

SUPPLEMENTAL INFORMATION

1. Supplemental figure legends
2. Supplemental figures
3. Table S1 – list of diapause DEGs

Figure S1

- A) Additional cisplatin and etoposide dual titrations across an expanded panel of SCLC cell lines: H146, H209, H524, and H1417.
- B) Additional EdU labeling across time points in response recovery time course in H526 and H1963 cell lines.
- C) Gating strategy for the quantification of viable cells at each time point.
- D) Representative flow cytometry scatterplots with 7-AAD signal plotted against forward scatter demonstrating viable population gate at various time points in H82.

Figure S2

- A) Distance clustering separated by cell line demonstrating samples to be excluded in downstream analysis in each response-recovery time course.
- B) Plots of principal components 1 and 2 for each cell line time course dataset.

Figure S3

- A) Pearson correlation heatmap of expression of all ETS group transcription factors among 49 SCLC cell lines from the Cancer Cell Line Encyclopedia (CCLE).
- B) Pearson correlation heatmap of expression of all ETS group transcription factors among 47 primary SCLC samples from George et al.
- C) Dependencies across 25 SCLC lines on ETV4 and ETV5 RNAi perturbation, ASCL1 and NEUROD1 included as positive controls.
- D) Dependencies across 19 SCLC lines on ETV4 and ETV5 CRISPR perturbation, ASCL1 and NEUROD1 included as positive controls.

Figure S4

- A) Summary of frameshift mutations in four evaluated H526 sublines at ETV4 exon 5.
- B) Summary of frameshift mutations in four evaluated H526 sublines at ETV5 exon 6.
- C) Evaluation of off-target editing at ENO2 and WDR93.
- D) Quantitative polymerase chain reaction of H82 and H526 lines stably transduced with shRNA targeting ETV4 and ETV5.
- E) Quantitative polymerase chain reaction of H526 line stably transduced with cDNA for overexpression of ETV4 and ETV5.
- F) Cellular growth curves of stably-transduced shRNA lines generated from H82 and H526 parental lines by CellTiter-Glo. Each time point was measured in quadruplicate.
- G) Cellular growth curves of stably-transduced cDNA lines generated from H526 parental line by CellTiter-Glo. Each time point was measured in quadruplicate.

Figure S5

- A) Summary of measured *in vitro* IC₅₀ values for target binding of selected tyrosine kinase inhibitors.
- B) Dual titrations of pan-FGFR inhibitors infogatinib and erdafitinib against lucitinib in H82 (left) and H526 (right).

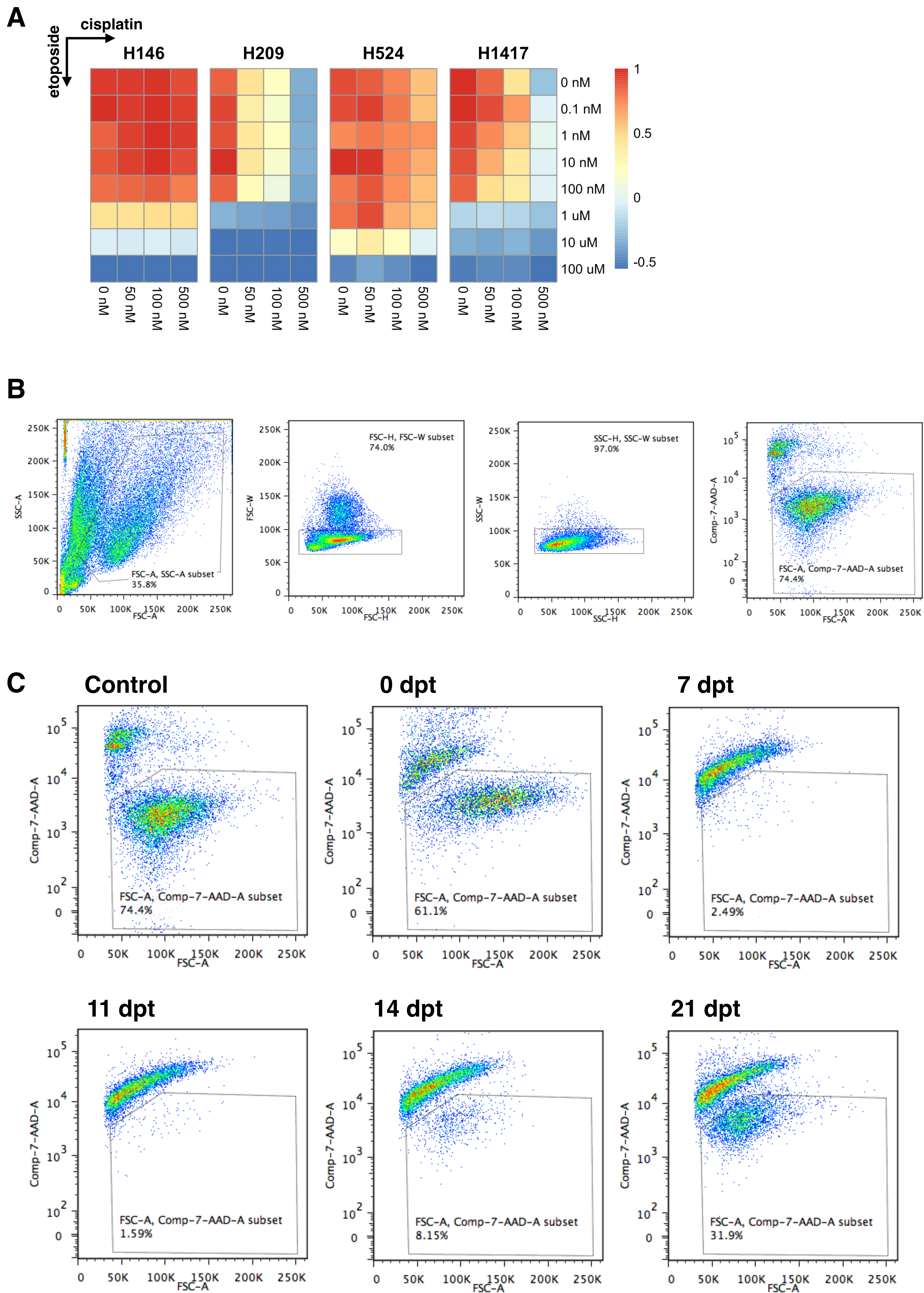
Figure S6

- A) Time course analysis of phosphorylation of Erk1/2 (T202/Y204) and Akt (S473) following exposure to 500 nM LY2874455 in H82 (left) and H526 (right).
- B) Clonogenic regrowth assay in stably-transduced H526 lines expressing the following cDNA: GFP, ETV4, ETV5, ETV4 and ETV5. As above, cells were treated with 500 nM cisplatin and etoposide for 72 hours and then seeded in 1% methylcellulose prepared with a final concentration of 500 nM LY2874455 for quantification of clonogenic regrowth. Non-parametric t-test was used to determine statistical significance between groups.

Figure S7

- A) H209 xenograft tumor growth comparing daily intraperitoneal administration of 12 mg/kg LY2874455 in combination with cisplatin and etoposide (n=5) compared to only cisplatin and etoposide (n=6). Error bars represent standard error of the mean.

