Supplementary Figure 1 - The cloning and sequencing strategy of the experiments.

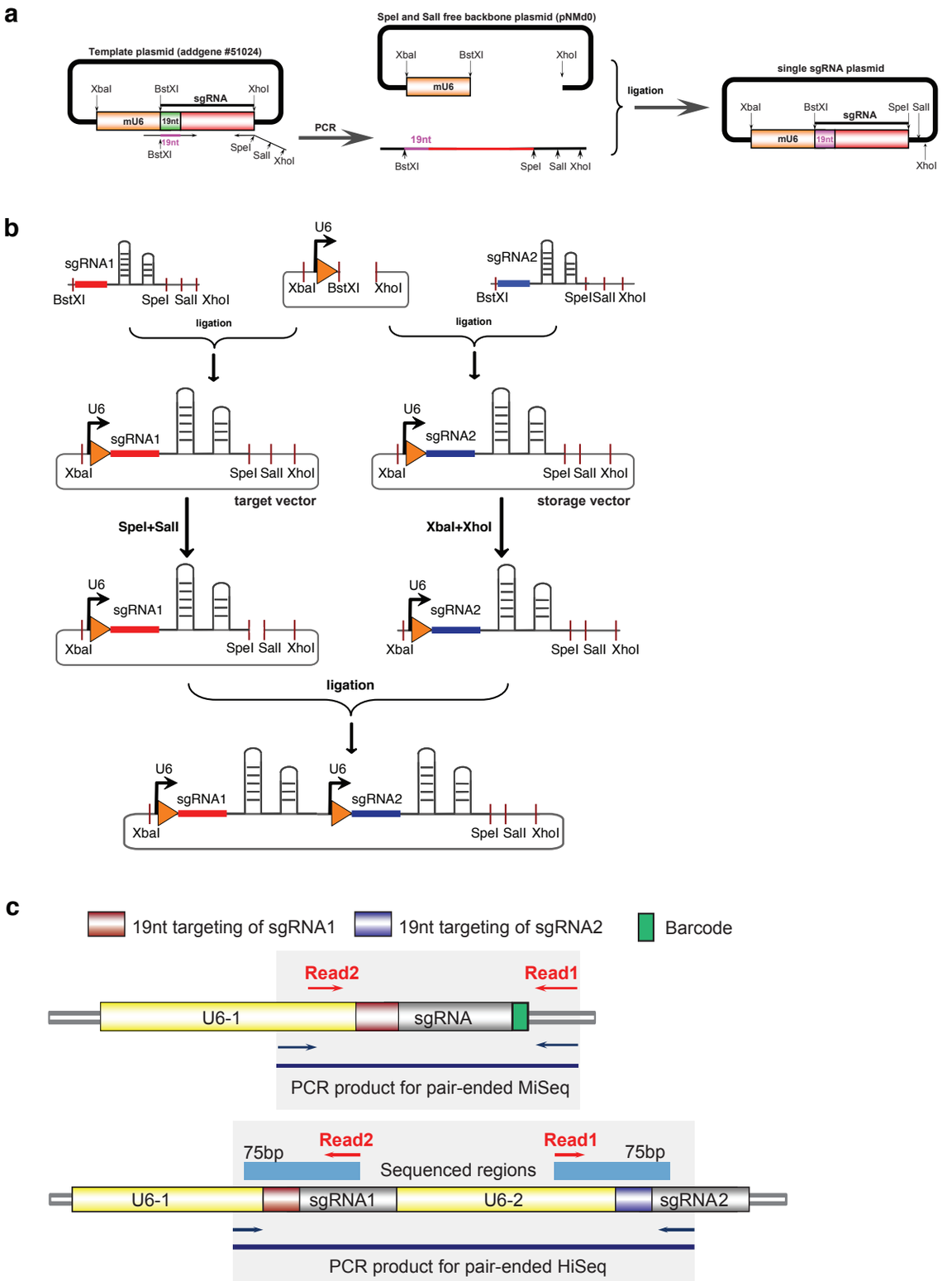

Figure S1 | The cloning and sequencing strategy of the experiments.
(**a**) Construction of the sgRNAs by introducing additional restriction enzyme sites (SpeI and SalI). (**b**) Cloning strategy for generating the double sgRNA library. Two pairs of compatible restriction enzyme sites are used here: SpeI + XbaI, and XhoI + SalI. The strategy can allow insertion of more sgRNAs sequentially onto the vector. (**c**) Sequencing strategy to analyze the sgRNA sequences for the single sgRNA library (top) and the double sgRNA library (bottom).

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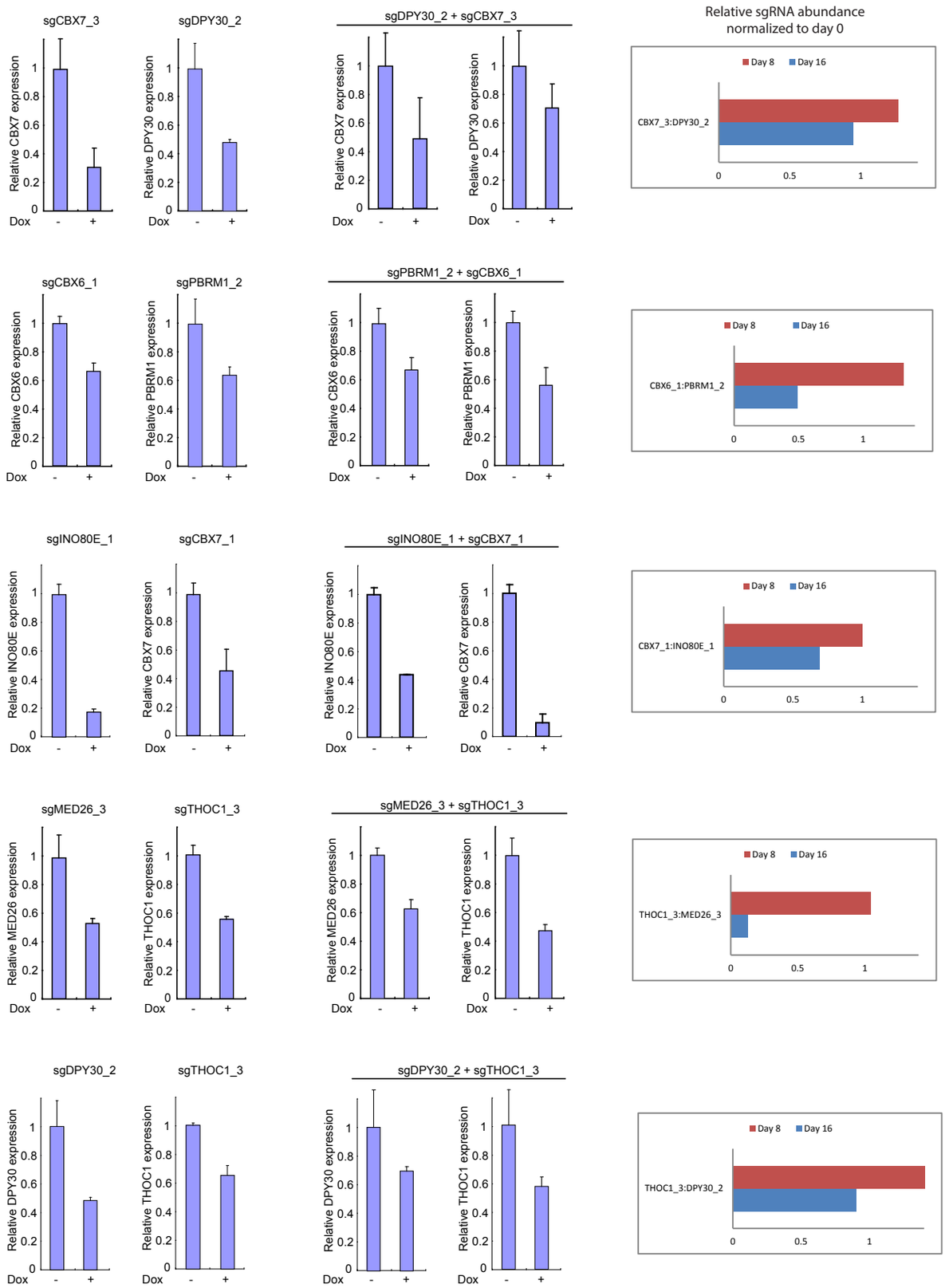
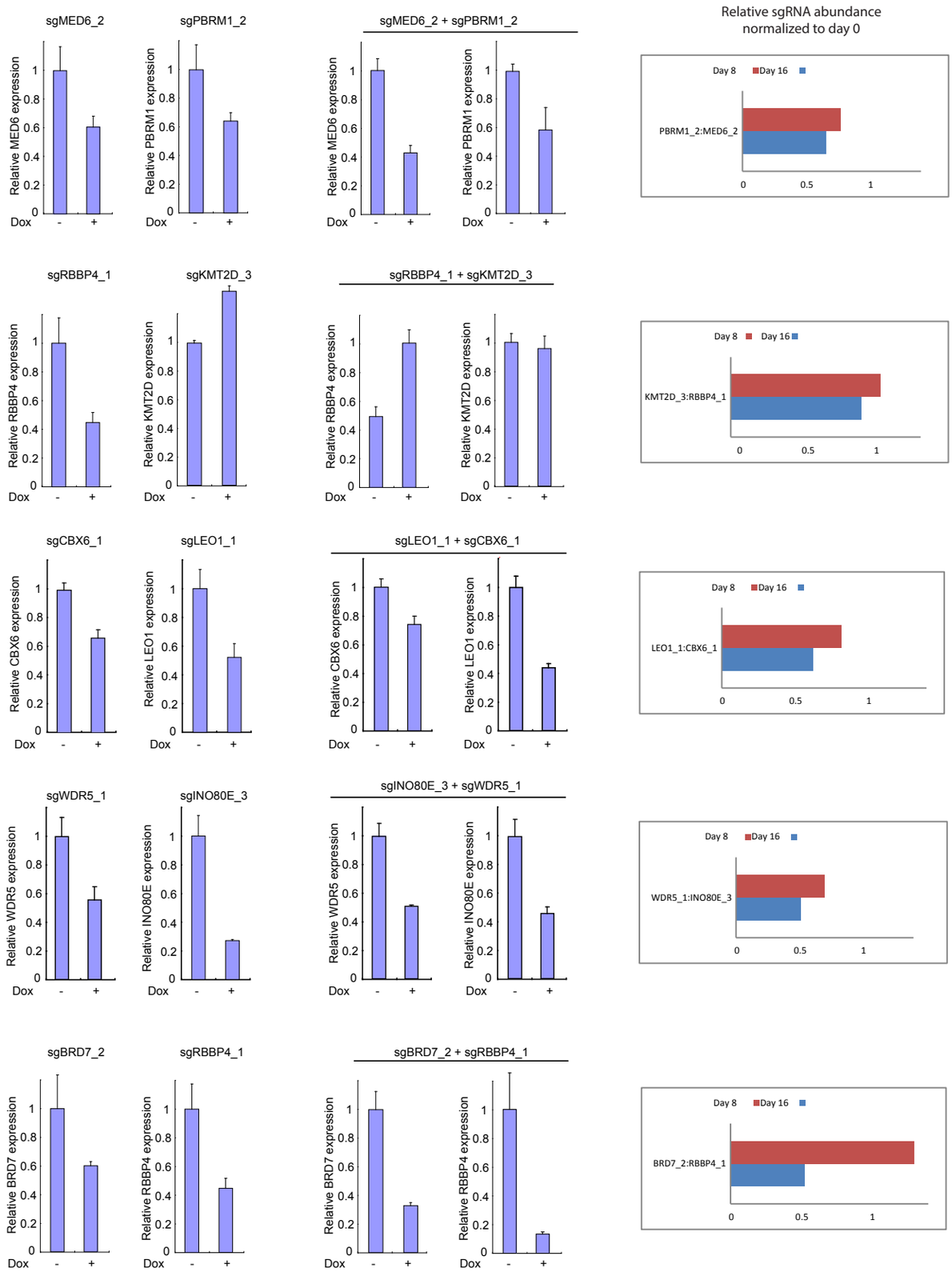


Figure S2 | Gene repression efficiencies of single and double sgRNA constructs.
(a) Quantitative PCR measurement of transcriptional repression efficiency for a set of single (28) and double (42) sgRNA constructs. Each row represents a pair of sgRNAs introduced into cells individually or as a pair. Error bars indicate standard deviation. Horizontal bar charts represent growth phenotypes as observed in the pooled growth competition assay (similar to Figure S5f).

a (page 2 of 9)


sgMED6_2
sgPBRM1_2
sgMED6_2 + sgPBRM1_2
Relative sgRNA abundance normalized to day 0
Relative MED6 expression
Relative PBRM1 expression
Dox
Day 8
Day 16
PBRM1_2:MED6_2
sgRBBP4_1
sgKMT2D_3
sgRBBP4_1 + sgKMT2D_3
Relative RBBP4 expression
Relative KMT2D expression
KMT2D_3:RBBP4_1
sgCBX6_1
sgLEO1_1
sgLEO1_1 + sgCBX6_1
Relative CBX6 expression
Relative LEO1 expression
LEO1_1:CBX6_1
sgWDR5_1
sgINO80E_3
sgINO80E_3 + sgWDR5_1
Relative WDR5 expression
Relative INO80E expression
WDR5_1:INO80E_3
sgBRD7_2
sgRBBP4_1
sgBRD7_2 + sgRBBP4_1
Relative BRD7 expression
Relative RBBP4 expression
BRD7_2:RBBP4_1

