

Supplementary Information

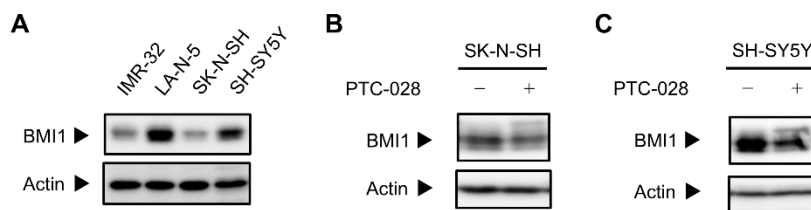
Pharmacologic inhibition of BMI1 exerts antitumor effects against MYCN-amplified neuroblastoma, with activation of the p53 pathway

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Components

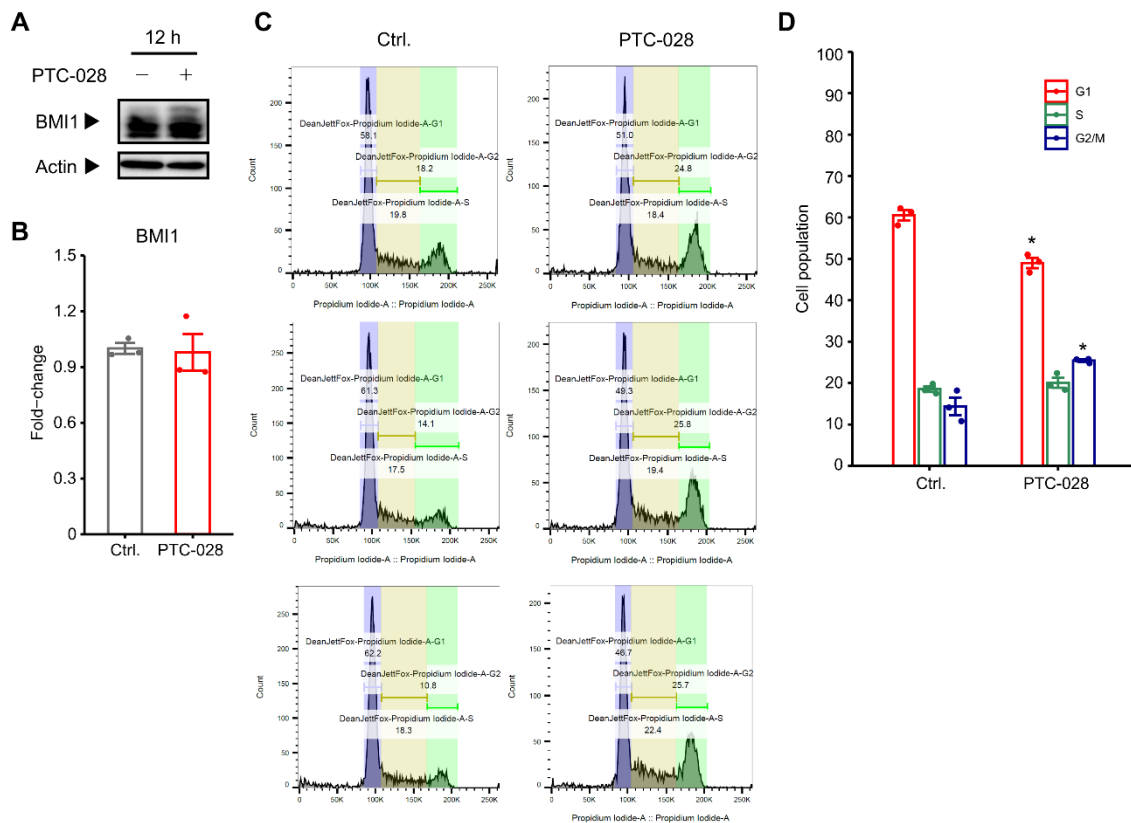
Twelve Supplementary Figures

Six Supplementary Tables



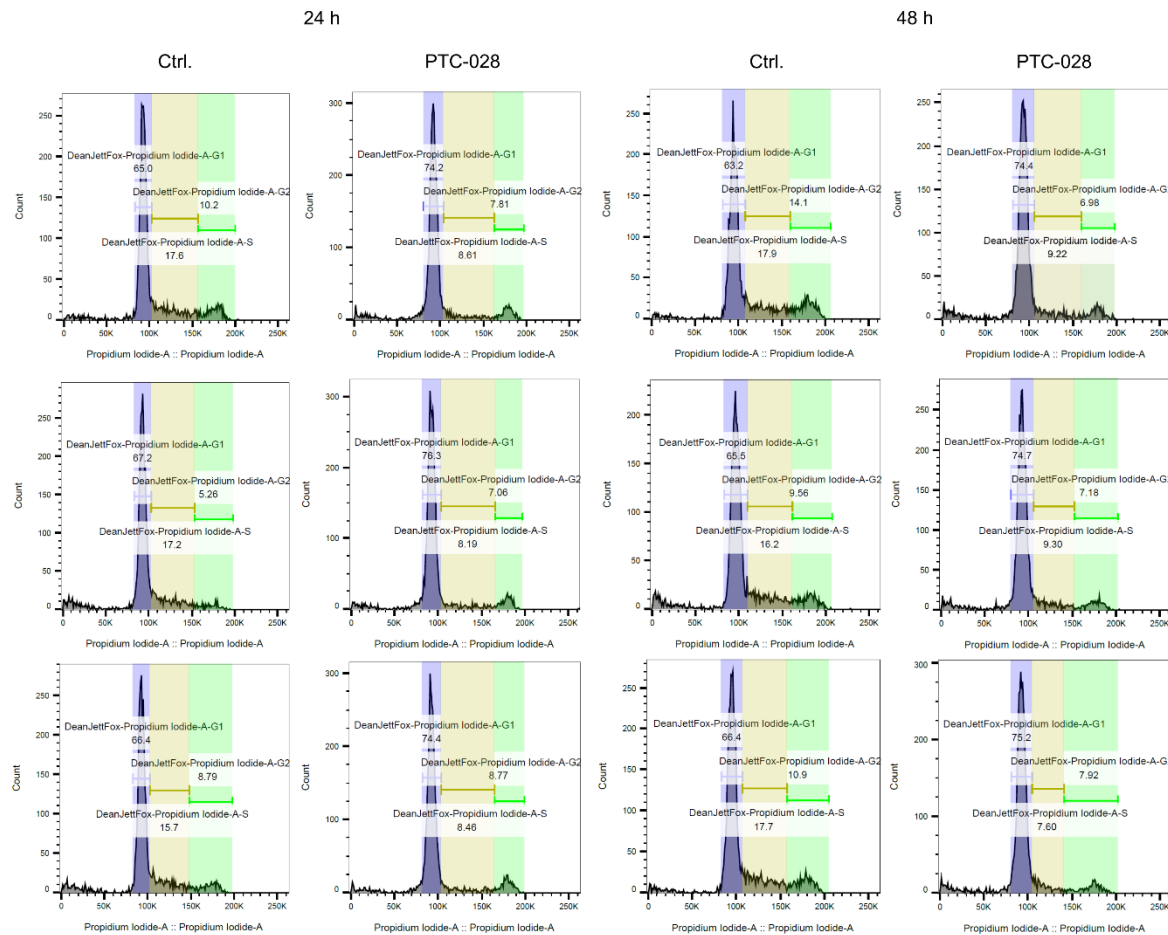
Supplementary Figure 1. Expression of BMI1 in four cell lines.

(A) Western blotting analysis of BMI1 expression in IMR-32, LA-N-5, SK-N-SH, and SH-SY5Y cells at steady state. Uncropped blots are shown in Figure S8. (B) Western blotting analysis of BMI1 in SK-N-SH cells 24 h after initiation of PTC-028 treatment. Uncropped blots are shown in Figure S8. (C) Western blotting analysis of BMI1 in SH-SY5Y cells 24 h after initiation of PTC-028 treatment. Uncropped blots are shown in Figure S8.



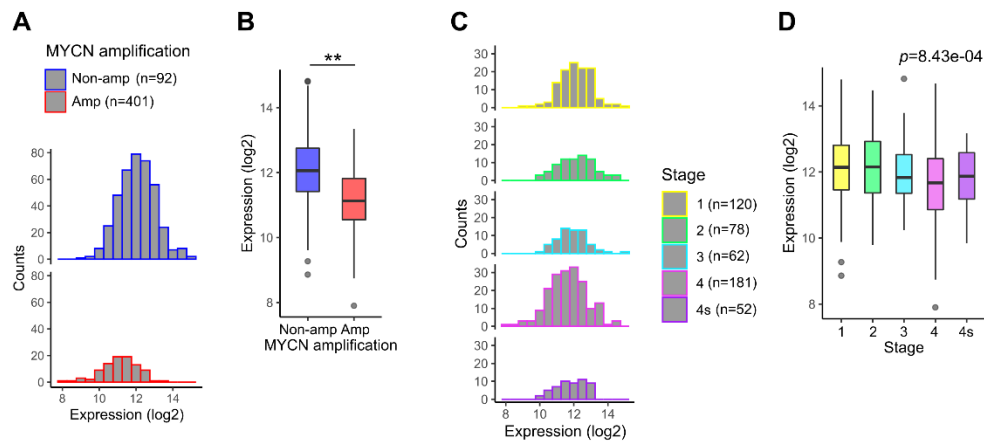
Supplementary Figure 2. Analysis of cell cycle progression in MYCN-amplified neuroblastoma following 12 h of treatment with PTC-028.

(A) Western blotting analysis of BMI1 in IMR-32 cells 12 h after initiation of PTC-028 treatment. Uncropped blots are shown in Figure S8. (B) Quantification of BMI1 as determined by Western blotting analysis. Protein level was normalized to that of actin. Data are presented as mean $\pm$ SE ($n = 3$; * $p < 0.05$, ** $p < 0.01$ vs. control; Student's t -test). (C) Original plots of assays of cell cycle progression of IMR-32 cells 12 h after initiation of PTC-028 treatment, as determined by flow cytometry using PI staining. (D) Percentage of IMR-32 cells in each cell cycle phase, as determined by PI staining. Data are presented as mean $\pm$ SE ($n = 3$; * $p < 0.05$, vs. control; Tukey's multiple comparison test).



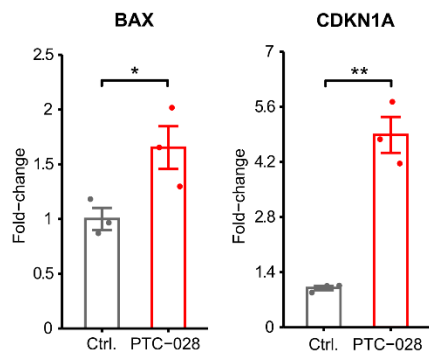
Supplementary Figure 3. Original data from cell cycle progression assays after 24 h or 48 h of treatment with PTC-028.

Original plots of assays of cell cycle progression of IMR-32 cells 24 h or 48 h after initiation of PTC-028 treatment, as determined by flow cytometry using PI staining.