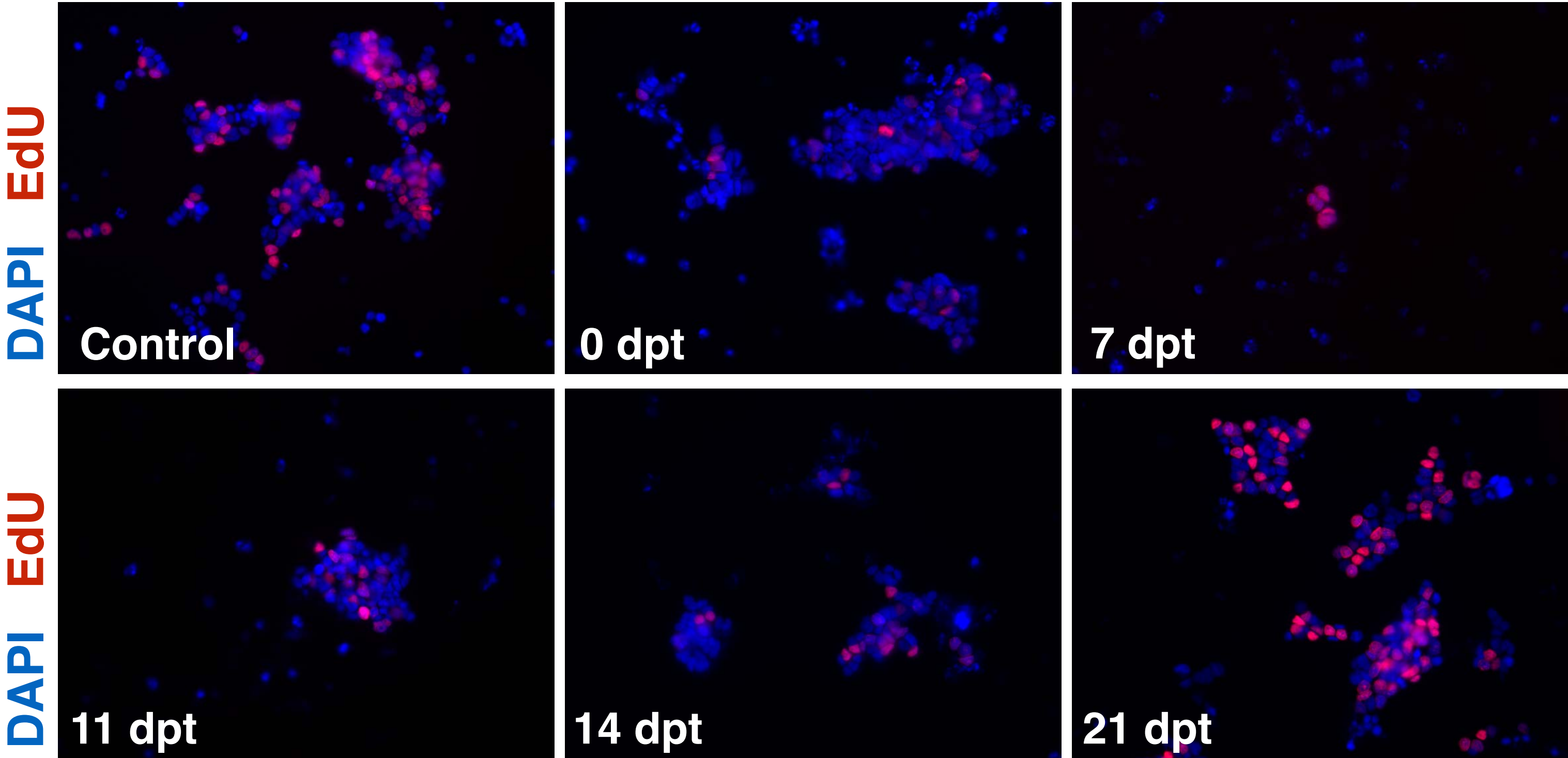
Supplementary Figure 1



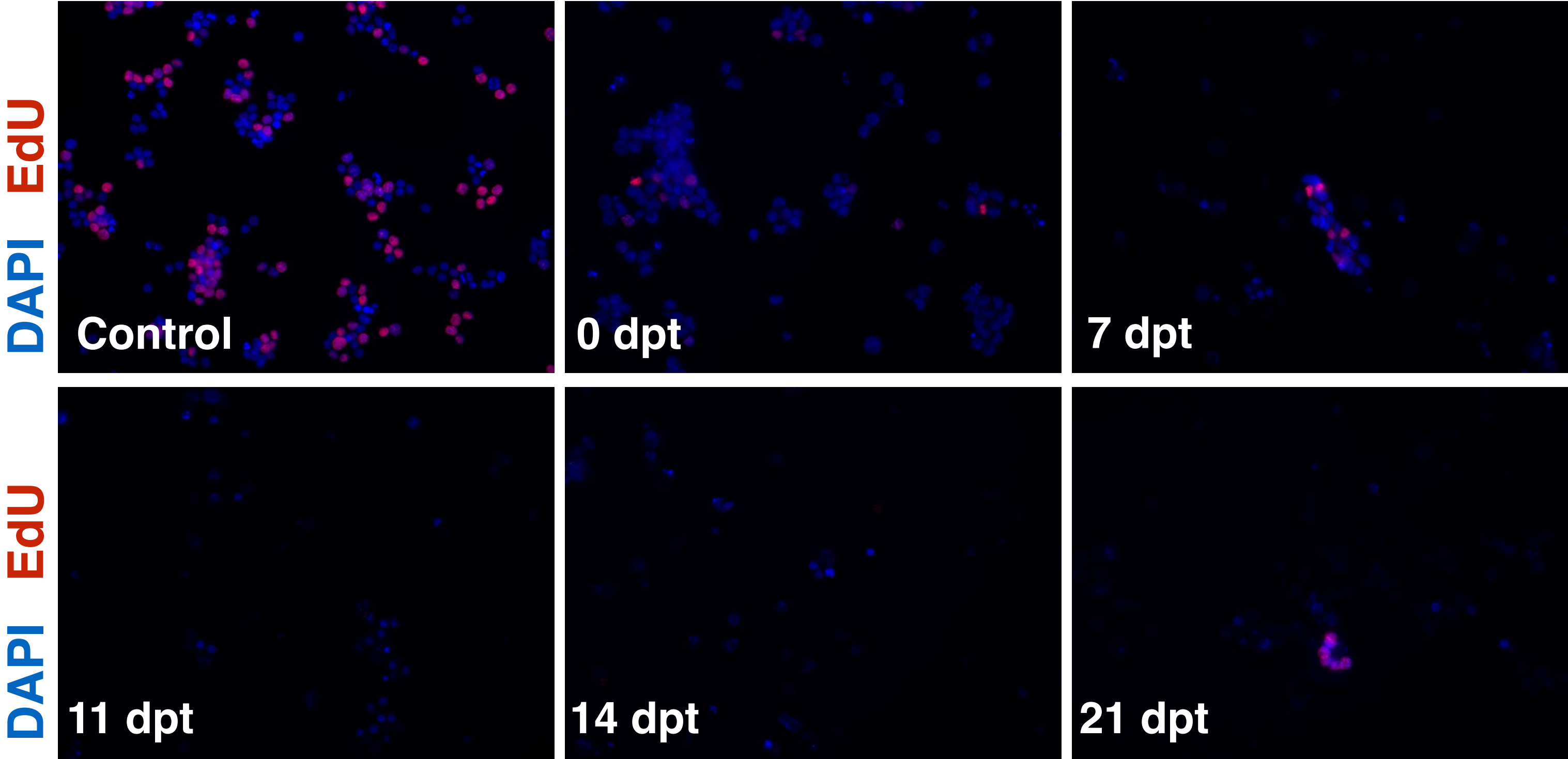
Supplementary Figure 1 (continued)