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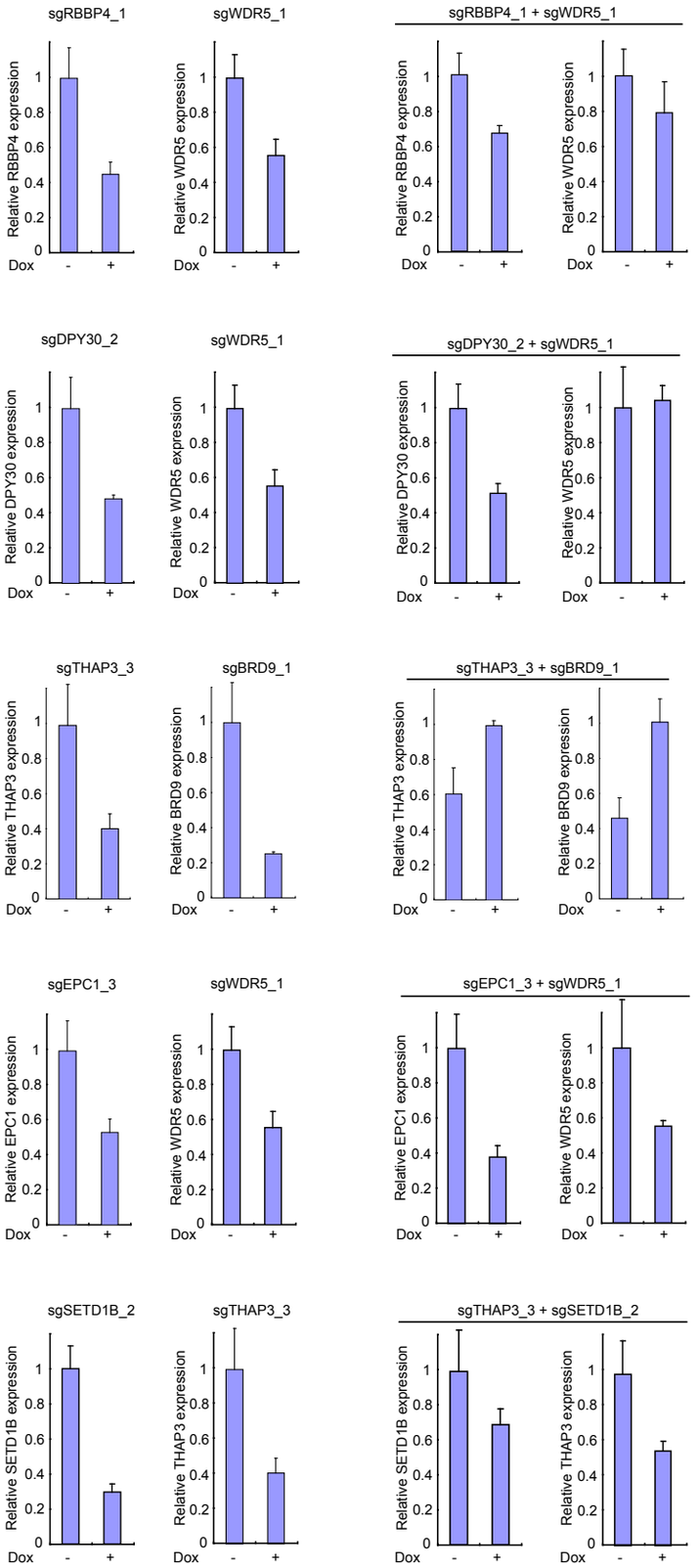
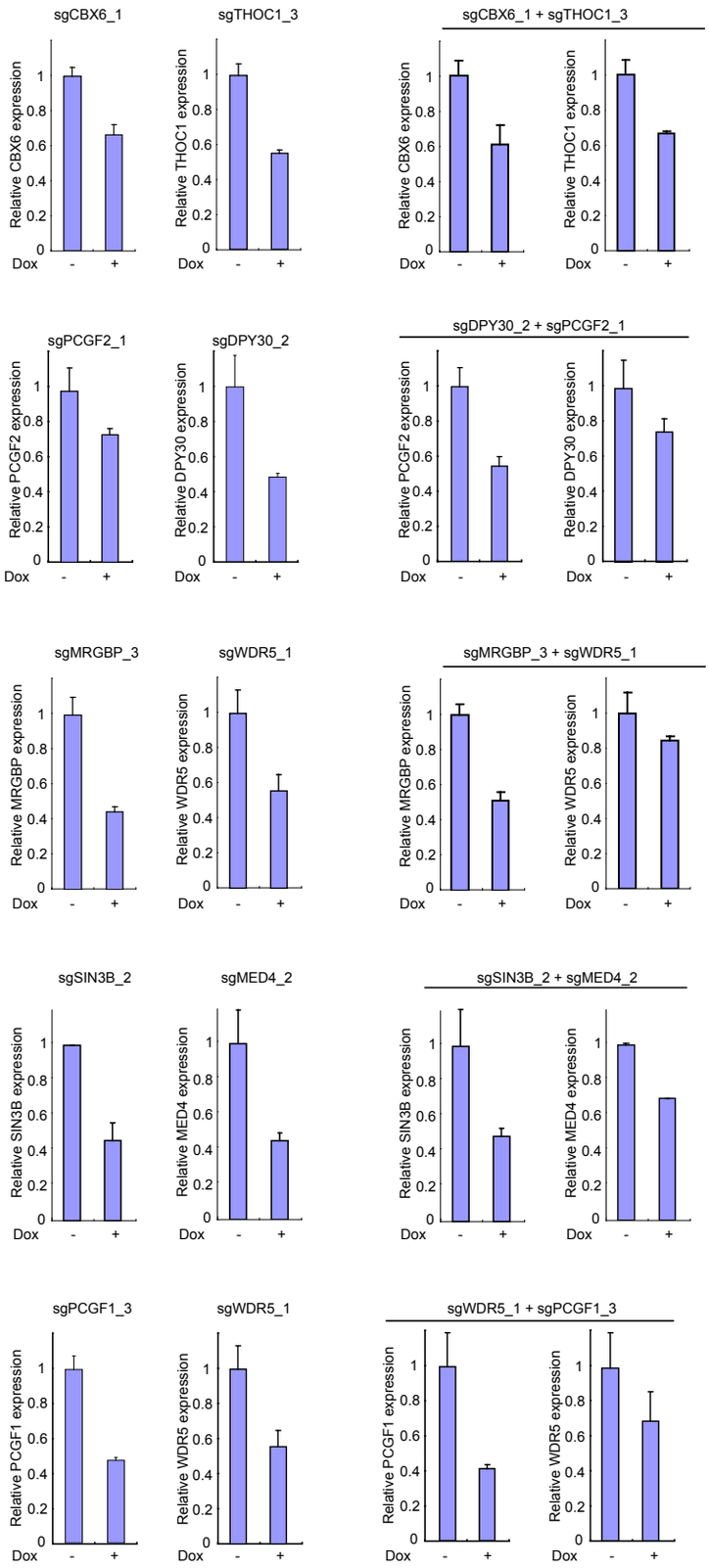
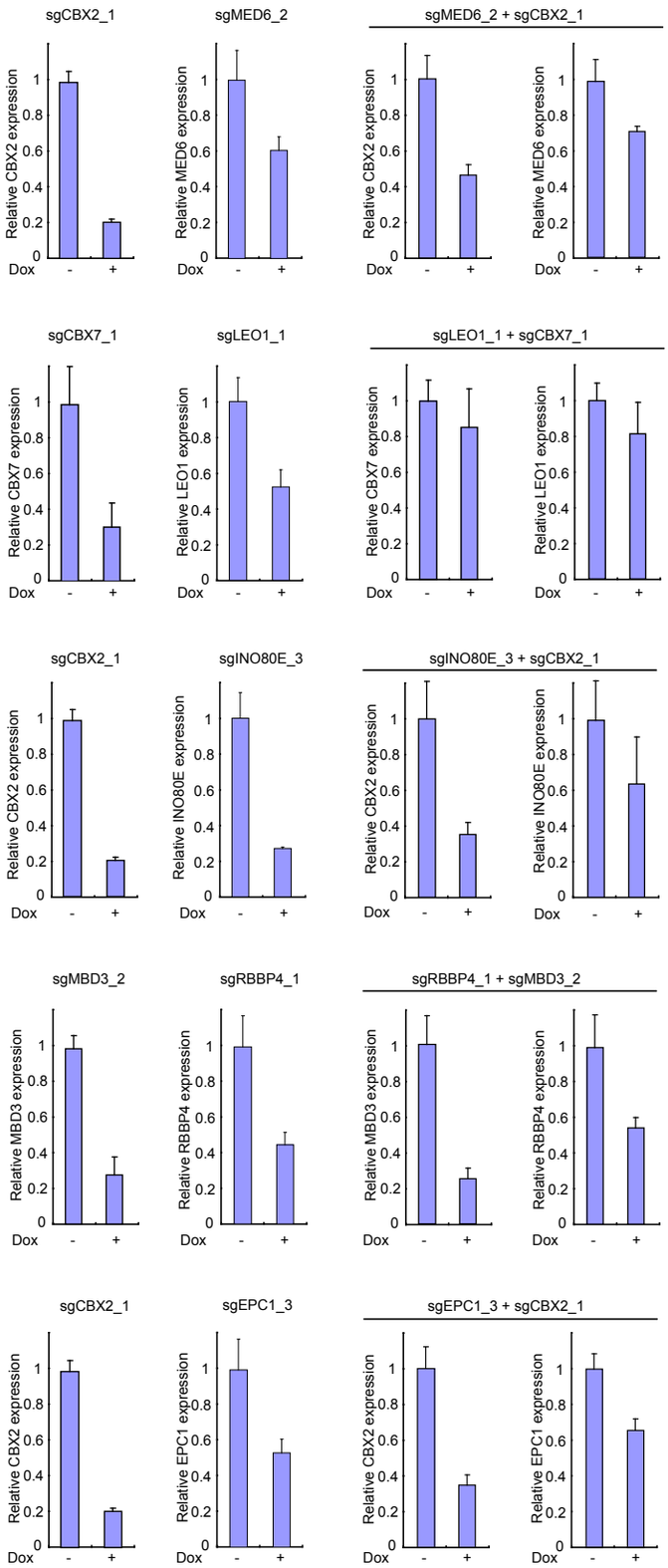

sgRBBP4_1
Relative RBBP4 expression
sgWDR5_1
Relative WDR5 expression
sgRBBP4_1 + sgWDR5_1
Relative RBBP4 expression
Relative WDR5 expression
sgDPY30_2
Relative DPY30 expression
sgWDR5_1
Relative WDR5 expression
sgDPY30_2 + sgWDR5_1
Relative DPY30 expression
Relative WDR5 expression
sgTHAP3_3
Relative THAP3 expression
sgBRD9_1
Relative BRD9 expression
sgTHAP3_3 + sgBRD9_1
Relative THAP3 expression
Relative BRD9 expression
sgEPC1_3
Relative EPC1 expression
sgWDR5_1
Relative WDR5 expression
sgEPC1_3 + sgWDR5_1
Relative EPC1 expression
Relative WDR5 expression
sgSETD1B_2
Relative SETD1B expression
sgTHAP3_3
Relative THAP3 expression
sgTHAP3_3 + sgSETD1B_2
Relative SETD1B expression
Relative THAP3 expression
0
0.2
0.4
0.6
0.8
1
Dox
-
+

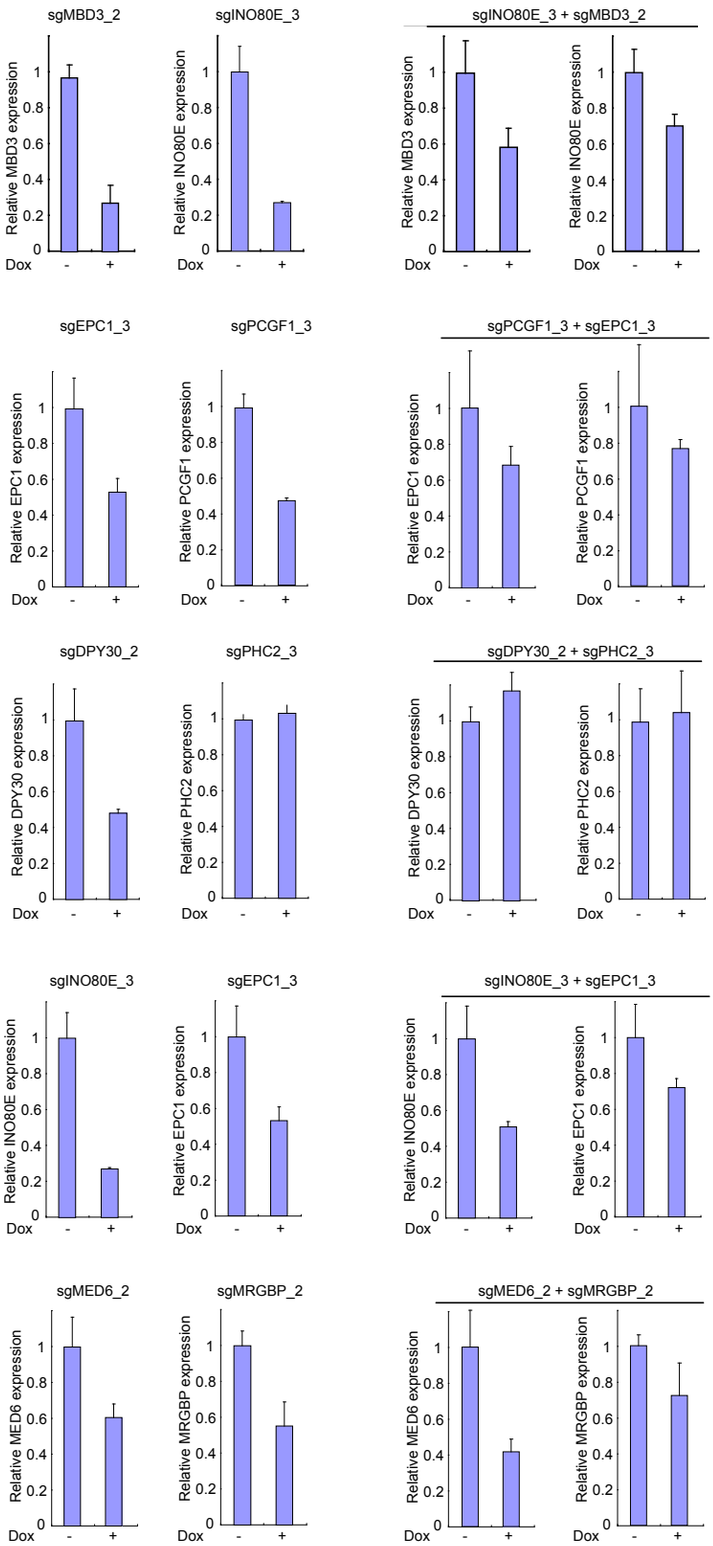
a (page 4 of 9)


sgCBX6_1
sgTHOC1_3
sgCBX6_1 + sgTHOC1_3
Relative CBX6 expression
Relative THOC1 expression
sgPCGF2_1
sgDPY30_2
sgDPY30_2 + sgPCGF2_1
Relative PCGF2 expression
Relative DPY30 expression
sgMRGBP_3
sgWDR5_1
sgMRGBP_3 + sgWDR5_1
Relative MRGBP expression
Relative WDR5 expression
sgSIN3B_2
sgMED4_2
sgSIN3B_2 + sgMED4_2
Relative SIN3B expression
Relative MED4 expression
sgPCGF1_3
sgWDR5_1
sgWDR5_1 + sgPCGF1_3
Relative PCGF1 expression
Dox
0
0.2
0.4
0.6
0.8
1
-
+

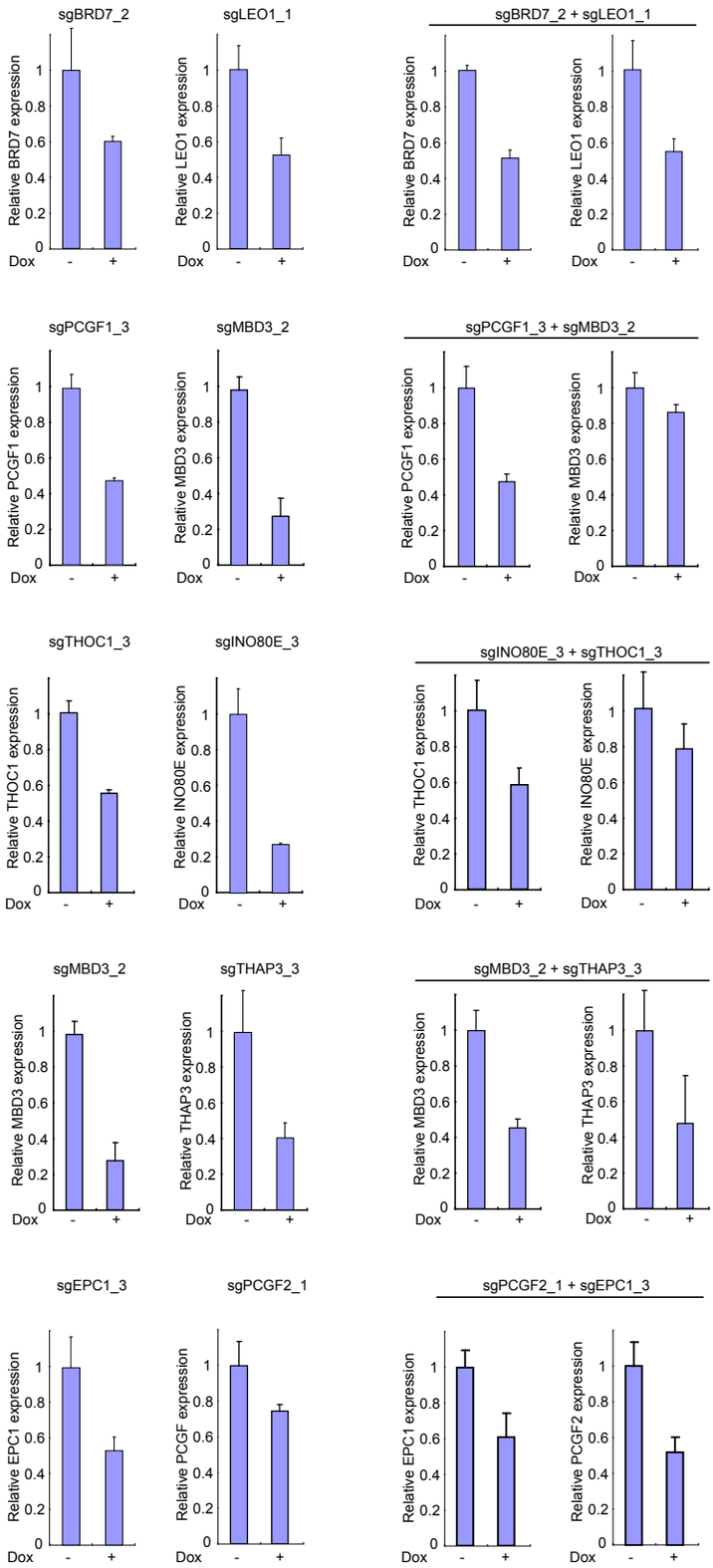
a (page 5 of 9)


sgCBX2_1
sgMED6_2
sgMED6_2 + sgCBX2_1
Relative CBX2 expression
Relative MED6 expression
sgCBX7_1
sgLEO1_1
sgLEO1_1 + sgCBX7_1
Relative CBX7 expression
Relative LEO1 expression
sgCBX2_1
sgINO80E_3
sgINO80E_3 + sgCBX2_1
Relative INO80E expression
sgMBD3_2
sgRBBP4_1
sgRBBP4_1 + sgMBD3_2
Relative MBD3 expression
Relative RBBP4 expression
sgCBX2_1
sgEPC1_3
sgEPC1_3 + sgCBX2_1
Relative EPC1 expression
0
0.2
0.4
0.6
0.8
1
Dox
-
+

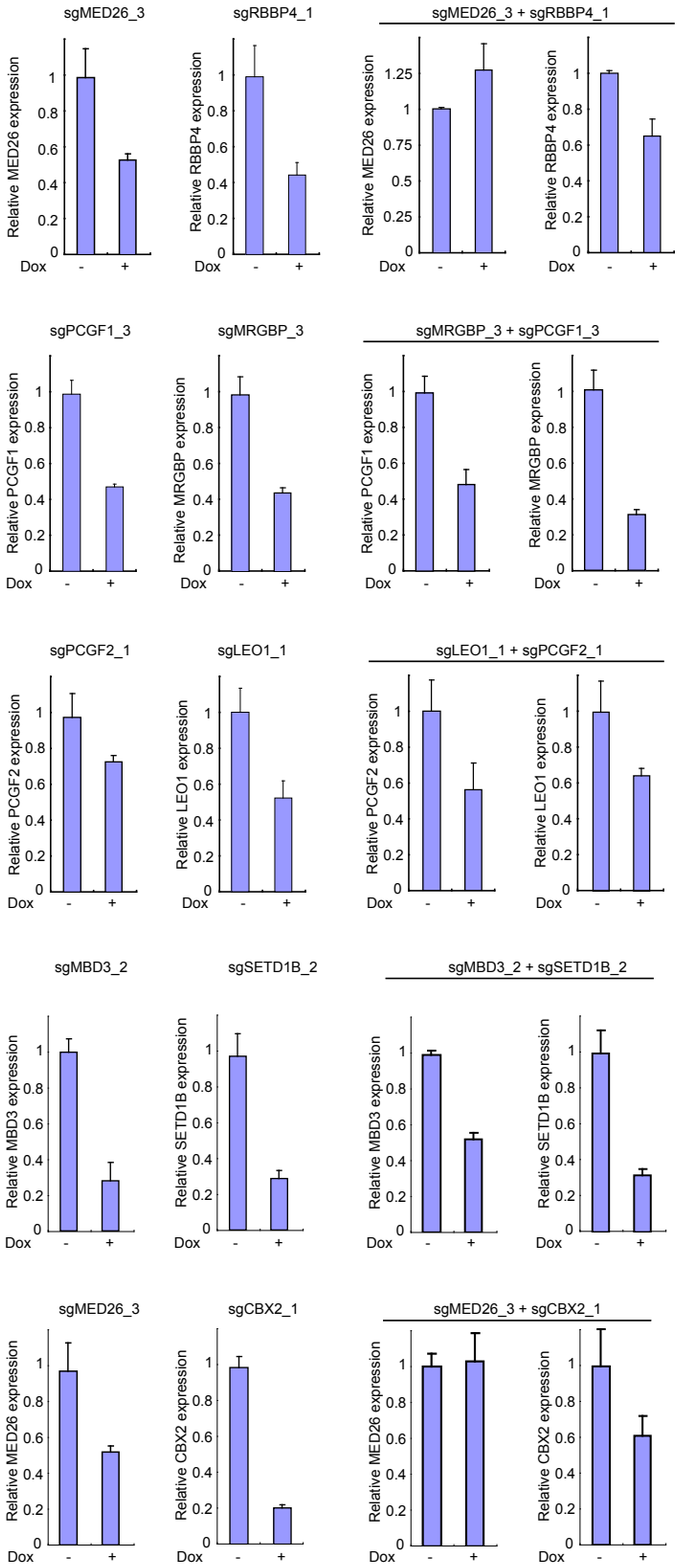
a (page 6 of 9)


sgMBD3_2
sgINO80E_3
sgINO80E_3 + sgMBD3_2
Relative MBD3 expression
Relative INO80E expression
sgEPC1_3
sgPCGF1_3
sgPCGF1_3 + sgEPC1_3
Relative EPC1 expression
Relative PCGF1 expression
sgDPY30_2
sgPHC2_3
sgDPY30_2 + sgPHC2_3
Relative DPY30 expression
Relative PHC2 expression
sgINO80E_3
sgEPC1_3
sgINO80E_3 + sgEPC1_3
sgMED6_2
sgMRGBP_2
sgMED6_2 + sgMRGBP_2
Relative MED6 expression
Relative MRGBP expression
Dox
-
+
0
0.2
0.4
0.6
0.8
1

a (page 7 of 9)


sgBRD7_2
sgLEO1_1
sgBRD7_2 + sgLEO1_1
Relative BRD7 expression
Relative LEO1 expression
sgPCGF1_3
sgMBD3_2
sgPCGF1_3 + sgMBD3_2
Relative PCGF1 expression
Relative MBD3 expression
sgTHOC1_3
sgINO80E_3
sgINO80E_3 + sgTHOC1_3
Relative THOC1 expression
Relative INO80E expression
sgMBD3_2
sgTHAP3_3
sgMBD3_2 + sgTHAP3_3
Relative THAP3 expression
sgEPC1_3
sgPCGF2_1
sgPCGF2_1 + sgEPC1_3
Relative EPC1 expression
Relative PCGF expression
Relative PCGF2 expression
Dox
0
0.2
0.4
0.6
0.8
1
-
+

a (page 8 of 9)


sgMED26_3
sgRBBP4_1
sgMED26_3 + sgRBBP4_1
Relative MED26 expression
Relative RBBP4 expression
sgPCGF1_3
sgMRGBP_3
sgMRGBP_3 + sgPCGF1_3
Relative PCGF1 expression
Relative MRGBP expression
sgPCGF2_1
sgLEO1_1
sgLEO1_1 + sgPCGF2_1
Relative PCGF2 expression
Relative LEO1 expression
sgMBD3_2
sgSETD1B_2
sgMBD3_2 + sgSETD1B_2
Relative MBD3 expression
Relative SETD1B expression
sgMED26_3
sgCBX2_1
sgMED26_3 + sgCBX2_1
Relative CBX2 expression
Dox
-
+

a (page 9 of 9)