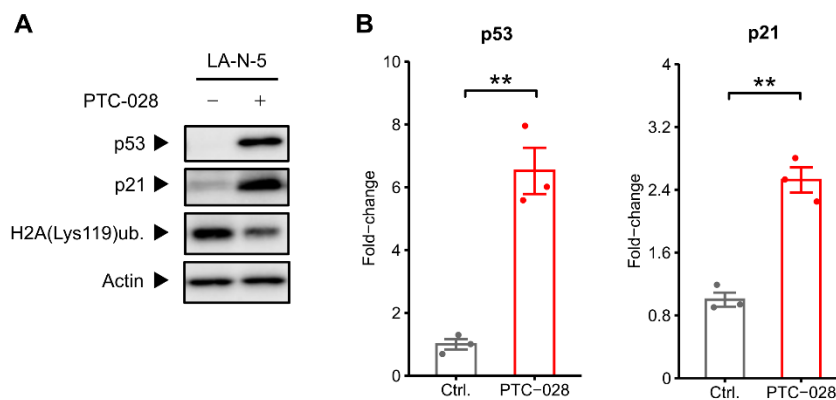


Supplementary Figure 4. Analysis of CDKN1A expression in clinical samples.

(A-D) Analysis of CDKN1A expression using a microarray data set, SEQC (Tumor Neuroblastoma-SEQC-498-custom-ag44kcwof). Histograms (A) and box plot (B) showing the relationship between CDKN1A expression level and MYCN amplification in neuroblastoma (** $p < 0.01$; Student's t -test). Another set of histograms (C) and box plot (one-way ANOVA) (D) show the relationship between CDKN1A expression and neuroblastoma stage (INSS).

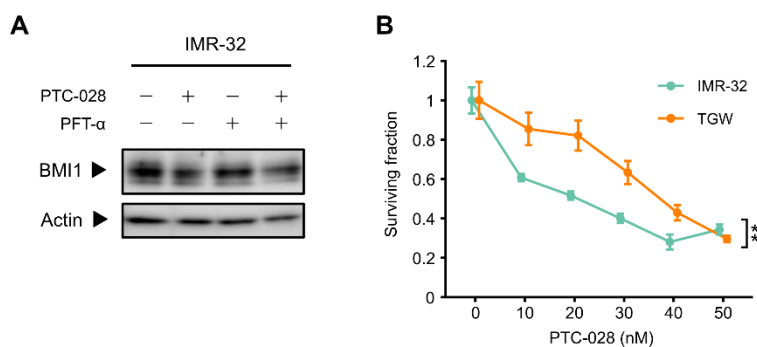


Supplementary Figure 5. Validation of RNA-seq results by PCR analysis of BAX and CDKN1A expression. Relative quantitation of BAX and CDKN1A mRNA expression following 24 h of treatment with PTC-028. mRNA levels were normalized to that of GAPDH. Data are presented as mean $\pm$ SE ($n = 3$; * $p < 0.05$, ** $p < 0.01$; Student's t -test).



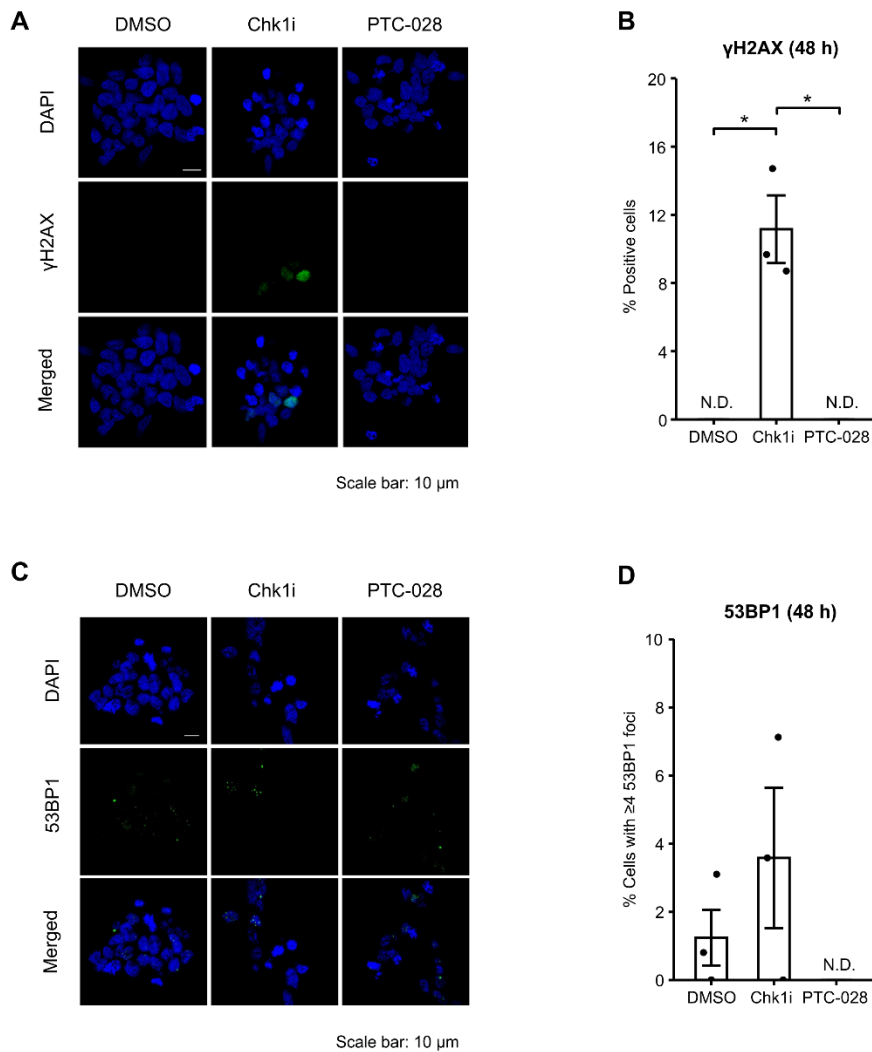
Supplementary Figure 6. Expression of proteins related to the p53 pathway in LA-N-5 cells following treatment with PTC-028.

(A) Western blotting analysis of p53, p21, and H2Aub.(K119) in LA-N-5 cells 48 h after initiation of PTC-028 treatment. Uncropped blots are shown in Figure S8. (B) Relative quantitation of p53 and p21 as determined by Western blotting analysis. Protein levels were normalized to that of actin. Data are presented as mean $\pm$ SE ($n = 3$; ** $p < 0.01$; Student's t -test).



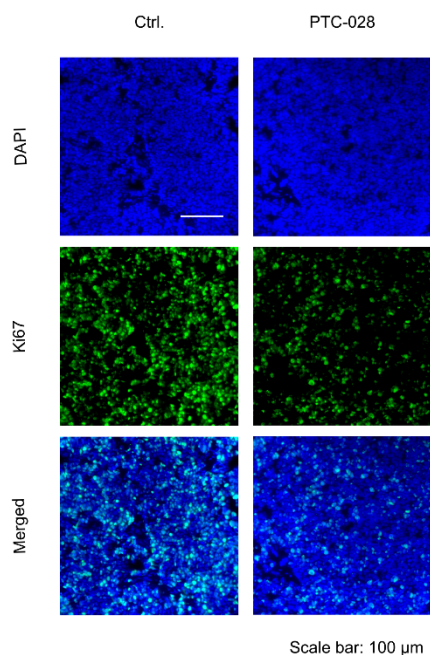
Supplementary Figure 7. Analysis of PTC-028 toxicity against MYCN-amplified neuroblastoma cell lines with p53 dysfunction.

(A) Western blotting analysis of BMI1 in IMR-32 cells 48 h after initiation of PTC-028 alone, pifithrin- α (PFT- α), or combined PTC-028 and pifithrin- α . Uncropped blots are shown in Figure S8. (B) Surviving fraction of TGW cells and IMR-32 cells under PTC-028 treatment for 48 h, as determined using the WST-8 assay. Data are presented as mean $\pm$ SE ($n = 6$; ** $p < 0.01$ vs. IMR-32 group; two-way ANOVA).



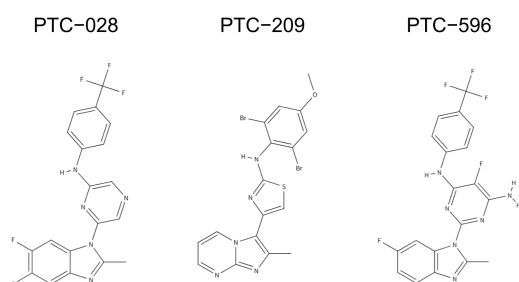
Supplementary Figure 8. Analysis of DNA damage in MYCN-amplified neuroblastoma cells following 48 h of treatment with PTC-028.

(A) Immunofluorescence staining of γ H2AX (green) in LA-N-5 cells treated with PTC-028 for 48 h. DAPI = blue. Scale bar = 10 μ m. (B) Ratio (%) of γ H2AX-positive LA-N-5 cells. Data are presented as mean $\pm$ SE ($n = 3$; 3 fields/well; $*p < 0.05$, vs. control; Tukey's multiple comparison test; N.D., not detected). (C) Immunofluorescence staining of 53BP1 (green) in LA-N-5 cells treated with PTC-028 for 48 h. DAPI = blue. Scale bar = 10 μ m. (D) Ratio (%) of LA-N-5 cells with four or more 53BP1 foci. Data are presented as mean $\pm$ SE ($n = 3$; 3 fields/well; $*p < 0.05$, vs. control; Tukey's multiple comparison test; N.D., not detected)



Supplementary Figure 9. Analysis of Ki67 expression in tumor xenografts.

Representative images of immunohistochemical staining of Ki67 (green) in tumor xenografts 14 days after the commencement of treatment. DAPI = blue. Scale bar = 100 μm .



Supplementary Figure 10. Chemical structures of three BMI1 inhibitors.

Chemical structures of PTC-028, PTC-209, and PTC-596.

