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Supplementary Information for

DNA methyltransferase inhibitors induce a BRCAness phenotype that sensitizes NSCLC to PARP inhibitor and ionizing radiation

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Supplementary Experimental Procedures

Materials

	Company	**Cat. #**	**Dilution**
Immunoblotting			
FANCD2 (Fl17)	Santa Cruz	sc-20022	1:200
Ku80 (Ku86 B-1)	Santa Cruz	sc-5280	1:200
Ku80 (111)	Thermo Fisher	MA5-12933	1:200
β-actin	Millipore Sigma	A1978	1:5000
Immunofluorescence			
RAD51	Abcam	ab63801	1:1000
γH2AX (Ser139, clone JBW301)	Millipore Sigma	05-636	1:100
Goat anti-rabbit IgG (H+L), DyLight 488	Seracare KPL	5230-0385	1:100
Goat anti-mouse IgG (H+L), DyLight 594	Invitrogen	35511	1:200
Proximity ligation assay			
PARP1 (3G4)	Millipore Sigma	WH0000142M1	1:200
γH2AX (Ser139, clone 20E3)	Cell Signaling	CST-9718	1:200
DNMT1 (H-300)	Santa Cruz	sc-20701	1:200
DNA fiber			
Anti-BrdU (B44): IdU	BD Biosciences	347580	1:40
Anti-BrdU (BU1/75 ICR1): CldU	Abcam	ab6326	1:200
Sheep anti-mouse IgG Cy3	Millipore Sigma	C2181	1:500
Goat anti-rat IgG Alexa Fluor 488	Thermo Fisher	A11006	1:200

Table S1. Antibodies used during experimental procedures.

Gene	**Company**	**Cat. #**	**Forward sequence**	**Reverse sequence**
ATM	Qiagen	Hs_ATM_1_SG		
ATR	Qiagen	Hs_ATR_2_SG		
BRCA1	Qiagen	Hs_BRCA1_vb.1_SG		
BRCA2	Qiagen	Hs_BRCA2_1_SG		
FANCC	IDT		5'-TGG AGG CTC TCC TCA TCT GT	5'-GCA TTC GAT CCT TCT CAG ACA
FANCD2	Qiagen	Hs_FANCD2_va.1_SG		
FANCE	IDT		5'-ATG AGA AGG AGA GAC CCG AA	5'-GAA GTC AAG GAG AGG ATC CG
FANCF	Qiagen	Hs_FANCF_1_SG		
FANCG	Qiagen	Hs_FANCG_1_SG		
Ku70	Qiagen	Hs_XRCC6_1_SG		
Ku80	Qiagen	Hs_XRCC5_1_SG		
RAD50	Qiagen	Hs_RAD50_1_SG		
XRCC4	Qiagen	Hs_XRCC4_1_SG		
B2M	Qiagen	Hs_B2M_1_SG		
Actin	Qiagen	Hs_ACTB_1_SG		
GAPDH	IDT		5'-GTC TCC TCT GAC TTC AAC AGC G	5'-ACC ACC CTG TTG CTG TAG CCA A
MYC	Qiagen	Hs_MYC_1_SG		
IFI27			5’-ATC AGC AGT GAC CAG TGT GG	5’-TGG CCA CAA CTC CTC CAA TC
OASL			5’-TCG TGA AAC ATC GGC CAA CT	5’-TCG TGA AAC ATC GGC CAA CT
EJ5	IDT		5’-CTG CTA ACC ATG TTC ATG CC	5’-AAG TCG TGC TGC TTC ATG TG
EJ5-Ctrl	IDT		5’-GTG CGC GGA ACC CCT ATT TG	5’-AGG GAA TAA GGG CGA CAC GG

Table S2. Quantitative real time PCR primers used during experimental procedures. All Qiagen primers are QuantiTect Primer Assays. IDT = Integrated DNA Technologies.

Supplementary Experimental Procedures

Immunoblotting

Cells were lysed in RIPA buffer (Sigma-Aldrich) containing Halt protease and phosphatase inhibitors (ThermoFisher) for 1h at 4°C, then cleared by centrifugation at 13000rpm for 20min. Proteins were boiled for 5min in 1X lithium dodecyl sulphate buffer containing 0.1M dithiothreitol (DTT), loaded on 4-15% SDS-PAGE gels (BioRad), and transferred onto PVDF membrane (GE Life Sciences). Membranes were blocked in 5% non-fat milk in tris buffered saline-0.1% Tween 20 (TBST) for 1 hr. Primary antibodies were applied overnight at 4°C. Membranes were washed 3 times in TBST and secondary antibodies applied for 1 hr. Following 3 washes in TBST, chemiluminescent detection of HRP was performed using Hi/Lo Digital-ECL Western Blot Detection Kit acquired on a KwikQuant imager (both KindleBio).

For immunoblotting of proteins extracted from xenograft tissue, frozen samples were ground using a mortar and pestle, and resuspended in lysis buffer (NaCl 150 mM, Tris-HCl pH 7.5 10 mM, EDTA 1 mM, NP-40 1%, EGTA 1 mM, sodium fluoride 50 mM, β-glycerophosphate 40 mM, sodium pyrophosphate 10 mM, sodium vanadate 1 mM, PMSF 8mM, 1x Halt phosphatase inhibitor). Homogenized samples were sonicated for 1min, incubated for 1h at 4C with agitation, and then cleared by centrifugation at 13000rpm for 30min. Subsequent processing proceeded as described above.

Immunofluorescence

NSCLC cell lines were cultured for 6 days in the presence of 5-azacytidine and/or talazoparib (or vehicle), then replated onto sterile coverslips. On day 7, cells were irradiated with a single 2 Gy fraction. After recovery for 2-48hr (time-course experiments) or 4hr (single time point experiments), cells were fixed for 10 min in 4% paraformaldehyde, washed 3 times in Dulbecco's phosphate-buffered saline (DPBS), and permeabilized for 10 min in permeabilization solution (50 mM NaCl, 3 mM $MgCl_2$, 10 mM HEPES, 200 nM sucrose, and 0.5% Triton X-100 in 1X PBS). Coverslips were washed 3 times in DPBS + 1% bovine serum albumin + 0.1% Triton X-100, blocked in DPBS + 10% FBS for 1h at room temperature, washed 3 times, and incubated overnight in primary antibody at 4°C. Coverslips were washed and incubated in secondary antibody for 1h at 37°C. After washing, coverslips were mounted on slides using ProLong Gold Antifade Reagent with DAPI (Cell Signaling Technology). Foci were examined using a Nikon fluorescent microscope Eclipse 80i (100×/1.4 oil, Melville, NY). Images of at least 50 cells/slide were captured using a CCD (charge-coupled device) camera and the imaging software NIS Elements (BR 3.00, Nikon).

Proximity ligation assay (PLA)

NSCLC cell lines were cultured for 3 days in the presence of 5-azacytidine (500 nM) and/or talazoparib (2nM or 100nM), then replated onto sterile coverslips. On day 4, cells were treated with 500 μM methyl methanesulphonate to induce DNA base damage. After 4hr, cells were fixed for 10 min in 4% paraformaldehyde, based 3 times in DPBS, and permeabilized for 15 min in 0.1% triton x-100 in PBS. Coverslips were washed 3 times in DPBS, blocked for 1hr at 37°C in Duolink In Situ PLA Blocking Solution (Sigma-Aldrich), and incubated overnight at 4°C in primary antibodies (mouse anti-PARP1/rabbit anti-H2AX, mouse anti-PARP1/rabbit anti γH2AX, mouse anti-PARP1/rabbit anti-DNMT1; all at 1:200 dilution in Duolink In Situ PLA Antibody Diluent). Following two washes in Duolink In Situ Wash Buffer A (also used for subsequent washes), coverslips were incubated for 1 hr in Duolink In Situ PLA Probes (PLUS anti-rabbit and MINUS anti-mouse, 1:5 in antibody diluent) at 37°C in a humidified chamber, then washed twice. Ligase was prepared 1:40 in Duolink Ligation buffer and incubated on coverslips for 1h at 37°C in a humidified chamber, then washed twice. Polymerase was prepared 1:80 in Duolink Amplification buffer and incubated on coverslips for 100 min at 37°C in a humidified chamber. Final washes were performed in Duolink In Situ Wash Buffer B, then coverslips were mountedon slides using ProLong Gold Antifade Reagent with DAPI. PLA foci were examined using a Nikon fluorescent microscope Eclipse 80i (100×/1.4 oil, Melville, NY). Images of at least 50 cells/slide were captured using a CCD (charge-coupled device) camera and the imaging software NIS Elements (BR 3.00, Nikon).

DNA fiber analysis

Cultured NSCLC cell lines were exposed to iodo-deoxyuridine (IdU; 25 μM) for 20 min, then washed and exposed to chloro-deoxyuridine (CldU; 250 μM) in fresh media in the presence or absence of 5-azacytidine (500 nM) and/or talazoparib (2 nM or 100 nM) for 30 min. Cells were collected in ice-cold PBS as a 7.5 x 10^5 cells/ml suspension, of which 2 μl were dotted onto one end of a microscope slide and allowed to air-dry for 5 min. Cells were lysed in lysis solution (50 mM EDTA, 200 mM Tris-HCl pH 7.4, SDS 0.5%) for 10 min, then slides were tilted to 15 degrees to allow fibers to spread down the length of the slide. After drying for 4h in the dark, fibers were fixed in 3:1 methanol:acetic acid for 10 min, and dried overnight. Subsequently, slides were washed in de-ionized water, immersed in 2.5N hydrochloric acid for 80 min, and then neutralized in 0.4 M Tris-HCl ph 7.4. Slides were washed twice in PBS-T, once in PBS, and then blocked for 1h at room temperature in blocking solution (5% bovine serum albumin, 10% goat serum in PBS-T) under parafilm. Fibers were incubated in primary antibody (rat anti-BrdU for CldU 1:200, mouse anti-BrdU for IdU 1:40) in blocking solution under parafilm for 1 hr at room temperature in a humidified chamber. Washes were repeated, then slides were incubated in secondary antibody (goat anti-rat Alexa 488 1:200, sheep anti-mouse Cy3 1:500) in blocking solution under parafilm for 1 hr at room temperature in a humidified chamber. Following repeat washes, slides were dehydrated in ethanol (2 min each in 70%, 90% and 100% v/v) and airdried, then mounted in Vectashield Antifade mounting medium.

Fibers were examined using a Nikon fluorescent microscope Eclipse 80i (100×/1.4 oil, Melville, NY). Images of at least 25 fibers/slide were captured using a CCD (charge-coupled device) camera and the imaging software NIS Elements (BR 3.00, Nikon). Fiber length was quantified using ImageJ software, and a ratio of CldU:IdU length was calculated.

Determination of apoptosis by annexin V staining

Cells were incubated in the presence of azacytidine (250 nM) and/or talazoparib (2.5 nM) for 4 days, after which they were irradiated at a dose of 4Gy. At the specified time point, cells were collected, washed twice in PBS, and resuspended in 100 µl binding buffer (PE Annexin V Apoptosis Detection Kit I, BD Biosciences) at 1 x 10^6 cells/ml. 5 µl each of annexin V-PE and 7-AAD were added and the suspension incubated for 15 min at room temperature in the dark. The suspension was made up to 500 µl with binding buffer. Analysis of annexin V and 7-AAD staining was performed using a BD FACSCanto II cytometer.