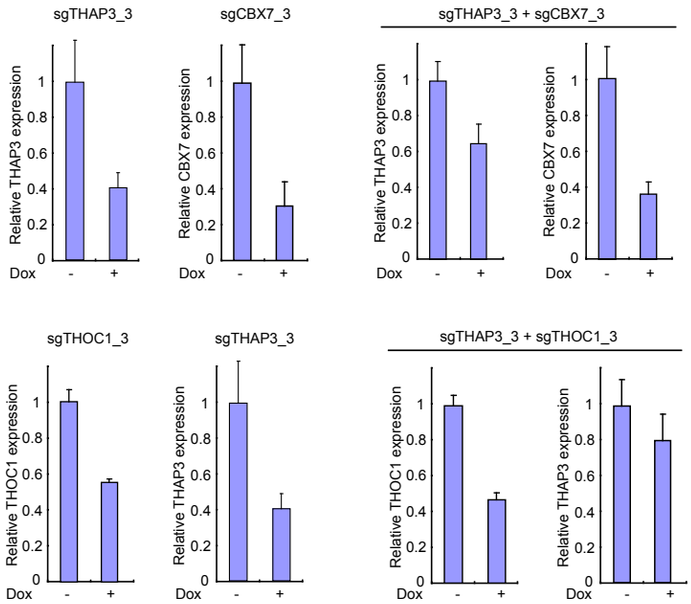
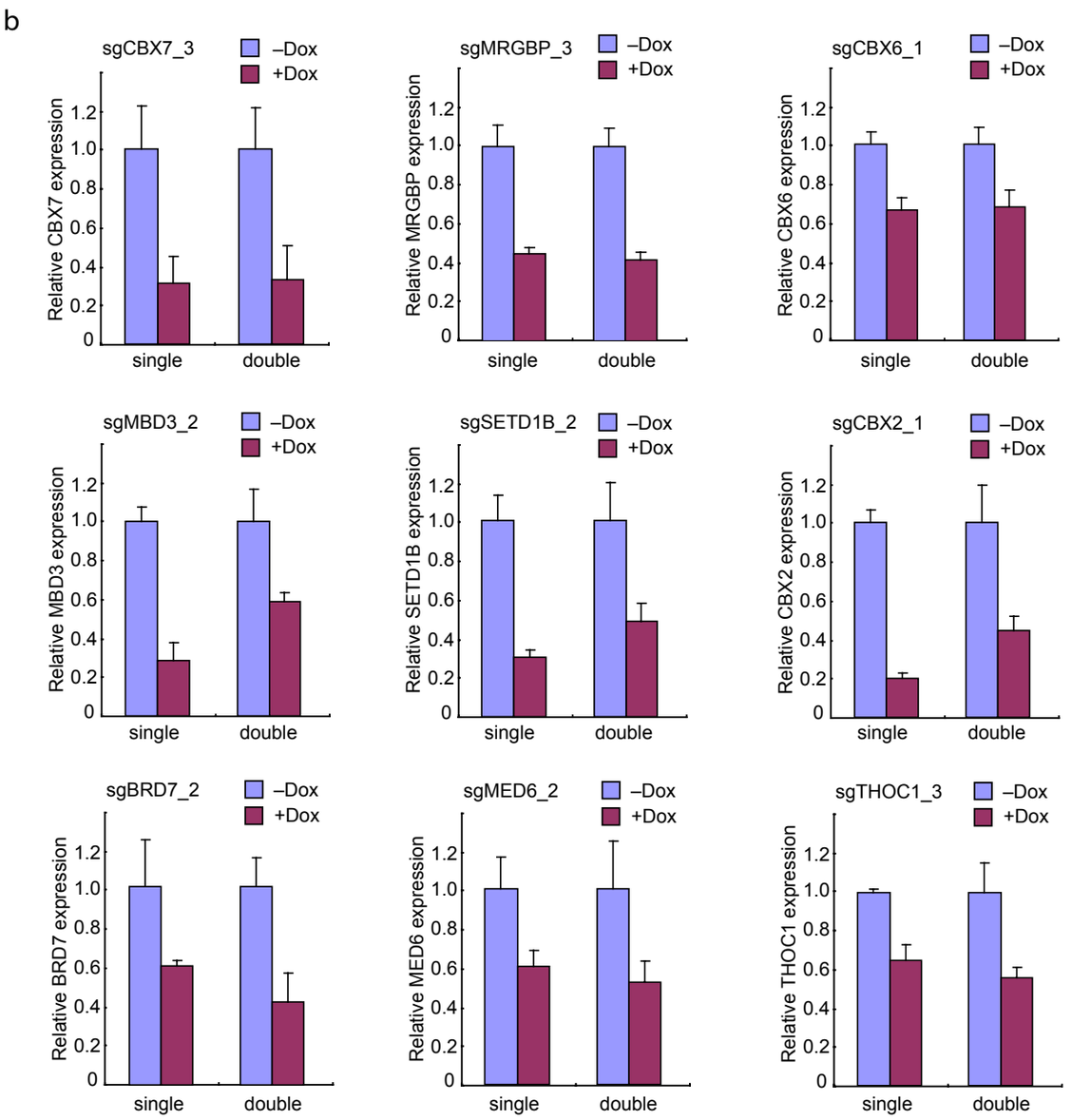


Figure S2 | Gene repression efficiencies of single and double sgRNA constructs.
(a) Quantitative PCR measurement of transcriptional repression efficiency for a set of single (28) and double (42) sgRNA constructs. Each row represents a pair of sgRNAs introduced into cells individually or as a pair. Horizontal bar charts represent growth phenotypes as observed in the pooled growth competition assay (similar to Figure S5f). (b) Representative examples of sgRNAs with similar (top), higher (middle) and lower (bottom) repression efficiencies comparing individual and pair-wise sgRNA knockdowns. The diagrams were replotted using the data in (a). (c) Overall (left) and cumulative (right) distribution of repression efficiency comparing individual and pair-wise sgRNA knockdowns based on the data in (a). Boxplot - red line: median; upper and lower box boundaries: 75th and 25th percentile of data; whiskers cover ca. 99% of the data assuming normal distribution (2.7 standard deviations); notches represent 95% confidence interval for the median; no outliers are shown (d) Doxycycline (Dox) induced growth phenotypes associated with positive (sgINTS9, sgGEMIN5 and sgPOLR1D) or negative control (sgNC) sgRNAs. "-Dox" and "+Dox" denote without or with Dox induction respectively. Error bars on each panel (a,b,d) indicate standard deviation.



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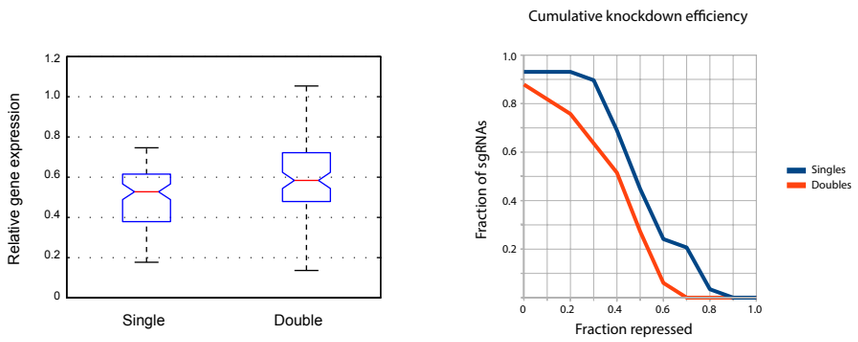
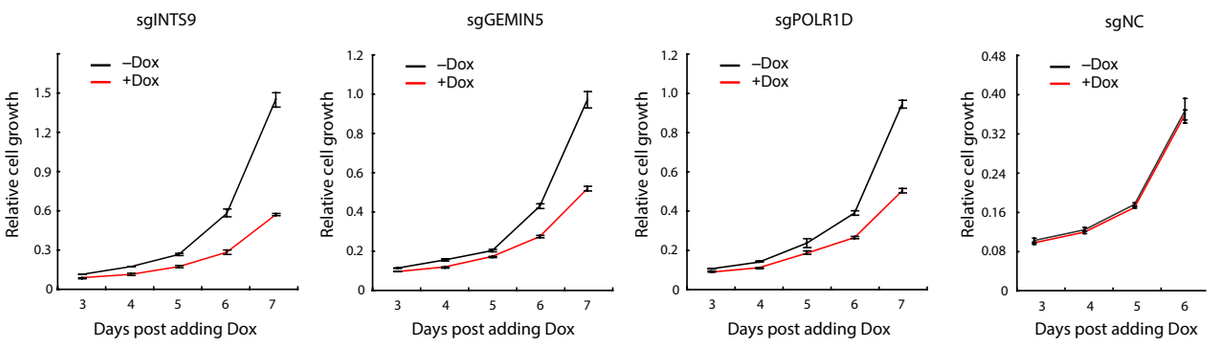
c



d



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Supplementary Figure 3 - Template switching and PCR conditions optimization.

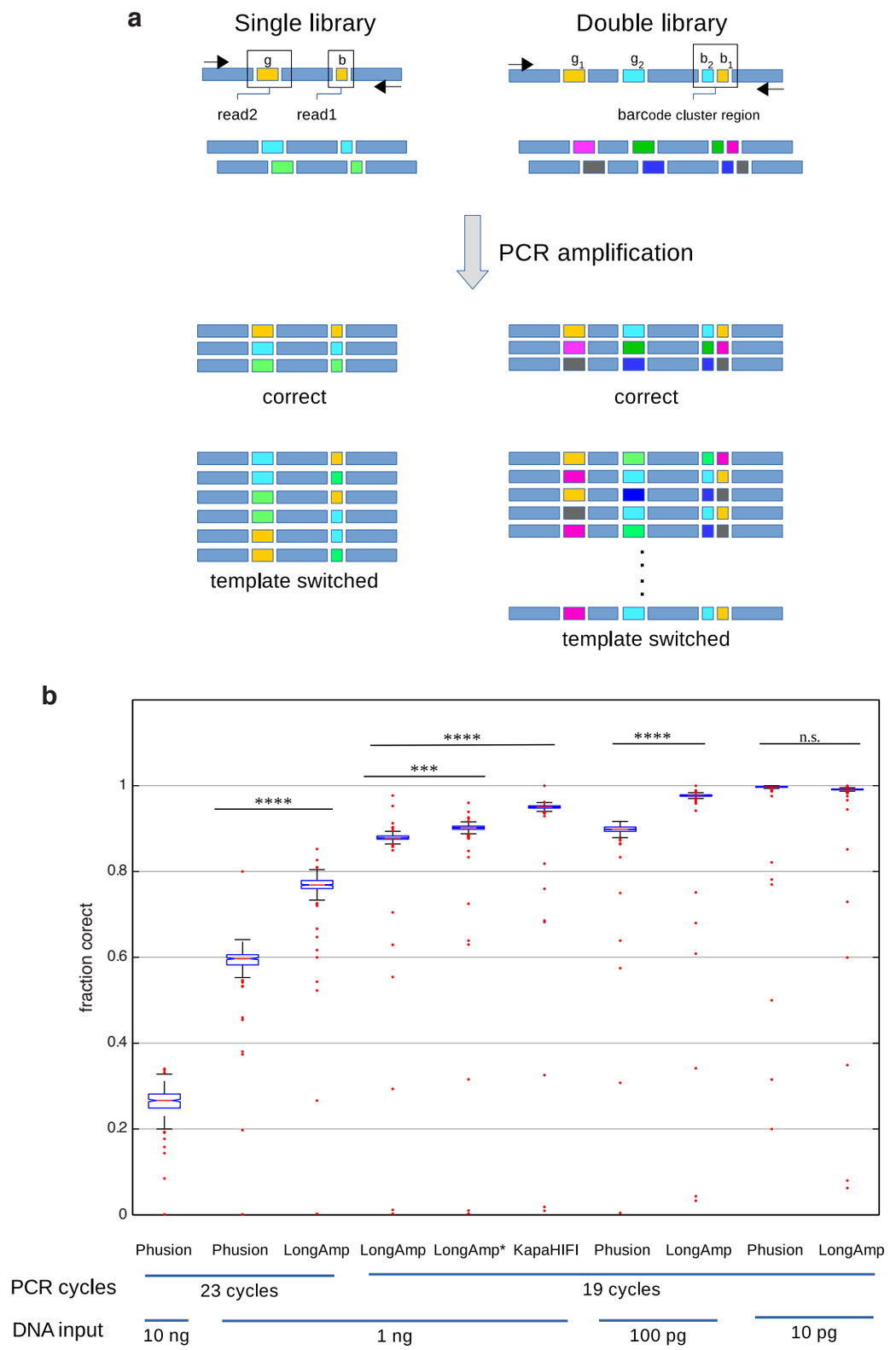


Figure S3 | Template switching and PCR conditions optimization.
(**a**) Schematic representation of the template switching phenomenon during PCR amplification for single (left) and double (right) sgRNA constructs. Upon PCR amplification both correct (top) and incorrect (bottom) products can be generated. sgRNAs and barcode sequences are denoted with g, g1, g2 and b, b1, b2 respectively. Regions with high sequence identity are shown in light blue. Sequenced regions are boxed. (**b**) Optimization of PCR conditions. The fraction of correct products are plotted for each set of conditions (DNA polymerase used, PCR cycle number, and the amount of template DNA). Individual experimental conditions are compared using a t-test and p-values (*** ≤ 10^{-3}; **** ≤ 10^{-4}; n.s. - not significant).