D

H526

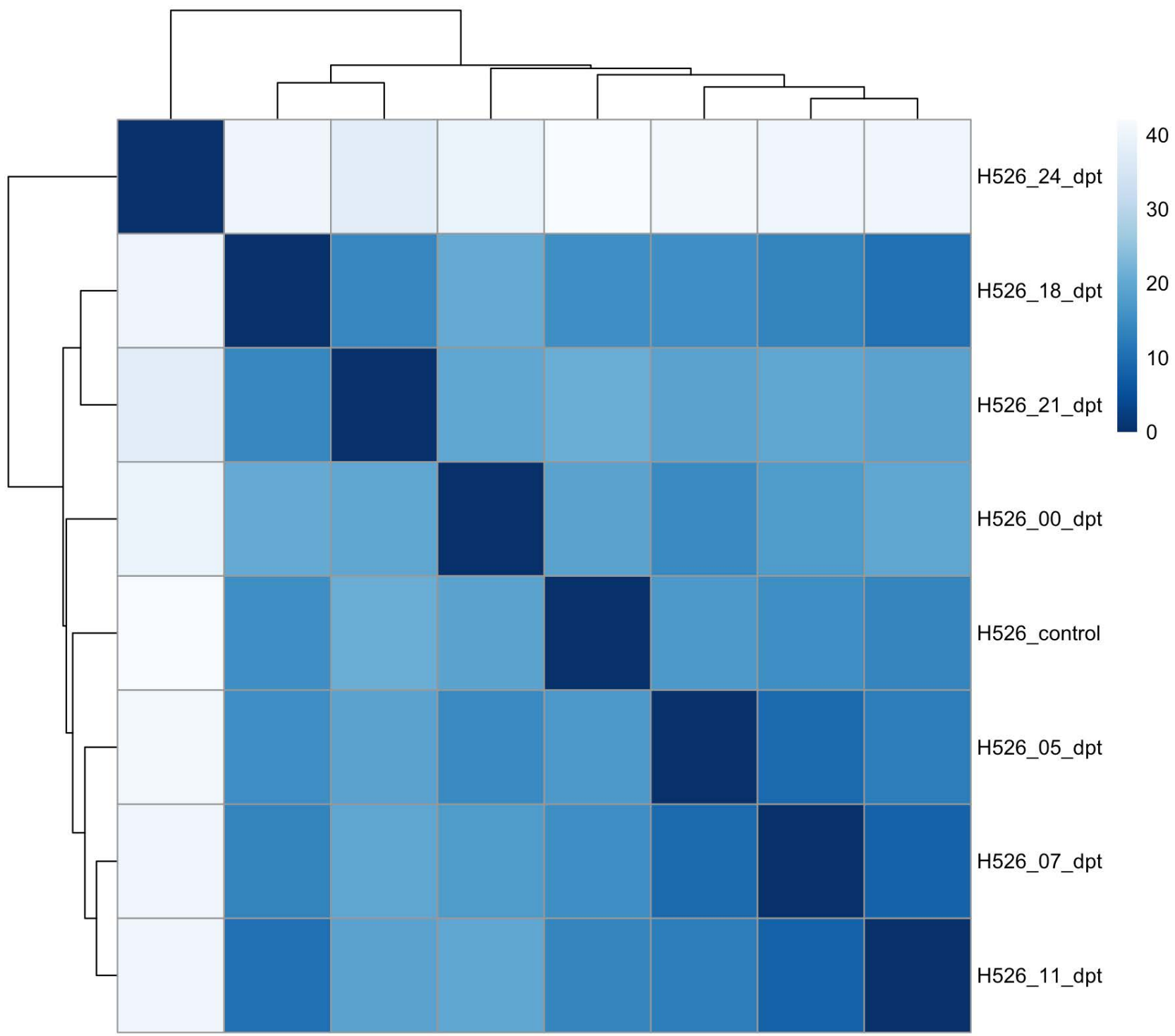
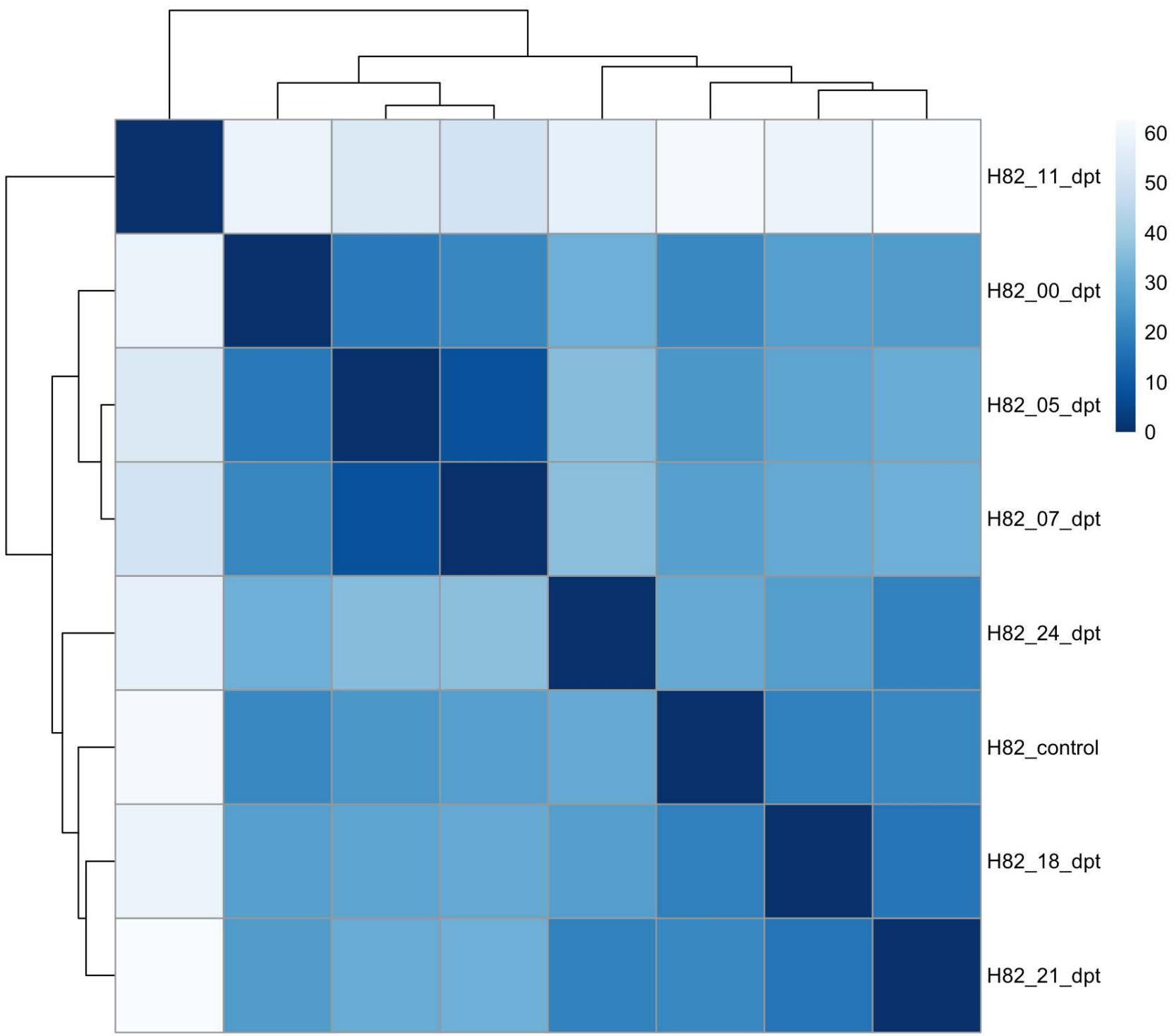