Figure 2A

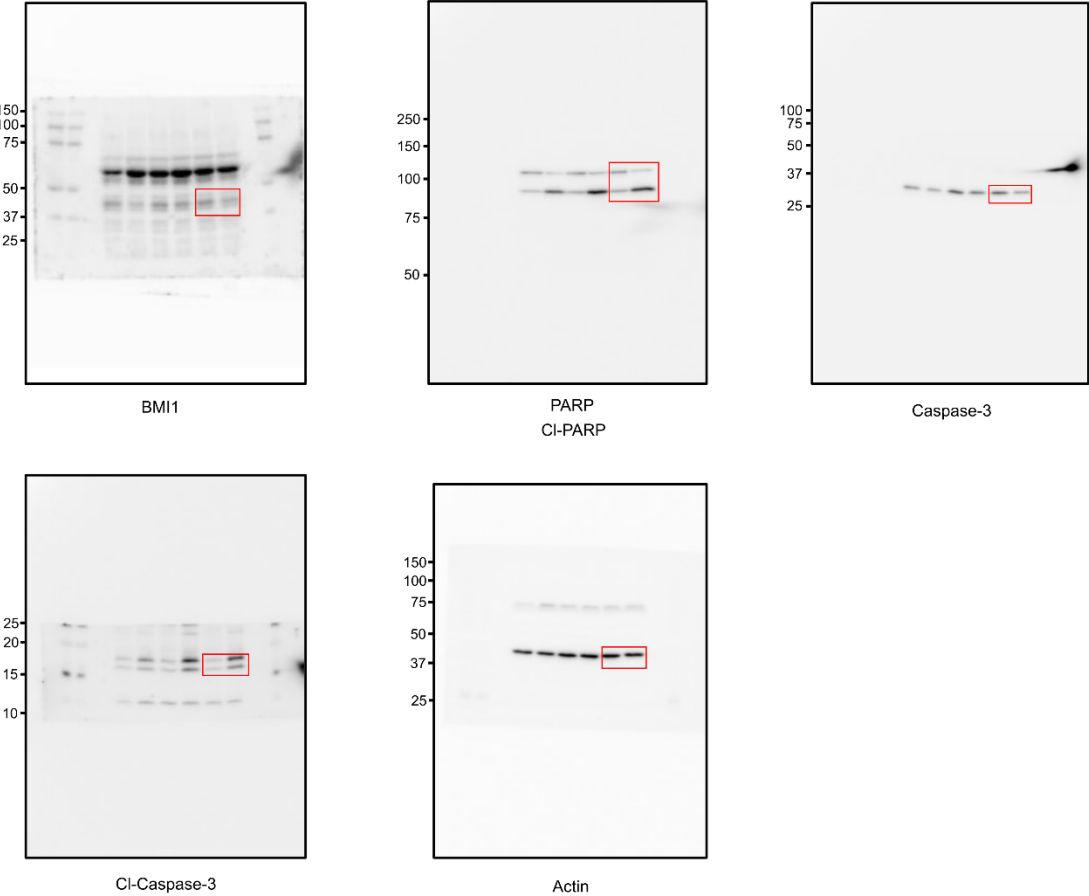
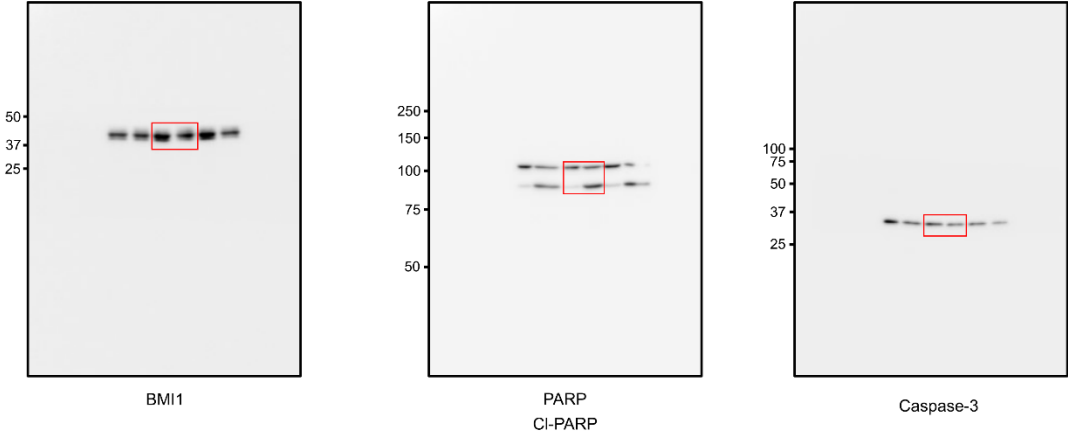
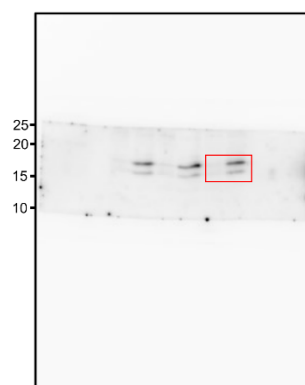
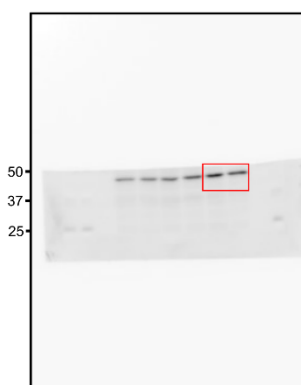


Figure 2C



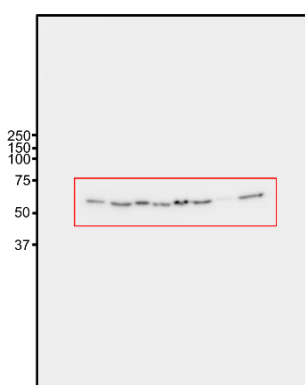


Cl-Caspase-3

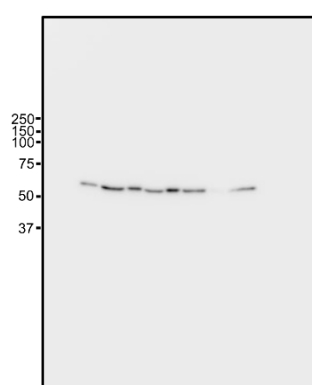


Actin

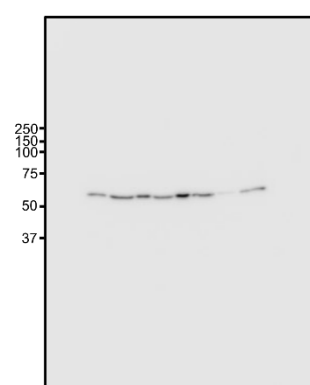
Figure 2F



α-Tubulin #1

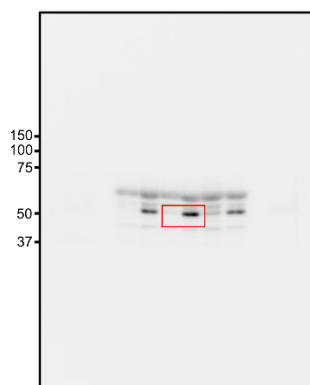


α-Tubulin #2

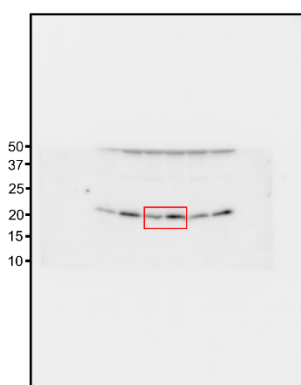


α-Tubulin #3

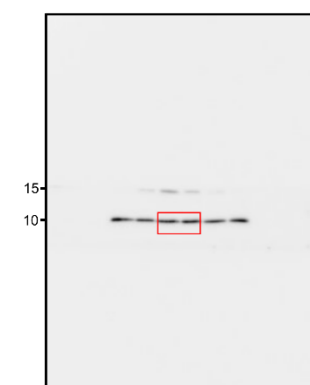
Figure 4A (24 h)



p53



p21



NOXA

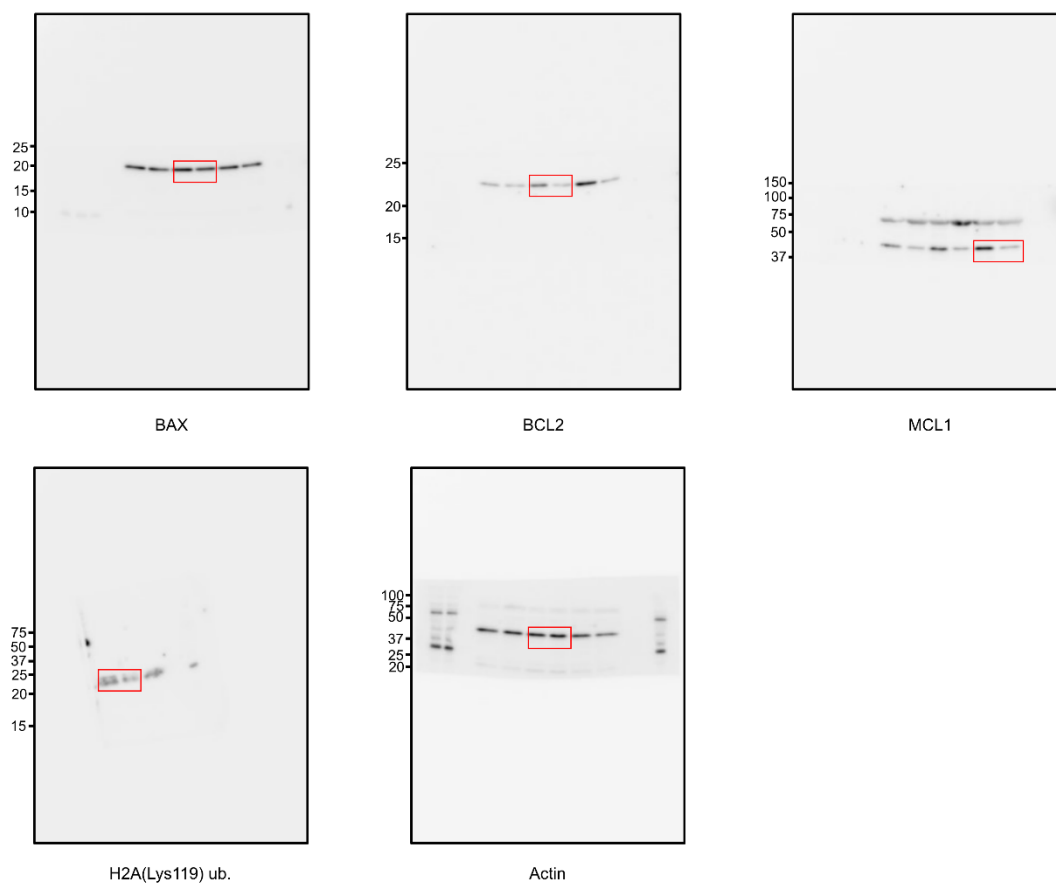
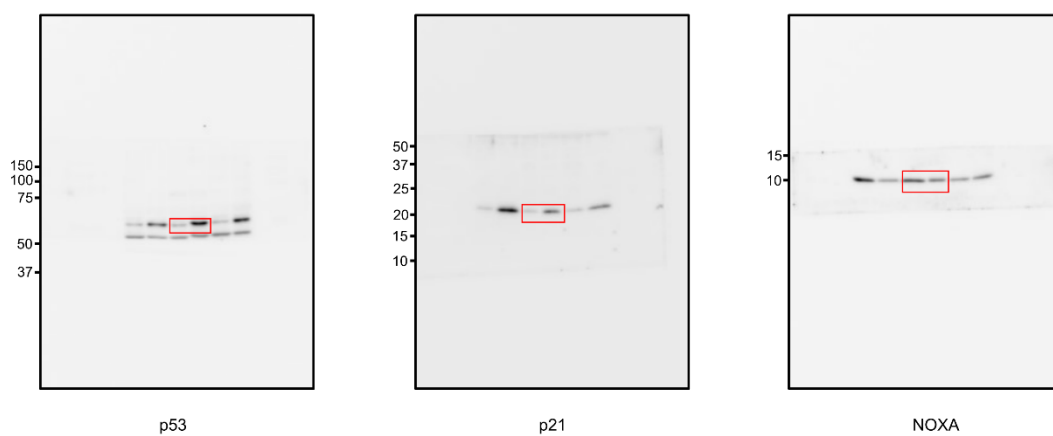
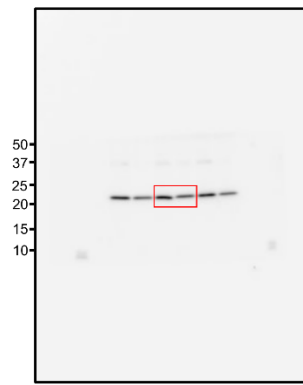
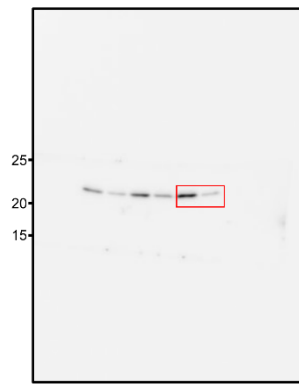