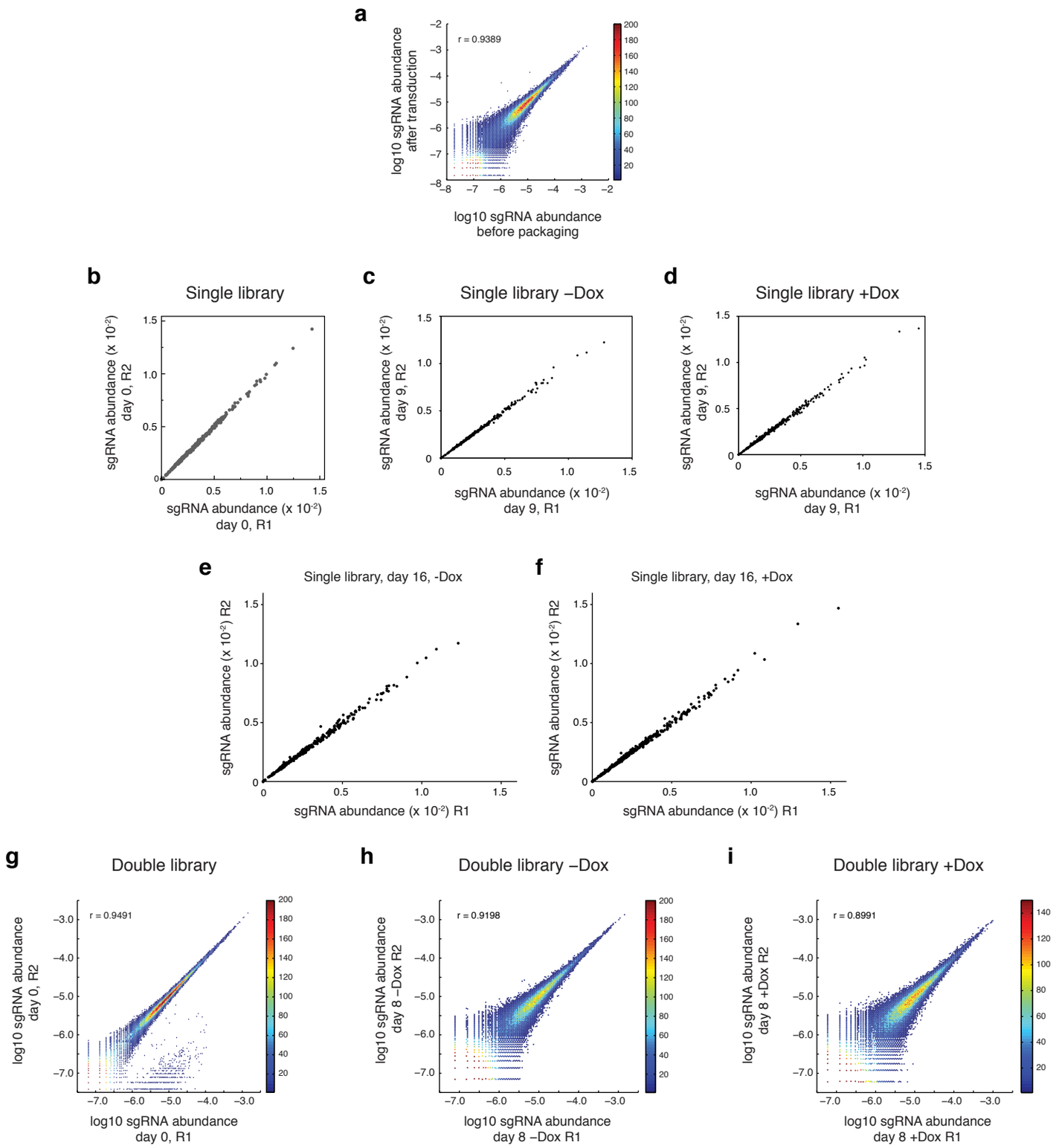
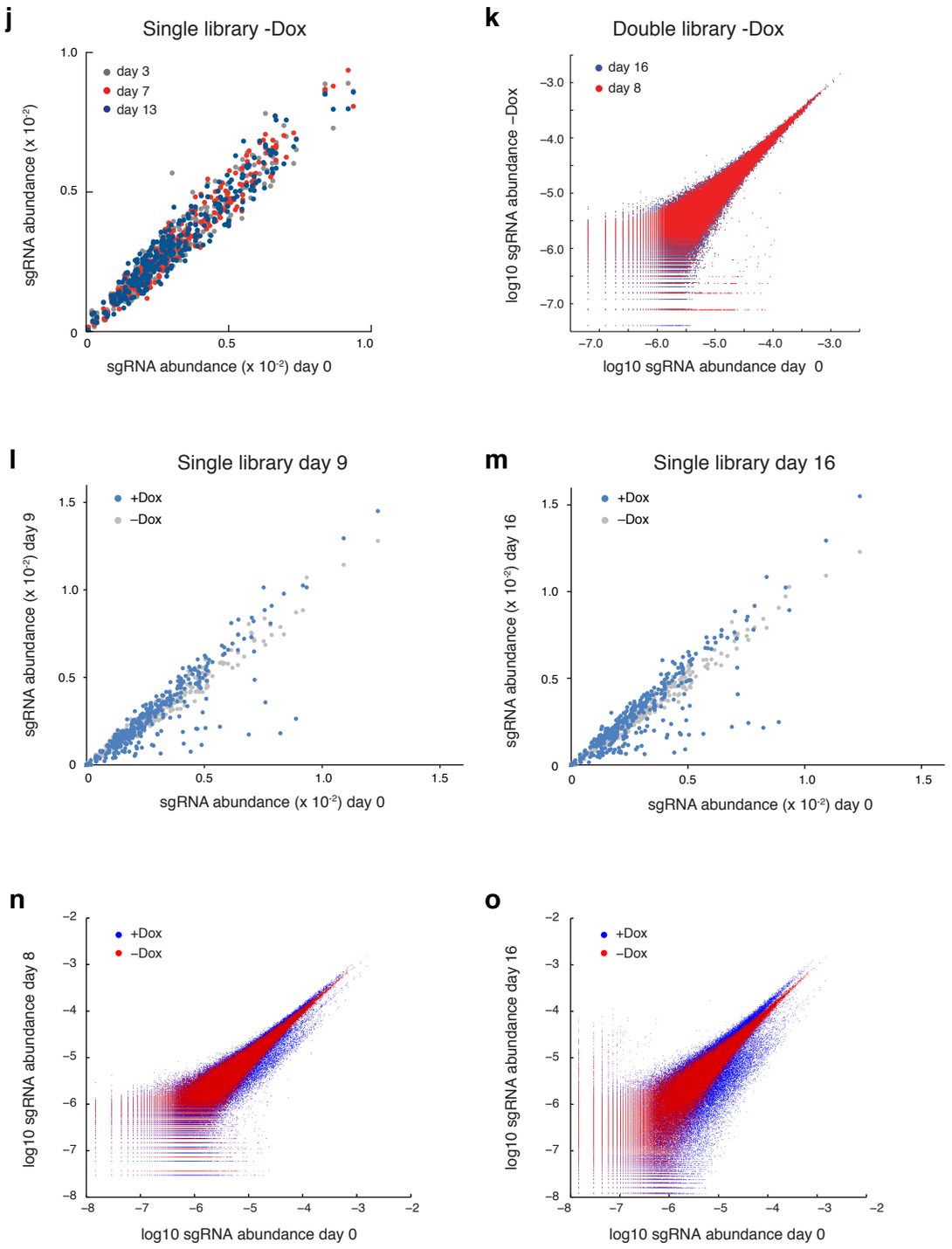


Figure S4 | Platform quality control.

(**a**) Correlation of double sgRNA construct abundance in the double library before packaging and after packaging and transduction into HEK293-dCas9-KRAB cells. (**b**-**f**) Replicate correlations for single sgRNA library at different time points without (-Dox) and with (+Dox) induction. (**g**-**i**) Replicate correlations for double sgRNA library at different time points without (-Dox) and with (+Dox) induction. (**j**-**k**) Comparison of single (**j**) and double (**k**) sgRNA library abundance without Dox induction at different time points to the day 0 sample. (**l**-**m**) Comparison of single sgRNA library abundance without Dox (-Dox, grey) or with Dox (+Dox, blue) induction at day 9 (**l**) and day 16 (**m**) to day 0. (**n**-**o**) Comparison of double sgRNA library distribution without Dox (-Dox, red) or with Dox (+Dox, blue) at day 8 (**n**) and day 16 (**o**) to day 0. (**p**-**q**) Reproducibility of enrichment/depletion patterns of +Dox/-Dox at day 16 between two biological replicates for single (**p**) and double (**q**) sgRNA libraries.The data in (**q**) was subjected to initial filtering as described in 'Data processing and analysis'.



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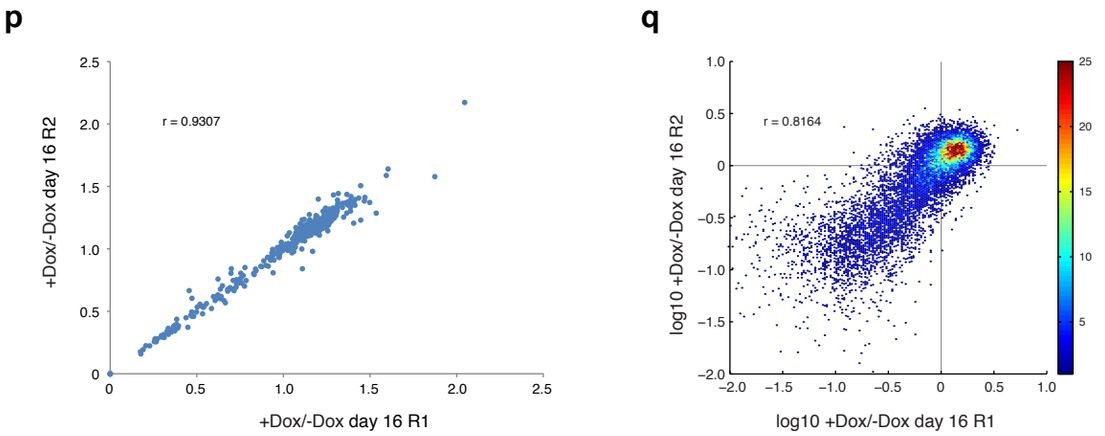

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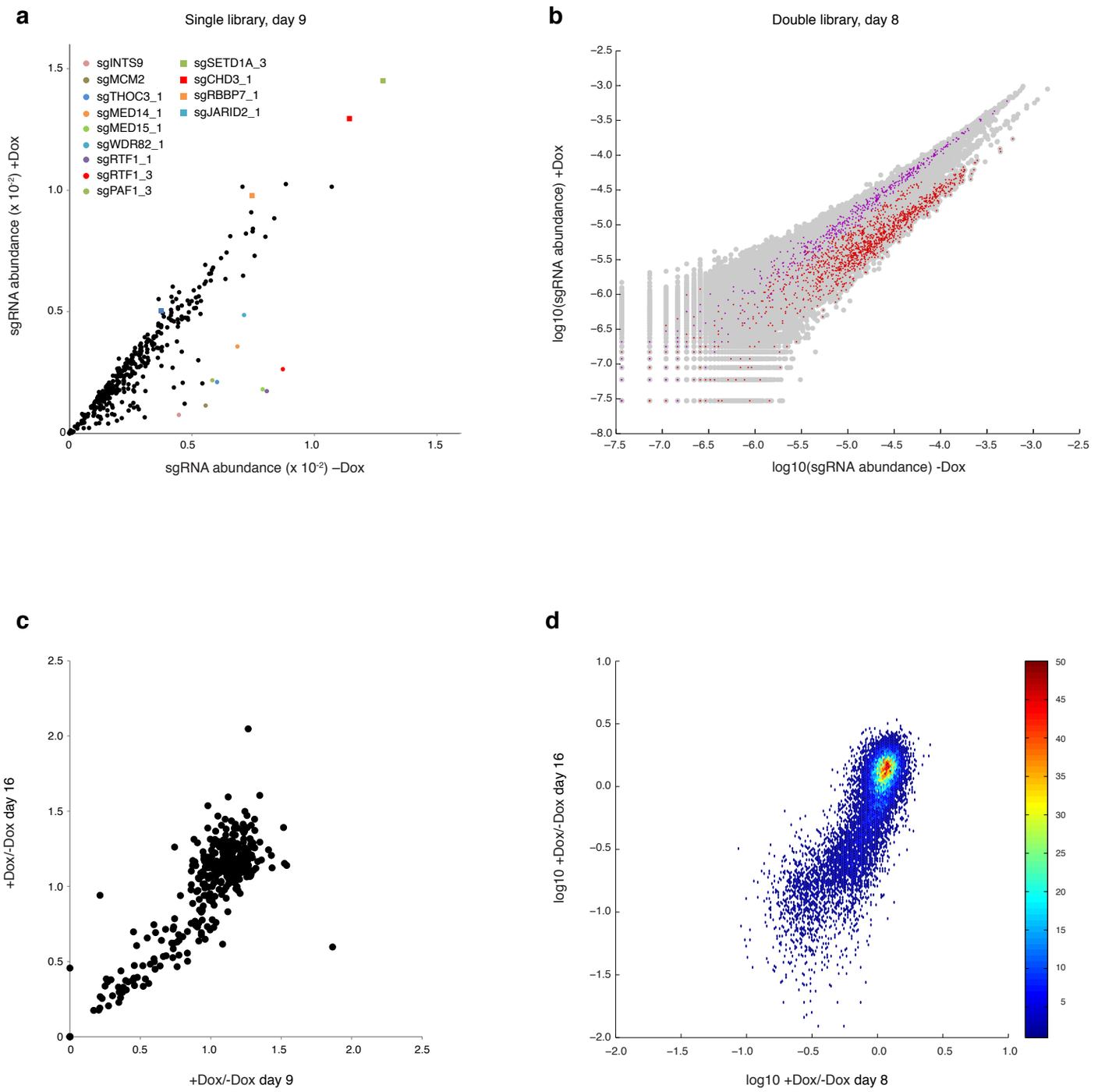
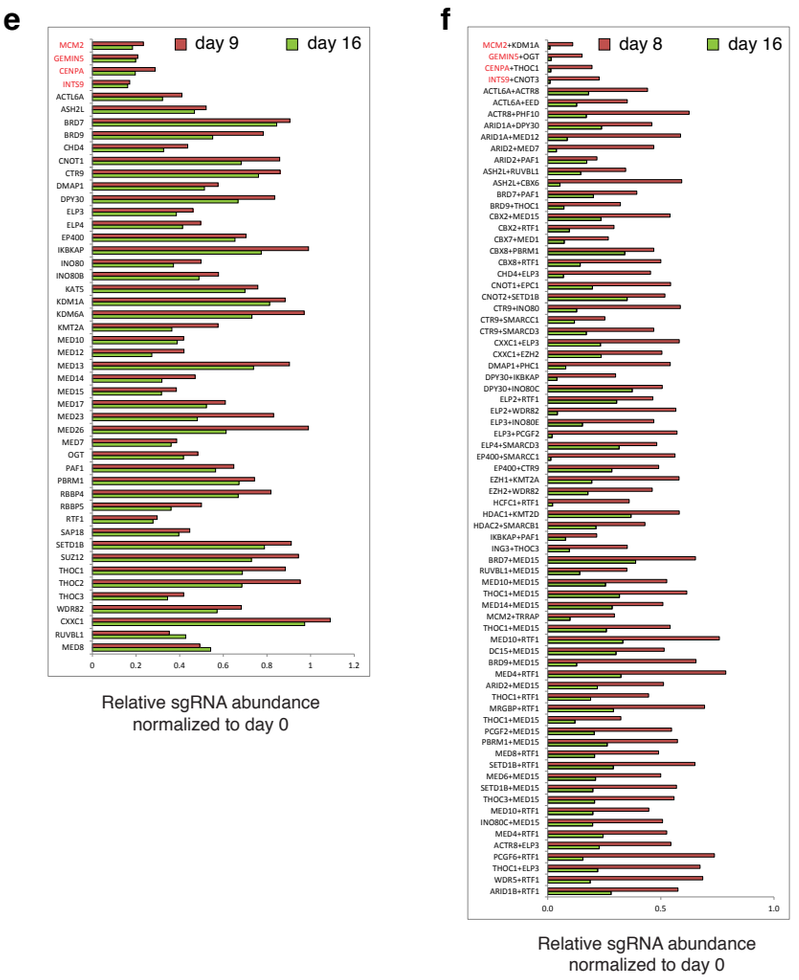


Figure S5 | Comparison of single and double sgRNA libraries at intermediate time points.
(**a**) Comparison of the single sgRNA library with and without Dox at day 9. The colored dots show representative depleted sgRNAs and the colored squares show enriched sgRNAs. (**b**) Comparison of the double sgRNA library (grey) with and without Dox at day 8. Purple dots, negative control sgRNA pairs; red dots, positive control sgRNA pairs. (**c**-**d**) Time-dependent enrichment/depletion patterns (+Dox/-Dox) for single (**c**) and double (**d**) sgRNA screens. The data in (**d**) was subjected to initial filtering as described in 'Data processing and analysis'.(**e-f**) The time-dependent depletion pattern of single sgRNAs (**e**) and pairs of sgRNAs (**f**). Positive controls are marked in red.



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Supplementary Figure 6 - Choice of two pairs for validation by CRISPRi of gene expression and growth effects.

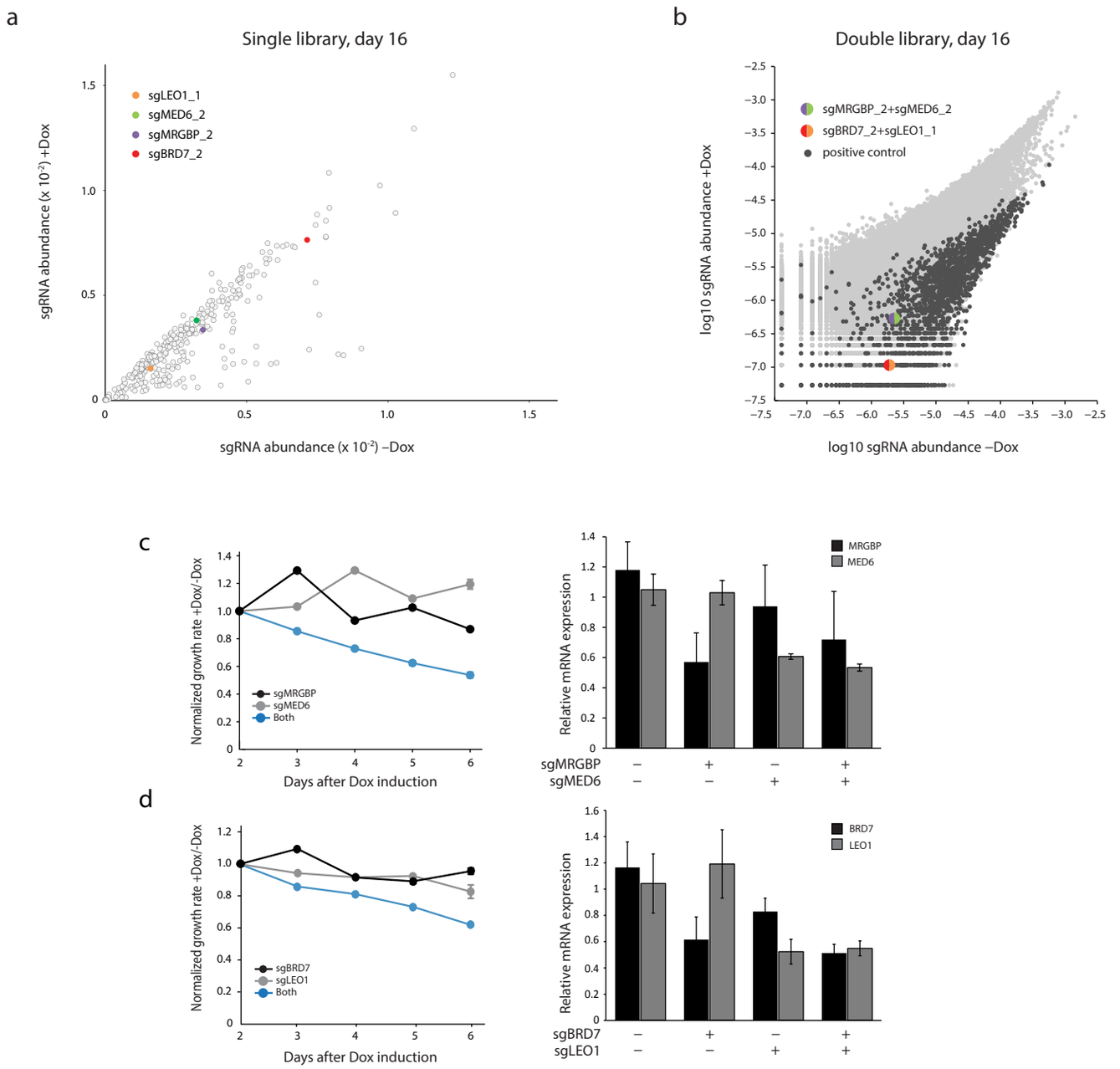

Figure S6 | Choice of two pairs for validation by CRISPRi of gene expression and growth effects.
The colored dots show their sgRNA (pairs) enrichment in the single screen (a) and the double screen (b). (c-d) Measurement of two pairwise sgRNAs combinations (MRGBP & MED6 and BRD7 & LEO1) for cell proliferation suppression (left) and target gene repression (right).