H1963

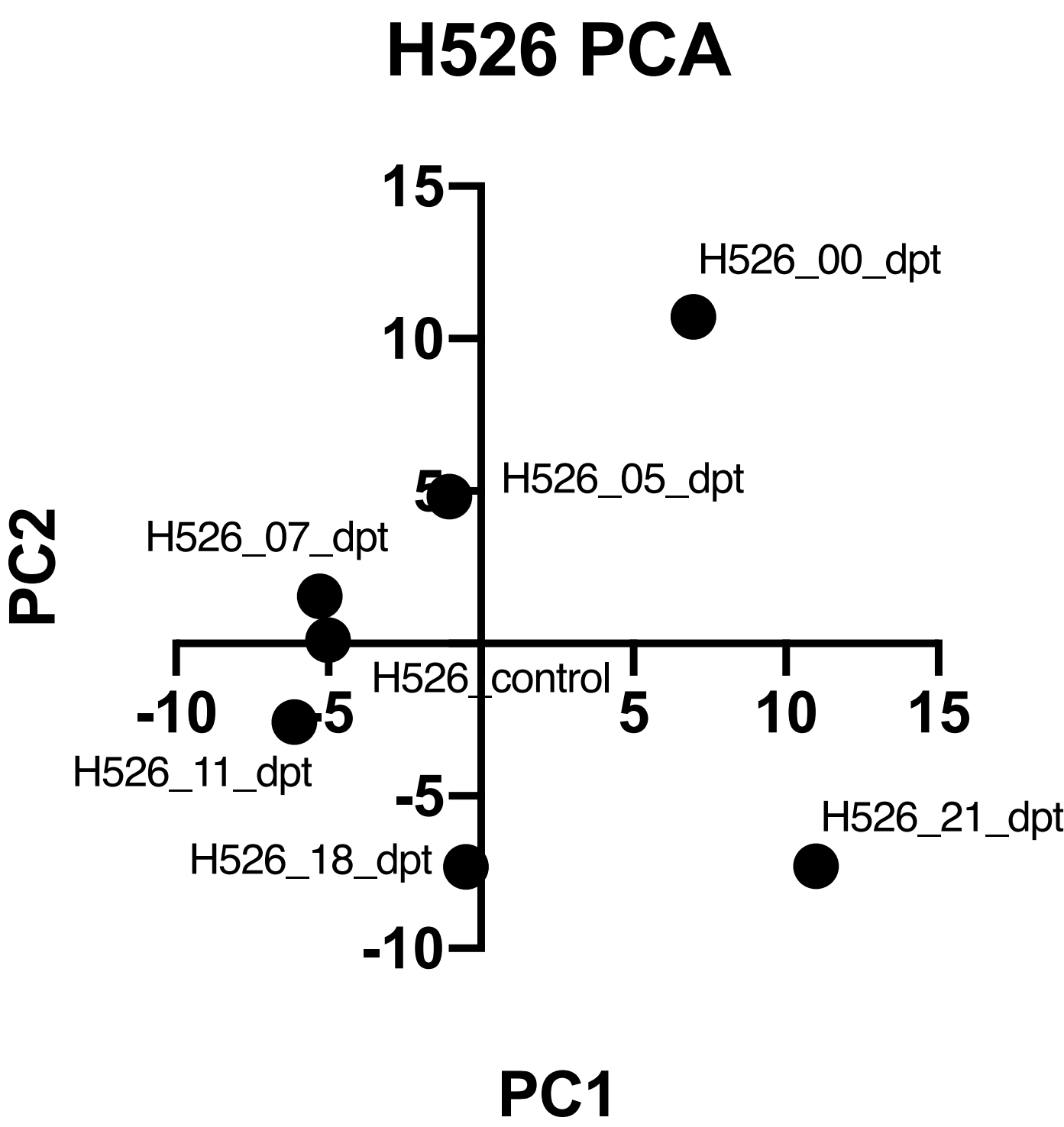
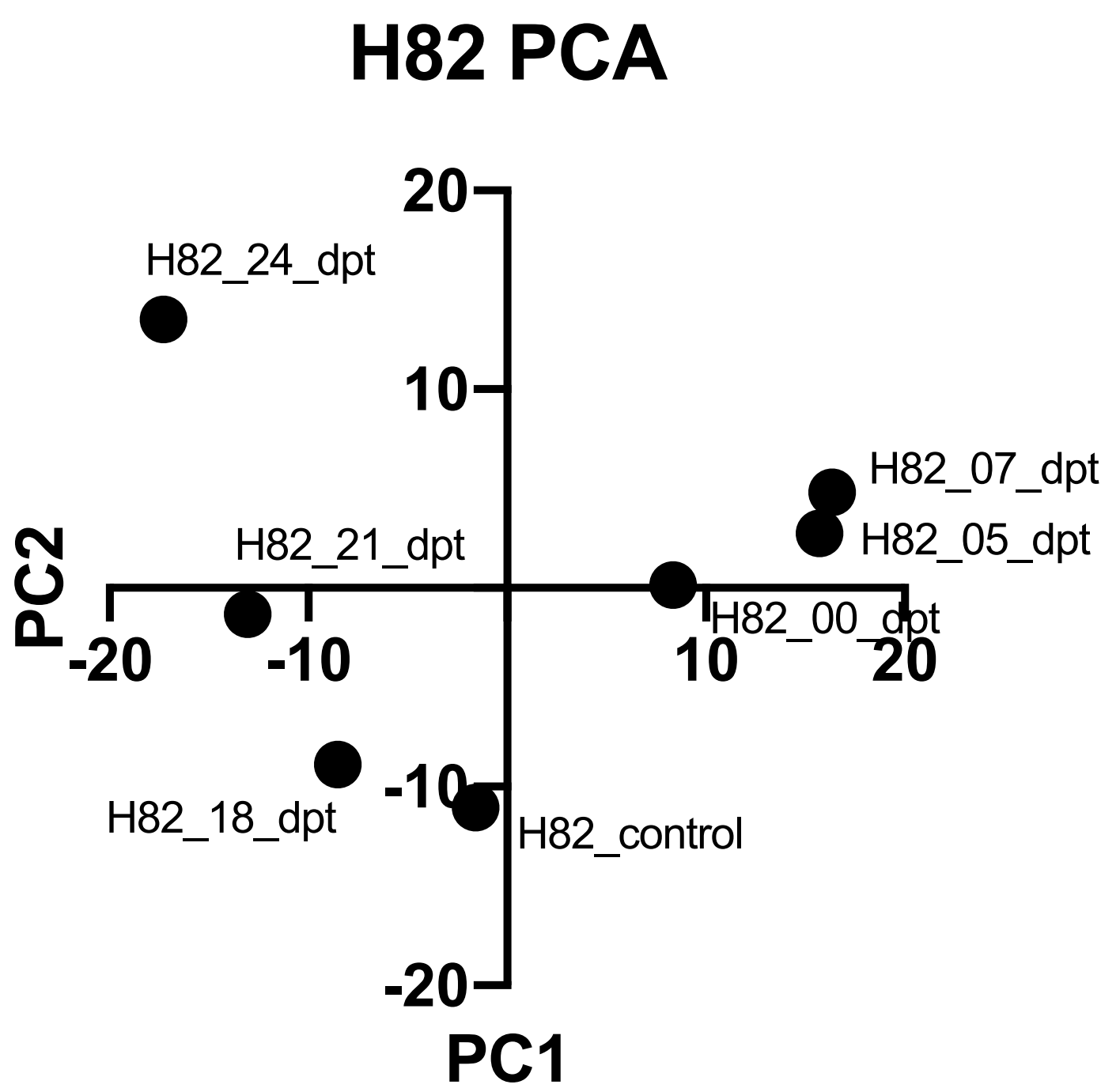