Figure 4A (48 h)

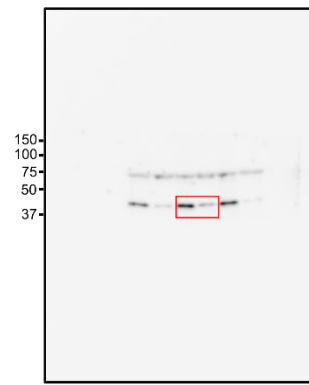




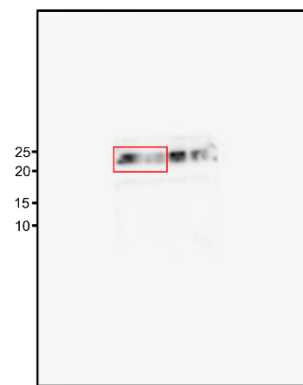
BAX



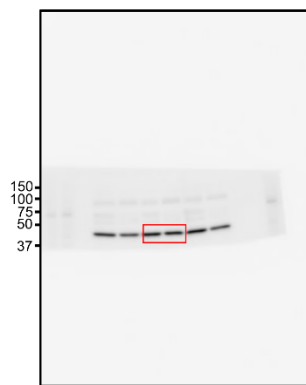
BCL2



MCL1

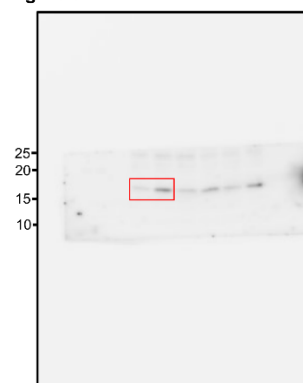


H2A(Lys119) ub.

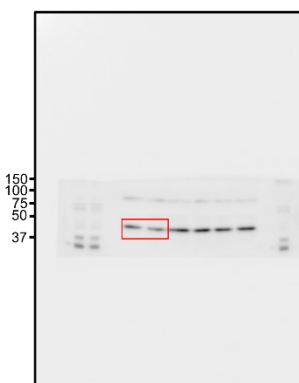


Actin

Figure 5A



γH2AX



Actin

Figure 5B

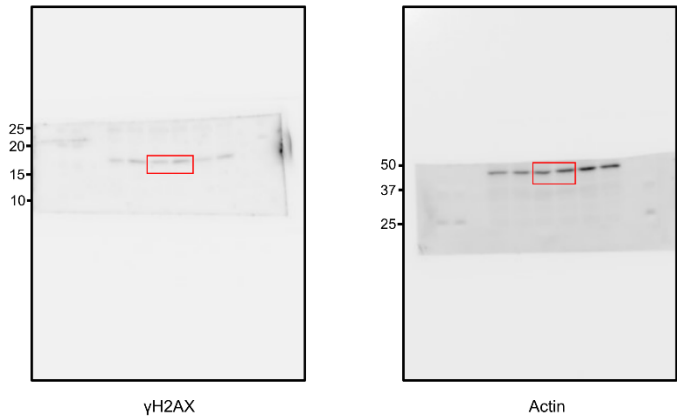


Figure S2A

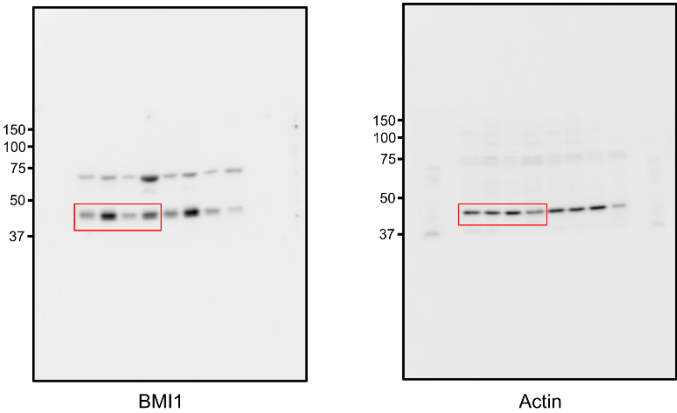


Figure S2B,C

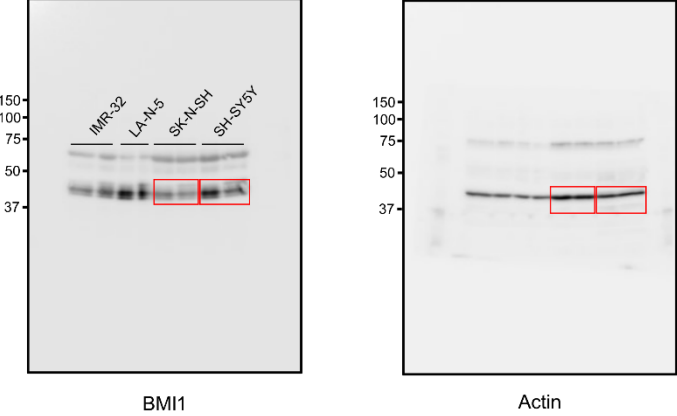


Figure S3A

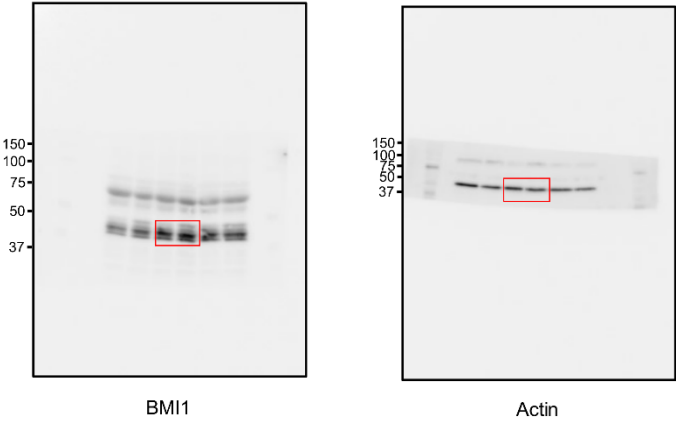


Figure S7A

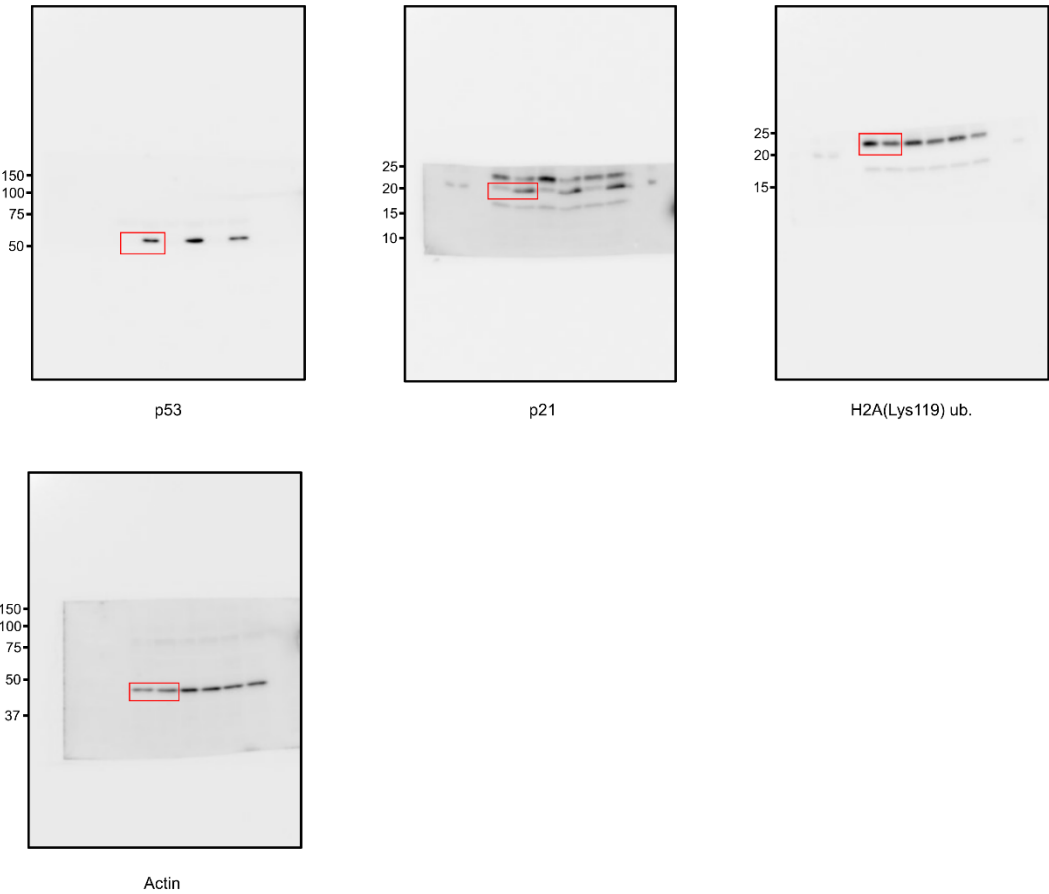
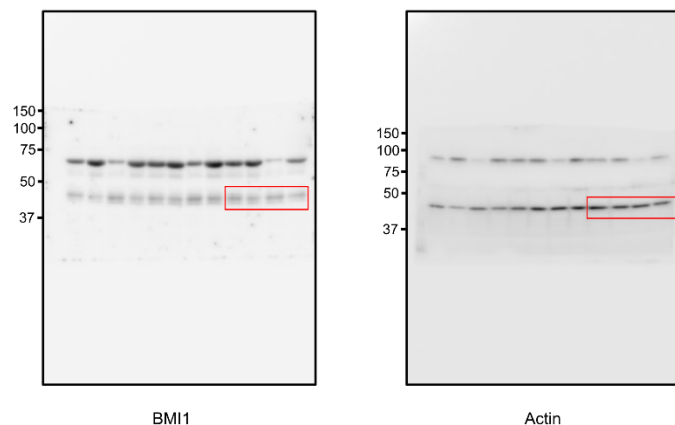
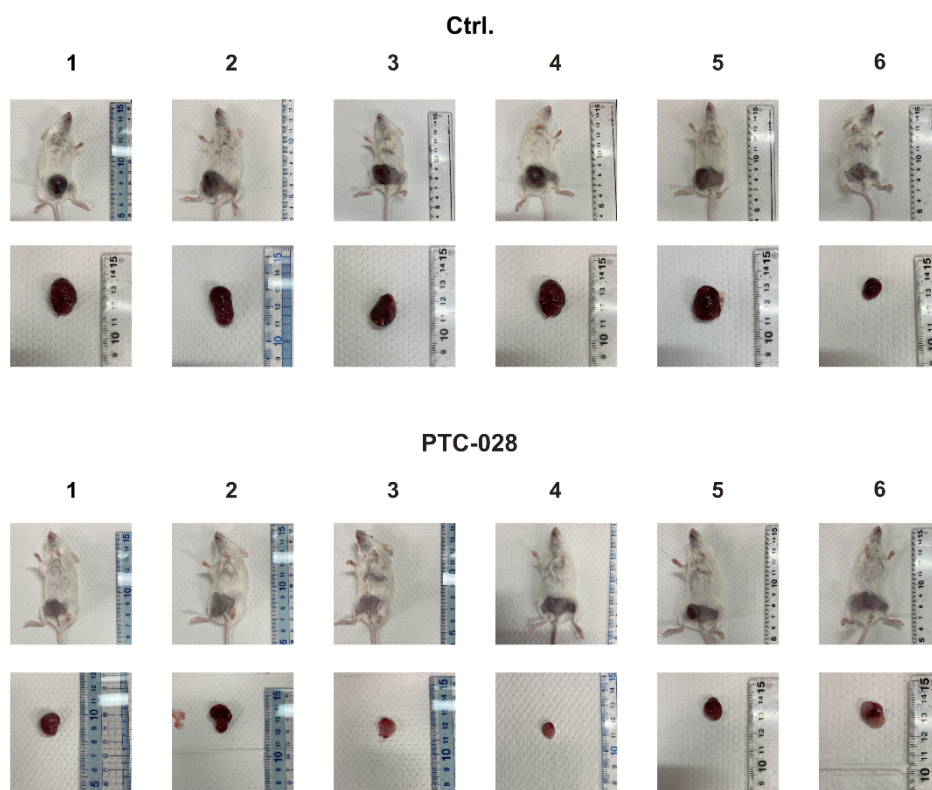