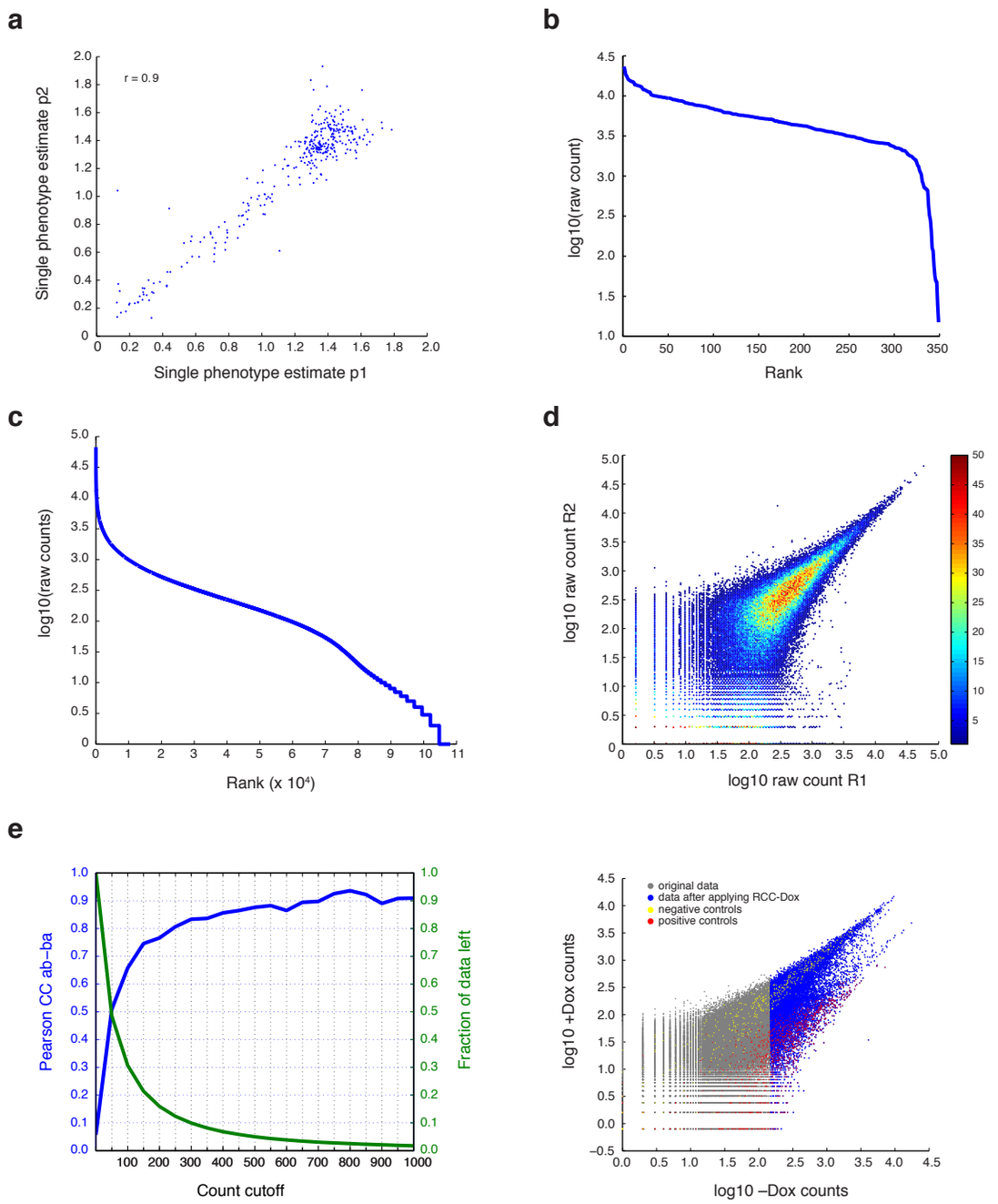

Figure S7 | Data processing and analysis.

(**a**) Comparison of single phenotype estimates derived from pairs where a given sgRNA is either in position 1 (p1, x-axis) or position 2 (p2, y-axis). The Pearson correlation coefficient (r) is also shown. (**b**) Distribution of raw sgRNA counts for the single sgRNA library (log10 scale). (**c**) Distribution of raw sgRNA counts for the double sgRNA library (log10 scale). (**d**) Data reproducibility of +Dox/-Dox between biological replicates of double sgRNAs screens. The low counts region shows a high level of variability. (**e**) Initial data filtering. (Left) Dataset CCAB-BA (blue) and fraction remaining data (green) as a function of the raw count cutoff for the -Dox sample (RCC-Dox). Higher RCC-Dox values produce a better overall quality dataset at the expense of losing a fraction of the raw data (green, as percentage of all observed pairs); (Right) A scatter plot of log transformed raw counts before (grey) and after (blue) filtering by RCC-Dox. The positive controls (red) and negative controls (yellow) are annotated. (**f**) Data filtering based on number of replicates (in this case ≥ 3). Replicate count matrices where each data point represents the number of replicate data points available for each sgRNA-A:sgRNA-B combination before (left) and after the filtering (right) are shown. Missing data is in black. (**g**) Selection of T1 and T2 during the data collapsing step. To saturate the combinatorial space T1 was sampled in the interval [0.1:1] with a step of 0.1 and T2 in interval [0:T1-0.1] (missing data is in black). (Left) CCAB-BA as a function of T1 and T2; (Right) Number of genes in the final dataset as a function of T1 and T2.

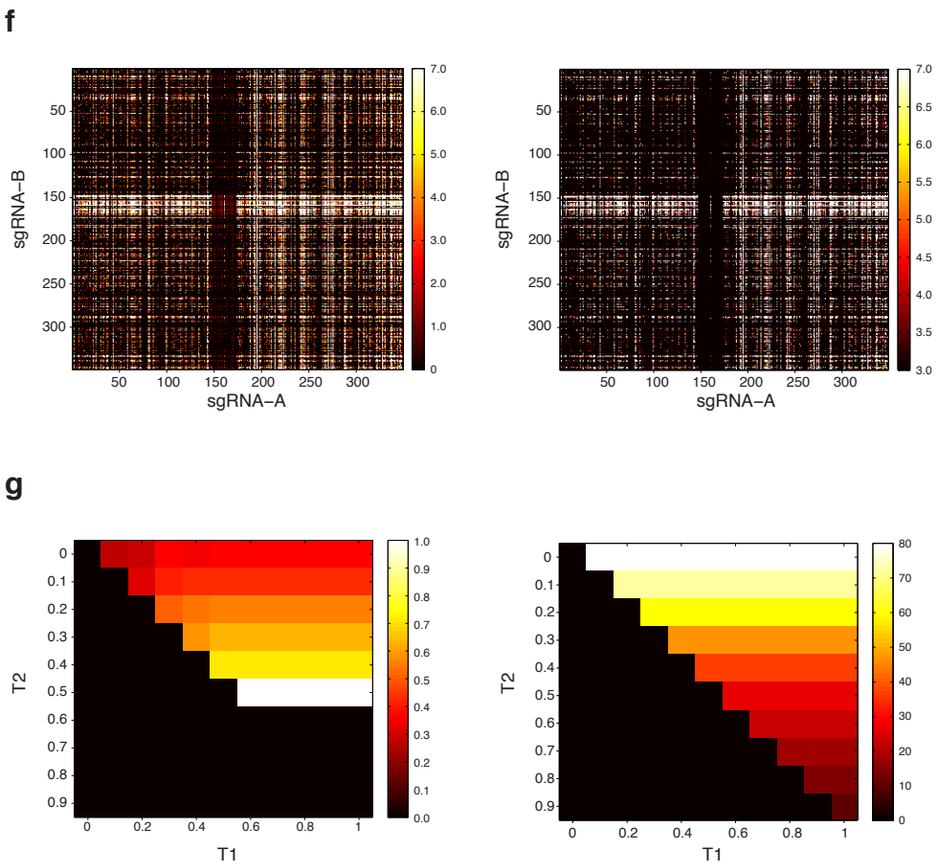

Figure S7 | Data processing and analysis.
(**a**) Comparison of single phenotype estimates derived from pairs where a given sgRNA is either in position 1 (p1, x-axis) or position 2 (p2, y-axis). The Pearson correlation coefficient (r) is also shown. (**b**) Distribution of raw sgRNA counts for the single sgRNA library (log10 scale). (**c**) Distribution of raw sgRNA counts for the double sgRNA library (log10 scale). (**d**) Data reproducibility of +Dox/-Dox between biological replicates of double sgRNAs screens. The low counts region shows a high level of variability. (**e**) Initial data filtering. (Left) Dataset CCAB-BA (blue) and fraction remaining data (green) as a function of the raw count cutoff for the -Dox sample (RCC-Dox). Higher RCC-Dox values produce a better overall quality dataset at the expense of losing a fraction of the raw data (green, as percentage of all observed pairs); (Right) A scatter plot of log transformed raw counts before (grey) and after (blue) filtering by RCC-Dox. The positive controls (red) and negative controls (yellow) are annotated. (**f**) Data filtering based on number of replicates (in this case ≥ 3). Replicate count matrices where each data point represents the number of replicate data points available for each sgRNA-A:sgRNA-B combination before (left) and after the filtering (right) are shown. Missing data is in black. (**g**) Selection of T1 and T2 during the data collapsing step. To saturate the combinatorial space T1 was sampled in the interval [0.1:1] with a step of 0.1 and T2 in interval [0:T1-0.1] (missing data is in black). (Left) CCAB-BA as a function of T1 and T2; (Right) Number of genes in the final dataset as a function of T1 and T2.

Supplementary Figure 8 - Rapamycin-genetic screen using CRISPRi platform.

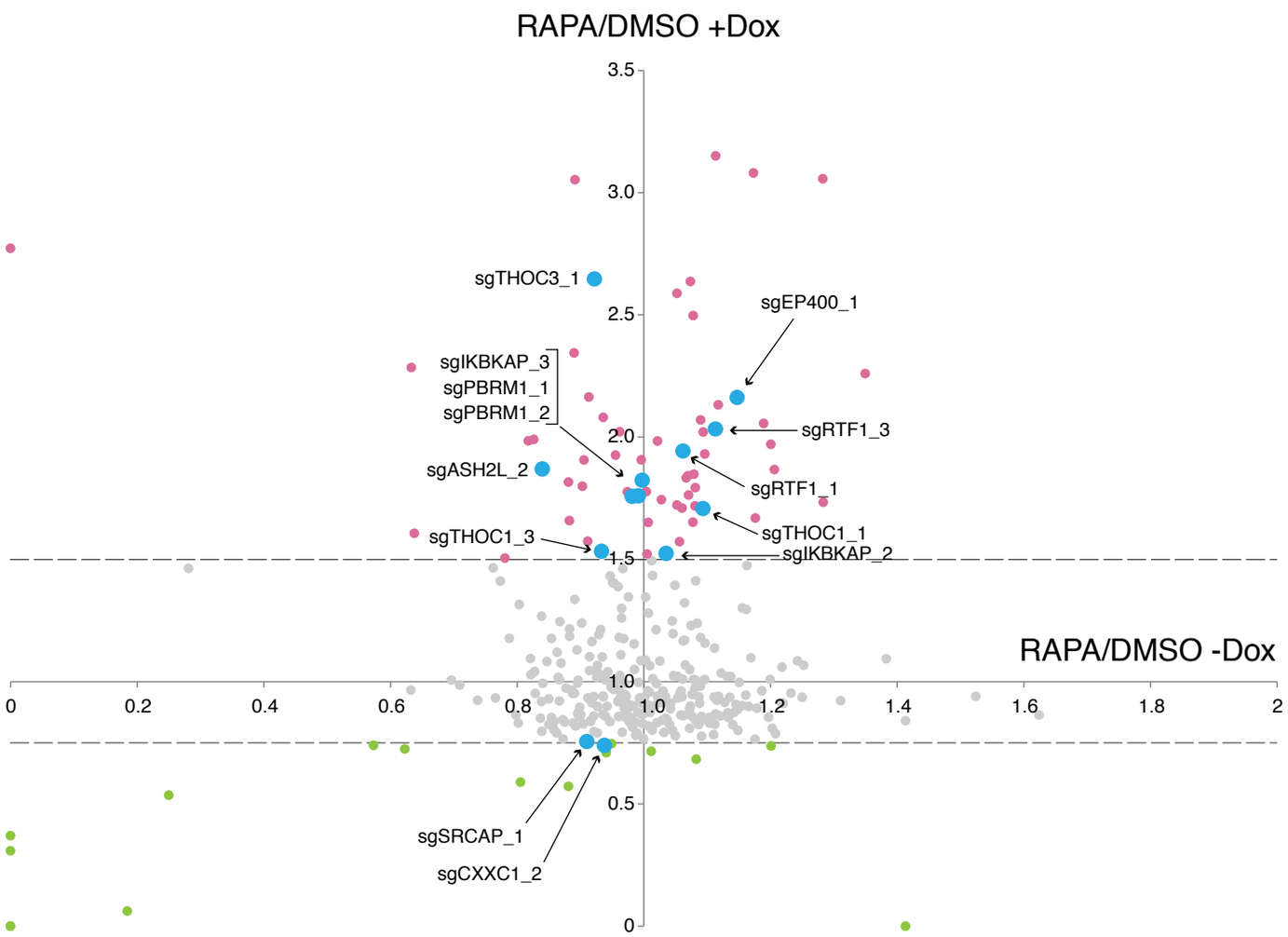

Figure S8 | Rapamycin-genetic screen using CRISPRi platform.
Comparison of single library with and without Dox induction after 20 days of Rapamycin treatment. The sgRNA representations were normalized using DMSO control with and without Dox induction to normalize out the sgRNA-mediated growth effects. Cutoffs for protective/sensitizing hits were set at 1.5 and 0.75 respectively and data points falling outside of these values are colored in pink (>1.5) and in green (<0.75). Hits listed in Supplementary Tables 4 and 5 are also annotated.

Supplementary Table 1 | Target genes and sgRNA sequences

sgRNA name	sgRNA sequence
ACTL6A_1	GTGGGTGGCGGTGGAAGTTA
ACTL6A_2	GGCCGCGACTGCGAGTCTCG
ACTL6A_3	GCGCCGGCAGCAGCCATGAG
ACTR8_1	GCGCTGCAGCCACGACTGCC
ACTR8_2	GTCTCCGGCCATAATGACCC
ACTR8_3	GCGGCCCATCGTGCCCGCGC
ARID1A_1	GGCTCTGTAGGCTCGGGACC
ARID1A_2	GGAGAAGACGAAGACAGGGC
ARID1A_3	GCCCCCCTCATTCCCAGGCA
ARID1B_1	GCATCCTCTTCCTCCTCGTC
ARID1B_2	GGGGAGCAGCCCCGTCTCCA
ARID1B_3	GAGGCGGCTCTCAAGGAGGG
ARID2_1	GGAACTGCCGCAGCTCGTCC
ARID2_2	GAACCGGGGGGGCAGCGCCG
ARID2_3	GGGGTCCCGGCTGACAAGTG
ASH2L_1	GGAGCGGTCGCAAATGCAAC
ASH2L_2	GCAGCCGCTCCTCCTGGAGA
ASH2L_3	GTGGCCGTGATGGCGGCGGC
BRD7_1	GTCGGACAAACACCTCTACG
BRD7_2	GGGCTTCCGCTCTTTCCCAG
BRD7_3	GCAGGCCCAGGCCGGCGAAG
BRD9_1	GCTGGCACCCGGTCGGACCT
BRD9_2	GAGTGGCGCTCGTCCTACGA
BRD9_3	GCGAGCGCGGGCGGCCAGCC
CBX2_1	GTACTCCAGCTTGCCCTGCG
CBX2_2	GCTGAGCAGCGTGGGCGAGC
CBX6_1	GTGGGTGCCGCTGAGCAAGA
CBX6_2	GCTGTCTGCAGTGGGCGAGC
CBX6_3	GCATCGAGTACCTGGTGAAA
CBX7_1	GCTGTCAGCCATCGGCGAGC
CBX7_2	GTGCGGAAGGTGAGGCTGCC
CBX7_3	GCACCGCTCCCTCCACGCTG
CBX8_1	GCTCCTGGAAGCGGCCAAGG
CBX8_2	GGTGGGGGAGCGGGTGTTCG
CBX8_3	GCACGGAGGCCCTAGGCCCG
CHD3_1	GCTCCCACTCGGGCTTGGGG
CHD3_2	GTCTGCCGCCTTCATCACAC
CHD3_3	GAGGAAAAGAAATCCTCAGC