Extrachromosomal homologous recombination and non-homologous end joining assays

NSCLC cell lines were cultured for 3 days in the presence of 5-azacytidine (500 nM). Nuclear extracts were prepared using the Cell Lytic NuCLEAR Extraction Kit (Sigma-Aldrich). Nuclear extracts were dialysed for two hours using the Plus One Mini Dialysis Kit 1kDa (GE Healthcare) in dialysis solution (20 mM HEPES pH9, 100 mM KCl, 0.2 mM EDTA, 20% glycerol. 0.5 mM DTT, 0.1 mM PMSF). Protein content was quantified by Nanodrop and diluted to 0.5 µg/µl in DNase/RNase-free water. For HR assay, diluted nuclear extracts were incubated with 5 µl each of dl-1 and dl-2 plasmid (Homologous Recombination Assay Kit, Norgen Biotek) in reaction buffer (for 2 hours at 30°C. For NHEJ assay, pimEJ5GFP was linearized overnight with I-SceI followed by end dephosphorylation using shrimp alkaline phosphatase, then diluted nuclear extracts (2 µg) were incubated with 5ul plasmid in ligation buffer (1x T4 ligase buffer, 2 mM ATP, 50 µM deoxynucleotide triphosphates) for 2 hours at 37°C. Plasmid DNA was recovered by QIAamp DNA mini kit (Qiagen), and the relative quantity of recombined product was determined by quantitative real-time PCR CFX384 Real Time System (BioRad) using PCR primers spanning the repair site, normalized against amplification of a distant site (for HR, primers supplied by Norgen Biotek; for NHEJ, see Supplementary Experimental Procedures Table S2 for primer details).

Double strand break repair reporter assays

Stable cell lines expressing pDRGFP (a gift from Maria Jasin; Addgene plasmid # 26475), EJ2GFP-puro, or pimEJ5GFP (gifts from Jeremy Stark; Addgene plasmids #44025 and #44026) were created using a Nucleofector II system (Amaxa). Cells were pretreated for 4 days in the presence of 5-azacytidine (500 nM), then transfected with ISceI using Lipofectamine 3000 (Thermo Scientific). After 72 hours, the repair product was quantified as GFP positivity as determined by flow cytometry using a BD FACSCanto II cytometer.

Supplementary Figures

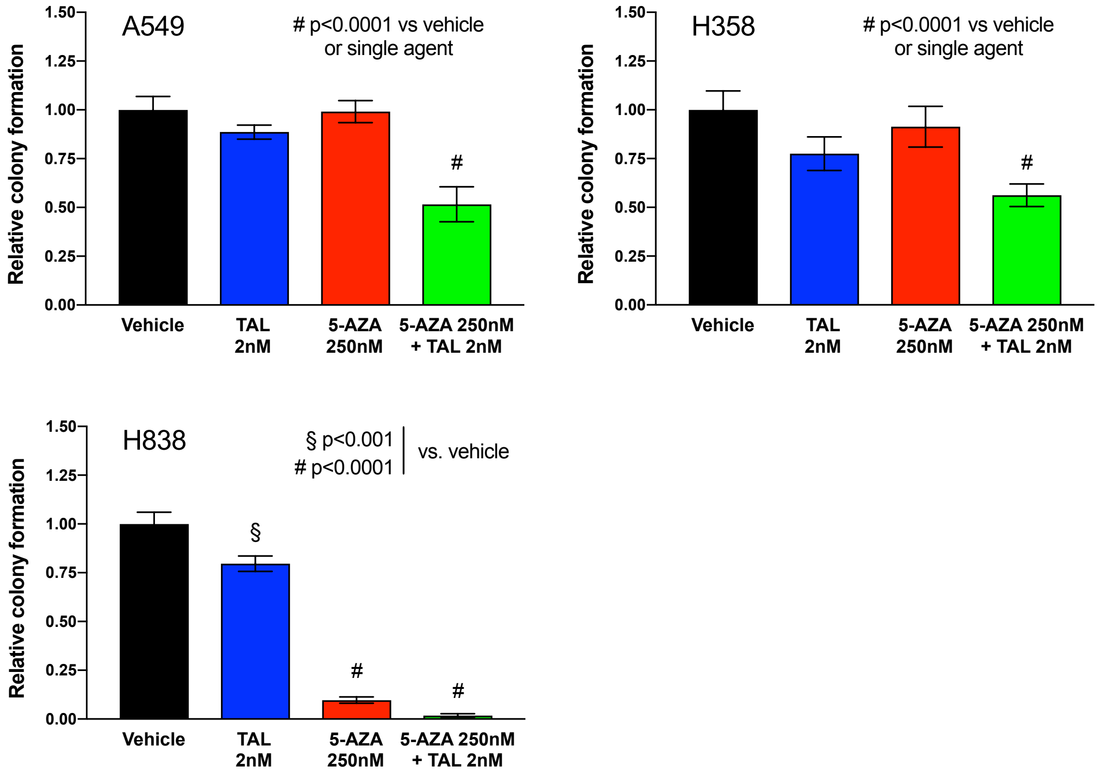


Fig. S1. Colony forming assay in NSCLC cell lines. 5-AZA+TAL significantly reduces clonogenicity compared to single agents alone.

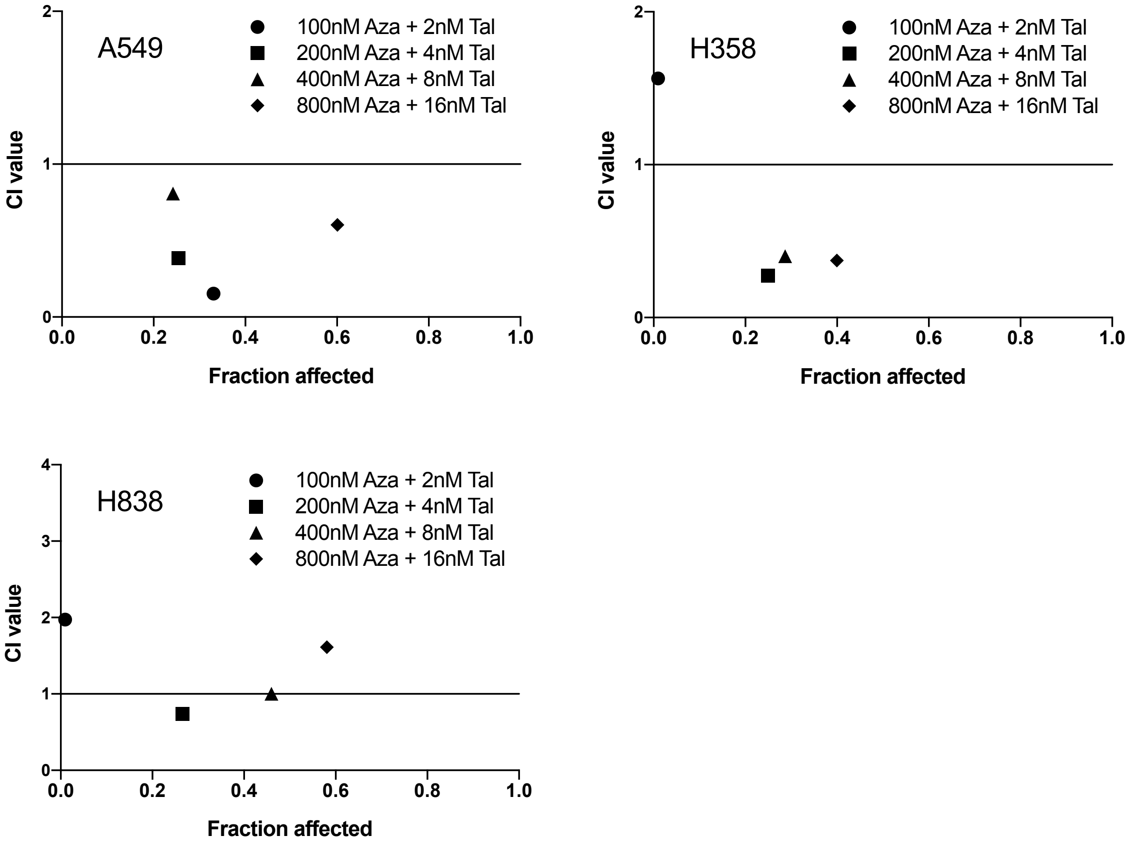


Fig. S2. Combination index analysis of 5-AZA+TAL combination in NSCLC. The data indicate that the cytotoxic effect of the 5-AZA+TAL combination is synergistic in A549 and H358 cell lines. H838, which is highly sensitive to single agent 5-AZA, does not exhibit synergistic cytotoxicity in response to the combination.

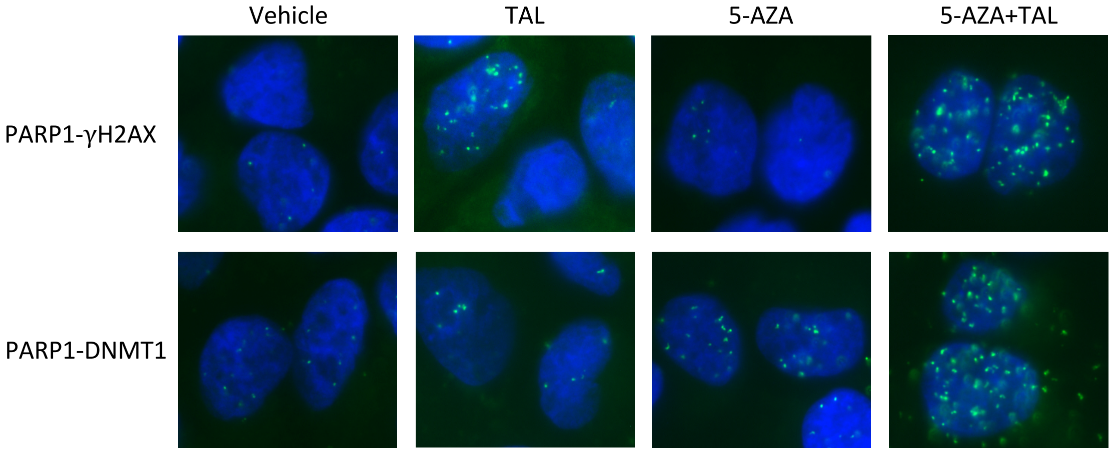


Fig. S3. Proximity ligation assay for PARP1-γH2AX and PARP1-DNMT1 colocalization in H460 cells following treatment with TAL, 5-AZA, or combination.

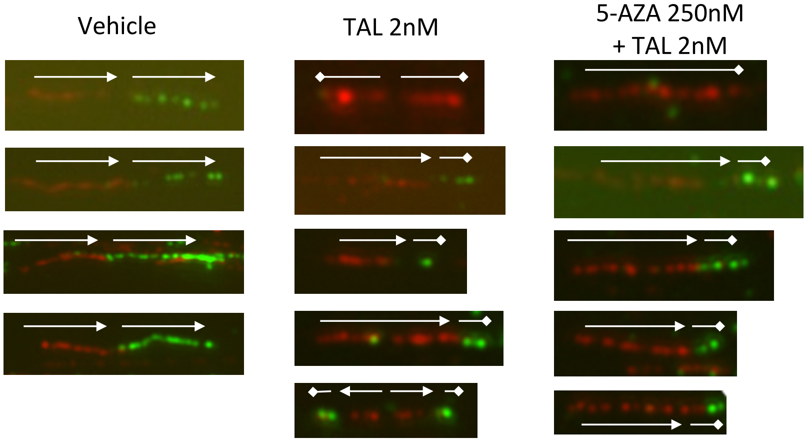


Fig. S4. Examples of DNA replication forks following TAL +/- 5-AZA exposure. Red tracts represent IdU incorporation in absence of drug. Green forks represent CldU incorporation following addition of drug. Square arrows indicate abbreviated tract length indicating fork stalling.

