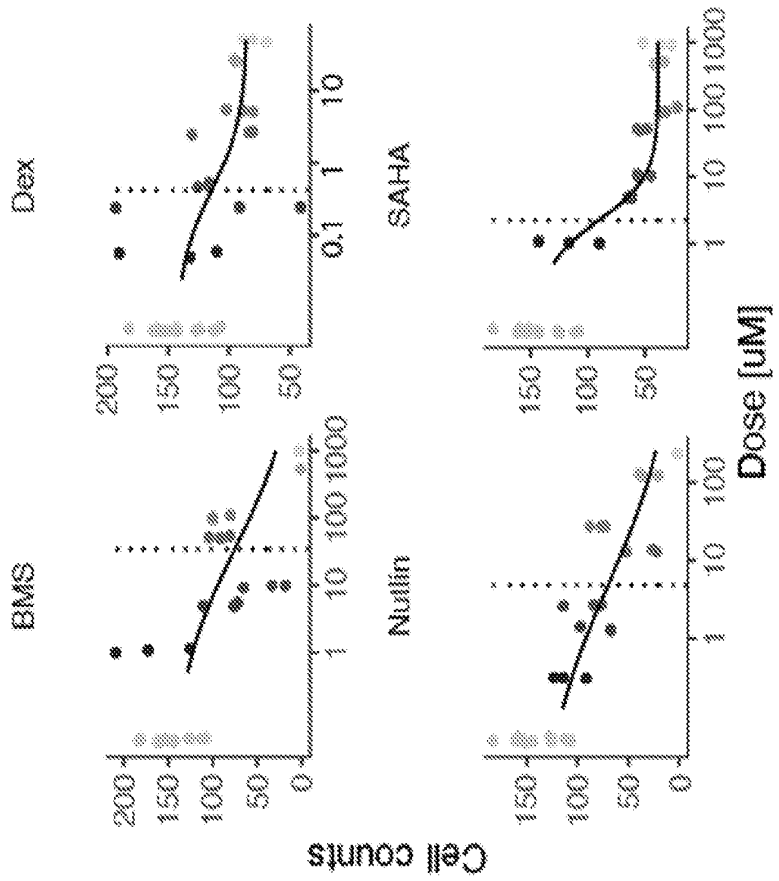
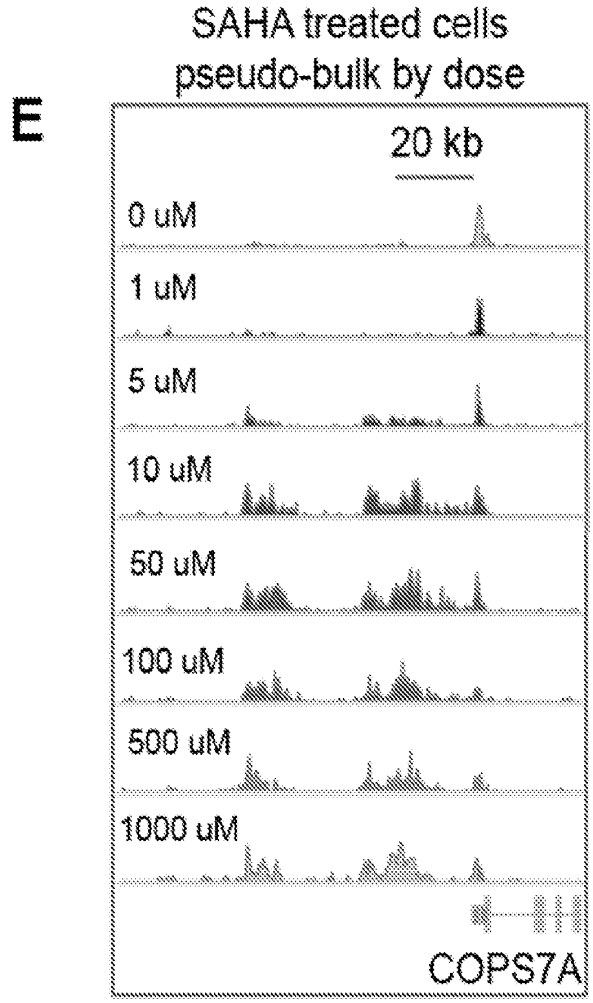


Fig. 42D

Fig. 42E


E
SAHA treated cells
pseudo-bulk by dose
20 kb
0 uM
1 uM
5 uM
10 uM
50 uM
100 uM
500 uM
1000 uM
COPS7A