CHD3_4	GTTTTAGGCTACTTGGGAGG
CHD4_1	GCTCCGGCTCCTCCTCGCCG
CHD4_2	GCGCGACCTGCGGCGGCTCC
CHD4_3	GGCCGTGAGGGGCGTCTCTT
CNOT1_1	GTCGAGGAGAGCCGGAGTCG
CNOT1_2	GGAGCCGCCTGAGGTGAGGC
CNOT1_3	GTTTCTCTACAAAATGGCGC
CNOT2_1	GAGCCTAGGGGAGTGGAGTC
CNOT2_2	GCCGCCTTCTCTTCTCCCCC
CNOT2_3	GCAGCTCCAGATCCTAGGCC
CNOT3_1	GTCAGCTTCCGCGGAGCCAT
CNOT3_2	GTTGTTCTGACGACGGGGGT
CNOT3_3	GCCGCTATCGCGATAGCGCC
CTR9_1	GTGAGTGACGGCTCCGGCTC
CTR9_2	GGAGACTACCGGCTGCGGAG
CTR9_3	GATGGAGCCCCGCGACATGA
CXXC1_1	GAATGAATACAACTTGATCC
CXXC1_2	GAACCTCTCTGCCTGACAAA
CXXC1_3	GGCAGGCTGTGTGCCTTGCG
DMAP1_1	GGCCGTTAGGAACATCCAAG
DMAP1_2	GCGGGCCAAGAGGAGAAGGG
DMAP1_3	GACCCAGGTGCGGAAGTGCG
DPY30_1	GAGTGGGACAGTCCACGACT
DPY30_2	GTGCTCCCGCGCCCAGGTGG
DPY30_3	GATTTCAACACGAAGACTCC
EED_1	GAGAAGAGGCGAAACTCAAA
EED_2	GCTGAAACGTCTTTGGAAGG
EED_3	GTAAGGTCCGTTGGATTAAG
ELP2_1	GGACTCCCCGCACCCGGTTT
ELP2_2	GTCATAGAGCACCACGGAGC
ELP2_3	GGTGCCACCATGTCGCCAAC
ELP3_1	GAAGCGGAAAGGTGCGAAAG
ELP3_2	GCCTGGGCGTTCGCCCCTTT
ELP3_3	GCAGCCACAAACTCAGACCA
ELP4_1	GCCAGCGTGACCAACGACAG
ELP4_2	GGTAGTGTTGCCGCGAGTAC
ELP4_3	GCAACGTCACCAGTTTCCAG
EP400_1	GCGTCAGGAGGGCGGGAGGA
EP400_2	GGTAAGTGAGGGCGGAGGCG
EP400_3	GGCTACGCGACCCCGGACCC
EPC1_1	GGCACTAACACCAGCCGGGA

EPC1_2	GCTGCCGGGGACTTGAGGGG
EPC1_3	GTTGGCTGAAGAGCGCACAG
EZH1_1	GTGAGTAAACAAGCCTGGGC
EZH1_2	GGAAATTGGAAGGAATCCGA
EZH1_3	GGCGCCCCTCCTCATTCCGA
EZH2_1	GGATTTCGGGGTGCGTCGTG
EZH2_2	GCTGCCCTCGCCGCCTGGTC
EZH2_3	GGGGATGTACACAATGAAGT
HCFC1_1	GAAAGGAGCCACAAGCGCCG
HCFC1_2	GGGCTACGACTGAGGAAGGG
HDAC1_1	GGGACGGGAGGCGAGCAAGA
HDAC1_2	GGCTGAGGCTGGAGCGCCGA
HDAC1_3	GCTCGGAGAGGAGGCTGCGA
HDAC2_1	GGCTCGGTACCACCCGGCAG
HDAC2_2	GGCGATAGTCCCGCGGGGAA
HDAC2_3	GGCACCAACTCGCGAGGAGG
IKBKAP_1	GTTTGGGCAGATGGGCAAGA
IKBKAP_2	GCCTGGCACCGTAGAGGTAG
IKBKAP_3	GGCGAGGCCGGGCCCGCTTC
ING3_1	GAGGGAACAAGGGGGTCCAG
ING3_2	GGAAAGTGAGTGCGCGGCGC
ING3_3	GAGTTTTGTCCCCTCCAATA
INO80_1	GGGGTCCCAGGAGCCGCGGA
INO80_2	GGTTCGCTCTCTGAGGCCGT
INO80B_1	GAAAGGGGACTAGAAATGGT
INO80B_2	GCGGCGTGGGAGCACCTCTG
INO80B_3	GCGAATAGATCAAGCAATTT
INO80C_1	GAAGACTCGGAGTGCGATGG
INO80C_2	GTTCCGGACTATTCCGGGAG
INO80C_3	GGAAGTTCCAAGGCCCGCGC
INO80D_1	GGCTGACAGATCAGAGTGAG
INO80D_2	GGAGCCCGGGGATGTGGGCC
INO80E_1	GGTAGCGGGAGGGCAGACTC
INO80E_2	GTCATGAACGGGCCGGCGGA
INO80E_3	GTGCTGCCGCGGGAAGGCTG
JARID2_1	GACTCGGCGAGCCCTCGCTG
JARID2_2	GTTACATCTTGGAAAAGAAA
JARID2_3	GGGGGGGGAGTGAAGGGCGT
KAT5_1	GCAAGACTGCCCCTGTGACT
KAT5_2	GCCTCACGAAGCCCCTGTAG
KAT5_3	GCCACTGGCTGTGCACGTTA

KDM1A_1	GACAGAGCGAGCGGCCCCTA
KDM1A_2	GGCGGCCCGAGATGTTATCT
KDM1A_3	GCGTGAAGCGAGGCGAGGCA
KDM2B_1	GCTCGGCTTCCATACCTATA
KDM2B_2	GCGGACCCGCCATGTGGAGG
KDM2B_3	GTCGGCCACACAGGTAATGT
KDM6A_1	GCAGCCACAGGCGGGGACGG
KDM6A_2	GAAAGCCGCCGCTGCCGACC
KDM6A_3	GGAGCACTGAGGGGATTCGT
KMT2A_1	GAGGCGGCGGCCGCTCCCCC
KMT2A_2	GGCCGGCCCTGAAGAGGCTG
KMT2A_3	GGCGCTTCCCCGCCCGACCC
KMT2D_1	GATAAAGATTCAGAACCGGC
KMT2D_2	GTGCCAGGACCAGAAATGTA
KMT2D_3	GAGATTATCCAAAACCTGAG
LEO1_1	GTGAGCGATAATGGCGGATA
LEO1_2	GCGAAGCTGAGCGTAAAGGT
LEO1_3	GCGTGGCAGGCCTTCCGCTG
MBD2_1	GGATTCCAAGGGCTCGGTTA
MBD2_2	GGGCTGGATGCGCGCGCACC
MBD2_3	GGACCTAAGAGGCGGTGGCC
MBD3_1	GGAAGAAGTGCCCAGAAGGT
MBD3_2	GAGCCCGTTGAGGCCCTGCG
MBD3_3	GCGCAATGGAGCGGAAGAGG
MED1_1	GATCAATCTGAAGTCCCCGG
MED1_2	GGCTCGGGATCCCGGGACGC
MED1_3	GAAGCTAGATCCGCCACAAA
MED10_1	GGAGAAGTTTGACCACCTAG
MED10_2	GTTGAGCCCGGCCTGGCTGC
MED10_3	GGTCTCCCCAGGGCCTGGCC
MED12_1	GCGGCCGAGAGACAACAAGG
MED12_2	GAGGGAGCCGAAAAGGGGGG
MED12_3	GTAGCGCCGGAGGCACCAGC
MED13_1	GCCGGCGGCGGCTGCTGTGA
MED13_2	GGTTACAGTGACAATCTTCC
MED13_3	GGTGCGCCCTTGGGCCGTGG
MED14_1	GACTCTGCCCGCTCCCGTTT
MED14_2	GTGTGCCGTTGCGCCAAGCC
MED14_3	GTGGTTCTCCAGCTGCACTG
MED15_1	GATACGGGCGGCGGGAGCTG
MED15_2	GGTCAGTCAAATGTGAGTAG

MED15_3	GCCGCCTCAGTCACAGAGCC
MED17_1	GGGAGCTTGCGGTGCGTTCT
MED17_2	GCGTTGCGTTCGGTTTCCCG
MED17_3	GAGGCTTCCCTGCGGAGAGC
MED23_1	GGAATATAGGGGCAGAGGGG
MED23_2	GGCGGGGGTGATAGTACAGA
MED26_1	GGCGGCTCCTCCTCCTCCTT
MED26_2	GTCACTCACTCGCCGGCCTC
MED26_3	GGCGTCTCCGCAGCAGATCA
MED4_1	GCGGCTGCTGTCTGCGCTTG
MED4_2	GGCGAGCCTGAGAGCCGGGC
MED4_3	GGAGCGGCTGGGAGGCGGTT
MED6_1	GTTTCGCTAGATCACAGCCT
MED6_2	GATTGTCTGTGGACCAGTTT
MED6_3	GCGTTTACAGGTTCTCTTTC
MED7_1	GAAAGACGAAAGACCGCCTT
MED7_2	GTGCGGTCTCTCCGAGAGCG
MED7_3	GGCTCTAAGCGTGGCAGTCT
MED8_1	GACCGAGAGTGGGCTGGCTA
MED8_2	GGCAGAACCCACGGCTGATA
MED8_3	GCGTTGGGCGTACTAGCGGC
MEN1_1	GTGGGATGTAAGCGCGGAGG
MEN1_2	GACAGACTTTACAGCCCCGG
MEN1_3	GGACTCTCCTTGGGGTTTGG
MRGBP_1	GCTCGGCCGGGCCGCGGCCA
MRGBP_2	GCCGCAGGCGACAAGGGCCC
MRGBP_3	GACAGTGGTGTGGAGCCCCG
MTA1_1	GCCGCCAACATGTACAGGGT
MTA2_1	GTTGGGCTCTGCCGGCCGCA
MTA2_2	GAACGAGCTCGGCTCCTGCC
MTA2_3	GCCTCAGCGTCCCGGGAGTG
MTA3_1	GCCCCAGAACGTGGGGGCCG
MTA3_2	GTCCAGGCGCGCTACACGTT
MTA3_3	GGGGAGGAACGCCTTGTCAC
NCOA6_1	GTCGGGCTGGCTTCGCGGGG
NCOA6_2	GACCGTGCCACTCGGTCGCC
NCOA6_3	GACGGCGGCGCGGGCCCGTA
OGT_1	GCTCTGGAGGGCTTGAGCGG
OGT_2	GCTCCAGATGGCGTCTTCCG
OGT_3	GATGGTCAATTAGAGTTCCC
PAF1_1	GTGAACGCGCAGGCAGCACC

PAF1_2	GCGGAAAGTGGGTTGAGATG
PAF1_3	GCGGCCTGAGGAGACCCGTT
PBRM1_1	GGGTAAGGCCGGGCCCAGGG
PBRM1_2	GGCCCGGCAGCTGACCAAGG
PBRM1_3	GCAGGTGCGACAAGGCTACT
PCGF1_1	GCCTCATCGCGATCGCAATC
PCGF1_2	GATGGACCCGCTACGGAACG
PCGF1_3	GTCGGCCAGCGGTGCGAATT
PCGF2_1	GCTTACCTGGGTTCGGGGTC
PCGF2_2	GCCTGTAACCCTCTGGGGAT
PCGF2_3	GGGGGGTGCGAAGGCAGGAT
PCGF6_1	GTAGGCGCTGCCAAAACCGA
PCGF6_2	GGCGCCTCTGTCTGAGACGG
PCGF6_3	GGTGTCTCTCCCGACCATGG
PHC1_1	GAAGGTAACCGGGCGACCGA
PHC1_2	GGGCGTTACACAGATGGAGG
PHC1_3	GCTCAGCGCCGGAGGTAGGC
PHC2_1	GACTGGCAGCTCATTCTCCA
PHC2_2	GTACACAGAAATCTGGGGCC
PHC2_3	GGTAAGAGTCTAATTGATCT
PHC3_1	GTGACTGATGTCGTAACTAG
PHF10_1	GGGCCCACGCCCCGGCACCC
PHF10_2	GTCGCTGTCGCACGGCCGCG
RBBP4_1	GGCACCCTCACCTTCCTTGT
RBBP4_2	GCTGAGCCGCGGCCTCGACA
RBBP4_3	GGGGGCGCAGGAAACAATAG
RBBP5_1	GTTGTTGCCGGAGCTGAGAC
RBBP5_2	GCTGCGTTTTAGAGAAGCGT
RBBP5_3	GGTGGACGCCGCGAAGAGAC
RBBP7_1	GGAGCGCAGCCGCTGGAGGA
RBBP7_2	GCGCGCGCGTTGACCGCCTC
RBBP7_3	GCCCTTGTCCGGGGGTTGCT
RTF1_1	GGCGGGCAAGAGGGGAGTCC
RTF1_2	GGACCACCATGGTAAAGAAG
RTF1_3	GCGCGGGCCGGCGGAGCCAG
RUVBL1_1	GGGCGCACTGTCCTAGCTGC
RUVBL1_2	GCCTCCCACAGCCACGTGAA
RUVBL1_3	GCAGGCGGCCTCAGGGCTTG
SAP18_1	GGTCAGGGCGAGCGTCTCGC
SAP18_2	GGAGTCGCGCGTTACCCAGG
SAP18_3	GATCGACCGCGAGAAGGTGA

SAP30_1	GTGAGCGGGGTCCCCGCTCC
SAP30_2	GGCCCGGGACAGTTGGTGTT
SAP30_3	GCAGAGTGAATTGCCGCTGC
SETD1A_1	GAATAGCCCGCTTCTGTCCC
SETD1A_2	GCCAGCAGGGATTGGCTAAC
SETD1A_3	GACTCCACCAAGGCGGATGA
SETD1B_1	GGTTCCTCCTCTCGCCCGAA
SETD1B_2	GATTGACCCGGCTCTGAAAA
SETD1B_3	GCACGGCTGGGGGGGCGCGC
SIN3A_1	GGGCTAGTCCGCCGGCCGCT
SIN3A_2	GCTCGGTCCCAGGGCCCGCA
SIN3A_3	GGCCTGTCCCTCGCCTACCT
SIN3A_4	GCGGCCGCTTCTCTGTTACC
SIN3A_5	GCCTGTGACCGCTTCGTTAG
SIN3B_1	GGGACGCCACTCACGTGCAC
SIN3B_2	GAGGGCCGAGGTGAGAGGTG
SMARCA4_1	GGGCGGTTTGAATGGAGCCG
SMARCA4_2	GGCGCGCCCTGTGCGGGGCC
SMARCA4_3	GGGAAGGCCACAGTGTCGCG
SMARCB1_1	GGCCTGGTCGTCGTCTGCGG
SMARCB1_2	GGGCCGAGGGAAACCGAAGC
SMARCB1_3	GCGAGGGATCAGGAGGGCTG
SMARCC1_1	GCTGTTTATCGACGGAAGGA
SMARCC1_2	GACGGTGTCCCAGCTGGATT
SMARCC1_3	GGTGGGTTCGCGCGCCCGTG
SMARCC2_1	GACAACGTGCGGCTGTGGCT
SMARCC2_2	GACCGCGGCCCTGCAGCCCC
SMARCC2_3	GCCTCGTAGTACTTCACGTT
SMARCD1_1	GTGGCTCCAAGCGGCGGCGC
SMARCD1_2	GCCGCACAAAGAACCGGAAC
SMARCD2_1	GACTCGGGCGGCCAAACCTC
SMARCD2_2	GCCCGGGAGATTCCGGATCC
SMARCD2_3	GGAACTCGCGAACTTGGATT
SMARCD3_1	GAATGGGAGTCTGCCAGTCA
SMARCD3_2	GCCAGGCAGCGATGGGGAGG
SMARCD3_3	GAAAGTGCTCGGCAGGGGGG
SMARCE1_1	GCGGGTGAGTGTTTCCAAGT
SMARCE1_2	GAACTCGGGGTCTAGCCAAG
SMARCE1_3	GGCCTCAAGGAGGCCTCAAC
SRCAP_1	GTCAGTCCGTCGGGAGGGCT
SRCAP_2	GCTCGGGTCTTGGGAACGTG

SRCAP_3	GTGTGAACCCGCAGGAGGCC
SUZ12_1	GGGCGAGCGGTTGGTATTGC
SUZ12_2	GGCGGGTAGCTGGCGGGGGG
SUZ12_3	GCCTCAGAAGCACGGCGGTG
THAP1_1	GTGATGGTGGCCTCCCTCGG
THAP1_2	GTTCTCAGTGTCGCTGCGCT
THAP1_3	GCTAATGCAAACAACAAAAC
THAP3_1	GCTGCCCCCAACAAAGATGG
THAP3_2	GGGTCCCCGCCTCTTACCGG
THAP3_3	GGGCCCGCGGACCGACTCCG
THOC1_1	GCTTCGGGCAAACTGAAGAG
THOC1_2	GGCAAAATTCGAGTAATTTC
THOC1_3	GTCCGCCTCAGCGTCCGCTC
THOC2_1	GAGGCGAATTGTGAGTGTTC
THOC2_2	GCTGCACTCTCACCTGTAGT
THOC2_3	GACCATCCACGCCCGCCGCC
THOC3_1	GCTGCTGCAGTGTTGTGAGT
THOC3_2	GGCGGTCCCCGCTGCAGCCA
THOC3_3	GCCCCGGCTCGATGGCCCCG
TRRAP_1	GGGTCGCGGGCCGGGCCTGC
TRRAP_2	GGCGGGCGTCCGAACGGCCC
TRRAP_3	GCGGCCGAGCGGTTGCGACG
WDR5_1	GGCCGCACAGGAGACAAGGG
WDR5_2	GCTCTGGCGGCCTCGGTCTC
WDR5_3	GGCACGCACCTTGCTCTGAG
WDR82_1	GAGGTGGCTGTGAGGACGAA
WDR82_2	GGAGGAGGCGGCCCAACTGT
WDR82_3	GCGGAGCTTCCGCGTCGCTA
NC_1 (DC13_1)	GGGCTGAACGCGTATTCGCG
NC_2 (DC14_1)	GGCGATTCGGCGACCTTAGT
NC_3 (DC14_2)	GGCGCGAGTACGAAATTAAT
NC_4 (DC14_3)	GATTATCAGACGCGCTGCGT
NC_5 (DC15_1)	GCGCGGCTAGAATAGACTTG
NC_6 (DC15_2)	GGTTCGTGCGGTAGTGTGCG
NC_7 (DC15_3)	GTATCGTCTTCCGTCCTCGT
NC_8 (DC15_4)	GGCTACTCTATGCGTCGATT
NC_9 (DC15_5)	GCTTAACAAAGCGAGCGACC
NC_10 (DC15_6)	GGCACTGGACGATATCCGAC
NC_11 (DC15_7)	GTTCATCTCAACGGTAATCG
NC_12 (DC1617_1)	GGTTATATTGACGTCCTGCC
NC_13 (LC_1)	GCTAGTCTGCGTGACGCGTCT