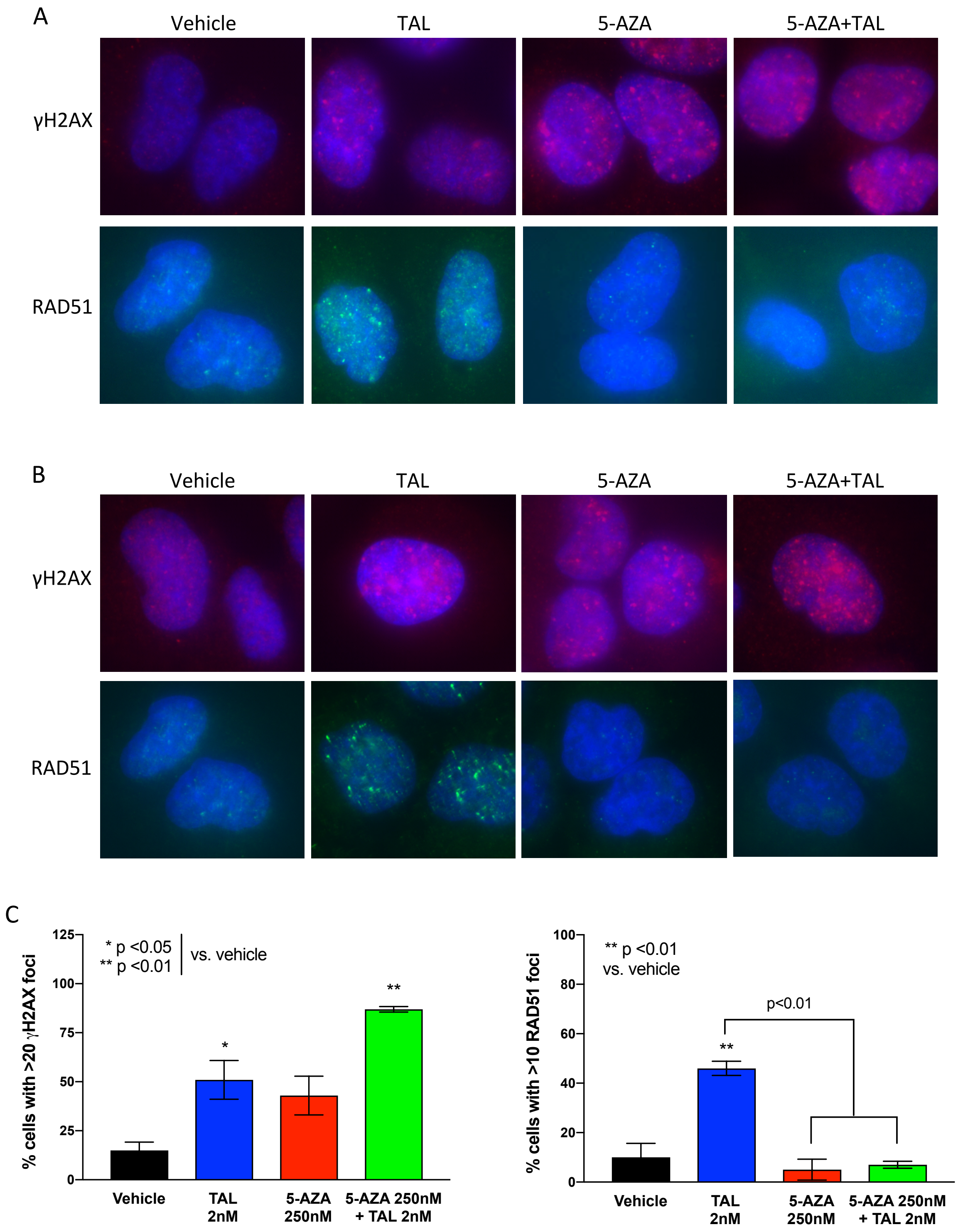


Fig. S5. A. γH2AX and RAD51 foci in H460 cells following 5-AZA, TAL, or combination. B. γH2AX and RAD51 foci in A549 cells following 5-AZA, TAL, or combination. C. Quantification of γH2AX and RAD51 foci in A549 cells.

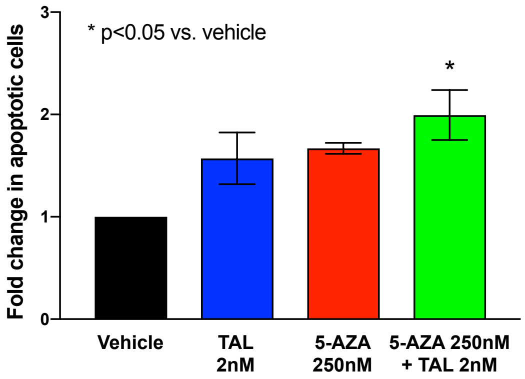


Fig. S6. Annexin V flow cytometry indicates a two-fold increase in apoptosis in H460 cells treated with 5-AZA+TAL combination (p <0.05 compared to vehicle control).

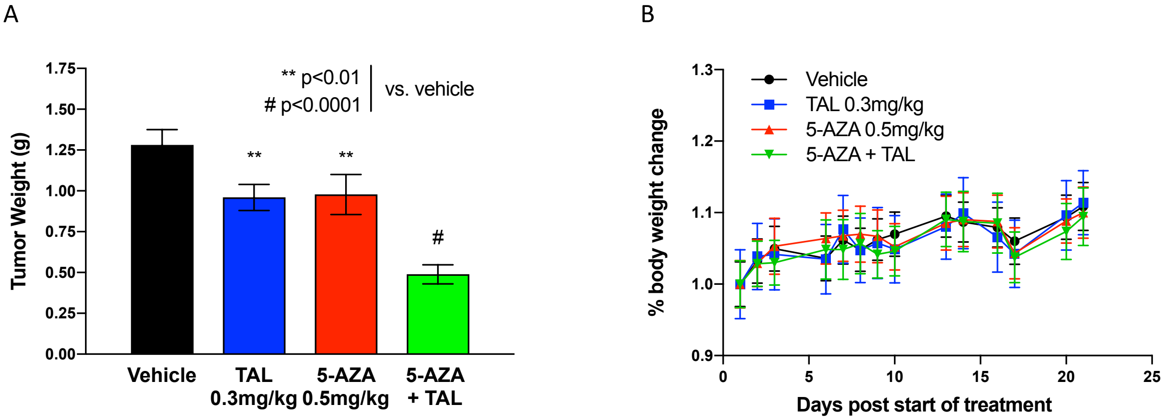


Fig. S7. H460 xenograft model treated with TAL and/or 5-AZA. A. Excised tumor weight at study endpoint. B. Body weight on study.

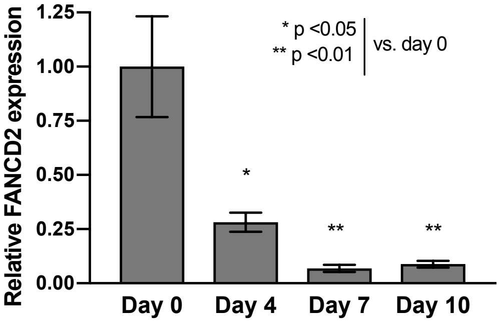


Fig. S8. RNA expression of FANCD2 in A549 cells after 5-AZA treatment (250 nM).

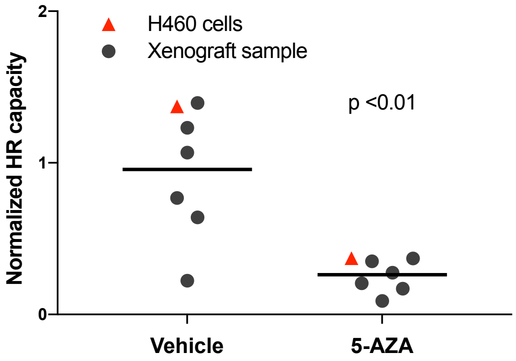


Fig. S9. Homologous recombination repair capacity by extrachromosomal assay in samples from *in vivo* H460 NSCLC model (n=8) treated with 5-AZA (0.5mg/kg SC). Data represented as mean per sample over three experiments performed in triplicate, overlaid with group mean ± SEM. P value calculated using two-way ANOVA.

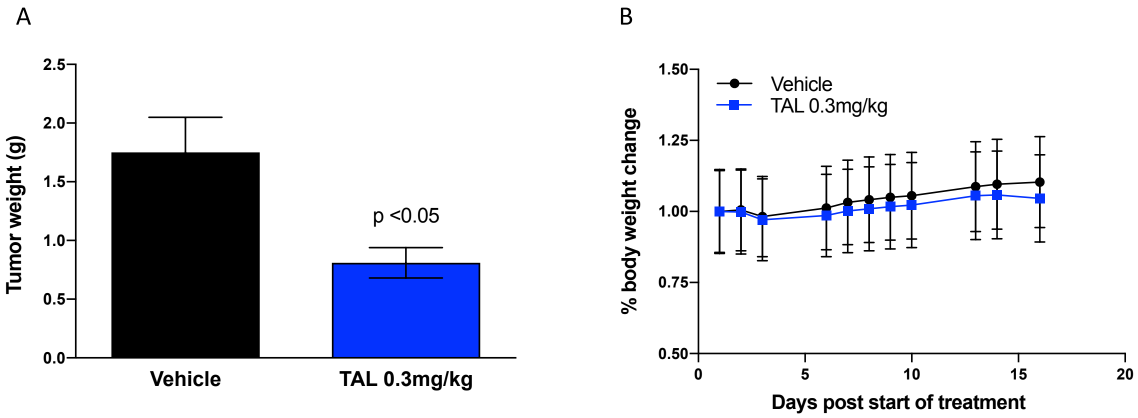


Fig. S10. FANCD2-KD H460 xenograft model treated with TAL. A. Excised tumor weight at study endpoint. B. Body weight on study.

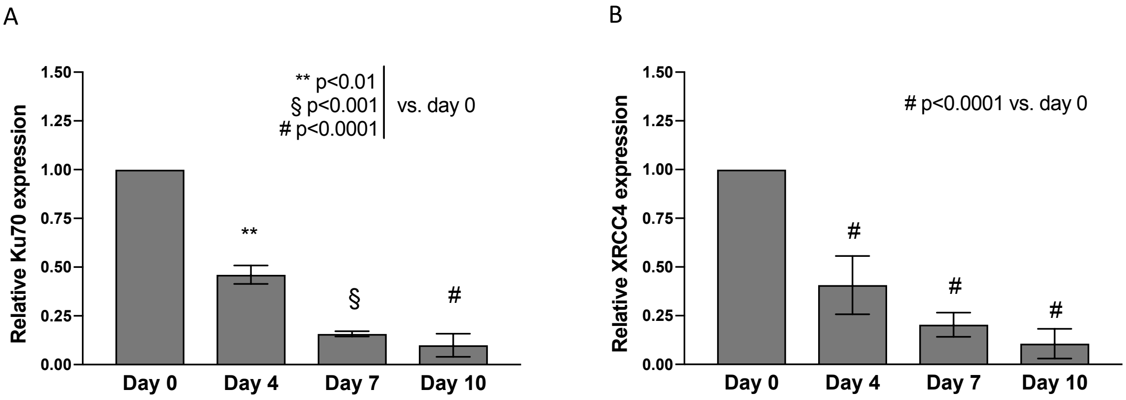


Fig. S11. RNA expression of NHEJ factors after 5-AZA treatment (250 nM). A. Ku70 expression. B. XRCC4 expression.

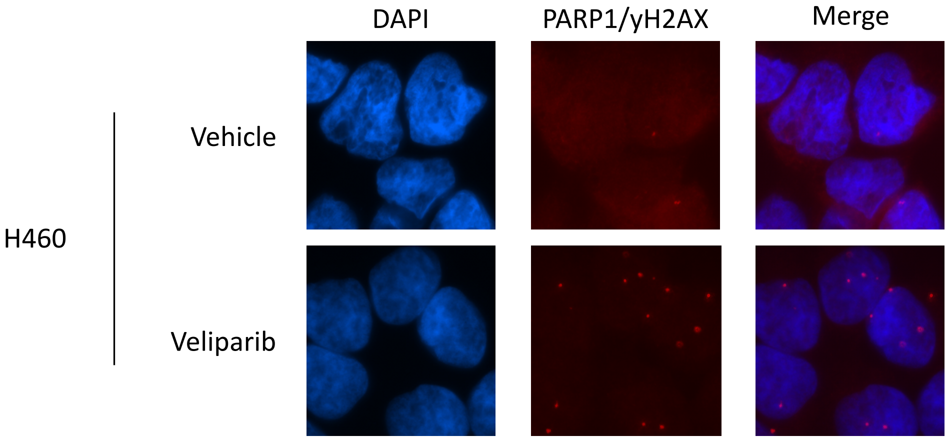


Fig. S12. Proximity ligation assay for PARP1-γH2AX colocalization in H460 cells following treatment with veliparib (15nM).