Figure S8A



Supplementary Figure 11. Uncropped blots of cropped images shown in the figures.

Uncropped images of all Western blots shown in the figures. Cropped areas presented in the figures are indicated by red boxes.



Supplementary Figure 12. Images of all mice and tumors examined in the study.
 Images of mice before tumor dissection in the xenograft experiment and tumors after dissection.

Supplementary Table 1. Upregulated genes in PTC-028-treated IMR-32 cells

ENSG	Symbol	log2FC	<i>p</i> value	q value
ENSG00000124762.13	CDKN1A	1.887004145	1.48E-138	3.47E-134
ENSG00000275430.3	MUC20	1.742672701	0.000101216	0.006372558
ENSG00000145632.14	PLK2	1.565889648	4.15E-19	4.44E-16
ENSG00000105327.17	BBC3	1.514401936	2.53E-28	9.94E-25
ENSG00000229524.10	BAG6	1.388813893	1.04E-09	2.57E-07
ENSG00000131080.14	EDA2R	1.352116099	4.19E-24	9.86E-21
ENSG00000163046.15	ANKRD30BL	1.339320811	1.31E-13	6.84E-11
ENSG00000205592.14	MUC19	1.325605906	8.11E-21	1.01E-17
ENSG00000107796.13	ACTA2	1.250117504	3.33E-09	7.62E-07
ENSG00000158373.8	HIST1H2BD	1.247209903	2.44E-08	4.56E-06
ENSG00000168918.13	INPP5D	1.228731818	1.48E-17	1.24E-14
ENSG00000241790.2	ENO1P4	1.216035805	1.61E-08	3.15E-06
ENSG00000184678.10	HIST2H2BE	1.201965566	7.18E-10	1.90E-07
ENSG00000080546.13	SESN1	1.15821759	1.09E-26	3.20E-23
ENSG00000164938.13	TP53INP1	1.15750419	3.11E-40	3.67E-36
ENSG00000180573.9	HIST1H2AC	1.147182645	4.16E-07	5.77E-05
ENSG00000274487.1	AC244154.1	1.146480422	1.99E-05	0.001652001
ENSG00000174307.6	PHLDA3	1.111613957	7.38E-22	1.24E-18
ENSG00000143217.8	NECTIN4	1.097236106	8.87E-11	2.79E-08
ENSG00000163071.10	SPATA18	1.091922335	4.28E-10	1.25E-07
ENSG00000270276.2	HIST2H4B	1.071922429	4.59E-06	0.000507554
ENSG00000142627.12	EPHA2	1.066373041	7.00E-09	1.51E-06
ENSG00000120738.7	EGR1	1.063159668	6.48E-10	1.73E-07
ENSG00000132510.10	KDM6B	1.04509415	1.05E-18	9.92E-16
ENSG00000120875.8	DUSP4	1.029358746	4.26E-18	3.71E-15
ENSG00000172667.10	ZMAT3	1.002790094	6.21E-22	1.12E-18
ENSG00000148400.10	NOTCH1	1.000075098	5.51E-17	4.32E-14
ENSG00000139318.7	DUSP6	0.988104146	5.66E-06	0.00060295
ENSG00000283515.1	AC020915.5	0.97330587	7.65E-05	0.005074582
ENSG00000185432.11	METTL7A	0.963244474	6.39E-19	6.27E-16
ENSG00000141232.4	TOB1	0.955678733	3.36E-23	6.59E-20
ENSG00000123384.13	LRP1	0.951454725	7.18E-34	3.38E-30

ENSG00000198576.3	ARC	0.934006536	5.12E-13	2.23E-10
ENSG00000146006.7	LRRTM2	0.930318445	6.58E-09	1.45E-06
ENSG00000198075.9	SULT1C4	0.917342151	1.43E-08	2.82E-06
ENSG00000120889.12	TNFRSF10B	0.912654843	1.99E-39	1.56E-35
ENSG00000130766.4	SESN2	0.90813527	8.11E-10	2.12E-07
ENSG00000173846.12	PLK3	0.903665621	6.20E-06	0.000654473
ENSG00000186529.15	CYP4F3	0.902211355	2.09E-08	3.96E-06
ENSG00000189060.5	H1F0	0.885090295	4.33E-35	2.55E-31
ENSG00000136048.13	DRAM1	0.877031031	2.25E-13	1.12E-10
ENSG00000180747.15	SMG1P3	0.856380823	1.24E-09	3.01E-07
ENSG00000159388.5	BTG2	0.847274746	4.19E-13	1.89E-10
ENSG00000161513.11	FDXR	0.83217522	5.42E-15	3.19E-12
ENSG00000197093.10	GAL3ST4	0.806950347	1.92E-05	0.001607155
ENSG00000244405.7	ETV5	0.803452681	6.43E-07	8.66E-05
ENSG00000164070.11	HSPA4L	0.80099516	2.71E-11	9.40E-09
ENSG00000185088.13	RPS27L	0.788075905	9.23E-16	6.39E-13
ENSG00000240303.7	ACAD11	0.782398754	3.73E-06	0.000439149
ENSG00000049130.15	KITLG	0.769337645	3.76E-08	6.80E-06
ENSG00000055163.19	CYFIP2	0.75249592	2.97E-21	4.37E-18
ENSG00000170385.9	SLC30A1	0.746223487	6.13E-10	1.66E-07
ENSG00000181218.5	HIST3H2A	0.735767628	2.91E-05	0.002245645
ENSG00000284917.1	EEF1AKMT4-ECE2	0.702912928	7.98E-09	1.69E-06
ENSG00000135679.23	MDM2	0.692366531	5.90E-19	6.04E-16
ENSG00000164674.15	SYTL3	0.683520795	1.83E-07	2.67E-05
ENSG00000105270.14	CLIP3	0.679656606	5.49E-05	0.003833746
ENSG00000157168.18	NRG1	0.677200956	2.76E-06	0.000328443
ENSG00000048392.11	RRM2B	0.638433406	1.21E-08	2.46E-06
ENSG00000005339.14	CREBBP	0.622802374	1.66E-05	0.001427723
ENSG00000105204.13	DYRK1B	0.62076599	2.04E-06	0.000250499
ENSG00000087245.12	MMP2	0.615686352	7.04E-12	2.59E-09
ENSG00000164237.8	CMBL	0.599004563	8.26E-10	2.14E-07
ENSG00000168016.14	TRANK1	0.598200312	7.65E-08	1.27E-05
ENSG00000263465.4	SRSF8	0.596188254	1.56E-10	4.82E-08

ENSG00000168209.4	DDIT4	0.588360861	6.45E-11	2.11E-08
ENSG00000113328.18	CCNG1	0.580226266	7.13E-11	2.30E-08
ENSG00000171617.13	ENC1	0.580135374	1.44E-05	0.001300095
ENSG00000117139.16	KDM5B	0.572362905	3.09E-14	1.73E-11
ENSG00000124067.16	SLC12A4	0.569902635	1.52E-05	0.001362084
ENSG00000100647.7	SUSD6	0.569883479	6.76E-06	0.000704826
ENSG00000109670.14	FBXW7	0.56157258	3.80E-06	0.000439346
ENSG00000135968.20	GCC2	0.553181878	1.50E-05	0.001350114
ENSG00000072364.12	AFF4	0.548308778	5.20E-06	0.000559531
ENSG00000166833.19	NAV2	0.548206759	4.55E-06	0.000507554
ENSG00000149256.15	TENM4	0.546420422	0.000129372	0.007920866
ENSG00000146278.10	PNRC1	0.541507594	7.25E-06	0.000729702
ENSG00000135111.15	TBX3	0.54124369	1.14E-05	0.001075462
ENSG00000087088.19	BAX	0.533277877	8.16E-08	1.33E-05
ENSG00000205918.9	PDPK2P	0.524377143	4.57E-05	0.003279552
ENSG00000160789.19	LMNA	0.522169861	9.52E-08	1.54E-05
ENSG00000134369.15	NAV1	0.51067205	2.63E-06	0.000313917
ENSG00000167654.17	ATCAY	0.509855251	9.33E-06	0.000907524
ENSG00000173114.12	LRRN3	0.496513889	0.000142373	0.008596048
ENSG00000179094.15	PER1	0.491157167	3.82E-06	0.000439346
ENSG00000215397.3	SCRT2	0.490790366	1.50E-05	0.001350114
ENSG00000138829.11	FBN2	0.489066988	3.46E-05	0.002576903
ENSG00000134574.11	DDB2	0.488236037	3.83E-06	0.000439346
ENSG00000109654.14	TRIM2	0.485633757	1.30E-05	0.001196735
ENSG00000181827.14	RFX7	0.485083107	1.83E-05	0.001554223
ENSG00000170734.11	POLH	0.481762601	2.32E-06	0.000280019
ENSG00000167548.14	KMT2D	0.478188423	3.16E-07	4.45E-05
ENSG00000170836.11	PPM1D	0.47769887	5.78E-07	7.96E-05
ENSG00000181026.14	AEN	0.473582722	7.57E-09	1.62E-06
ENSG00000163171.7	CDC42EP3	0.470393709	2.90E-05	0.002242904
ENSG00000078549.14	ADCYAP1R1	0.464767229	8.99E-10	2.30E-07
ENSG00000284454.2	AC256236.3	0.463318239	7.91E-05	0.005201794
ENSG00000124942.13	AHNAK	0.460604473	4.71E-09	1.06E-06
ENSG00000164236.11	ANKRD33B	0.45584171	4.88E-06	0.000529555