NC_14 (LC_2)	GAAGTAACTGAAGGATCAATAT
NC_15 (LC_3)	GCGGGAAAACCGCGCCCCGGA
NC_16 (LC_4)	GCTCAGGGCCGTGAGCGTGGG
NC_17 (LC_5)	GTAGGAGCGCGTGCTGATTGT
NC_18 (LC_6)	GGACGAACTAATGTATTGTGGC
NC_19 (LC_7)	GGTTTATGGACCTTCAGGGAG
NC_20 (LC_8)	GGCGTACCCGTGGTTTCACCGT
NC_21 (LC_9)	GCTTGGGAGCAAGCCGGCGGTA
NC_22 (LC_10)	GTGTGGCGACCCTGGTCTCAT
NC_23 (LC_11)	GGGCCTCTGTGAGGTCGTGGT
NC_24 (LC_12)	GTATGATACTCGTGCTTAGT
NC_25 (LC_13)	GCGAAGTCGAATGTTGGTCG
NC_26 (LC_14)	GGCCCAACATCCTCGTGTCCA
NC_27 (LC_15)	GTGGCGGAGCCTAGCCGAGAGT
NC_28 (LC_16)	GGCGCGAACTTTAAGGTGGAC
NC_29 (LC_17)	GATTAGTTCGCGTATGGCAGCA
NC_30 (LC_18)	GCCGTAAGGACGGGTAGAGGT
NC_31 (LC_19)	GGGGGCGGAAATCGAGCCCT
NC_32 (LC_20)	GAAGTGAGAGGAGGGAGCAGCC
NC_33 (LC_21)	GTAAATCCCGGGAGTCAGA
NC_34 (LC_22)	GTGAGCGGCGACCCCCCCTG
NC_35 (LC_23)	GGTGCGGACCCCCGCCGGGGG
NC_36 (LC_24)	GGTGAGCCGGTTTGTGAGAAG
NC_37 (LC_25)	GAGAGTGCGCTGCAATGGATAT
NC_38 (LC_26)	GGATGTGCCATGGTGAGGGCTG
NC_39 (LC_27)	GGATGCGCCTAGGCGAAAGAAA
NC_40 (LC_28)	GAGCCGATGCAGGGCGTAGGG
NC_41 (LC_29)	GCCATTCTCTATGTTCGATAAG
MCM2_PC	GGATCGTGGTACTGCTATGG
INTS9_PC	GGCAGGTGGCGGAGATTGCAC
GEMIN5_PC	GGCGTGAGGCTACGAGCGGT
CENPA_PC	GCCAAGCACCGGCTCATGTG
POLR1D_PC	GGAAGCAAGGACCGACCGA

Supplementary Table 2 | Manually curated functional complexes and members

Complex	Genes within the complex
CNOT	*CNOT1, CNOT2, CNOT3*
Elongator	*IKBKAP, ELP2, ELP3, ELP4*
THO	*THOC1, THOC2, THOC3*
INO80	*INO80B, INO80E, INO80, ACTL6A, ACTR8, RUVBL1, INO80C, INO80D*
SRCAP	*SRCAP*
NuA4	*ING3, EP400, TRRAP, KAT5, RUVBL1, RUVBL2, EPC1, MRGBP, ACTL6A, DMAP1*
PAF1C	*PAF1, CTR9, LEO1, RTF1*
SET1A/B	*ASH2L, SETD1A, SETD1B, DPY30, RBBP5, WDR82, CXXC1, WDR5*
MLL1/2	*DPY30, RBBP5, WDR5, ASH2L, KMT2A, KMT2D, MEN1*
MLL2/3	*DPY30, RBBP5, WDR5, ASH2L, NCOA6, KDM6A*
HCFC-OGT	*HCFC1, OGT, THAP1, THAP3*
Mediator	*MED1, MED4, MED6, MED7, MED8, MED10, MED12, MED13, MED14, MED15, MED17, MED23, MED26*
esBAF	*PBRM1, ARID2, PHF10, SMARCC1, SMARCA4, BRD7, SMARCD1 , SMARCD2, ARID1A, ARID1B, SMARCB1 , SMARCE1, BRD9*
cardiac BAF	*SMARCD3*
neuronal progenitor BAF	*SMARCC2*
NURD	*MBD2, MBD3, HDAC2, MTA1, MTA3, HDAC1, MTA2, RBBP4, RBBP7, CHD3, CHD4, LSD1*
PRC1	*PHC1, PHC2, PHC3, CBX2, CBX6, CBX7, CBX8, PCGF1, PCGF2, PCGF6, KDM2B*
PRC2	*SUZ12, EED, RBBP4, RBBP7, EZH1, EZH2, JARID2*
SIN3	*SIN3A, SIN3B, RBBP4, RBBP7, HDAC2, HDAC1, SAP30, SAP18*

Supplementary Table 3 | Comparison with orthogonal dataset (S-score)

Gene pairs	esiRNA [1]	CRISPRi (this study)
RBBP7+RBBP4	-3.021379	-3.4432042717
PAF1+MBD2	-1.924307	-1.9275465243
MRGBP+MBD2	-1.154774	-1.5088420949
TRRAP+RTF1	3.387044	2.6769924866
SUZ12+HCFC1	2.01163	2.6803257052
RTF1+PAF1	8.762486	2.7472714405
RTF1+ELP3	2.850101	2.8665793965
RUVBL1+PAF1	4.067855	3.2018467106
RTF1+CNOT3	3.817132	3.2039785564

References

1. Roguev, A. *et al.* Quantitative genetic-interaction mapping in mammalian cells. *Nat. Methods* 10, 432–437 (2013).

Supplementary Table 4 | Yeast orthologs have similar Rapamycin resistance/sensitization phenotypes to the hits uncovered by CRISPRi screen

Gene name	CRISPRi screen phenotype	Yeast ortholog name	Yeast knockout phenotype
CXXC1	sensitization	*SPP1*	Sensitization [1]
SRCAP	sensitization	*SWR1*	Sensitization [2]
RTF1	resistance	*RTF1*	Resistance [2]
ASH2L	resistance	*BRE2*	Resistance [3]
IKBKAP	resistance	*IKI3*	Resistance [3]
PBRM1	resistance	*RSC1*	Resistance [2]
MED12	resistance	*SRB8*	Resistance [2]

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Supplementary Table 5 | Genes confer Rapamycin resistance in the CRISPRi screen are downregulated upon Rapamycin treatment.

Gene name	CRISPRi screen phenotype	Gene expression change upon Rapamycin treatment
THOC1	resistance	Decreased [1]
EP400	resistance	Decreased (https://dx.doi.org/10.7272/Q6TD9V7J)
THOC3	resistance	Decreased [2]
ASH2L	resistance	Decreased [2]

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Supplementary Table 6 | Primers used for cloning and sequencing

Primers used to clone single sgRNA (5'-3'):	
Forward primer (N19 is the targeting sequence):	GGAGAACCACCTTGTTGGN$_{19}$GTTTAAGAGCTATGCTGGAAACAGCA
Reverse primer (N10 is the barcode sequence):	CTAGTACTCGAGNNNNNNNNNNGCGTCGACCCTAGGGCTAGCACTAGTA AAAAAAGCACCGACTCGGTGCCAC
Primers used to amplify genomic DNA for single sgRNA screens (5'-3'):	
Forward primer:	AATGATACGGCGACCACCGAGATCTACACGGTAATACGGTTATCCACGC GG
Reverse primer (NNNNNNNN is the index):	CAAGCAGAAGACGGCATACGAGATNNNNNNNNGCACAAAAGGAAACTCA CCCT
Custom primers for Mi-seq (5'-3'):	
Read1 primer:	CCACGCGGCCGCCTAATGGATCCTAG
Read2 primer:	GTGTGTTTTGAGACTATAAGTATCCCTTGGAGAACCACCTTGTTGG
Index read primer:	GTCTCAAAACACACAATTACTTTACAGTTAGGGTGAGTTTCCTTTTGTGC'
Primers used to amplify genomic DNA for sgRNA double screens (5'-3'):	
Forward primer:	AATGATACGGCGACCACCGAGATCTACACTGAGACTATAAGTATCCCTTG GAGA
Reverse primer (NNNNNN is the index):	CAAGCAGAAGACGGCATACGAGATNNNNNNCTGGCGAACTACTTACTCT AGCTTCCCGGCAACGCCTTATTTAAACTTGCTATGCTGT'
Custom primers for Hi-Seq 2500 (5'-3'):	
Read1 primer:	CGAAGTTATAAACAGCACAAAAGGAAACTCACCCTAACTGTAAAGTAATT GTGTG
Read2 primer:	GCACCGACTCGGTGCCACTTTTTCAAGTTGATAACGGAC
Index read primer:	GTTTAAATAAGGCGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAG

Supplementary Table 7 | qPCR primer sequences

Gene Name	Forward primer (5'-3')	Reverse primer (5'-3')
BRD7	AAGCACAAGTCGGACAAACAC	CGTTCCCTCCTACTTTGAGGAC
BRD9	GCAATGACATACAATAGGCCAGA	GAGCTGCCTGTTTGCTCATCA
CBX2	GCAAGCTGGAGTACCTGGTC	GGCTCCCAGCTGTTATGTTT
CBX6	CTCTTCCTCCCGGTGTTTG	CCGTGGTCAGAAGCAAAAG
CBX7	CGTCATGGCCTACGAGGA	TGGGTTTCGGACCTCTCTT
DPY30	GGAGGGACAAACGCAGGTT	GGTAGGCACGAGTTGGCAA
EPC1	ATGAGTAAACTGTCGTTTCGGG	GAGGCGTATTCGTGCAGGTC
HDAC2	CAGATCGTGTAATGACGGTATCA	CCTTTTCCAGCACCAATATCC
INO80E	TACCGGAATCTGAAGCGGAAG	TCTAGGAGGAAACTCTTGTCCC
KMT2D	GAGCTACGGCGCTTTGAGTT	AGGGAAACCAATCTGTGATAGGT
LEO1	CGGATATGGAGGATCTCTTCGG	CAGAGGCATTACTGCCAGAGG
MBD3	ACCATGGACCTCCCCAAG	CGACAGCAGCGTCTCATC
MED26	CGGTGCTGGAAGTCATCTC	TTCCCAAGTCGTGTTTCCTC
MED4	GGTGGTAACAGCACACGAGA	TTGCCAGCATTTCTATAAGTTCC
MED6	TGCAGAGGCTAACATTAGAACAC	GCTGTTGCTTCCGAATGATGA
MRGBP	TGAACCGACACTTCCACATGA	TGGTCCCAGATGACCTTGGAT
PBRM1	AGGAGGAGACTTTCCAATCTTCC	CTTCGCTTTGGTGCCCTAATG
PCGF1	CGCTACGGAACGAGGAGGA	CCGGTCCAGTTTGAGGTTGAG
PCGF2	TTCTCCGCAACAAGATGGAT	AGTGGCTCGTCCTCGTACA
PHC2	AGGGAACGGAAACTCTGCCT	TCGATAACATGCGTCAGGATTTG
RBBP4	ATGACCCATGCTCTGGAGTG	GGACAAGTCGATGAATGCTGAAA
RPL19	TCGCCTCTAGTGTCCTCCG	GCGGGCCAAGGTGTTTTTC
SETD1B	CTGGCTTAACGACACGCTCT	CCATCGTCCCGTTTCTTCT
SIN3A	TTACTGCATGTCCAAGTTCAAGA	CCAGGTGTCGTTCAGTACCC
SMARCD1	TGGGAGCTTCGGGTAGAAG	TGGCATCATATTTGGACAAGG
THAP3	CAGTGCTGCAACCGCTACA	CATTGTGCTTTAGGTTCTTGCG
THOC1	CGGACGCGGTTTACGAAGT	AAAAGGTGTAGATGCGGTACAAA
WDR5	GAGGAGAAGAAGCCCGAGAC	GCATAGTTTGGCTTCACAGGT

Supplementary Table 8 | Primers used to generate esiRNA

Gene Symbol	Gene ID (Entrez)	Forward Primer (5'-3')	Reverse Primer (5'-3')
ACTR8	93973	GGGCGGGTACTGCTG ACCGAAAGTCTGC	GGGCGGGTCCTCCTTT CCATGCAATCAG
BRD7	29117	GGGCGGGTCCAAGTG ATTTCAGCATCCA	GGGCGGGTGGGACCCA AGAGACAGATCA
CNOT3	4849	GGGCGGGTCCCCTCT GACTCTGAGCGTA	GGGCGGGTGCGGTACT CAAAGGTGAAGC
DPY30	84661	GGGCGGGTCAGATGC TGGAGGGACAAAC	GGGCGGGTTCTGTTGT CCGGAAGGTTCT
EPC1	80314	GGGCGGGTGGTGTATT GGATTTGCACGA	GGGCGGGTAGTGCCAG TTGCTGTTGATG
EP400	57634	GGGCGGGTTTAACTCA GCGAACCATCCA	GGGCGGGTTGGTGTAA GCTGCTCCATGA
HDAC1	3065	GGGCGGGTCGAATCC GCATGACTCATAA	GGGCGGGTTGTACAGC ACCCTCTGGTGA
INO80D	54891	GGGCGGGTCTGAAGA GAGCGGAGAGGAA	GGGCGGGTTTGTTAGC GCACTGTTCACC
KAT5	10524	GGGCGGGTGTCACCC GGATGAAGAACAT	GGGCGGGTGTTAGGAT GCAGGCCACATT
KDM1A	23028	GGGCGGGTGCCCAAA GAAACTGTGGTGT	GGGCGGGTCCCAAAAA CTGGTCTGCAAT
LEO1	123169	GGGCGGGTTGACACT GAGGTGCCAAAAG	GGGCGGGTTGCTTCCA TCTGACCACTTG
MED4	29079	GGGCGGGTGCTGTTTA CCAAGCGAAGGA	GGGCGGGTACTGCTTG AGGAGTCCGTTG
MED14	9282	GGGCGGGTATGTTCCA TGGCGTCTTCTC	GGGCGGGTGAATCAGA AGCTGGCAAAGG
MED15	51586	GGGCGGGTATTCTGAC AGACCCCTCGAA	GGGCGGGTATCCAGCT TGCAGATCAGGT
MED17	9440	GGGCGGGTCTTAGCAA GCCGAATTGAGG	GGGCGGGTCTGCCACT TTCAGGTCCATT
PHC1	1911	GGGCGGGTCATCTCCT GGGCCTTTATCA	GGGCGGGTTCTTCCCT GCAAAGTCTGCT
eGFP (Non-Targeting Control)		GGGCGGGTCCACATG AAGCAGCACGA	GGGCGGGTCGTCCTCG ATGTTGTGGC

REAGENTS AND EQUIPMENT

DNA constructs

1. pNMd0 (sgRNA expression backbone vector)
2. pSLQ1643 (TetON-dCas9-KRAB-P2A-mCherry)

Reagents

1. PCR primers for sgRNA cloning (Integrated DNA Technologies (IDT), custom DNA oligonucleotides)
2. Phusion (New England Biolabs, cat. no. M0536L)
3. LongAmp Hot Start Taq DNA Polymerase (New England Biolabs, cat. no. M0534L)
4. XhoI, XbaI, SpeI-HF, SalI-HF, BstXI (New England Biolabs, cat. no. R0146L, R0145L, R3133L, R3138L, R0113L)
5. Alkaline Phosphatase, Calf Intestinal (CIP) (New England Biolabs, cat. no. M0290L)
6. T4 DNA ligase (New England Biolabs, cat. no. M0202L)
7. QIAquick gel extraction kit (Qiagen, cat. no. 28706)
8. QIAquick PCR purification kit (Qiagen, cat. no. 28106)
9. QIAprep spin miniprep kit (Qiagen, cat. no. 27106)
10. HiSpeed Plasmid Maxi Kit (Qiagen, cat no. 12662)
11. UltraPure 10× TAE buffer (Invitrogen, cat. no. 15558-026)
12. UltraPure agarose (Invitrogen, cat. no. 16500500)
13. Ethidium bromide solution, 10 mg ml−1 (Sigma-Aldrich, cat. no. E8751)
14. All-purpose HI-LO DNA mass ladder (Bionexus, cat. no. BN2050)
15. LB medium (Sigma-Aldrich, cat. no. L3022)
16. LB agar medium (Sigma-Aldrich, cat. no. L2897)
17. Carbenicillin, sterile filtered, 100 mg ml−1 (Sigma-Aldrich, cat. no. C1613)
18. α-Select Electrocompetent Cells (BIOLINE USA Inc, cat. no. BIO-85028)
19. Mirus TransIT-LT1 transfection reagent (Mirus, cat. no. 2300)
20. DMEM-high glucose medium (Invitrogen, cat. no. 11960-044)
21. Penicillin-streptomycin (Invitrogen, cat. no. 15070-063)
22. Trypsin-EDTA solution, 0.05% (wt/vol) (Invitrogen, cat. no. 25300-062)
23. Puromycin (Sigma-Aldrich, cat. no. P9620-10ML)
24. Doxycycline (Sigma-Aldrich, cat. no. D3447-500MG)
25. ddH2O, sterile

Equipment

1. Microcentrifuge tubes, 1.7 ml (Axygen Scientific, cat. no. MCT-175-C-S)
2. Microcentrifuge (Thermo Scientific, cat. no. 75002431)
3. Manual Pipettes (P2, P20, P200, P1000) & tips
4. Multichannel pipettes (Rainin, cat. nos. L12-10 XLS+, L12-200 XLS+ and L12-1200 XLS)
5. Thermocycler with programmable temperature control, 96 wells (Bio-Rad, T100)
6. CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad)
7. Strip PCR tubes, 8 wells (Applied Biosystems, cat. no. N801-0580)

8. Gel electrophoresis system (PowerPac basic power supply, Bio-Rad, cat. no. 164-5050 and Sub-Cell GT system gel tray, Bio-Rad, cat. no. 170-4401)
9. 6 well plates (Greiner Bio One International GmbH, cat. no. 657160)
10. Incubator for bacteria plates (Thermo Scientific, cat. no. 50125590)
11. NanoDrop 8000 UV-visible spectrophotometer (Thermo Scientific)
12. Digital gel imaging system (GE)
13. Dark reader (Clare Chemical Research, Inc. DR22A)
14. BD FACSAria II sorter (BD Biosciences)
15. Tissue Culture Hood/Biosafety Cabinet
16. CO2 incubator at 37°C and 5% CO2 for mammalian cell culture
17. Cell counting system
18. Electroporator (Bio-Rad)
19. Bioanalyzer (Agilent)
20. Miseq and HiSeq2500 (Illumina)

PROCEDURE

Preparation of single and double sgRNA library

Library design

We designed a library of 358 sgRNAs targeting a set of 107 genes encoding epigenetic regulators (1~3 sgRNAs/gene) using top prediction hits from the CRISPR-ERA algorithm [7]. The library also included 41 non-targeting negative control sgRNAs (NC_1 to NC_41) and 5 positive controls targeting genes (*MCM2*, *GEMIN5*, *CENPA*, *INTS9* and *POLR1D*) strongly affecting cell proliferation. We excluded any sgRNAs containing XbaI, XhoI, SpeI, and SalI restriction sites, which were used for double sgRNA library construction.