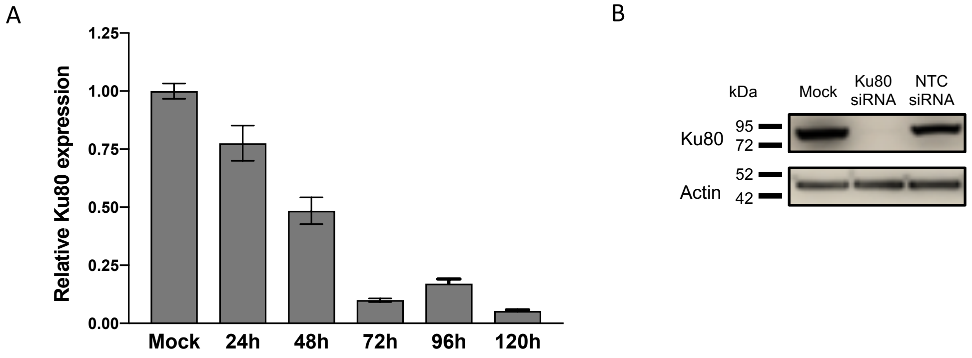


Fig. S13. A. Ku80 expression in H460 cells following transfection with Ku80 siRNA. A. Ku80 RNA expression by qRT-PCR. Data represented as mean expression ± SEM, normalized against pre-treatment expression level (n=3). B. Ku80 protein expression. NTC = non-targeting control.

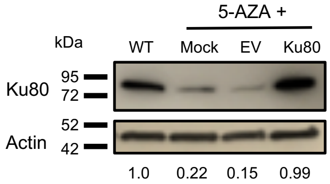


Fig. S14. Ku80 protein expression in H460 cells following 5-AZA treatment (250nM, 4 days) followed by nucleofection with Ku80 or empty vector (EV) expression plasmid.

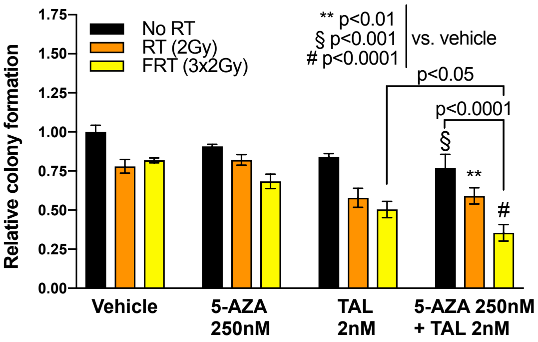


Fig. S15. Colony formation in A549 cells is significantly reduced by 5-AZA+TAL in combination with single fraction 2Gy RT or 3x2Gy FRT.

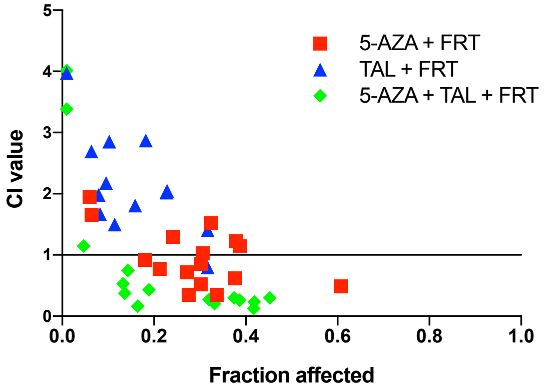


Fig. S16. Combination index (CI) plot for 5-AZA+TAL+FRT in H460 cells (n=9).

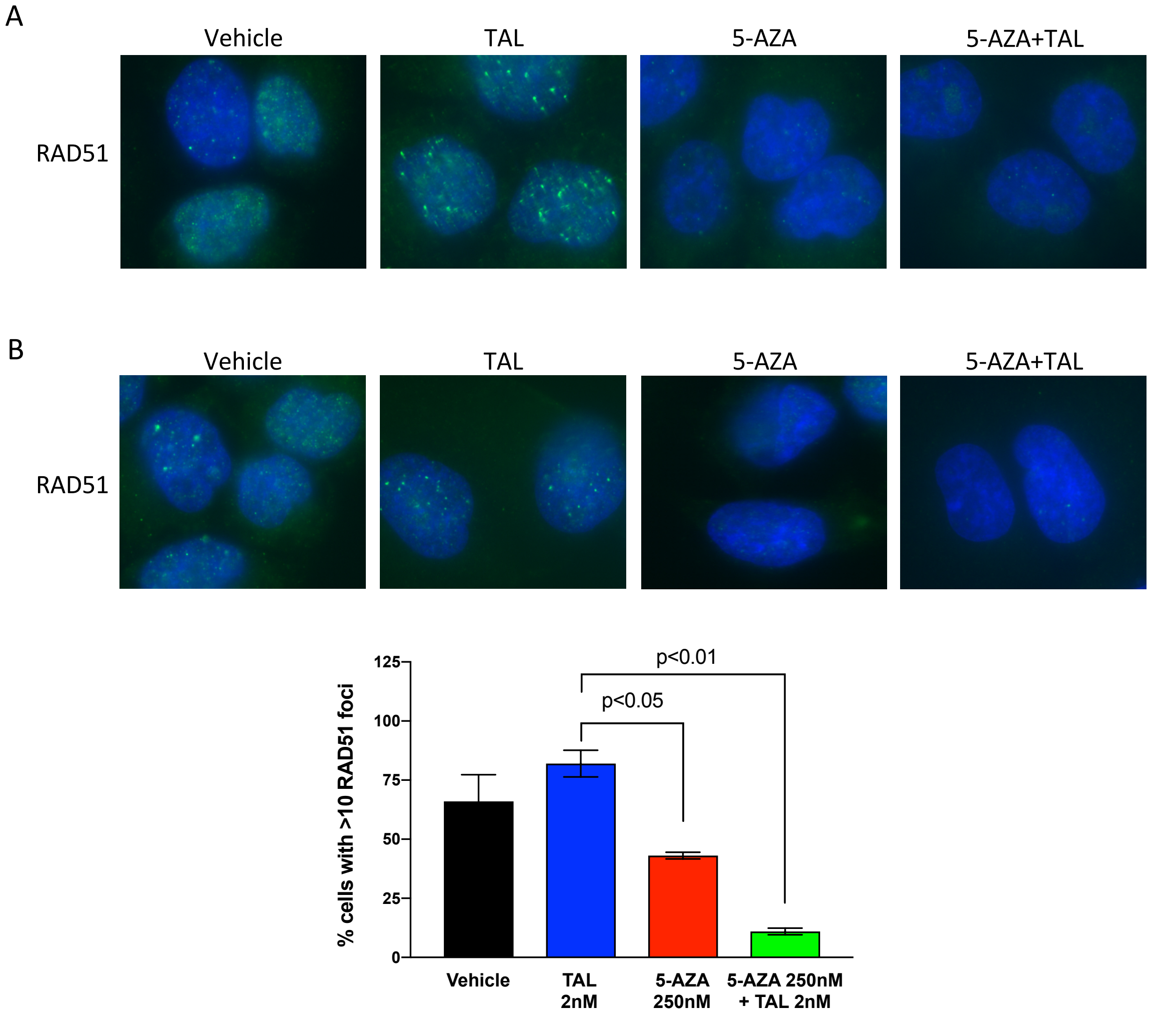
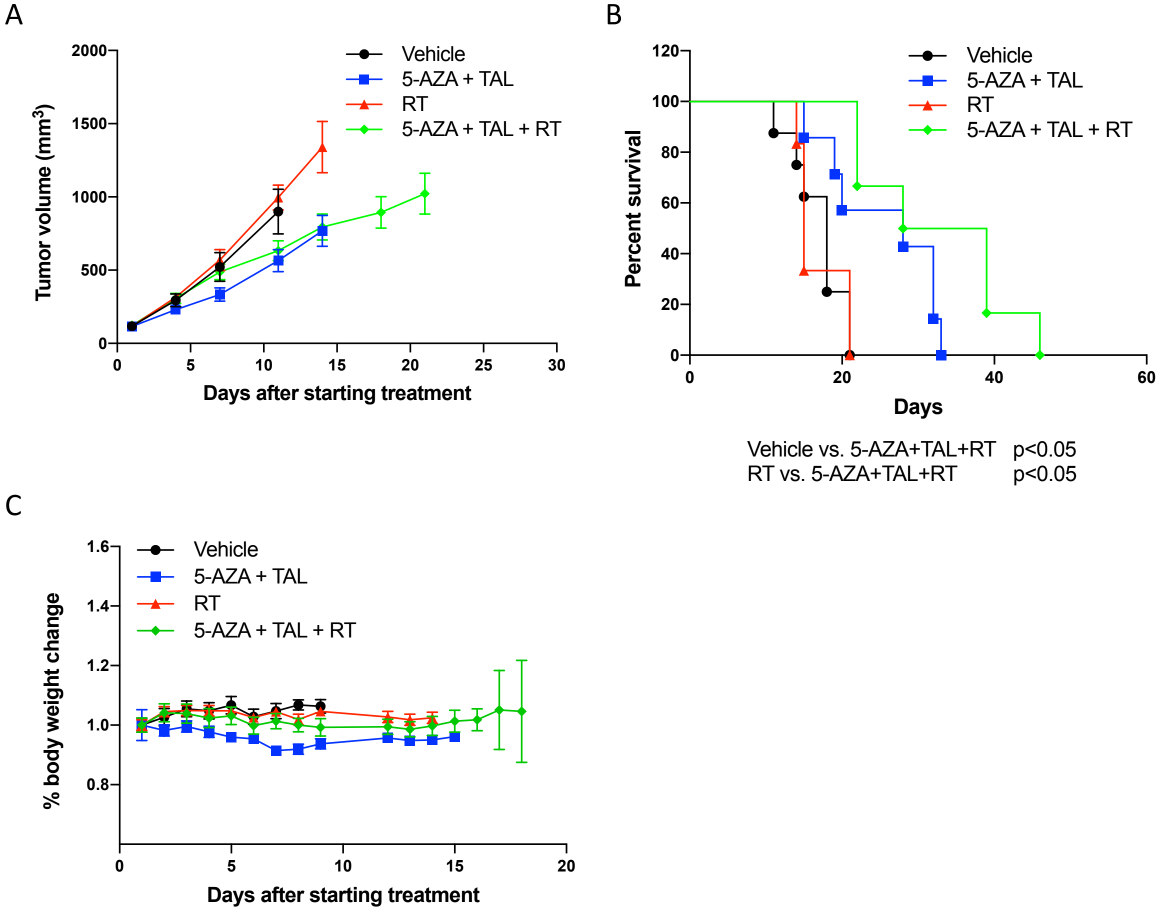


Fig. S17. RAD51 foci burden 4 hours following 2Gy RT is decreased in A549 cells treated with 5-AZA and 5-AZA+TAL.



Vehicle vs. 5-AZA+TAL+RT $p<0.05$
RT vs. 5-AZA+TAL+RT $p<0.05$

Fig. S18. *In vivo* H460 subcutaneous flank injection model, treated with vehicle, 5-AZA (0.5mg/kg) + TAL (0.3mg/kg), RT (2Gy single dose), or 5-AZA+TAL+RT. A. Tumor volume on study. B. Kaplan-Meier survival curve. C. Body weight on study.

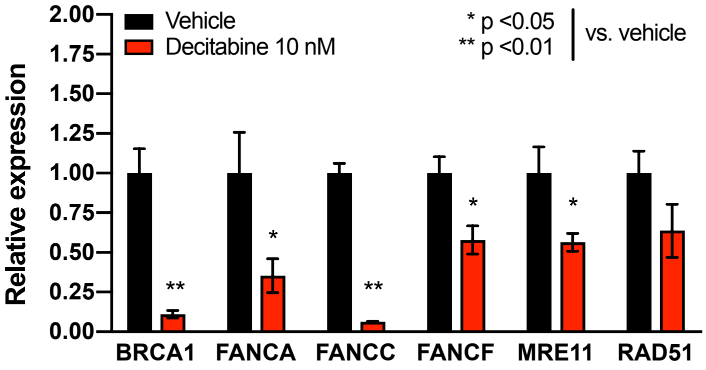


Fig. S19. Relative RNA expression of select DNA repair factors in MOLM14 AML cells following decitabine exposure (10 nM; 7 days). Data represented as mean expression ± SEM, normalized against GAPDH expression (n=3).