Supplementary Figure 2

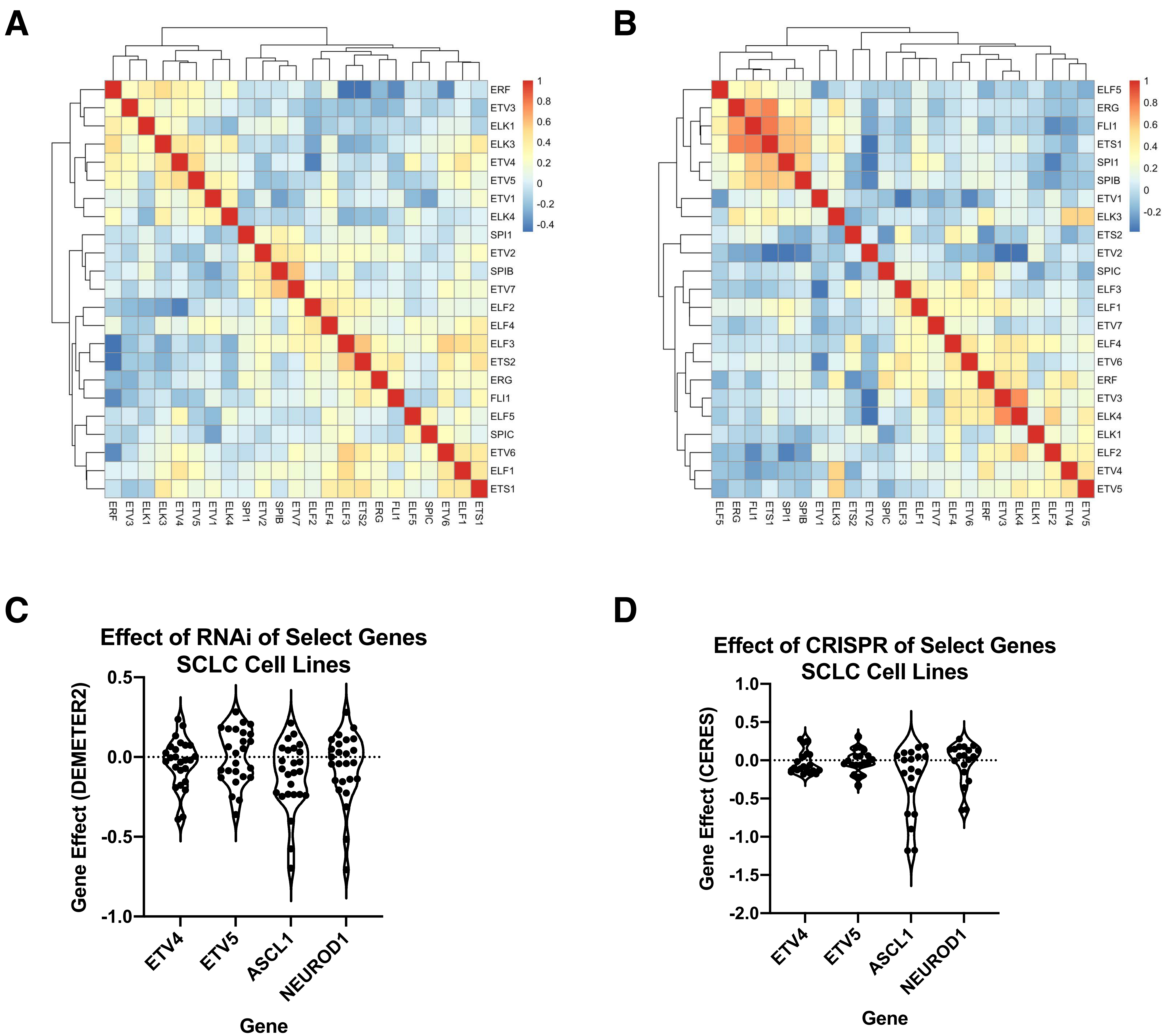
A



B



Supplementary Figure 3



Supplementary Figure 4

A

SAMPLE ?	GUIDE TARGET ?	PAM SEQUENCE?	INDEL % ?	MODEL FIT (R ²) ?	KNOCKOUT-SCORE ?
✓ AC5	CTTTCCACAGCCCCACCACC	AGG	96	0.96	96
✓ AD5	CTTTCCACAGCCCCACCACC	AGG	97	0.97	97
✓ BD2	CTTTCCACAGCCCCACCACC	AGG	97	0.97	97
✓ DC2	CTTTCCACAGCCCCACCACC	AGG	98	0.98	25

Cell Line

AC5



AD5



BD2



DC2



B

SAMPLE ?	GUIDE TARGET ?	PAM SEQUENCE?	INDEL % ?	MODEL FIT (R ²) ?	KNOCKOUT-SCORE ?
✓ AC5	GCTACAAGACGACAGCTCAG	AGG	97	0.97	97
✓ AD5	GCTACAAGACGACAGCTCAG	AGG	99	0.99	99
✓ BD2	GCTACAAGACGACAGCTCAG	AGG	95	0.95	64
✓ DC2	GCTACAAGACGACAGCTCAG	AGG	99	0.99	99

Cell Line

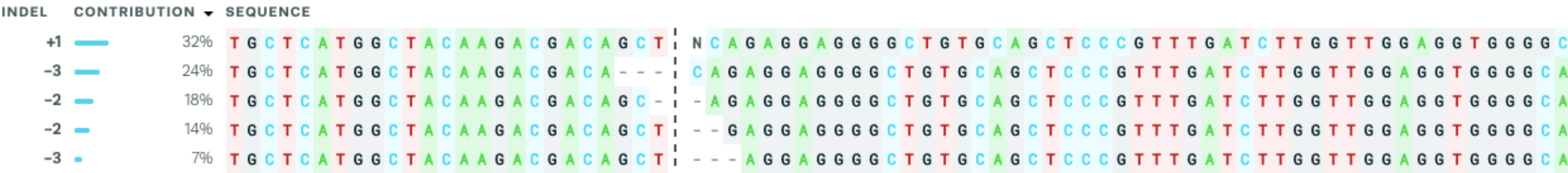
AC5



AD5



BD2



DC2



C

ENO2

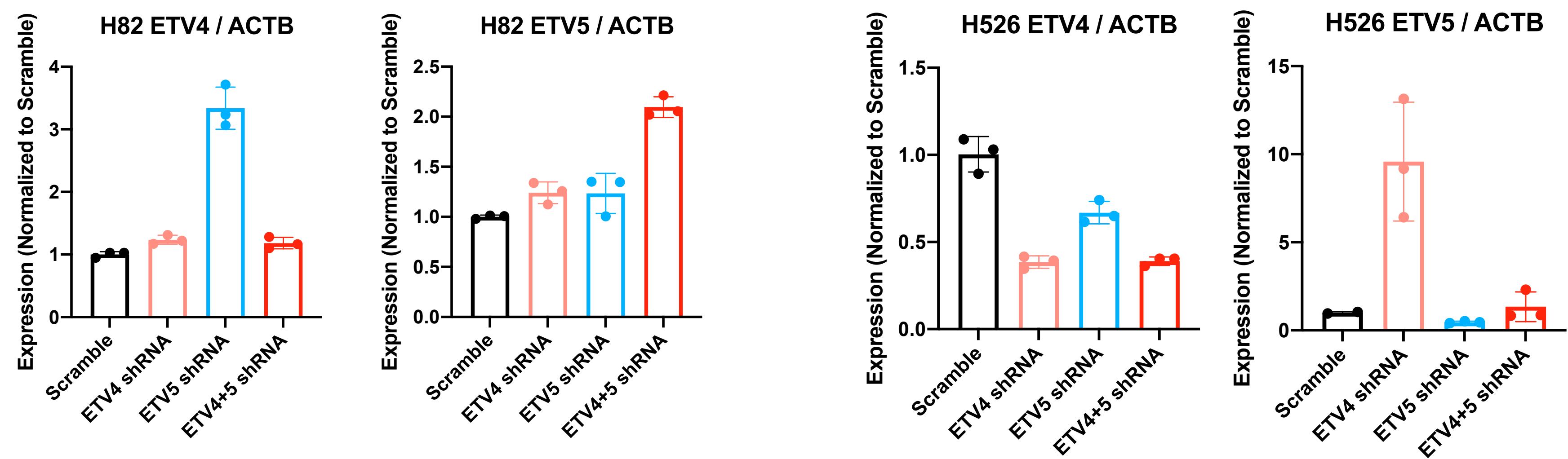
SAMPLE ?	GUIDE TARGET ?	PAM SEQUENCE?	INDEL % ?	MODEL FIT (R ²) ?	KNOCKOUT-SCORE ?
✓ AC5	CTGTGCACAGCCCCACCACC	AGG	0	1	0
✓ AD5	CTGTGCACAGCCCCACCACC	AGG	0	1	0
✓ BD2	CTGTGCACAGCCCCACCACC	AGG	0	1	0
✓ DC2	CTGTGCACAGCCCCACCACC	AGG	0	1	0