ENSG00000284832.1	POLR2A	0.455233167	1.21E-06	0.000152563
ENSG00000102858.12	MGRN1	0.454573938	1.35E-05	0.001239033
ENSG00000055609.17	KMT2C	0.454002045	0.000164519	0.009518265
ENSG00000136367.13	ZFHX2	0.451809513	4.98E-05	0.003545133
ENSG00000173714.7	WFIKK2	0.450140107	2.14E-07	3.07E-05
ENSG00000177606.6	JUN	0.449250572	1.32E-05	0.001211355
ENSG00000088854.12	C20orf194	0.443451024	2.86E-05	0.002226435
ENSG00000015133.18	CCDC88C	0.439704017	5.47E-06	0.000585174
ENSG00000181222.15	POLR2A	0.439037911	1.73E-07	2.57E-05
ENSG00000148143.12	ZNF462	0.437646779	6.03E-05	0.004124679
ENSG00000172831.11	CES2	0.436717263	0.000161135	0.009368504
ENSG00000107984.9	DKK 1.00	0.434925639	2.63E-10	8.05E-08
ENSG00000080298.15	RFX3	0.433807302	5.85E-05	0.004039128
ENSG00000198853.11	RUSC2	0.426116681	1.80E-07	2.65E-05
ENSG00000009413.15	REV3L	0.42480962	0.000154461	0.009184587
ENSG00000248905.8	FMN1	0.424595306	7.42E-08	1.25E-05
ENSG00000116717.11	GADD45A	0.423935864	2.59E-05	0.002042213
ENSG00000124766.6	SOX4	0.423799565	2.39E-09	5.62E-07
ENSG00000162641.18	AKNAD1	0.42149604	8.74E-05	0.005666773
ENSG00000100393.12	EP300	0.420993493	0.000120469	0.007504444
ENSG00000146083.11	RNF44	0.407506496	7.84E-06	0.000782447
ENSG00000107282.7	APBA1	0.406151371	2.17E-05	0.001759363
ENSG00000127663.14	KDM4B	0.404134228	9.19E-07	0.000119507
ENSG00000113369.8	ARRDC3	0.403784774	0.000156665	0.009205848
ENSG00000149212.11	SESN3	0.400720843	8.88E-05	0.005712795
ENSG00000121068.13	TBX2	0.400717657	1.00E-07	1.60E-05
ENSG00000159409.14	CELF3	0.397761375	3.48E-07	4.87E-05
ENSG00000166851.14	PLK1	0.397440322	7.34E-08	1.24E-05
ENSG00000158859.9	ADAMTS4	0.395365697	0.000160041	0.009351064
ENSG00000112249.13	ASCC3	0.394546695	6.03E-08	1.05E-05
ENSG00000167196.13	FBXO22	0.389059493	8.80E-05	0.005690502
ENSG00000076604.14	TRAF4	0.386873512	9.01E-05	0.005749342
ENSG00000167566.16	NCKAP5L	0.381554585	7.39E-05	0.004957152
ENSG00000162783.10	IER5	0.380492485	3.91E-05	0.002850681

ENSG00000155980.11	KIF5A	0.375216238	0.000156496	0.009205848
ENSG00000139767.9	SRRM4	0.374106	9.28E-05	0.005908445
ENSG00000154767.14	XPC	0.373025586	1.45E-07	2.22E-05
ENSG00000144406.18	UNC80	0.372479513	0.000144905	0.008704289
ENSG00000149639.14	SOGA1	0.370746058	9.55E-05	0.006026976
ENSG00000038382.19	TRIO	0.367503413	8.59E-05	0.005605193
ENSG00000086758.15	HUWE1	0.361079136	7.32E-06	0.000733487
ENSG00000163050.16	COQ8A	0.357570592	2.72E-05	0.002130094
ENSG00000276876.4	MYT1	0.353673989	3.72E-05	0.002723613
ENSG00000107485.16	GATA3	0.353365628	1.61E-06	0.000199971
ENSG00000131018.22	SYNE1	0.34820818	2.12E-05	0.001721024
ENSG00000112245.10	PTP4A1	0.347885342	7.19E-06	0.000726464
ENSG00000197102.11	DYNC1H1	0.347024751	2.05E-08	3.92E-06
ENSG00000112984.11	KIF20A	0.345603035	1.07E-05	0.001028923
ENSG00000254726.2	MEX3A	0.344227389	1.65E-05	0.001427723
ENSG00000166963.12	MAP1A	0.328953364	5.25E-05	0.003710685
ENSG00000128591.15	FLNC	0.319965856	2.54E-05	0.002009931
ENSG00000110900.14	TSPAN11	0.310722201	7.70E-05	0.005092628
ENSG00000173064.12	HECTD4	0.309898345	7.03E-06	0.000718358
ENSG00000103222.18	ABCC1	0.309726077	1.43E-05	0.001300095
ENSG00000076356.6	PLXNA2	0.297854062	3.52E-06	0.000416425
ENSG00000091136.13	LAMB1	0.289795522	6.79E-05	0.004604928
ENSG00000196576.14	PLXNB2	0.287517199	3.84E-06	0.000439346
ENSG00000196498.13	NCOR2	0.279745594	2.20E-05	0.001777831
ENSG00000115266.11	APC2	0.279101948	1.86E-06	0.000228906
ENSG00000112159.11	MDN1	0.274872707	6.75E-06	0.000704826
ENSG00000167658.15	EEF2	0.270880321	1.15E-05	0.001081874
ENSG00000150995.18	ITPR1	0.270729233	4.68E-06	0.000514148
ENSG00000154358.20	OBSCN	0.263978791	6.08E-07	8.33E-05
ENSG00000083857.13	FAT1	0.262674264	7.97E-07	0.000104878
ENSG00000215077.10	BRD2	0.26089571	0.000125075	0.007770848
ENSG00000198408.13	MGEA5	0.259265221	3.67E-05	0.002697166
ENSG00000162981.13	FAM84A	0.244034658	5.49E-05	0.003833746
ENSG00000171634.17	BPTF	0.238212662	3.06E-05	0.002340125

ENSG00000186635.14	ARAP1	0.231608939	8.44E-06	0.000835434
ENSG00000240891.7	PLCXD2	0.216733924	5.96E-05	0.004103698
ENSG00000197081.12	IGF2R	0.206696201	1.61E-05	0.001395696
ENSG00000272333.5	KMT2B	0.16227339	4.65E-05	0.003330143
ENSG00000197694.15	SPTAN1	0.161516925	1.86E-05	0.001567102
ENSG00000167978.16	SRRM2	0.074780079	4.47E-06	0.000501522

Supplementary Table 2. Downregulated genes in PTC-028–treated IMR-32 cells

ENSG	Symbol	log2FC	<i>p</i> value	q value
ENSG00000134058.11	CDK7	-1.4501349	1.1205E-06	0.00014339
ENSG00000262771.5	SSBP1	-1.4038973	9.2148E-13	3.8747E-10
ENSG00000274615.1	AC233968.1	-1.396803	6.4968E-08	1.1249E-05
ENSG00000276497.3	APBA1	-0.9582578	0.00013515	0.00822342
ENSG00000175305.17	CCNE2	-0.8875421	3.7571E-13	1.7347E-10
ENSG00000277909.4	SPC25	-0.7655879	2.399E-05	0.00191487
ENSG00000093009.9	CDC45	-0.7486501	1.5429E-13	7.898E-11
ENSG00000112029.9	FBXO5	-0.7452132	6.0041E-21	7.8544E-18
ENSG00000285089.1	VAR52	-0.7342569	3.5313E-05	0.00261485
ENSG00000159147.17	DONSON	-0.7331852	2.2894E-08	4.3127E-06
ENSG00000159259.7	CHAF1B	-0.7326396	5.1949E-15	3.1366E-12
ENSG00000104738.16	MCM4	-0.7228392	8.0182E-26	2.0978E-22
ENSG00000259316.11	AC087632.1	-0.7047272	2.2871E-14	1.3135E-11
ENSG00000168496.3	FEN1	-0.7009313	2.3156E-27	7.7892E-24
ENSG00000167900.11	TK1	-0.6968409	2.2641E-17	1.8383E-14
ENSG00000206282.11	RGL2	-0.6951607	7.9625E-05	0.00522264
ENSG00000162073.13	PAQR4	-0.6719052	2.7879E-15	1.8235E-12
ENSG00000143476.17	DTL	-0.6645417	3.3334E-13	1.5698E-10
ENSG00000175643.8	RMI2	-0.652444	1.8804E-08	3.6594E-06
ENSG00000092470.11	WDR76	-0.6481685	2.2739E-13	1.1155E-10
ENSG00000131470.14	PSMC3IP	-0.6461149	8.0534E-13	3.4479E-10
ENSG00000156802.12	ATAD2	-0.6430373	5.2218E-16	3.8424E-13
ENSG00000277953.4	PRPF31	-0.640548	1.0801E-05	0.00102968
ENSG00000136982.5	DSCC1	-0.6388579	3.3817E-08	6.1727E-06
ENSG00000174371.16	EXO1	-0.6364759	4.2481E-16	3.2268E-13
ENSG00000137310.11	TCF19	-0.6251032	2.5802E-09	5.9566E-07
ENSG00000014138.8	POLA2	-0.618993	1.5439E-11	5.5082E-09
ENSG00000076248.10	UNG	-0.6114577	1.5952E-21	2.5041E-18
ENSG00000167513.8	CDT1	-0.6092724	1.031E-08	2.1296E-06
ENSG00000223802.7	CERS1	-0.6085905	6.1586E-07	8.3824E-05
ENSG00000127564.16	PKMYT1	-0.6084484	3.4679E-15	2.207E-12
ENSG00000123374.10	CDK2	-0.601066	4.7889E-15	2.9675E-12