Supplementary tables

H460 5-AZA Enriched Pathways	ES	NES	NOM p-val	FDR q-val
REACTOME_CYTOSOLIC_TRNA_AMINOACYLATION	-0.7913	-2.2294	0.0000	0.0000
KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	-0.7070	-2.2174	0.0000	0.0000
REACTOME_TRNA_AMINOACYLATION	-0.7052	-2.2038	0.0000	0.0000
REACTOME_MITOTIC_PROMETAPHASE	-0.6028	-2.1668	0.0000	0.0000
REACTOME_FANCONI_ANEMIA_PATHWAY	-0.7782	-2.1278	0.0000	0.0000
REACTOME_MITOTIC_M_M_G1_PHASES	-0.5243	-2.0485	0.0000	0.0014
REACTOME_AMINO_ACID_TRANSPORT_ACROSS_THE_PLASMA_MEMBRANE	-0.6873	-2.0344	0.0000	0.0012
REACTOME_DNA_REPLICATION	-0.4992	-2.0308	0.0000	0.0010
KEGG_ONE_CARBON_POOL_BY_FOLATE	-0.7937	-2.0196	0.0000	0.0004
REACTOME_CELL_CYCLE_MITOTIC	-0.4672	-1.9644	0.0000	0.0036
REACTOME_BILE_ACID_AND_BILE_SALT_METABOLISM	-0.6949	-1.9543	0.0000	0.0041
REACTOME_AMINO_ACID_SYNTHESIS_AND_INTERCONVERSION_TRANSAMINATION	-0.7965	-1.9532	0.0000	0.0037
REACTOME_G2_M_CHECKPOINTS	-0.6261	-1.9308	0.0000	0.0049
REACTOME_MITOCHONDRIAL_PROTEIN_IMPORT	-0.5853	-1.8968	0.0000	0.0074
REACTOME_3_UTR_MEDIATED_TRANSLATIONAL_REGULATION	-0.5080	-1.8830	0.0000	0.0080
REACTOME_DNA_REPAIR	-0.5093	-1.8771	0.0000	0.0081
REACTOME_ACTIVATION_OF_GENES_BY_ATF4	-0.6649	-1.8686	0.0000	0.0094
KEGG_RIBOSOME	-0.5153	-1.8398	0.0000	0.0127
REACTOME_CELL_CYCLE	-0.4237	-1.8350	0.0000	0.0154
REACTOME_SYNTHESIS_OF_BILE_ACIDS_AND_BILE_SALTS	-0.6936	-1.8334	0.0000	0.0148
REACTOME_MITOCHONDRIAL_TRNA_AMINOACYLATION	-0.6683	-1.8319	0.0000	0.0143
REACTOME_PEPTIDE_CHAIN_ELONGATION	-0.5087	-1.8309	0.0000	0.0136
REACTOME_PERK_REGULATED_GENE_EXPRESSION	-0.6378	-1.8254	0.0000	0.0139
REACTOME_CHOLESTEROL_BIOSYNTHESIS	-0.6605	-1.8249	0.0000	0.0133
KEGG_STEROID_BIOSYNTHESIS	-0.7042	-1.7978	0.0000	0.0172
REACTOME_APC_CDC20_MEDIATED_DEGRADATION_OF_NEK2A	-0.6582	-1.7900	0.0020	0.0205
KEGG_PROPANOATE_METABOLISM	-0.5894	-1.7789	0.0000	0.0184
REACTOME_AMINO_ACID_AND_OLIGOPEPTIDE_SLC_TRANSPORTERS	-0.5454	-1.7543	0.0000	0.0304
KEGG_GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS	-0.6170	-1.7477	0.0066	0.0240
REACTOME_DOUBLE_STRAND_BREAK_REPAIR	-0.6311	-1.7448	0.0020	0.0320
REACTOME_HOMOLOGOUS_RECOMBINATION_REPAIR_OF_REPLICATION_INDEPENDENT_DOUBLE_STRAND_BREAKS	-0.6834	-1.7420	0.0098	0.0318
REACTOME_DEADENYLATION_DEPENDENT_MRNA_DECAY	-0.5474	-1.7411	0.0000	0.0311
KEGG_BUTANOATE_METABOLISM	-0.5824	-1.7407	0.0021	0.0216
KEGG_CELL_CYCLE	-0.4552	-1.7396	0.0000	0.0191
REACTOME_ACTIVATION_OF_ATR_IN_RESPONSE_TO_REPLICATION_STRESS	-0.5706	-1.7385	0.0000	0.0308
REACTOME_ACTIVATION_OF_THE_MRNA_UPON_BINDING_OF_THE_CAP_BINDING_COMPLEX_AND_EIFS_AND_SUBSEQUENT_BINDING_TO_43S	-0.5170	-1.7347	0.0024	0.0313
KEGG_PRIMARY_BILE_ACID_BIOSYNTHESIS	-0.7084	-1.7310	0.0041	0.0188
REACTOME_GENERIC_TRANSCRIPTION_PATHWAY	-0.4012	-1.7231	0.0000	0.0348
REACTOME_RNA_POL_I_TRANSCRIPTION_TERMINATION	-0.6463	-1.7143	0.0041	0.0365
REACTOME_NONSENSE_MEDIATED_DECAY_ENHANCED_BY_THE_EXON_JUNCTION_COMPLEX	-0.4570	-1.7109	0.0000	0.0367
REACTOME_RNA_POL_I_TRANSCRIPTION_INITIATION	-0.6252	-1.7086	0.0021	0.0364
REACTOME_EXTENSION_OF_TELOMERES	-0.5808	-1.6994	0.0064	0.0394
REACTOME_MITOTIC_G2_G2_M_PHASES	-0.4677	-1.6833	0.0000	0.0451
REACTOME_FATTY_ACYL_COA_BIOSYNTHESIS	-0.6431	-1.6818	0.0043	0.0443
REACTOME_METABOLISM_OF_RNA	-0.4049	-1.6816	0.0000	0.0432

REACTOME_GLOBAL_GENOMIC_NER_GG_NER	-0.5700	-1.6810	0.0044	0.0423
KEGG_MISMATCH_REPAIR	-0.6111	-1.6727	0.0166	0.0319
KEGG_PYRUVATE_METABOLISM	-0.5287	-1.6651	0.0048	0.0318
REACTOME_INTERACTIONS_OF_VPR_WITH_HOST_CELLULAR_PROTEINS	-0.5572	-1.6599	0.0043	0.0512
KEGG_CITRATE_CYCLE_TCA_CYCLE	-0.5683	-1.6594	0.0064	0.0306
REACTOME_POST_TRANSLATIONAL_MODIFICATION_SYNTHESIS_OF_GPI_ANCHORED_PROTEINS	-0.5882	-1.6547	0.0046	0.0528
REACTOME_TRANSLATION	-0.4238	-1.6544	0.0000	0.0517
KEGG_N_GLYCAN_BIOSYNTHESIS	-0.5099	-1.6520	0.0086	0.0297
REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	-0.5603	-1.6463	0.0089	0.0550
REACTOME_DEADENYLATION_OF_MRNA	-0.6203	-1.6453	0.0210	0.0541
REACTOME_INHIBITION_OF_THE_PROTEOLYTIC_ACTIVITY_OF_APC_C_REQUIRED_FOR_THE_ONSET_OF_ANAPHASE_BY_MITOTIC_SPINDLE_CHECKPOINT_COMPONENTS	-0.6273	-1.6377	0.0165	0.0565
KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS	-0.6589	-1.6357	0.0101	0.0327
REACTOME_CELL_CYCLE_CHECKPOINTS	-0.4324	-1.6230	0.0000	0.0636
REACTOME_CITRIC_ACID_CYCLE_TCA_CYCLE	-0.6161	-1.6077	0.0108	0.0727
KEGG_PURINE_METABOLISM	-0.4039	-1.5983	0.0000	0.0448
REACTOME_CYCLIN_A_B1_ASSOCIATED_EVENTS_DURING_G2_M_TRANSITION	-0.6330	-1.5933	0.0329	0.0811
REACTOME_G1_S_TRANSITION	-0.4252	-1.5854	0.0025	0.0856
REACTOME_SYNTHESIS_OF_GLYCOSYLPHOSPHATIDYLINOSITOL_GPI	-0.6125	-1.5817	0.0279	0.0863
KEGG_DNA_REPLICATION	-0.5195	-1.5681	0.0175	0.0547
REACTOME_FORMATION_OF_THE_TERNARY_COMPLEX_AND_SUBSEQUENTLY_THE_43S_COMPLEX	-0.4881	-1.5664	0.0177	0.0955
REACTOME_PYRUVATE_METABOLISM_AND_CITRIC_ACID_TCA_CYCLE	-0.5041	-1.5664	0.0089	0.0937
REACTOME_SMAD2_SMAD3_SMAD4_HETEROTRIMER_REGULATES_TRANSCRIPTION	-0.5576	-1.5661	0.0172	0.0920
REACTOME_FORMATION_OF_INCISION_COMPLEX_IN_GG_NER	-0.5880	-1.5507	0.0262	0.1019
REACTOME_METABOLISM_OF_MRNA	-0.3790	-1.5455	0.0000	0.1038
REACTOME_FORMATION_OF_ATP_BY_CHEMIOSMOTIC_COUPLING	-0.6112	-1.5366	0.0356	0.1099
KEGG_HOMOLOGOUS_RECOMBINATION	-0.5322	-1.5349	0.0328	0.0682
REACTOME_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE	-0.4071	-1.5328	0.0071	0.1116
KEGG_NUCLEOTIDE_EXCISION_REPAIR	-0.4763	-1.5302	0.0200	0.0673
REACTOME_CHROMOSOME_MAINTENANCE	-0.4065	-1.5261	0.0026	0.1156
REACTOME_INFLUENZA_VIRAL_RNA_TRANSCRIPTION_AND_REPLICATION	-0.4146	-1.5140	0.0050	0.1244
REACTOME_S_PHASE	-0.4009	-1.5062	0.0077	0.1298
REACTOME_SYNTHESIS_OF_BILE_ACIDS_AND_BILE_SALTS_VIA_7ALPHA_HYDROXYCHOLESTEROL	-0.6075	-1.5046	0.0427	0.1290
REACTOME_LOSS_OF_NLP_FROM_MITOTIC_CENTROSOMES	-0.4593	-1.4993	0.0156	0.1320
REACTOME_MITOTIC_G1_G1_S_PHASES	-0.3910	-1.4930	0.0051	0.1356
KEGG_GLYOXYLATE_AND_DICARBOXYLATE_METABOLISM	-0.5917	-1.4925	0.0464	0.0858
REACTOME_TRIGLYCERIDE_BIOSYNTHESIS	-0.4823	-1.4921	0.0213	0.1342
KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	-0.4768	-1.4920	0.0172	0.0816
REACTOME_SYNTHESIS_OF_PIPS_AT_THE_GOLGI_MEMBRANE	-0.5854	-1.4867	0.0540	0.1373
REACTOME_METABOLISM_OF_NON_CODING_RNA	-0.4663	-1.4845	0.0207	0.1375
REACTOME_INFLUENZA_LIFE_CYCLE	-0.3830	-1.4820	0.0097	0.1381
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	-0.4358	-1.4771	0.0208	0.0864
REACTOME_NEP_NS2_INTERACTS_WITH_THE_CELLULAR_EXPORT_MACHINERY	-0.5132	-1.4754	0.0409	0.1426
REACTOME_TCA_CYCLE_AND_RESPIRATORY_ELECTRON_TRANSPORT	-0.3872	-1.4710	0.0000	0.1453
REACTOME_NA_CL_DEPENDENT_NEUROTRANSMITTER_TRANSPORTERS	-0.5699	-1.4502	0.0817	0.1663
REACTOME_NUCLEOTIDE_EXCISION_REPAIR	-0.4610	-1.4442	0.0414	0.1712
REACTOME_METABOLISM_OF_NUCLEOTIDES	-0.4149	-1.4388	0.0238	0.1752