WDR93

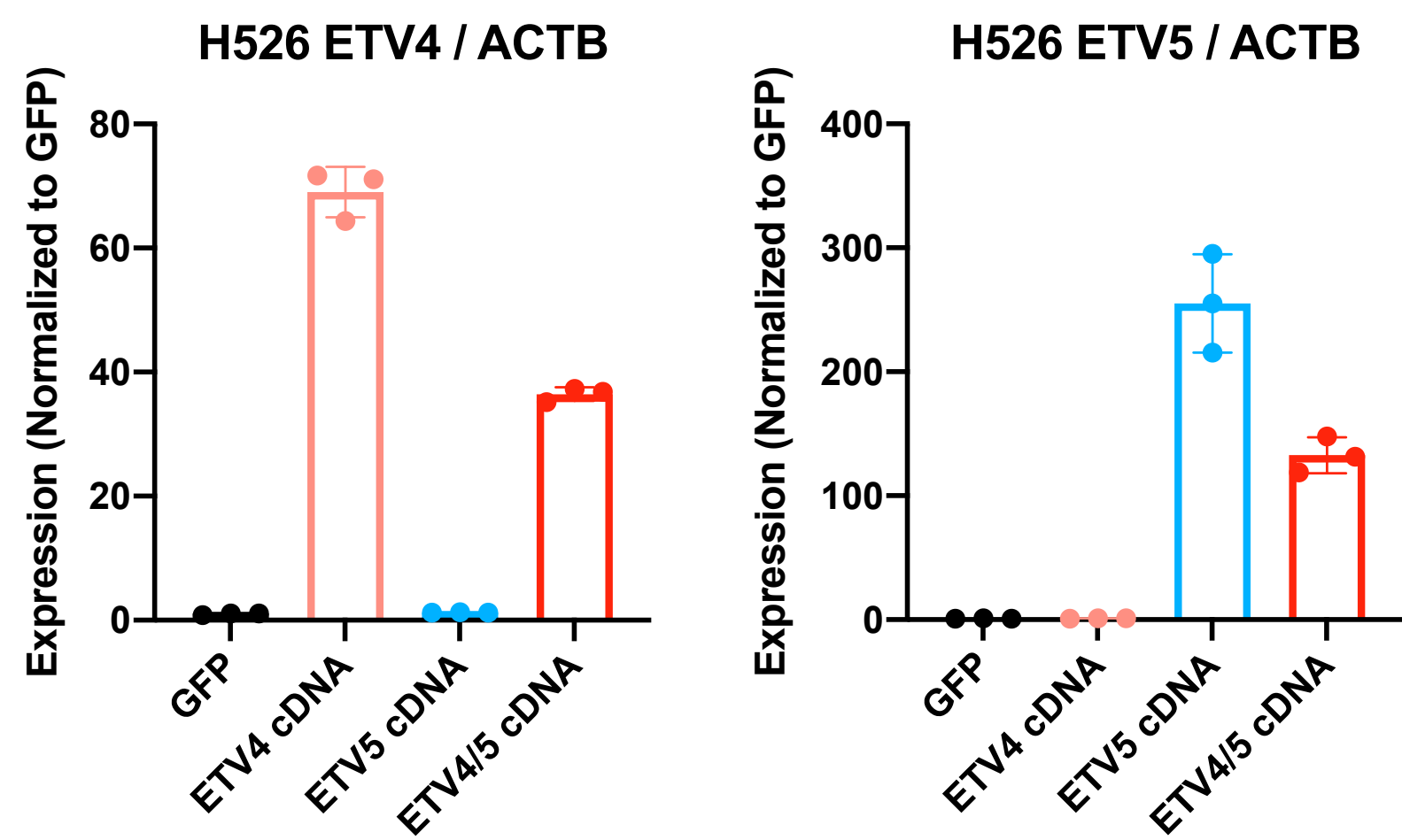
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✓ AC5	CTTTCCCCGCCCCCCCACC	AGG	0	1	0
✓ AD5	CTTTCCCCGCCCCCCCACC	AGG	0	1	0
✓ BD2	CTTTCCCCGCCCCCCCACC	AGG	0	1	0
✓ DC2	CTTTCCCCGCCCCCCCACC	AGG	0	1	0

Supplementary Figure 4 (continued)