Cloning Step 1: Construct single gRNA vector

The sgRNA expressing constructs have been previously described [8,9]. The SpeI and SalI sites were removed in the sgRNA expression construct pNMd0. The single sgRNA expression constructs were cloned as described previously with minor modifications (cloning strategy is shown in **Supplementary Fig. 1a**).

1. Assemble the following reaction (volumes shown are per reaction) in a 0.2 mL PCR tube using the following primers:

   Forward primer (sgRNA-F, N_{19} is the targeting sequence):
   5′- GGAGAACCACCTTGTTGGN$_{19}$GTTTAAGAGCTATGCTGGAAACAGCA -3′

   Reverse primer (sgRNA-R, N_{10} is the barcode sequence):
   5′-CTAGTACTCGAGN$_{10}$GCGTCGACCCTAGGGCTAGCACTAGTAAAAAAAGCACCGACTCGG TGCCAC -3′

   Assemble the following reaction:

0.5 µL	template (addgene #51024, 100 ng/µL)
2.5 µL	Forward primer (sgRNA-F) (10 µM)
2.5 µL	Reverse primer (sgRNA-R) (10 µM)
2 µL	dNTPs (10 mM)
0.5 µL	Phusion high-fidelity polymerase (2 U/µL)
42 µL	Nuclease-free water
50 µL	TOTAL VOLUME

   Cycling conditions

1 cycle	98°C	30 sec
25 cycles	98°C	10 sec
	62°C	30 sec
	72°C	10 sec
1 cycle	72°C	5 min
1 cycle	4°C	Forever

2. Check reaction products by running 5 µL of the reaction on a 1% agarose gel. Successful PCR reactions should show a ~185 bp DNA product.
3. Add 1µL DpnI (20 U/µL) into each PCR reaction, incubate at 37°C for 1 h.

4. Purify PCR products using QIAquick PCR purification kit by following the manufacturer's instructions.
5. To digest pNMd0 sgRNA backbone assemble the following reaction:

2 µL	pNMd0 sgRNA backbone (1 µg/µL)
2 µL	BstXI (10 U/µL)
1 µL	XhoI (20 U/µL)
5 µL	10x Buffer 3
40 µL	Nuclease-free water
50 µL	TOTAL VOLUME

Incubate at 37°C for 1 hour.

6. Gel-purify ~9.7 kbp products by 0.8% agarose gel electrophoresis and QIAquick gel extraction kit following the manufacturer's instructions.
7. Measure the concentrations of the sgRNA backbone vector and sgRNA PCR fragments using a NanoDrop 8000 spectrophotometer.
8. To clone the new sgRNA fragments into the sgRNA expression vector, assemble the following In-Fusion cloning reaction::

1 µL	5X In-Fusion HD enzyme premix
50 ng	Linearized sgRNA backbone vector
25 ng	Purified new sgRNA PCR fragments
x µL	ddH2O
5 µL	TOTAL VOLUME

Incubate for 15 min at 50°C followed by 5 min incubation on ice.

9. Transform the In-Fusion reactions into chemically competent E. coli cells according to the manufacturer's instructions.Plate onto a LB agar plate supplemented with 100 µg/mL carbenicillin and Incubate at 37°C overnight.
10. Confirms successful cloning by Sanger sequencing 2-3 bacterial colonies. Construct the single sgRNA library by mixing equal amounts of each of the single sgRNA constructs. This pool is then split in two and used as storage and target vector pools.

Cloning Step 2: Construct double gRNA library

In order to enable the insertion of the mU6-sgRNA expression cassettes and construct higher order (double) sgRNA constructs we utilize unique SpeI and SalI sites introduced in the sgRNA expressing vector. Constructs for mU6-driven expression of pairs of sgRNAs were generated by digesting the storage vectors with XbaI and XhoI enzymes and ligating the mU6-sgRNA cassettes into the target vectors backbone digested with SpeI and SalI (**Supplementary Fig. 1b)**.

1. Prepare single sgRNA library in target vector pool and storage vector pool.
2. Digest target vector pool with SpeI-HF and SalI-HF:

Assemble the following reaction:

2 µL	target vector pool (1 µg/µL)
1 µL	SpeI-HF (20 U/µL)

1 µL	SalI-HF (20 U/µL)
5 µL	10x CutSmart Buffer
41 µL	Nuclease-free water
50 µL	TOTAL VOLUME

Incubate at 37°C for 1 hour.

3. Gel-purify ~10 kbp DNA products using 1% agarose gel electrophoresis and QIAquick gel extraction kit by following the manufacturer's instructions.
4. Digest storage vector pool with XbaI and XhoI:

2 µL	storage vector pool (1 µg/µL)
1 µL	XbaI (20 U/µL)
1 µL	XhoI (20 U/µL)
5 µL	10x CutSmart Buffer
41 µL	Nuclease-free water
50 µL	TOTAL VOLUME

Incubate at 37°C for 1 hour.

5. Gel-purify ~480 bp DNA products using 1% agarose gel electrophoresis and QIAquick gel extraction kit by following the manufacturer's instructions.
6. Ligate the pooled inserts and pooled backbones:

Assemble the following reaction:

2 µL	10X T4 DNA Ligase Buffer
100ng	pooled inserts
300ng	pooled backbones
1 µL	T4 DNA Ligase
X µL	Nuclease-free water
20 µL	TOTAL VOLUME

Incubate at 16°C for 12-16 hours followed by heat inactivation at 65°C for 10 minutes.

7. Transform 2 µL of the ligation reaction into 100 µL of α-Select Electrocompetent Cells according to the manufacturer's protocol using a Bio-Rad Electroporator. Spread a small fraction (100µL) of cultures on carbenicillin (100 µg/ml) LB plates and grow overnight at 30°C. Calculate the ligation and transformation efficiency, and scale up the ligation and transformation to reach at least 50x double library coverage.
8. Extract plasmid DNA using HiSpeed Plasmid Maxi Kit (Qiagen). Library diversity is determined by deep sequencing.

Lentivirus production

Note: it is important to use mycoplasma-free HEK 293T cells for the production of lentiviral particles. This protocol is for 6 well plates. The experiment can be scaled up.

1. Seed a six-well tissue-culture plate with 2~3 x 10^5 HEK 293T cells in 2 mL DMEM high-glucose medium containing 10% FBS per well 24 h before transfection. Incubate at

37°C and 5% CO2 in a CO2 incubator, overnight.

2. 24 h after plating the cells, prepare a 3 μg DNA mixture by adding 1.32 μg dR8.91, 165 ng MD2.G lentiviral packaging plasmids and 1.51 μg dCas9 or sgRNA expression vector. Add the mixture to 250 μL Opti-MEM reduced-serum medium in a microcentrifuge tube. Mix well by pipetting up and down.
3. Add 7.5 μL Mirus TransIT-LT1 transfection reagent into the 250 μL Opti-MEM reduced-serum medium. Mix well by pipetting up and down. Allow transfection complexes to form for 30 min at room temperature.
4. Add 250 μL of Opti-MEM with DNA and transfection reagent mixture to the well in the six-well plate. Mix the well by rocking the plate gently back and forth. Incubate at 37°C and 5% CO2 in a CO2 incubator for 24 h.
5. Replace the transfection medium with 2.5 mL fresh DMEM medium with 10% FBS to collect lentiviruses. Harvest the viral supernatant at 24~48 h after medium replacement using a sterile syringe. Filter the medium through a 0.45 μm syringe filter into a conical tube to avoid transferring HEK 293T cells to target cells.

Generation of TetON-dCas9-KRAB HEK 293 cells

1. Package TetON-dCas9-KRAB-P2A-mCherry expressing lentiviral vector (pSLQ1643) and rtTA expressing vector into viral particles as described in '**Lentivirus production**'
2. Plate 1.5~2 x 10^5 HEK 293 cells per well in a six-well plate with 2 mL DMEM medium supplemented with 10% FBS per well 16 h before transduction.
3. Replace the medium with 1 mL DMEM with 10% FBS and 1 mL filtered viral supernatant (TetON-dCas9-KRAB-P2A-mCherry : rtTA is 1:1), and incubate overnight at 37°C and 5% CO2 in a CO2 incubator.
4. Replace the viral supernatant with 2 mL fresh DMEM with 10% FBS and incubate at 37°C and 5% CO2 in a CO2 incubator.
5. 24 hours after lentivirus transduction, add 1 μg/μL Dox to induce dCas9-KRAB-P2A-mCherry expression. 24h later, sort the red fluorescent protein (mCherry) positive cells into 96 well plates by using a BD FACSAria II sorter, and incubate the clonal cells collected at 37°C and 5% CO2 in a CO2 incubator.
6. Clones displaying high mCherry expression upon Dox induction and undetectable mCherry expression in the absence of Dox were selected for further characterization.

Competitive growth experiments

Note: It is important to maintain high cell coverage (> 1000X) at all stages of the competitive growth experiment. Also, at least 2 biological replicates are needed for each growth assay.

1. Package the pooled library of single and double gRNA constructs into lentivirus (see '**Lentivirus production'**)
2. Titer the library virus in the TetON-dCas9-KRAB HEK 293 cells by serial dilution.
3. The target TetON-dCas9-KRAB HEK 293 cells were transduced with the packaged libraries in the presence of 8 μg/ml polybrene (Sigma) at a multiplicity of infection (MOI) of about 0.3 (corresponding to an infection efficiency of 30-40%) to ensure single copy integration in most infected cells.
4. 48h after infection, add 1 μg/mL Puromycin for 3 days.
5. After Puromycin selection, the cells were split into 2 pools treated with Dox or without

Dox. Cells were maintained for minimum desired coverage (1000X library size) and harvested at 0, 9 or 16 days for single sgRNA library screening, or at 0, 8 or 16 days for double sgRNA screening.

6. Extract DNA from cells harvested at 0, 9, 16day (for single screen) or 0, 8, 16day (for double screen) time points using the Blood and Cell Culture DNA Mini (for single screen) or Maxi (for double screen) Kit (Qiagen) according to manufacturer instructions.

NGS library preparation

1. Digest the genomic DNA (gDNA) with MfeI-HF restriction enzyme. Adjust volumes of gDNA using ddH_2O, and set up reactions using NEB CutSmart buffer as below. The reaction volume can be scaled up or down.

   Assemble the following reaction:

1.2 mL	gDNA sample
134 µL	10X CutSmart Buffer
5 µL	MfeI-HF (20 U/µL)
1.34 mL	TOTAL VOLUME

   Incubate at 37°C overnight.

2. Run all the samples in 0.8% agarose gel, stain the gel with EtBr, and excise region of interest around ~1000-3000 bp (CRISPR sgRNA fragment size ~ 1650 bp) using blue light to visualize the DNA.
3. Gel-purify by using QIAGEN Gel extraction kit. Concentrate the purified gDNA fragment to 30 µL (for single screen sample) or 1.5 mL (for double screen sample).
4. Setup 100 µL PCR reactions (in multiples) using purified gDNA template (**Supplementary Fig. 1c**):
   Note: split reactions into 50 wells of 8-tube PCR strips (100 µL / well) for double screen gDNA.

Name	**Sequence (5'-3')**
Single forward primer (single-F):	*AATGATACGGCGACCACCGAGATCTACACGGTAATACGGTTATCCACGCGG*
Single reverse primer (single-R, N_8 is the index):	*CAAGCAGAAGACGGCATACGAGATN_8GCACAAAAGGAAACTCACCCT*
Double forward primer (double-F):	*AATGATACGGCGACCACCGAGATCTACACTGAGACTATAAGTATCCCTTGGAGA*
Double reverse primer (double-R, N_6 is the index):	*CAAGCAGAAGACGGCATACGAGAT N_6CTGGCGAACTACTTACTCTAGCTTCCCGGCAACGCCTTATTTAAACTTGCTATGCTGT*

Assemble the following reaction:

30 µL	Template gDNA
20 µL	5X LongAmp *Taq* Reaction Buffer
3 µL	10 mM dNTPs
4 µL	Forward primer (10 µM)
4 µL	Reverse primer (10 µM)
4 µL	LongAMP *Taq* (2.5 U/µL)
35 µL	Milli-Q Water
100 µL	total volume

Cycling conditions

1 cycle	94°C	30 sec
19 cycles	94°C	25 sec
	60°C	25 sec
	65°C	1 min
1 cycle	65°C	10 min
1 cycle	4°C	Forever

5. Purify pooled PCR reactions using QIAquick PCR purification kit according to manufacturer protocols.
6. Run the purified sample in 1.5% agarose gel, stain the gel with EtBr, and excise the band of interest around ~ 350 bp (for single screen) or ~ 650 bp (for double screen).
7. Gel-purify using QIAGEN Gel extraction kit according to manufacturer protocols and measure the DNA concentrations using the Nanodrop.
8. Determine DNA purity and ~350 bp fragment (for single screen) and ~ 650 bp (for double screen) concentrations using Bioanalyzer.
9. Pool samples for sequencing, according to Bioanalyzer results.

Next-generation sequencing (NGS)

To identify both gRNA on each construct 75 bp paired-end reads are required. The sequencing primers and strategy are shown in **Supplementary Fig. 1c**. Given the lack of base diversity in the amplicon it is necessary to spike in ~20% PhiX when sequencing using Illumina HiSeq Rapid run. Sequencing primers are as follows:

Name	Sequence (5'-3')
Single read1 primer	CCACGCGGCCGCCTAATGGATCCTAG
Single read2 primer	GTGTGTTTTGAGACTATAAGTATCCCTTGGAGAACCACCTTGTTGG
Single index read primer	GTCTCAAAACACACAATTACTTTACAGTTAGGGTGAGTTTCCTTTTGTGC
Double read1 primer	CGAAGTTATAAACAGCACAAAAGGAAACTCACCCTAACTGTAAAGTAATTGTGTG
Double read2 primer	GCACCGACTCGGTGCCACTTTTTCAAGTTGATAACGGAC
Double index read primer	GTTTAAATAAGGCGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAG

Data processing and calculation of genetic interaction scores

Raw counts were extracted from FASTQ files using a software pipeline (code available upon request). Briefly, reads containing sgRNA sequences are identified, paired reads are matched, sgRNA sequences are extracted and matched to their respective targets.

Raw counts were processed and scored using the S-score [10] framework. Detailed explanation of all the steps can be found in the **Supplementary Materials and Methods** section accompanying the manuscript.

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Figure	panel	data
Figure 1		
	b	Supplementary_Dataset_3:day16_r2-3
	c	Supplementary_Dataset_3:day16_r2-3
	d	Supplementary_Dataset_3:Figure 1d.xlsx
	e	Supplementary_Dataset_3:day16_r1-8
	f	Supplementary_Dataset_3:Figure 1f.xlsx
	g	Supplementary_Dataset_3:day16_r2-3
		Supplementary_Dataset_3:day0_r1
		Supplementary_Dataset_3:day8_r1-2
Figure 2		
	a	Supplementary_Dataset_3:day16_r1-7
		Supplementary_Dataset_1
	b	Supplementary_Dataset_3:Figure 2b.xlsx
	c	Supplementary_Dataset_3:Figure 2c.xlsx
Supplementary Figure 2		
	a	Supplementary_Dataset_3:Figure S2a qPCR raw data.xlsx
		Supplementary_Dataset_3:Figure S2a 19 growth bargraph.xlsx
	b	Supplementary_Dataset_3:Figure S2b.xlsx
	c	Supplementary_Dataset_3:Figure S2c.xlsx
	d	Supplementary_Dataset_3:Figure S2d.xlsx
Supplementary Figure 3		
	b	Supplementary_Dataset_3:Figure S3b.xlsx
Supplementary Figure 4		
	a	Supplementary_Dataset_3:day0_r1-2

		Supplementary_Dataset_3:double_lib_before_pack
	b	Supplementary_Dataset_3:Figure S4b.xlsx
	c-d-e-f	Supplementary_Dataset_3:Figure S4c-f.xlsx
	g	Supplementary_Dataset_3:day0_r1-2
	h	Supplementary_Dataset_3:day8_r1-2
	i	Supplementary_Dataset_3:day8_r1-2
	j	Supplementary_Dataset_3:Figure S4j.xlsx
	k	Supplementary_Dataset_3:day8_r1
		Supplementary_Dataset_3:day0_r1
		Supplementary_Dataset_3:day16_r1
	l-m	Supplementary_Dataset_3:Figure S4l-m.xlsx
	n	Supplementary_Dataset_3:day0_r1-2
		Supplementary_Dataset_3:day8_r1-2
	o	Supplementary_Dataset_3:day0_r1-2
		Supplementary_Dataset_3:day16_r1-8
	p	Supplementary_Dataset_3:Figure S4p.xlsx
	q	Supplementary_Dataset_3:day16_r2
		Supplementary_Dataset_3:day16_r3
Supplementary Figure 5		
	a	Supplementary_Dataset_3:Figure S5a.xlsx
	b	Supplementary_Dataset_3:day8_r1-2
	c	Supplementary_Dataset_3:Figure S5c.xlsx
	d	Supplementary_Dataset_3:day8_r2

		Supplementary_Dataset_3:day16_r3
	e	Supplementary_Dataset_3:Figure S5e.xlsx
	f	Supplementary_Dataset_3:day0_r1
		Supplementary_Dataset_3:day8_r2
		Supplementary_Dataset_3:day16_r3
		Supplementary_Dataset_3:Figure S5f.xlsx
Supplementary Figure 6		
	a	Supplementary_Dataset_3:Figure S6a.xlsx
	b	Supplementary_Dataset_3:day16_r1
	c-d	Supplementary_Dataset_3:Figure S6c-d growth validation curve.xlsx
		Supplementary_Dataset_3:Figure S6c-d qPCR for growth validation pairs.xlsx
Supplementary Figure 7		
	a	Supplementary_Dataset_3:day16_r1-7
	b	Supplementary_Dataset_2:Day0 day9 day16 replicates:day0
	c	double_lib_before_pack
	d	Supplementary_Dataset_3:day16_r1
		Supplementary_Dataset_3:day16_r8
	e	Supplementary_Dataset_3:day16_r3
Supplementary Figure 8		
	a	Supplementary_Dataset_3:Figure S8.xlsx