KEGG_CYSTEINE_AND_METHIONINE_METABOLISM	-0.4709	-1.4353	0.0621	0.1138
REACTOME_RECRUITMENT_OF_MITOTIC_CENTROSOME_PROTEINS_AND_COMPLEXES	-0.4302	-1.4325	0.0156	0.1808
KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM	-0.4906	-1.4319	0.0521	0.1119
REACTOME_PKB_MEDIATED_EVENTS	-0.4963	-1.4282	0.0551	0.1838
KEGG_PYRIMIDINE_METABOLISM	-0.3859	-1.4222	0.0234	0.1151
KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM	-0.4633	-1.4184	0.0650	0.1136
KEGG_RNA_DEGRADATION	-0.4282	-1.4069	0.0304	0.1195
REACTOME_METABOLISM_OF_PROTEINS	-0.3209	-1.4052	0.0000	0.2128
REACTOME_DESTABILIZATION_OF_MRNA_BY_KSRP	-0.5354	-1.3986	0.0911	0.2198
REACTOME_GLUCOSE_TRANSPORT	-0.4476	-1.3945	0.0641	0.2228
KEGG_SELENOAMINO_ACID_METABOLISM	-0.5027	-1.3924	0.0699	0.1284
REACTOME_LAGGING_STRAND_SYNTHESIS	-0.5276	-1.3902	0.1049	0.2260
KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	-0.3856	-1.3882	0.0295	0.1272
REACTOME_DEPOSITION_OF_NEW_CENPA_CONTAINING_NUCLEOSOMES_AT_THE_CENTROMERE	-0.4165	-1.3824	0.0474	0.2358
REACTOME_REGULATION_OF_MITOTIC_CELL_CYCLE	-0.3938	-1.3799	0.0313	0.2363
KEGG_ABC_TRANSPORTERS	-0.4396	-1.3795	0.0505	0.1308
REACTOME_SULFUR_AMINO_ACID_METABOLISM	-0.4935	-1.3775	0.0903	0.2368
KEGG_ALANINE_ASPARTATE_AND_GLUTAMATE_METABOLISM	-0.4641	-1.3773	0.0882	0.1283
REACTOME_DNA_STRAND_ELONGATION	-0.4744	-1.3740	0.0732	0.2390
REACTOME_ASPARAGINE_N_LINKED_GLYCOSYLATION	-0.3893	-1.3711	0.0476	0.2403
REACTOME_TRANSPORT_OF_RIBONUCLEOPROTEINS_INTO_THE_HOST_NUCLEUS	-0.4909	-1.3705	0.0996	0.2383
REACTOME_FATTY_ACID_TRIACYLGLYCEROL_AND_KETONE_BODY_METABOLISM	-0.3495	-1.3704	0.0212	0.2355
REACTOME_E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION	-0.4666	-1.3631	0.0691	0.2441
REACTOME_APC_C_CDC20_MEDIATED_DEGRADATION_OF_CYCLIN_B	-0.5183	-1.3590	0.1225	0.2475
REACTOME_SLC_MEDIATED_TRANSMEMBRANE_TRANSPORT	-0.3283	-1.3558	0.0031	0.2494
REACTOME_PLATELET_SENSITIZATION_BY_LDL	-0.5341	-1.3540	0.1181	0.2491
REACTOME_TRANSCRIPTION_COUPLED_NER_TC_NER	-0.4374	-1.3517	0.0742	0.2499
KEGG_HISTIDINE_METABOLISM	-0.4601	-1.3277	0.1141	0.1751
KEGG_OOCYTE_MEIOSIS	-0.3474	-1.3238	0.0386	0.1745
KEGG_BASE_EXCISION_REPAIR	-0.4305	-1.3121	0.1052	0.1817
KEGG_LYSINE_DEGRADATION	-0.4012	-1.3039	0.0766	0.1859
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_HEPARAN_SULFATE	-0.4504	-1.2829	0.1553	0.2049
KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	-0.5102	-1.2814	0.1860	0.2014
KEGG_FATTY_ACID_METABOLISM	-0.4111	-1.2803	0.1295	0.1971
KEGG_SPLICEOSOME	-0.3327	-1.2641	0.0638	0.2123
KEGG_BIOSYNTHESIS_OF_UNSATURATED_FATTY_ACIDS	-0.4670	-1.2514	0.1912	0.2229
KEGG_VEGF_SIGNALING_PATHWAY	0.4259	1.3828	0.0626	0.2479
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	0.4004	1.3953	0.0376	0.2369
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION	0.3648	1.3987	0.0120	0.2397
KEGG_PRION_DISEASES	0.4966	1.4039	0.1028	0.2401
KEGG_TIGHT_JUNCTION	0.4035	1.4148	0.0286	0.2326
KEGG_PHOSPHATIDYLINOSITOL_SIGNALING_SYSTEM	0.4361	1.4231	0.0342	0.2278
KEGG_AXON_GUIDANCE	0.4069	1.4463	0.0159	0.2017
KEGG_ENDOCYTOSIS	0.3971	1.4506	0.0121	0.2036
KEGG_CYTOSOLIC_DNA_SENSING_PATHWAY	0.4768	1.4785	0.0477	0.1756
KEGG_GAP_JUNCTION	0.4474	1.4868	0.0070	0.1729
KEGG_VIRAL_MYOCARDITIS	0.4628	1.4869	0.0329	0.1811

KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	0.4581	1.4888	0.0294	0.1872
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	0.3922	1.4889	0.0073	0.1967
KEGG_SPHINGOLIPID_METABOLISM	0.5207	1.5118	0.0395	0.1746
KEGG_BLADDER_CANCER	0.5221	1.5153	0.0298	0.1809
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	0.4728	1.5373	0.0174	0.1606
KEGG_LYSOSOME	0.4409	1.5458	0.0047	0.1595
KEGG_TGF_BETA_SIGNALING_PATHWAY	0.4727	1.5491	0.0102	0.1663
KEGG_GRAFT_VERSUS_HOST_DISEASE	0.5326	1.5497	0.0297	0.1782
KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION	0.5174	1.5637	0.0203	0.1725
KEGG_DILATED_CARDIOMYOPATHY	0.4702	1.5938	0.0070	0.1452
KEGG_STARCH_AND_SUCROSE_METABOLISM	0.5468	1.5949	0.0189	0.1592
REACTOME_GASTRIN_CREB_SIGNALLING_PATHWAY_VIA_PKC_AND_MAPK	0.4343	1.6056	0.0016	0.2477
REACTOME_AMINE_DERIVED_HORMONES	0.6871	1.6148	0.0285	0.2452
KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS	0.4795	1.6295	0.0065	0.1281
REACTOME_OTHER_SEMAPHORIN_INTERACTIONS	0.6904	1.6298	0.0283	0.2326
KEGG_CELL_ADHESION_MOLECULES_CAMS	0.4644	1.6341	0.0000	0.1396
REACTOME_G_ALPHA_Q_SIGNALLING_EVENTS	0.4498	1.6497	0.0000	0.2098
KEGG_FOCAL_ADHESION	0.4495	1.6761	0.0000	0.1057
KEGG_AUTOIMMUNE_THYROID_DISEASE	0.5607	1.6836	0.0087	0.1146
REACTOME_CELL_SURFACE_INTERACTIONS_AT_THE_VASCULAR_WALL	0.5240	1.7151	0.0017	0.1215
REACTOME_FORMATION_OF_TUBULIN_FOLDING_INTERMEDIATES_BY_CCT_TRIC	0.7002	1.7163	0.0115	0.1306
KEGG_CARDIAC_MUSCLE_CONTRACTION	0.5395	1.7284	0.0017	0.0890
REACTOME_COLLAGEN_FORMATION	0.5672	1.7479	0.0035	0.1036
REACTOME_TRANSFERRIN_ENDOCYTOSIS_AND_RECYCLING	0.6590	1.7490	0.0038	0.1129
REACTOME_LATENT_INFECTION_OF_HOMO_SAPIENS_WITH_MYCOBACTERIUM_TUBERCULOSIS	0.6472	1.7684	0.0037	0.1045
REACTOME_MUSCLE_CONTRACTION	0.5923	1.7753	0.0037	0.1076
REACTOME_INTERFERON_ALPHA_BETA_SIGNALING	0.5767	1.7913	0.0053	0.1032
REACTOME_POST_CHAPERONIN_TUBULIN_FOLDING_PATHWAY	0.7479	1.8111	0.0079	0.0954
REACTOME_GLYCOSPHINGOLIPID_METABOLISM	0.6343	1.8299	0.0019	0.0902
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	0.5537	1.8327	0.0000	0.0292
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	0.5605	1.8376	0.0000	0.0372
KEGG_HEMATOPOIETIC_CELL_LINEAGE	0.5552	1.8569	0.0000	0.0423
KEGG_ECM_RECEPTOR_INTERACTION	0.5811	1.9147	0.0017	0.0348
REACTOME_DEGRADATION_OF_THE_EXTRACELLULAR_MATRIX	0.7120	1.9362	0.0000	0.0257
REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS	0.5901	1.9637	0.0000	0.0208
REACTOME_SMOOTH_MUSCLE_CONTRACTION	0.7577	2.0060	0.0000	0.0158
REACTOME_EXTRACELLULAR_MATRIX_ORGANIZATION	0.6051	2.0093	0.0000	0.0292

Table S1A: Top up and down regulated GSEA REACTOME and KEGG pathways by 5-AZA treatment in H460 cells. GSEA pathway cut-off of FDR ≤0.250 was used to delineate pathways with significant enrichment by 5-AZA. ES=Enrichment Score, NES=Normalized Enrichment Score, NOM p-Value= Nominal p Value, FDR q Value= False Discover Rate q Value.