ENSG00000094804.9	CDC6	-0.6002266	6.651E-20	7.4577E-17
ENSG00000276043.4	UHRF1	-0.5956985	4.6566E-21	6.45E-18
ENSG00000101412.12	E2F1	-0.5931925	1.2885E-13	6.8359E-11
ENSG00000031691.6	CENPQ	-0.5902118	6.2995E-06	0.00066221
ENSG00000104889.6	RNASEH2A	-0.5780458	4.0364E-07	5.6239E-05
ENSG00000204209.12	DAXX	-0.5772651	1.6168E-07	2.439E-05
ENSG00000171848.14	RRM2	-0.5696041	1.3662E-23	2.9244E-20
ENSG00000151725.11	CENPU	-0.566803	7.0048E-14	3.8359E-11
ENSG00000221829.9	FANCG	-0.563662	7.7083E-08	1.2693E-05
ENSG00000275045.4	GTF2H2	-0.558356	1.1725E-06	0.00014923
ENSG00000118513.18	MYB	-0.5581922	2.1108E-05	0.00172102
ENSG00000105011.8	ASF1B	-0.5565388	7.7023E-11	2.4509E-08
ENSG00000144554.10	FANCD2	-0.5482991	7.1273E-05	0.00479502
ENSG00000132646.10	PCNA	-0.5476239	3.3861E-20	3.9866E-17
ENSG00000162607.12	USP1	-0.5464642	8.8099E-16	6.2862E-13
ENSG00000105173.13	CCNE1	-0.5441165	1.9925E-05	0.001652
ENSG00000081870.11	HSPB11	-0.5426114	4.4222E-05	0.00319415
ENSG00000101773.18	RBBP8	-0.5419276	1.4277E-07	2.1973E-05
ENSG00000007968.6	E2F2	-0.5416712	1.3389E-08	2.6717E-06
ENSG00000111247.14	RAD51AP1	-0.5380465	1.8527E-07	2.693E-05
ENSG00000228867.8	NRM	-0.5374508	4.8165E-08	8.6576E-06
ENSG00000198056.13	PRIM1	-0.5352286	4.9537E-08	8.7702E-06
ENSG00000049541.10	RFC2	-0.5287221	9.7129E-08	1.5558E-05
ENSG00000100162.14	CENPM	-0.5281373	7.0116E-06	0.00071836
ENSG00000077514.8	POLD3	-0.521375	7.6588E-08	1.2693E-05
ENSG00000170312.15	CDK1	-0.5207021	1.6786E-12	6.8149E-10
ENSG00000100297.15	MCM5	-0.5201688	9.524E-13	3.9344E-10
ENSG00000131153.8	GIN52	-0.5166073	4.6945E-06	0.00051415
ENSG00000112312.9	GMNN	-0.5159151	3.2406E-11	1.0901E-08
ENSG00000129173.12	E2F8	-0.5147535	6.0482E-06	0.00064151
ENSG00000198554.11	WDHD1	-0.5063245	1.2665E-08	2.5489E-06
ENSG00000149636.15	DSN1	-0.5023395	7.2918E-08	1.2427E-05
ENSG00000163950.12	SLBP	-0.4984786	4.0904E-12	1.5535E-09
ENSG00000163918.10	RFC4	-0.4983198	1.1228E-07	1.7394E-05

ENSG00000111445.13	RFC5	-0.4947318	4.0911E-10	1.2042E-07
ENSG00000197299.10	BLM	-0.4922767	1.0954E-07	1.7195E-05
ENSG00000119969.14	HELLS	-0.4920444	2.0954E-11	7.3642E-09
ENSG00000164649.19	CDCA7L	-0.4883357	6.417E-07	8.6577E-05
ENSG00000101003.9	GIN51	-0.4863541	5.036E-10	1.4117E-07
ENSG00000085840.12	ORC1	-0.4822857	2.4118E-09	5.6229E-07
ENSG00000128708.12	HAT1	-0.4795727	1.0285E-07	1.6253E-05
ENSG00000170779.10	CDCA4	-0.477758	2.0037E-08	3.8674E-06
ENSG00000091651.8	ORC6	-0.4774898	1.015E-09	2.5427E-07
ENSG00000112118.18	MCM3	-0.4735438	1.9219E-15	1.293E-12
ENSG00000162062.14	TEDC2	-0.4719621	1.2527E-06	0.00015774
ENSG00000198885.9	ITPRIPL1	-0.4706067	7.5609E-05	0.00504352
ENSG00000177917.10	ARL6IP6	-0.469917	2.421E-06	0.00029086
ENSG00000110108.9	TMEM109	-0.4696454	0.00013809	0.00835871
ENSG00000161888.11	SPC24	-0.4685633	7.1361E-07	9.4934E-05
ENSG00000140525.17	FANCI	-0.4673771	1.2301E-18	1.114E-15
ENSG00000146670.9	CDCA5	-0.4665466	2.9953E-12	1.1562E-09
ENSG00000167325.14	RRM1	-0.4629214	3.994E-11	1.3246E-08
ENSG00000077152.10	UBE2T	-0.4552759	5.622E-09	1.2489E-06
ENSG00000012048.21	BRCA1	-0.4518512	3.0363E-11	1.0362E-08
ENSG00000051180.16	RAD51	-0.4514768	7.8146E-07	0.00010338
ENSG00000144354.13	CDCA7	-0.4514288	2.5033E-08	4.6413E-06
ENSG00000164045.11	CDC25A	-0.4499064	4.8169E-10	1.3832E-07
ENSG00000120437.8	ACAT2	-0.4486493	5.1763E-12	1.9347E-09
ENSG00000012963.14	UBR7	-0.448039	8.9686E-08	1.4564E-05
ENSG00000101057.15	MYBL2	-0.4431605	2.6191E-13	1.2586E-10
ENSG00000119333.11	WDR34	-0.4381672	9.571E-07	0.00012383
ENSG00000183527.11	PSMG1	-0.4372654	3.3365E-05	0.00249415
ENSG00000167670.15	CHAF1A	-0.4371537	7.2403E-12	2.6229E-09
ENSG00000176890.15	TYMS	-0.4370973	1.8082E-12	7.2164E-10
ENSG00000179958.8	DCTPP1	-0.4324201	4.9237E-08	8.7702E-06
ENSG00000181938.13	GIN53	-0.429721	6.9361E-09	1.5116E-06
ENSG00000092853.13	CLSPN	-0.4274956	9.3386E-05	0.00592711
ENSG00000165244.6	ZNF367	-0.4264815	8.8658E-05	0.00571279

ENSG00000160957.12	RECQL4	-0.4254505	4.5858E-06	0.00050755
ENSG00000112759.17	SLC29A1	-0.4240584	5.021E-10	1.4117E-07
ENSG00000169689.14	CENPX	-0.4220029	3.0807E-05	0.00234763
ENSG00000076003.4	MCM6	-0.421648	3.0007E-10	9.0586E-08
ENSG00000166803.12	PCLAF	-0.4205701	4.26E-13	1.8926E-10
ENSG00000186767.6	SPIN4	-0.4183367	5.5158E-05	0.00384265
ENSG00000074266.19	EED	-0.4181725	0.00015652	0.00920585
ENSG00000176974.19	SHMT1	-0.4170277	8.0448E-07	0.00010524
ENSG00000073111.13	MCM2	-0.4169083	2.6706E-12	1.0481E-09
ENSG00000213551.4	DNAJC9	-0.4140461	2.7392E-08	5.039E-06
ENSG00000228716.6	DHFR	-0.4112897	5.9893E-10	1.6399E-07
ENSG00000119326.14	CTNNAL1	-0.4112276	5.7219E-05	0.00396292
ENSG00000115687.13	PASK	-0.4111054	2.1189E-05	0.00172102
ENSG00000197256.10	KANK2	-0.4084874	1.6986E-07	2.5315E-05
ENSG00000006625.17	GGCT	-0.4084294	6.8808E-07	9.2059E-05
ENSG00000120539.14	MASTL	-0.407834	1.576E-06	0.00019634
ENSG00000188486.3	H2AFX	-0.4042715	1.0901E-08	2.232E-06
ENSG00000173207.12	CKS1B	-0.3985502	1.1965E-09	2.9348E-07
ENSG00000171241.8	SHCBP1	-0.3979558	3.0293E-05	0.00232351
ENSG00000204574.12	ABCF1	-0.3943999	1.5896E-05	0.00139143
ENSG00000122952.16	ZWINT	-0.3943494	8.457E-09	1.778E-06
ENSG00000127337.6	YEATS4	-0.393199	1.553E-07	2.3593E-05
ENSG00000138386.16	NAB1	-0.390158	2.0049E-05	0.00165651
ENSG00000184992.10	BRI3BP	-0.3876998	4.0942E-06	0.0004635
ENSG00000171320.14	ESCO2	-0.3856937	2.6163E-07	3.7337E-05
ENSG00000115392.11	FANCL	-0.3833203	5.7221E-05	0.00396292
ENSG00000123737.12	EXOSC9	-0.3821436	1.7387E-05	0.0014916
ENSG00000169683.7	LRRC45	-0.3808669	3.503E-05	0.00260203
ENSG00000165724.5	ZMYND19	-0.3799844	8.2572E-05	0.00540092
ENSG00000149554.12	CHEK1	-0.3784396	2.0732E-06	0.00025294
ENSG00000068137.14	PLEKHH3	-0.3771452	2.5851E-05	0.00204221
ENSG00000134291.11	TMEM106C	-0.3744224	1.0266E-06	0.00013209
ENSG00000165304.7	MELK	-0.3705784	2.6938E-05	0.00211433
ENSG00000144485.10	HES6	-0.368764	4.3033E-05	0.00311787

ENSG00000116667.12	C1orf21	-0.3680994	0.00012951	0.00792087
ENSG00000062822.13	POLD1	-0.3669004	0.00016595	0.00957778
ENSG00000116062.14	MSH6	-0.3639385	1.284E-09	3.0852E-07
ENSG00000128951.13	DUT	-0.3633418	2.1147E-09	5.0297E-07
ENSG00000178202.12	KDELC2	-0.3632044	1.9512E-05	0.00162926
ENSG00000125885.13	MCM8	-0.3597854	9.8804E-06	0.0009535
ENSG00000141858.11	SAMD1	-0.3590839	3.3197E-05	0.00248947
ENSG00000095002.14	MSH2	-0.3585449	7.1143E-06	0.00072207
ENSG00000123144.10	TRIR	-0.3552201	3.9993E-06	0.00045494
ENSG00000171161.12	ZNF672	-0.3539392	9.4911E-05	0.00600769
ENSG00000166736.11	HTR3A	-0.3535299	0.00015408	0.00918459
ENSG00000101868.10	POLA1	-0.3534741	3.3077E-05	0.00248836
ENSG00000013573.16	DDX11	-0.352708	2.2863E-06	0.00027751
ENSG00000065328.16	MCM10	-0.3526918	1.994E-07	2.8805E-05
ENSG00000118655.4	DCLRE1B	-0.3516549	0.00015341	0.00916865
ENSG00000153048.10	CARHSP1	-0.3431195	1.1054E-07	1.7238E-05
ENSG00000163655.15	GMPS	-0.3421656	6.576E-05	0.00448825
ENSG00000281013.2	NDUFA6	-0.3371376	2.5207E-05	0.00200522
ENSG00000198176.12	TFDP1	-0.3345566	3.106E-07	4.4058E-05
ENSG00000109805.9	NCAPG	-0.3344511	0.0001262	0.00778971
ENSG00000080986.12	NDC80	-0.3342412	0.00015881	0.00930245
ENSG00000160949.16	TONSL	-0.332902	2.7679E-05	0.00215812
ENSG00000004700.15	RECQL	-0.3324877	1.6262E-07	2.439E-05
ENSG00000100473.16	COCH	-0.3317449	1.3801E-05	0.00125954
ENSG00000164032.11	H2AFZ	-0.33119	9.1212E-09	1.9007E-06
ENSG00000146143.17	PRIM2	-0.3307584	0.00016063	0.00936247
ENSG00000105486.13	LIG1	-0.3285868	8.9362E-06	0.00087676
ENSG00000132780.16	NASP	-0.3255302	3.0797E-10	9.1794E-08
ENSG00000100075.9	SLC25A1	-0.3249034	0.00011517	0.00723206
ENSG00000116212.14	LRRC42	-0.3224324	0.00012638	0.00778971
ENSG00000080839.11	RBL1	-0.3221335	4.1399E-06	0.00046642
ENSG00000157851.16	DPYSL5	-0.3161919	1.171E-05	0.0010899
ENSG00000224156.10	TUBB	-0.3144299	5.6414E-10	1.5628E-07
ENSG00000123416.15	TUBA1B	-0.3144148	9.1895E-10	2.3267E-07