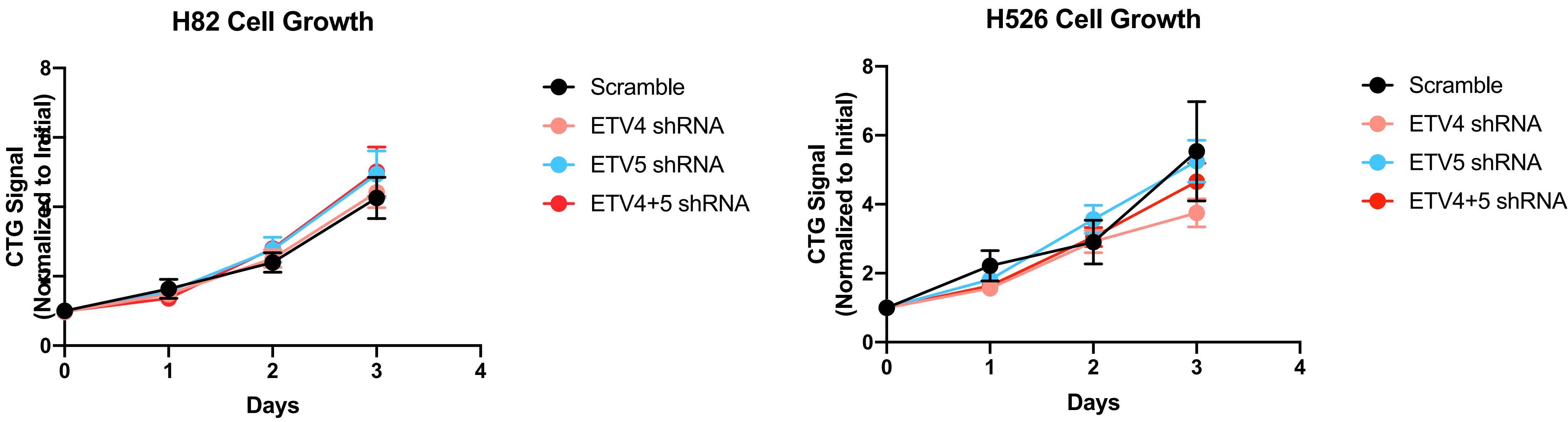
D



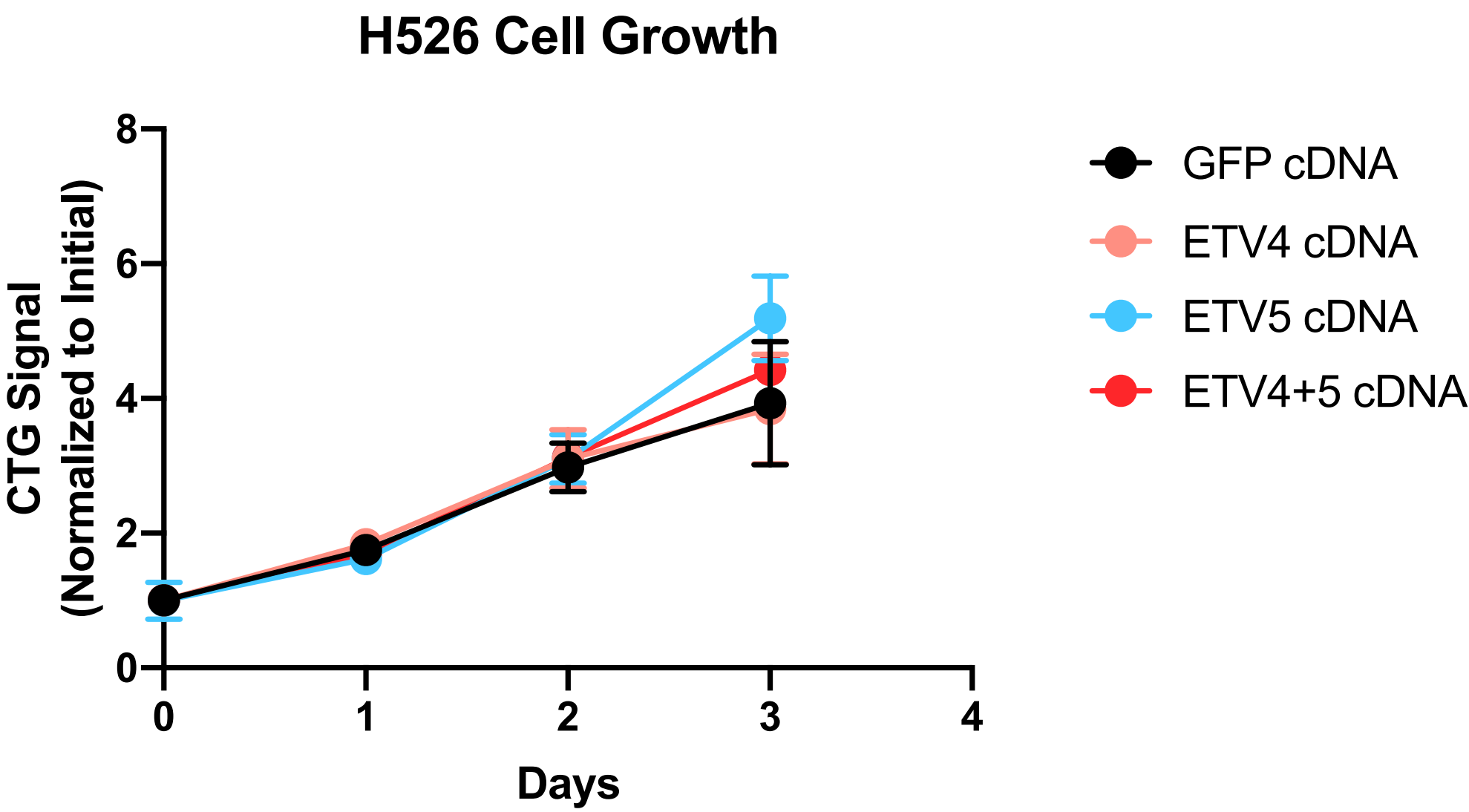
E



F



G



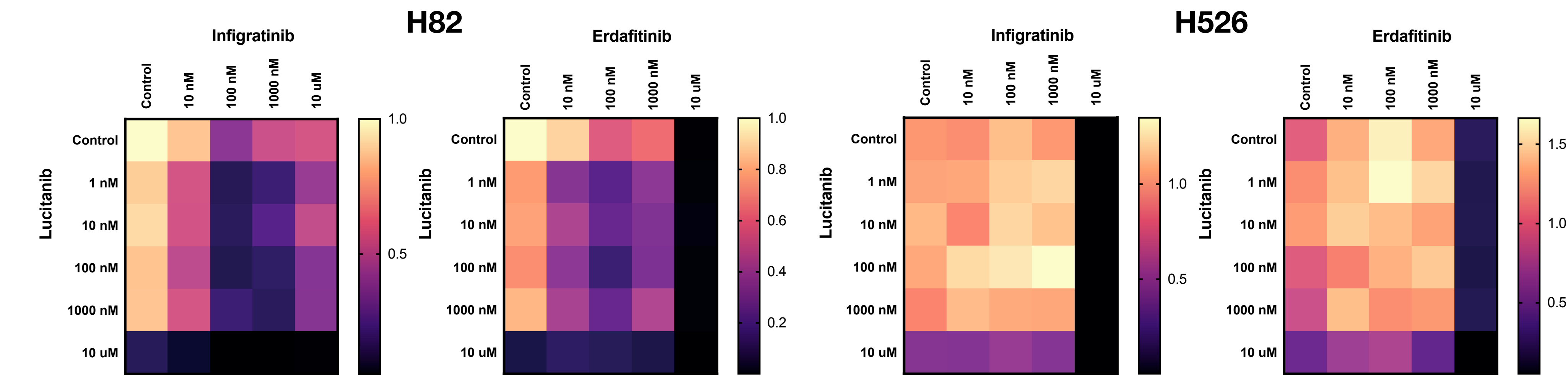
Supplementary Figure 5

A

Known IC50 for FGFR/VEGFR tyrosine kinase inhibitors (nM)

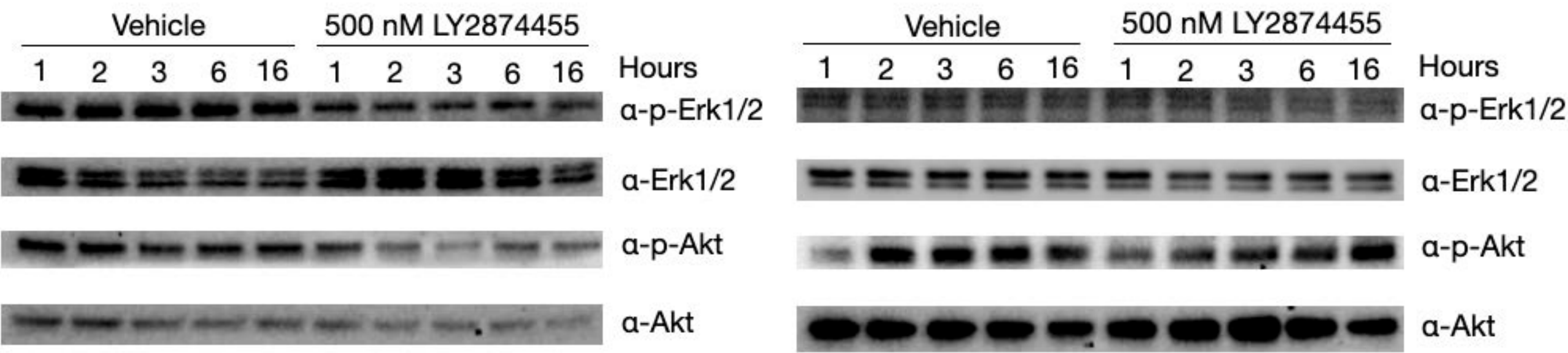
	FGFR1	FGFR2	FGFR3	FGFR4	VEGFR2	Notes
LY2874455	2.80	2.60	6.40	6.00	7.00	-
Infigratinib	0.90	1.40	1.00	-	-	40-fold selectivity for FGFR1/2/3 over FGFR4 and VEGFR2
Erdafitinib	1.20	2.50	3.00	5.70	36.80	20-fold selectivity for FGFR1/2/3/4 over VEGFRs
Roblitinib	-	-	-	1.10	-	1000-fold selectivity for FGFR4 over other FGFRs
Cabozantinib	-	-	-	-	0.035	-