A549 5-AZA Enriched Pathways	**ES**	**NES**	**NOM p-val**	**FDR q-val**
REACTOME_CELL_CYCLE_MITOTIC	-0.550	-2.448	0.000	0.000
REACTOME_DNA_REPLICATION	-0.574	-2.400	0.000	0.000
REACTOME_G2_M_CHECKPOINTS	-0.739	-2.386	0.000	0.000
REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	-0.769	-2.367	0.000	0.000
REACTOME_EXTENSION_OF_TELOMERES	-0.792	-2.339	0.000	0.000
REACTOME_DNA_STRAND_ELONGATION	-0.759	-2.337	0.000	0.000
REACTOME_MITOTIC_M_M_G1_PHASES	-0.563	-2.312	0.000	0.000
REACTOME_MITOTIC_PROMETAPHASE	-0.610	-2.304	0.000	0.000
REACTOME_ACTIVATION_OF_ATR_IN_RESPONSE_TO_REPLICATION_STRESS	-0.741	-2.304	0.000	0.000
KEGG_MISMATCH_REPAIR	-0.803	-2.271	0.000	0.000
KEGG_DNA_REPLICATION	-0.723	-2.264	0.000	0.000
REACTOME_CELL_CYCLE	-0.494	-2.243	0.000	0.000
KEGG_CELL_CYCLE	-0.556	-2.206	0.000	0.000
REACTOME_LAGGING_STRAND_SYNTHESIS	-0.801	-2.200	0.000	0.000
REACTOME_E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION	-0.704	-2.183	0.000	0.000
REACTOME_INTERACTIONS_OF_VPR_WITH_HOST_CELLULAR_PROTEINS	-0.703	-2.169	0.000	0.000
REACTOME_GLOBAL_GENOMIC_NER_GG_NER	-0.703	-2.135	0.000	0.000
REACTOME_G1_S_TRANSITION	-0.543	-2.133	0.000	0.000
REACTOME_MITOTIC_G1_G1_S_PHASES	-0.533	-2.120	0.000	0.000
REACTOME_S_PHASE	-0.548	-2.115	0.000	0.000
KEGG_NUCLEOTIDE_EXCISION_REPAIR	-0.640	-2.113	0.000	0.000
REACTOME_DNA_REPAIR	-0.536	-2.087	0.000	0.000
REACTOME_PROCESSIVE_SYNTHESIS_ON_THE_LAGGING_STRAND	-0.807	-2.080	0.000	0.000
REACTOME_CELL_CYCLE_CHECKPOINTS	-0.536	-2.068	0.000	0.000
REACTOME_SYNTHESIS_OF_DNA	-0.543	-2.051	0.000	0.000
REACTOME_CYTOSOLIC_TRNA_AMINOACYLATION	-0.698	-2.023	0.000	0.001
REACTOME_METABOLISM_OF_NON_CODING_RNA	-0.605	-2.012	0.000	0.001
REACTOME_TRNA_AMINOACYLATION	-0.622	-1.998	0.000	0.001
REACTOME_TRANSPORT_OF_RIBONUCLEOPROTEINS_INTO_THE_HOST_NUCLEUS	-0.676	-1.987	0.000	0.002
REACTOME_G0_AND_EARLY_G1	-0.699	-1.977	0.000	0.002
REACTOME_NUCLEOTIDE_EXCISION_REPAIR	-0.591	-1.976	0.000	0.002
REACTOME_HOMOLOGOUS_RECOMBINATION_REPAIR_OF_REPLICATION_INDEPENDENT_DOUBLE_STRAND_BREAKS	-0.742	-1.958	0.000	0.002
REACTOME_MITOTIC_G2_G2_M_PHASES	-0.535	-1.947	0.002	0.003
REACTOME_REGULATION_OF_GLUCOKINASE_BY_GLUCOKINASE_REGULATORY_PROTEIN	-0.653	-1.947	0.000	0.003
KEGG_SPLICEOSOME	-0.490	-1.934	0.000	0.003
KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	-0.596	-1.929	0.000	0.003
KEGG_HOMOLOGOUS_RECOMBINATION	-0.639	-1.910	0.004	0.003
REACTOME_PROCESSING_OF_CAPPED_INTRON_CONTAINING_PRE_MRNA	-0.472	-1.908	0.000	0.004
REACTOME_G1_S_SPECIFIC_TRANSCRIPTION	-0.724	-1.908	0.000	0.004
KEGG_BUTANOATE_METABOLISM	-0.607	-1.904	0.000	0.003
REACTOME_TRANSCRIPTION_COUPLED_NER_TC_NER	-0.582	-1.895	0.000	0.005
REACTOME_CHROMOSOME_MAINTENANCE	-0.484	-1.895	0.000	0.004
REACTOME_MRNA_PROCESSING	-0.463	-1.894	0.000	0.004
REACTOME_M_G1_TRANSITION	-0.514	-1.888	0.000	0.005
REACTOME_NEP_NS2_INTERACTS_WITH_THE_CELLULAR_EXPORT_MACHINERY	-0.629	-1.875	0.000	0.006
REACTOME_DOUBLE_STRAND_BREAK_REPAIR	-0.674	-1.863	0.002	0.007

REACTOME_TRANSPORT_OF_MATURE_TRANSCRIPT_TO_CYTOPLASM	-0.548	-1.855	0.000	0.007
KEGG_BASE_EXCISION_REPAIR	-0.590	-1.853	0.002	0.005
REACTOME_TRANSPORT_OF_MATURE_MRNA_DERIVED_FROM_AN_INTRONLESS_TRANSCRIPT	-0.602	-1.846	0.004	0.008
REACTOME_LOSS_OF_NLP_FROM_MITOTIC_CENTROSOMES	-0.548	-1.842	0.000	0.008
KEGG_PYRIMIDINE_METABOLISM	-0.474	-1.793	0.000	0.011
REACTOME_DEADENYLATION_OF_MRNA	-0.650	-1.792	0.008	0.014
REACTOME_RECRUITMENT_OF_MITOTIC_CENTROSOME_PROTEINS_AND_COMPLEXES	-0.523	-1.792	0.000	0.014
KEGG_ONE_CARBON_POOL_BY_FOLATE	-0.678	-1.787	0.010	0.011
KEGG_PURINE_METABOLISM	-0.439	-1.785	0.000	0.011
KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	-0.480	-1.765	0.000	0.011
REACTOME_REGULATION_OF_BETA_CELL_DEVELOPMENT	-0.577	-1.750	0.006	0.023
REACTOME_GRB2_SOS_PROVIDES_LINKAGE_TO_MAPK_SIGNALING_FOR_INTERGRINS_	-0.676	-1.746	0.002	0.023
KEGG_MATURITY_ONSET_DIABETES_OF_THE_YOUNG	-0.595	-1.731	0.004	0.017
KEGG_PANTOTHENATE_AND_COA_BIOSYNTHESIS	-0.654	-1.726	0.006	0.016
REACTOME_P130CAS_LINKAGE_TO_MAPK_SIGNALING_FOR_INTEGRINS	-0.674	-1.726	0.006	0.028
REACTOME_MRNA_SPLICING	-0.441	-1.699	0.002	0.036
REACTOME_AMINO_ACID_SYNTHESIS_AND_INTERCONVERSION_TRANSAMINATION	-0.646	-1.686	0.008	0.040
REACTOME_FANCONI_ANEMIA_PATHWAY	-0.608	-1.684	0.008	0.040
REACTOME_METABOLISM_OF_RNA	-0.391	-1.683	0.000	0.040
REACTOME_CLEAVAGE_OF_GROWING_TRANSCRIPT_IN_THE_TERMINATION_REGION_	-0.507	-1.668	0.004	0.045
KEGG_OOCYTE_MEIOSIS	-0.428	-1.656	0.007	0.031
REACTOME_ADHERENS_JUNCTIONS_INTERACTIONS	-0.544	-1.646	0.015	0.054
REACTOME_CYCLIN_A_B1_ASSOCIATED_EVENTS_DURING_G2_M_TRANSITION	-0.636	-1.639	0.024	0.057
REACTOME_SYNTHESIS_OF_PIPS_AT_THE_GOLGI_MEMBRANE	-0.624	-1.638	0.008	0.056
REACTOME_HIV_LIFE_CYCLE	-0.416	-1.629	0.002	0.061
REACTOME_SIGNALLING_TO_ERKS	-0.515	-1.626	0.011	0.062
KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS	-0.620	-1.625	0.010	0.041
REACTOME_KINESINS	-0.574	-1.624	0.006	0.062
REACTOME_REGULATION_OF_GENE_EXPRESSION_IN_BETA_CELLS	-0.591	-1.622	0.021	0.062
KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	-0.489	-1.610	0.010	0.045
KEGG_WNT_SIGNALING_PATHWAY	-0.391	-1.608	0.000	0.044
REACTOME_APC_CDC20_MEDIATED_DEGRADATION_OF_NEK2A	-0.573	-1.607	0.011	0.070
REACTOME_TELOMERE_MAINTENANCE	-0.441	-1.604	0.007	0.070
REACTOME_FORMATION_OF_INCISION_COMPLEX_IN_GG_NER	-0.581	-1.602	0.018	0.071
REACTOME_MITOCHONDRIAL_PROTEIN_IMPORT	-0.468	-1.595	0.013	0.073
KEGG_PYRUVATE_METABOLISM	-0.499	-1.592	0.012	0.048
REACTOME_DEADENYLATION_DEPENDENT_MRNA_DECAY	-0.472	-1.592	0.019	0.074
REACTOME_PROCESSING_OF_CAPPED_INTRONLESS_PRE_MRNA	-0.563	-1.584	0.018	0.079
REACTOME_PLATELET_SENSITIZATION_BY_LDL	-0.605	-1.575	0.038	0.084
REACTOME_NOTCH1_INTRACELLULAR_DOMAIN_REGULATES_TRANSCRIPTION	-0.485	-1.575	0.012	0.083
REACTOME_G1_PHASE	-0.500	-1.568	0.023	0.087
REACTOME_INHIBITION_OF_THE_PROTEOLYTIC_ACTIVITY_OF_APC_C_REQUIRED_FOR_THE_ONSET_OF_ANAPHASE_BY_MITOTIC_SPINDLE_CHECKPOINT_COMPONENTS	-0.571	-1.566	0.027	0.087
REACTOME_REGULATION_OF_MITOTIC_CELL_CYCLE	-0.428	-1.565	0.009	0.087
REACTOME_BASE_EXCISION_REPAIR	-0.573	-1.562	0.032	0.087
REACTOME_RNA_POL_II_TRANSCRIPTION	-0.396	-1.561	0.005	0.087
REACTOME_CTLA4_INHIBITORY_SIGNALING	-0.545	-1.558	0.029	0.088

REACTOME_PI3K_CASCADE	-0.426	-1.544	0.007	0.098
REACTOME_MITOCHONDRIAL_TRNA_AMINOACYLATION	-0.560	-1.531	0.044	0.108
REACTOME_HOST_INTERACTIONS_OF_HIV_FACTORS	-0.389	-1.530	0.002	0.108
KEGG_PROXIMAL_TUBULE_BICARBONATE_RECLAMATION	-0.536	-1.525	0.044	0.084
REACTOME_ACTIVATION_OF_THE_MRNA_UPON_BINDING_OF_THE_CAP_BINDING_COMPLEX_AND_EIFS_AND_SUBSEQUENT_BINDING_TO_43S	-0.436	-1.524	0.016	0.111
REACTOME_HIV_INFECTION	-0.356	-1.502	0.000	0.130
REACTOME_INSULIN_RECEPTOR_SIGNALLING_CASCADE	-0.402	-1.499	0.013	0.132
REACTOME_DESTABILIZATION_OF_MRNA_BY_KSRP	-0.576	-1.494	0.052	0.135
REACTOME_NUCLEAR_RECEPTOR_TRANSCRIPTION_PATHWAY	-0.438	-1.489	0.027	0.139
KEGG_COLORECTAL_CANCER	-0.419	-1.489	0.013	0.107
REACTOME_ACTIVATION_OF_BH3_ONLY_PROTEINS	-0.575	-1.482	0.047	0.145
REACTOME_RESOLUTION_OF_AP_SITES_VIA_THE_MULTIPLE_NUCLEOTIDE_PATCH_REPLACEMENT_PATHWAY	-0.558	-1.480	0.069	0.145
REACTOME_SIGNALING_BY_NOTCH	-0.388	-1.476	0.015	0.147
REACTOME_ANTIVIRAL_MECHANISM_BY_IFN_STIMULATED_GENES	-0.412	-1.475	0.023	0.147
REACTOME_CITRIC_ACID_CYCLE_TCA_CYCLE	-0.543	-1.472	0.049	0.147
REACTOME_INTEGRIN_ALPHAIIB_BETA3_SIGNALING	-0.491	-1.471	0.033	0.147
REACTOME_PHOSPHORYLATION_OF_THE_APC_C	-0.546	-1.469	0.071	0.147
REACTOME_SIGNALING_BY_CONSTITUTIVELY_ACTIVE_EGFR	-0.541	-1.466	0.049	0.149
KEGG_HEDGEHOG_SIGNALING_PATHWAY	-0.426	-1.462	0.036	0.127
REACTOME_DARPP_32_EVENTS	-0.511	-1.461	0.051	0.152
REACTOME_L1CAM_INTERACTIONS	-0.392	-1.461	0.020	0.151
REACTOME_SIGNALING_BY_NOTCH1	-0.404	-1.460	0.033	0.150
REACTOME_PKB_MEDIATED_EVENTS	-0.482	-1.457	0.042	0.152
REACTOME_MYOGENESIS	-0.486	-1.452	0.054	0.155
REACTOME_SIGNALLING_TO_RAS	-0.490	-1.452	0.066	0.154
REACTOME_ASSEMBLY_OF_THE_PRE_REPLICATIVE_COMPLEX	-0.411	-1.451	0.033	0.153
REACTOME_PLC_BETA_MEDIATED_EVENTS	-0.443	-1.449	0.041	0.154
KEGG_TGF_BETA_SIGNALING_PATHWAY	-0.384	-1.448	0.015	0.136
REACTOME_METABOLISM_OF_MRNA	-0.345	-1.448	0.002	0.154
KEGG_LYSINE_DEGRADATION	-0.441	-1.445	0.036	0.133
REACTOME_SIGNALING_BY_FGFR_MUTANTS	-0.441	-1.443	0.030	0.157
REACTOME_APOPTOTIC_CLEAVAGE_OF_CELLULAR_PROTEINS	-0.453	-1.440	0.041	0.159
KEGG_CHRONIC_MYELOID_LEUKEMIA	-0.402	-1.437	0.025	0.135
REACTOME_SIGNAL_AMPLIFICATION	-0.466	-1.433	0.056	0.165
REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS	-0.473	-1.418	0.068	0.181
REACTOME_CD28_CO_STIMULATION	-0.471	-1.415	0.048	0.183
REACTOME_INSULIN_SYNTHESIS_AND_PROCESSING	-0.503	-1.412	0.090	0.185
KEGG_ENDOMETRIAL_CANCER	-0.417	-1.408	0.052	0.160
REACTOME_SIGNALLING_BY_NGF	-0.327	-1.406	0.003	0.192
KEGG_BETA_ALANINE_METABOLISM	-0.495	-1.402	0.079	0.161
REACTOME_LATE_PHASE_OF_HIV_LIFE_CYCLE	-0.368	-1.402	0.022	0.194
REACTOME_DEVELOPMENTAL_BIOLOGY	-0.312	-1.398	0.000	0.198
REACTOME_ORC1_REMOVAL_FROM_CHROMATIN	-0.388	-1.378	0.036	0.223
KEGG_PANCREATIC_CANCER	-0.379	-1.377	0.039	0.183
REACTOME_DEPOSITION_OF_NEW_CENPA_CONTAINING_NUCLEOSOMES_AT_THE_CENTROMERE	-0.393	-1.377	0.049	0.222
REACTOME_IL_3_5_AND_GM_CSF_SIGNALING	-0.415	-1.377	0.063	0.220