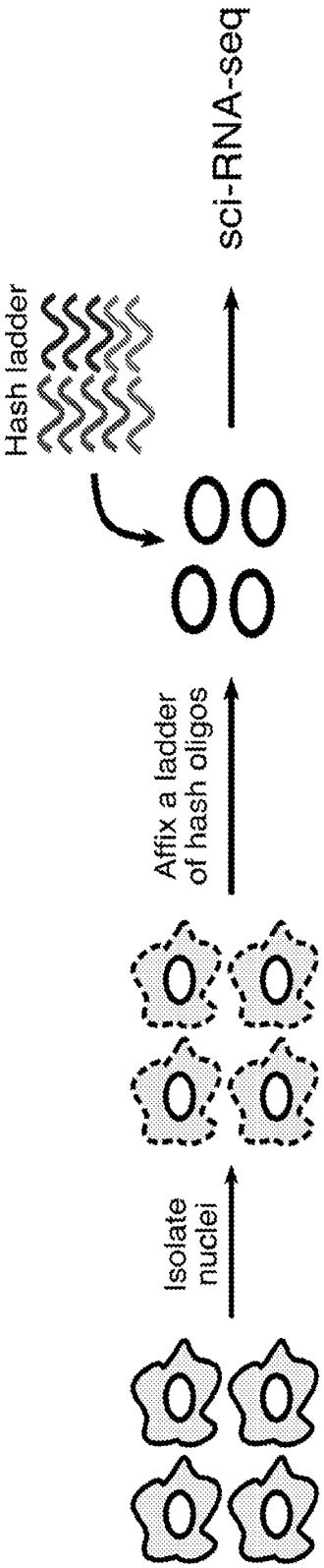


Fig. 43A

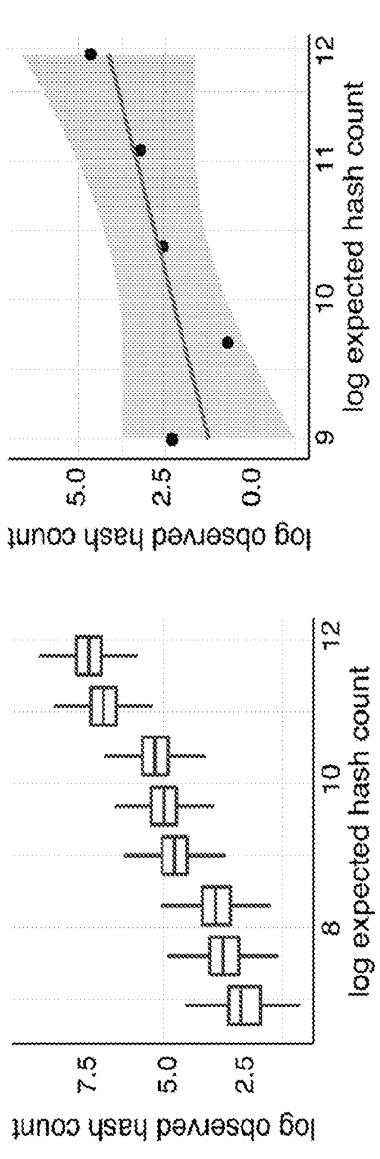


Fig. 43B

Fig. 43C

Fig. 44A

A