ENSG00000102054.17	RBBP7	-0.3124359	1.5459E-05	0.00136922
ENSG00000133119.12	RFC3	-0.311789	6.9698E-06	0.00071836
ENSG00000166508.17	MCM7	-0.3072455	4.4705E-09	1.0122E-06
ENSG00000128045.6	RASL11B	-0.3070574	5.1794E-06	0.00055945
ENSG00000147536.11	GINS4	-0.3063553	5.1486E-05	0.00365165
ENSG00000173786.16	CNP	-0.305845	6.944E-06	0.00071836
ENSG00000141560.14	FN3KRP	-0.3010695	0.00013568	0.00823424
ENSG00000153879.8	CEBPG	-0.3001438	6.8875E-05	0.00466031
ENSG00000175768.12	TOMM5	-0.2985786	2.0196E-05	0.00166278
ENSG00000165916.8	PSMC3	-0.2983497	9.5621E-06	0.00092658
ENSG00000131462.7	TUBG1	-0.2975362	3.7508E-06	0.00043935
ENSG00000213853.9	EMP2	-0.296616	1.5468E-05	0.00136922
ENSG00000092621.12	PHGDH	-0.2871143	1.0577E-05	0.00101654
ENSG00000136938.8	ANP32B	-0.2785786	9.2078E-06	0.00089965
ENSG00000227739.10	TUBB	-0.2778657	6.9435E-08	1.1934E-05
ENSG00000231617.8	DAXX	-0.2751135	7.0415E-05	0.00475086
ENSG00000164109.13	MAD2L1	-0.2739875	8.4305E-06	0.00083543
ENSG00000275895.6	U2AF1L5	-0.2736732	5.2995E-05	0.00373613
ENSG00000125450.10	NUP85	-0.2719251	1.1445E-05	0.00107795
ENSG00000182054.9	IDH2	-0.2710243	2.0271E-05	0.00166314
ENSG00000122378.13	FAM213A	-0.2703121	8.7904E-06	0.00086605
ENSG00000136492.8	BRIP1	-0.268073	4.7686E-05	0.00340261
ENSG00000164985.14	PSIP1	-0.2634604	4.5653E-05	0.00327955
ENSG00000115875.18	SRSF7	-0.2624978	3.8436E-06	0.00043935
ENSG00000105281.12	SLC1A5	-0.2595671	0.00013006	0.007934
ENSG00000163041.9	H3F3A	-0.2593759	3.2573E-05	0.00245829
ENSG00000124795.14	DEK	-0.2545359	5.005E-08	8.795E-06
ENSG00000169813.16	HNRNPF	-0.254514	1.1578E-05	0.00108187
ENSG00000097046.12	CDC7	-0.2519939	4.8794E-06	0.00052956
ENSG00000111602.11	TIMELESS	-0.2507445	4.2524E-05	0.00309045
ENSG00000099901.16	RANBP1	-0.2494924	7.7744E-05	0.00512783
ENSG00000144136.10	SLC20A1	-0.2465237	2.2905E-05	0.00184079
ENSG00000117054.13	ACADM	-0.2458944	1.6004E-05	0.0013957
ENSG00000183684.7	ALYREF	-0.2453652	0.0001267	0.00778971

ENSG00000160752.14	FDPS	-0.243602	0.00012595	0.00778971
ENSG00000115241.10	PPM1G	-0.2418759	0.00016315	0.00946212
ENSG00000177084.16	POLE	-0.239908	6.0032E-05	0.00412123
ENSG00000113456.18	RAD1	-0.2323713	8.9483E-05	0.00572568
ENSG00000138668.18	HNRNPD	-0.2268232	1.742E-05	0.0014916
ENSG00000116133.11	DHCR24	-0.2266153	7.5029E-05	0.00501902
ENSG00000197771.12	MCMBP	-0.2252846	2.3111E-05	0.00185099
ENSG00000143742.12	SRP9	-0.2241609	1.7879E-05	0.00152531
ENSG00000130024.14	PHF10	-0.2236121	1.2688E-06	0.00015891
ENSG00000128973.12	CLN6	-0.2225677	0.00015551	0.00920585
ENSG00000135446.16	CDK4	-0.2221273	7.0472E-06	0.00071836
ENSG00000171314.8	PGAM1	-0.2197512	3.7032E-05	0.00271651
ENSG00000142230.11	SAE1	-0.2171503	8.726E-05	0.00566677
ENSG00000189403.14	HMGB1	-0.2123089	0.00017014	0.00977163
ENSG00000128050.8	PAICS	-0.211459	1.585E-05	0.00139143
ENSG00000152795.17	HNRNPDL	-0.1950078	0.00015677	0.00920585
ENSG00000182481.8	KPNA2	-0.1893862	0.00014388	0.00866474
ENSG00000188529.14	SRSF10	-0.1882122	0.0001688	0.00971833
ENSG00000182199.10	SHMT2	-0.1850006	3.1256E-05	0.00237417
ENSG00000120253.13	NUP43	-0.1818481	8.9467E-05	0.00572568
ENSG00000206053.12	JPT2	-0.181442	1.2153E-05	0.00112666
ENSG00000105968.18	H2AFV	-0.1804915	5.4702E-05	0.00383375
ENSG00000145604.15	SKP2	-0.180424	6.6238E-05	0.00450779
ENSG00000109084.13	TMEM97	-0.1787136	0.00012045	0.00750444
ENSG00000120802.13	TMPO	-0.1713893	3.14E-05	0.00237744
ENSG00000187231.13	SESTD1	-0.1709456	3.5789E-05	0.00264173
ENSG00000137814.10	HAUS2	-0.1684091	2.9302E-05	0.00225485
ENSG00000275176.4	ACACA	-0.1652463	1.0855E-05	0.00103064
ENSG00000108179.13	PPIF	-0.1549263	1.7956E-05	0.00152642
ENSG00000161547.16	SRSF2	-0.1466375	1.5845E-05	0.00139143
ENSG00000213160.9	KLHL23	-0.1446441	7.6407E-05	0.00507458
ENSG00000154473.17	BUB3	-0.1340509	1.5367E-05	0.00136922
ENSG00000111786.8	SRSF9	-0.1210881	0.00011576	0.00724964
ENSG00000065911.11	MTHFD2	-0.1153833	0.0001511	0.0090531

ENSG00000127481.14	UBR4	-0.0077007	1.9112E-05	0.00160715
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Supplementary Table 3. Antibodies used for Western blotting analysis

Target protein	Dilution	Source	Supplier	Catalog number	Predicted band size (kDa)
BMI1	1:500	Mouse	Santa Cruz	sc-390443	41
Caspase-3	1:1000	Rabbit	CST	9662	35
Cleaved caspase-3 (Asp175)	1:1000	Rabbit	CST	9664	17, 19
PARP, Cleaved PARP (Asp214)	1:1000	Rabbit	CST	9542	116, 89
Actin	1:1000	Rabbit	Sigma-Aldrich	A5060	42
α -Tubulin	1:1000	Rabbit	CST	2144	52
p53	1:1000	Rabbit	CST	2527	53
p21 Waf1/Cip1	1:1000	Rabbit	CST	2947	21
NOXA	1:1000	Rabbit	CST	14766	10
BAX	1:1000	Rabbit	CST	2772	20
BCL2	1:1000	Rabbit	CST	4223	26
MCL1	1:1000	Rabbit	CST	5453	40
Ubiquityl-Histone H2A (Lys119)	1:2000	Rabbit	CST	8240	23
Phospho-histone H2A.X (Ser139)	1:1000	Rabbit	CST	9718	15

Abbreviation: CST, Cell Signaling Technology

Supplementary Table 4. Antibodies used for immunofluorescence analysis

Target protein	Dilution	Source	Supplier	Catalog number
Phospho-histone H2A.X (Ser139)	1:200	Rabbit	CST	9718
53BP1	1:100	Rabbit	CST	4937
Ki67	1:200	Mouse	BD	550609

Abbreviations: CST, Cell Signaling Technology; BD, BD Biosciences

Supplementary Table 5. Primers used for PCR analysis

Target gene	Forward (5'→3')	Reverse (5'→3')
GAPDH	GAAGGTGAAGGTCGGAGTCA	GAACATGTAAACCATGTAGTTGAGG
BAX	GGGGAGCAGCCCAGAGG	CGATCCTGGATGAAACCCTGA
CDKN1A	TGCCGAAGTCAGTTCCTTGT	GTTCTGACATGGCGCCTCC

Supplementary Table 6. Raw measurements of the tumors for every mouse

Day	Group	No.	Long diameter (mm)	Short diameter (mm)	Tumor volume (mm ³)
0	Ctrl.	1	8	7	196
	Ctrl.	2	11	5	137.5
	Ctrl.	3	8	5	100
	Ctrl.	4	6	6	108
	Ctrl.	5	9	6	162
	Ctrl.	6	7	5	87.5
	PTC-028	1	8	8	256
	PTC-028	2	9	5	112.5
	PTC-028	3	8	7	196
	PTC-028	4	8	7	196
	PTC-028	5	7	5	87.5
	PTC-028	6	7	6	126
3	Ctrl.	1	9	8	288
	Ctrl.	2	14	8	448
	Ctrl.	3	11	6	198
	Ctrl.	4	8	7	196
	Ctrl.	5	10	9	405
	Ctrl.	6	8	5	100
	PTC-028	1	10	7	245
	PTC-028	2	12	8	384
	PTC-028	3	8	7	196
	PTC-028	4	8	8	256
	PTC-028	5	8	5	100
	PTC-028	6	8	5	100
7	Ctrl.	1	14	12	1008
	Ctrl.	2	9	16	1152
	Ctrl.	3	13	12	936
	Ctrl.	4	10	9	405
	Ctrl.	5	13	11	786.5
	Ctrl.	6	10	8	320
	PTC-028	1	11	10	550
	PTC-028	2	13	5	162.5
	PTC-028	3	11	6	198
	PTC-028	4	8	9	324

	PTC-028	5	8	7	196
	PTC-028	6	10	8	320
10	Ctrl.	1	16	15	1800
	Ctrl.	2	12	19	2166
	Ctrl.	3	19	15	2137.5
	Ctrl.	4	16	11	968
	Ctrl.	5	19	14	1862
	Ctrl.	6	12	11	726
	PTC-028	1	12	11	726
	PTC-028	2	15	10	750
	PTC-028	3	11	7	269.5
	PTC-028	4	10	10	500
	PTC-028	5	10	7	245
	PTC-028	6	12	9	486
14	Ctrl.	1	18	20	3600
	Ctrl.	2	12	21	2646
	Ctrl.	3	20	19	3610
	Ctrl.	4	20	19	3610
	Ctrl.	5	20	16	2560
	Ctrl.	6	13	11	786.5
	PTC-028	1	14	15	1575
	PTC-028	2	13	19	2346.5
	PTC-028	3	10	12	720
	PTC-028	4	10	11	605
	PTC-028	5	13	10	650
	PTC-028	6	14	10	700