B

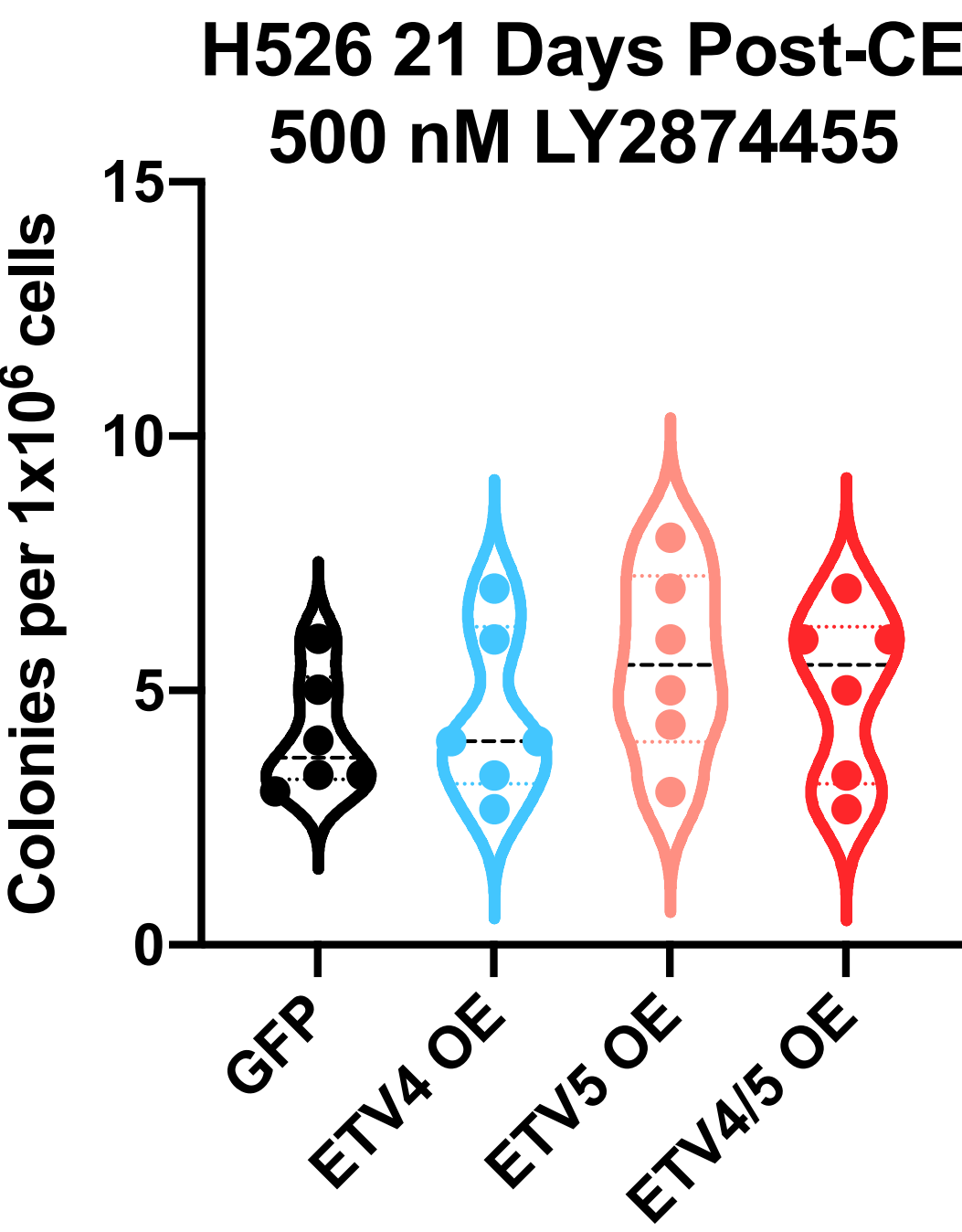


Supplementary Figure 6

A

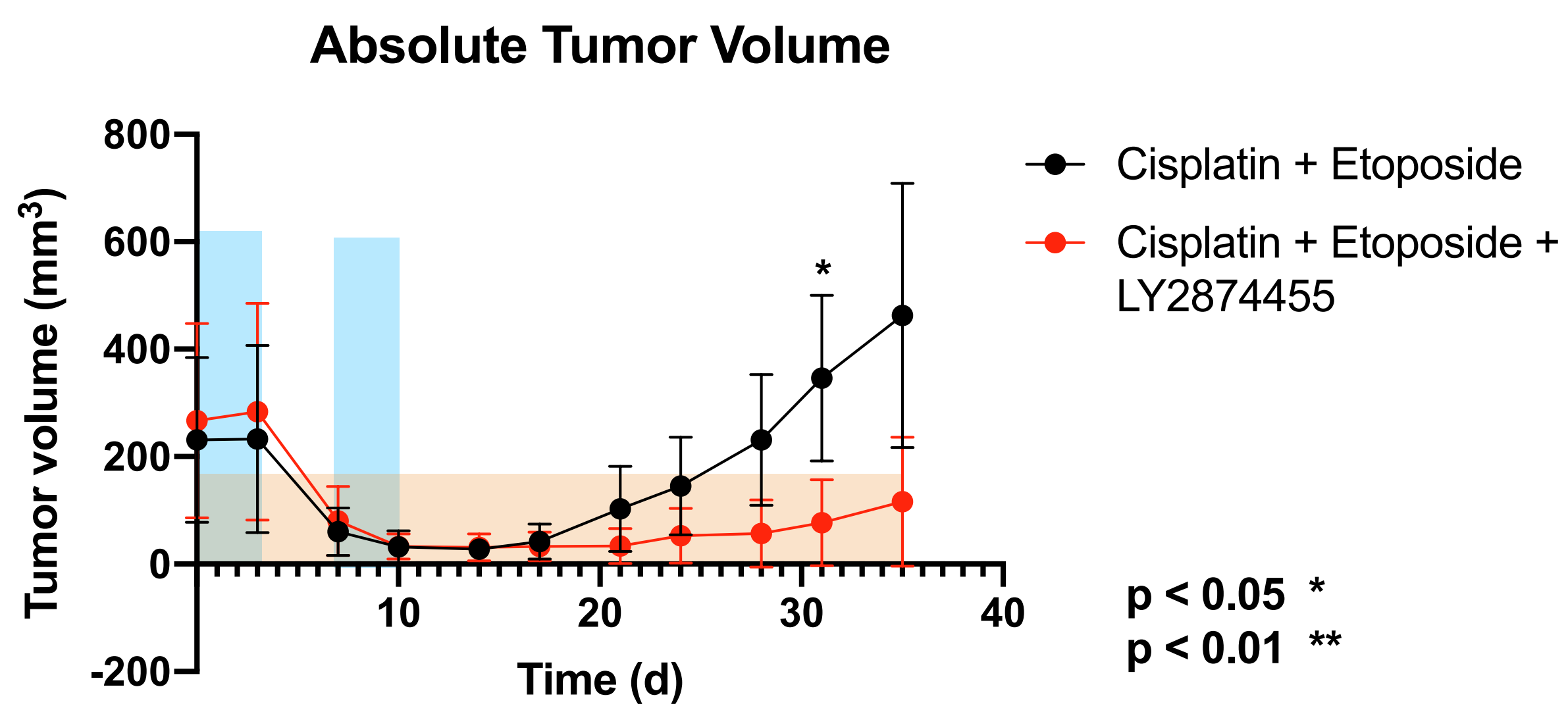


B



Supplementary Figure 7

A



SUPPLEMENTAL INFORMATION

1. Supplemental figure legends
2. Supplemental figures
3. Table S1 – list of diapause DEGs

C1orf210	ENSG00000253313
RPL3	ENSG00000100316
KHDC3L	ENSG00000203908
RAPH1	ENSG00000173166
EMC10	ENSG00000161671
MT1X	ENSG00000187193
ENO1	ENSG00000074800
C19orf25	ENSG00000119559
PSMD8	ENSG00000099341
RINL	ENSG00000187994
TRIM28	ENSG00000130726
WDR92	ENSG00000243667
SNRPD2	ENSG00000125743
RPL18A	ENSG00000105640
PPP2R1A	ENSG00000105568
MYC	ENSG00000136997
PSMD3	ENSG00000108344
RPL36	ENSG00000130255
ARFIP2	ENSG00000132254
ARFIP1	ENSG00000164144
EIF2D	ENSG00000143486
PGLYRP1	ENSG00000008438
ZFPL1	ENSG00000162300
PELO	ENSG00000152684
JMJD4	ENSG00000081692
NSMCE1	ENSG00000169189
ACTN4	ENSG00000130402
MIF	ENSG00000240972
JMJD8	ENSG00000161999
CLDN6	ENSG00000184697
MT1A	ENSG00000205362
CDC34	ENSG00000099804
DDX39B	ENSG00000198563
ARMC5	ENSG00000140691
ARMC6	ENSG00000105676
PPA1	ENSG00000180817
KCTD10	ENSG00000110906
CLPP	ENSG00000125656
GRWD1	ENSG00000105447
TXNIP	ENSG00000265972
MGARP	ENSG00000137463
TELO2	ENSG00000100726
EPHA2	ENSG00000142627
NECAB2	ENSG00000103154
GRB7	ENSG00000141738

CRABP2	ENSG00000143320
AIRE	ENSG00000160224
TWF2	ENSG00000247596
MRPL17	ENSG00000158042
PIK3R2	ENSG00000105647
PIK3R2	ENSG00000268173
ABCB8	ENSG00000197150
MRPL12	ENSG00000262814
PLA2G6	ENSG00000184381
ANAPC10	ENSG00000164162
MRPL20	ENSG00000242485
PRDX2	ENSG00000167815
PRDX5	ENSG00000126432
LDHA	ENSG00000134333
DPH3	ENSG00000154813
PLCG2	ENSG00000197943
NAALAD2	ENSG00000077616
RCE1	ENSG00000173653
TSPAN1	ENSG00000117472
NHEJ1	ENSG00000187736
PRELID1	ENSG00000169230
C19orf53	ENSG00000104979
PMM1	ENSG00000100417
PMM2	ENSG00000140650
MRPL28	ENSG00000086504
PA2G4	ENSG00000170515
PRDX6	ENSG00000117592
DERA	ENSG00000023697
TBL3	ENSG00000183751
SMTN	ENSG00000183963
AKR1B10	ENSG00000198074
EIF6	ENSG00000242372
STAG3	ENSG00000066923
WNK3	ENSG00000196632
OGDH	ENSG00000105953
ID3	ENSG00000117318
REN	ENSG00000143839
DUS1L	ENSG00000169718
ALDH18A1	ENSG00000059573
ANP32B	ENSG00000136938
C12orf75	ENSG00000235162
CD320	ENSG00000167775
ITM2C	ENSG00000135916
PIGO	ENSG00000165282
CITED1	ENSG00000125931

MRPS11	ENSG00000181991
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OLA1	ENSG00000138430
MRPL37	ENSG00000116221
ZCCHC17	ENSG00000121766
PANX1	ENSG00000110218
ZCWPW1	ENSG00000078487
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CHAF1A	ENSG00000167670
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HEATR1	ENSG00000119285
CAPG	ENSG00000042493
RBFA	ENSG00000101546
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PPP2CA	ENSG00000113575
PSMB4	ENSG00000159377
TUBA3D	ENSG00000075886
ARVCF	ENSG00000099889
PSMB3	ENSG00000277791
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GPAT2	ENSG00000186281
CCT7	ENSG00000135624
EMC8	ENSG00000131148
EXOSC2	ENSG00000130713
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WDR18	ENSG00000065268
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TBRG1	ENSG00000154144

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CHGA	ENSG00000100604
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CYB5B	ENSG00000103018
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SDC3	ENSG00000162512
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ACCSL	ENSG00000205126
FHIT	ENSG00000189283
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SOCS3	ENSG00000184557
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GPNMB	ENSG00000136235
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LRR8C	ENSG00000171488

SLC17A5	ENSG00000119899
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TCF4	ENSG00000196628
FXD6	ENSG00000137726
FGFR2	ENSG00000066468
C1orf116	ENSG00000182795
YPEL2	ENSG00000175155