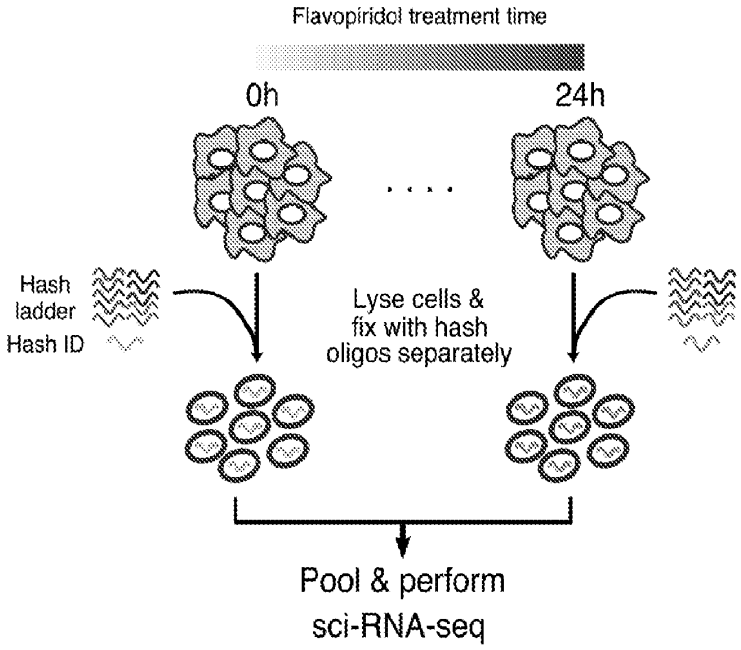


Fig. 44B

B

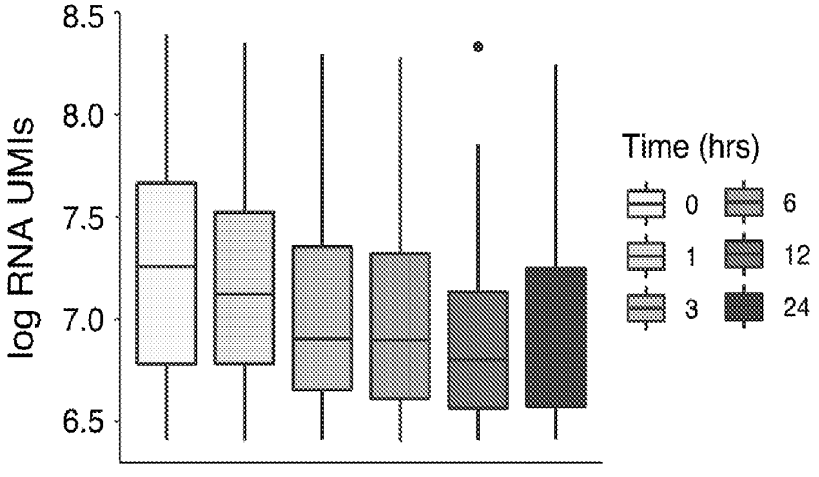


Fig. 44C

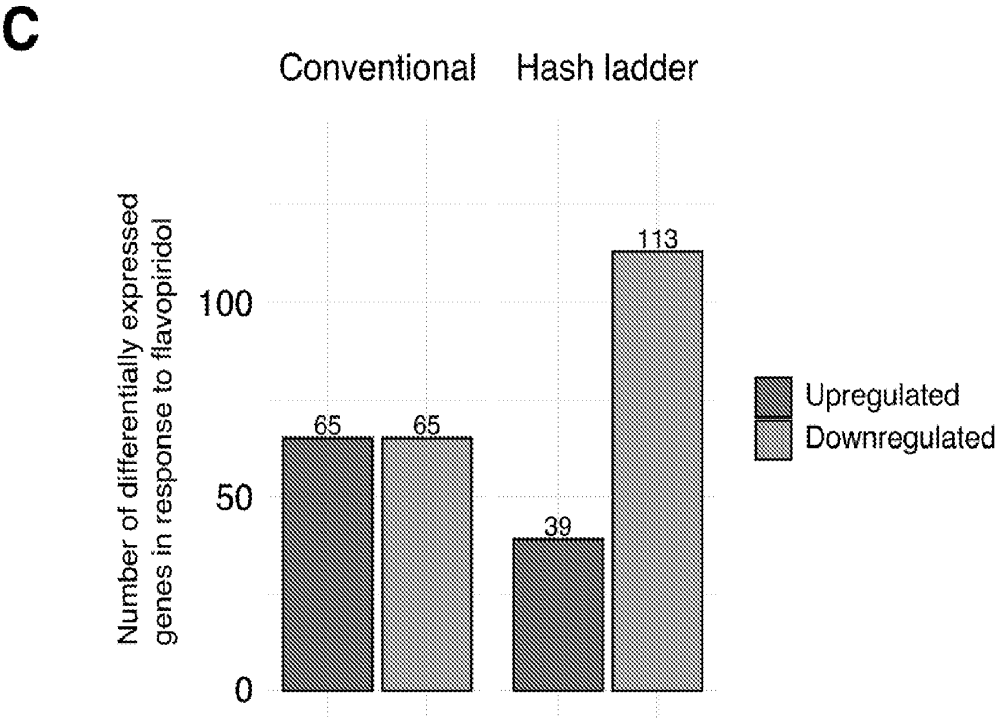


Fig. 44D