REACTOME_NGF_SIGNALLING_VIA_TRKA_FROM_THE_PLASMA_MEMBRANE	-0.339	-1.368	0.024	0.230
REACTOME_PRE_NOTCH_TRANSCRIPTION_AND_TRANSLATION	-0.475	-1.367	0.092	0.230
REACTOME_SIGNALING_BY_FGFR	-0.350	-1.365	0.036	0.232
REACTOME_MRNA_SPLICING_MINOR_PATHWAY	-0.415	-1.363	0.068	0.232
KEGG_PROPANOATE_METABOLISM	-0.450	-1.362	0.093	0.196
REACTOME_3_UTR_MEDIATED_TRANSLATIONAL_REGULATION	-0.346	-1.362	0.039	0.231
REACTOME_RNA_POL_I_TRANSCRIPTION_INITIATION	-0.477	-1.360	0.093	0.232
REACTOME_BOTULINUM_NEUROTOXICITY	-0.499	-1.359	0.083	0.231
REACTOME_APC_C_CDC20_MEDIATED_DEGRADATION_OF_CYCLIN_B	-0.503	-1.359	0.111	0.229
REACTOME_APC_C_CDC20_MEDIATED_DEGRADATION_OF_MITOTIC_PROTEINS	-0.380	-1.358	0.058	0.228
REACTOME_GAB1_SIGNALOSOME	-0.419	-1.358	0.075	0.227
REACTOME_CYCLIN_E_ASSOCIATED_EVENTS_DURING_G1_S_TRANSITION_	-0.381	-1.357	0.062	0.226
REACTOME_MRNA_3_END_PROCESSING	-0.425	-1.352	0.086	0.230
REACTOME_SIGNALING_BY_ERBB4	-0.351	-1.343	0.041	0.242
REACTOME_OPIOID_SIGNALLING	-0.372	-1.342	0.048	0.241
REACTOME_NEGATIVE_REGULATION_OF_FGFR_SIGNALING	-0.426	-1.338	0.101	0.245
REACTOME_N_GLYCAN_ANTENNAE_ELONGATION_IN_THE_MEDIAL_TRANS_GOLGI	-0.502	-1.338	0.119	0.244
KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM	-0.432	-1.337	0.107	0.224
REACTOME_SIGNALING_BY_ERBB2	-0.350	-1.337	0.043	0.243
KEGG_CITRATE_CYCLE_TCA_CYCLE	-0.436	-1.334	0.125	0.220
REACTOME_ABC_FAMILY_PROTEINS_MEDIATED_TRANSPORT	-0.424	-1.334	0.083	0.245
REACTOME_INFLUENZA_LIFE_CYCLE	-0.336	-1.332	0.029	0.247
REACTOME_INTRINSIC_PATHWAY_FOR_APOPTOSIS	-0.447	-1.332	0.101	0.245
REACTOME_REGULATION_OF_SIGNALING_BY_CBL	-0.493	-1.328	0.129	0.249
REACTOME_SIGNALING_BY_EGFR_IN_CANCER	-0.344	-1.327	0.055	0.248
KEGG_PPAR_SIGNALING_PATHWAY	-0.363	-1.320	0.084	0.233
KEGG_BASAL_CELL_CARCINOMA	-0.388	-1.318	0.096	0.228
KEGG_THYROID_CANCER	-0.437	-1.318	0.113	0.222
KEGG_NICOTINATE_AND_NICOTINAMIDE_METABOLISM	-0.459	-1.310	0.117	0.227
KEGG_MTOR_SIGNALING_PATHWAY	-0.383	-1.302	0.104	0.231
KEGG_STEROID_HORMONE_BIOSYNTHESIS	0.472	1.460	0.053	0.231
KEGG_CELL_ADHESION_MOLECULES_CAMS	0.402	1.499	0.022	0.191
KEGG_SPHINGOLIPID_METABOLISM	0.497	1.500	0.055	0.201
KEGG_CYTOSOLIC_DNA_SENSING_PATHWAY	0.486	1.512	0.037	0.196
REACTOME_LIPOPROTEIN_METABOLISM	0.555	1.572	0.042	0.246
KEGG_PORPHYRIN_AND_CHLOROPHYLL_METABOLISM	0.545	1.575	0.038	0.135
REACTOME_BIOLOGICAL_OXIDATIONS	0.435	1.602	0.003	0.212
REACTOME_TAK1_ACTIVATES_NFKB_BY_PHOSPHORYLATION_AND_ACTIVATION_OF_IKKS_COMPLEX	0.602	1.606	0.029	0.217
REACTOME_MYD88_MAL_CASCADE_INITIATED_ON_PLASMA_MEMBRANE	0.480	1.614	0.013	0.217
REACTOME_TRAF6_MEDIATED_NFKB_ACTIVATION	0.613	1.618	0.038	0.224
REACTOME_O_LINKED_GLYCOSYLATION_OF_MUCINS	0.501	1.634	0.015	0.213
KEGG_GLYCOSAMINOGLYCAN_DEGRADATION	0.615	1.639	0.029	0.090
KEGG_AMINO_SUGAR_AND_NUCLEOTIDE_SUGAR_METABOLISM	0.531	1.641	0.016	0.096
REACTOME_LATENT_INFECTION_OF_HOMO_SAPIENS_WITH_MYCOBACTERIUM_TUBERCULOSIS	0.582	1.650	0.015	0.202
KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0.509	1.654	0.015	0.093
REACTOME_INTERFERON_SIGNALING	0.448	1.675	0.002	0.181
REACTOME_INNATE_IMMUNE_SYSTEM	0.411	1.675	0.000	0.195

KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	0.494	1.685	0.004	0.079
REACTOME_COLLAGEN_FORMATION	0.525	1.691	0.008	0.185
REACTOME_EXTRACELLULAR_MATRIX_ORGANIZATION	0.490	1.692	0.003	0.201
REACTOME_PHASE_II_CONJUGATION	0.520	1.698	0.009	0.212
REACTOME_TERMINATION_OF_O_GLYCAN_BIOSYNTHESIS	0.648	1.707	0.012	0.219
REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS	0.504	1.717	0.000	0.231
KEGG_STARCH_AND_SUCROSE_METABOLISM	0.574	1.722	0.004	0.064
KEGG_O_GLYCAN_BIOSYNTHESIS	0.606	1.732	0.022	0.064
KEGG_GLYCOSPHINGOLIPID_BIOSYNTHESIS_GANGLIO_SERIES	0.697	1.752	0.010	0.061
KEGG_ASCORBATE_AND_ALDARATE_METABOLISM	0.726	1.758	0.014	0.067
KEGG_PENTOSE_AND_GLUCURONATE_INTERCONVERSIONS	0.677	1.765	0.015	0.074
KEGG_ECM_RECEPTOR_INTERACTION	0.512	1.772	0.000	0.084
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	0.533	1.800	0.000	0.082
KEGG_RETINOL_METABOLISM	0.585	1.857	0.002	0.061
REACTOME_INTERFERON_GAMMA_SIGNALING	0.580	1.887	0.000	0.115
REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL	0.578	1.889	0.000	0.166
KEGG_DRUG_METABOLISM_OTHER_ENZYMES	0.621	1.933	0.005	0.042
KEGG_LYSOSOME	0.564	2.087	0.000	0.007
REACTOME_INTERFERON_ALPHA_BETA_SIGNALING	0.737	2.393	0.000	0.000

Table S1C: Top up and down regulated GSEA REACTOME and KEGG pathways by 5-AZA treatment in A549 cells. GSEA pathway cut-off of FDR ≤0.250 was used to delineate pathways with significant enrichment by 5-AZA. ES=Enrichment Score, NES=Normalized Enrichment Score, NOM p-Value= Nominal p Value, FDR q Value= False Discover Rate q Value.

H23 5-AZA Enriched Pathways	**ES**	**NES**	**NOM p-val**	**FDR q-val**
REACTOME_G1_S_TRANSITION	-0.561	-2.205	0.000	0.002
REACTOME_S_PHASE	-0.545	-2.120	0.000	0.003
REACTOME_M_G1_TRANSITION	-0.558	-2.048	0.000	0.006
REACTOME_SYNTHESIS_OF_DNA	-0.539	-2.036	0.000	0.005
REACTOME_INTERACTIONS_OF_VPR_WITH_HOST_CELLULAR_PROTEINS	-0.653	-2.019	0.000	0.004
REACTOME_DNA_REPLICATION	-0.483	-2.019	0.000	0.004
REACTOME_FATTY_ACYL_COA_BIOSYNTHESIS	-0.745	-2.018	0.000	0.003
REACTOME_CELL_CYCLE_CHECKPOINTS	-0.513	-2.002	0.000	0.004
REACTOME_E2F_MEDIATED_REGULATION_OF_DNA_REPLICATION	-0.638	-1.974	0.000	0.005
REACTOME_MITOTIC_M_M_G1_PHASES	-0.473	-1.968	0.000	0.006
REACTOME_ACTIVATION_OF_ATR_IN_RESPONSE_TO_REPLICATION_STRESS	-0.620	-1.962	0.000	0.006
REACTOME_TRANSPORT_OF_MATURE_TRANSCRIPT_TO_CYTOPLASM	-0.563	-1.947	0.000	0.006
KEGG_SPLICEOSOME	-0.496	-1.941	0.000	0.011
REACTOME_PKA_MEDIATED_PHOSPHORYLATION_OF_CREB	-0.734	-1.931	0.000	0.007
REACTOME_ASPARAGINE_N_LINKED_GLYCOSYLATION	-0.527	-1.931	0.000	0.007
REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	-0.645	-1.931	0.002	0.006
REACTOME_TRANSPORT_OF_RIBONUCLEOPROTEINS_INTO_THE_HOST_NUCLEUS	-0.632	-1.919	0.000	0.007
REACTOME_ASSEMBLY_OF_THE_PRE_REPLICATIVE_COMPLEX	-0.540	-1.917	0.000	0.007
REACTOME_MITOTIC_G1_G1_S_PHASES	-0.480	-1.914	0.000	0.006
REACTOME_MRNA_PROCESSING	-0.461	-1.905	0.000	0.006
REACTOME_G2_M_CHECKPOINTS	-0.590	-1.901	0.000	0.007
REACTOME_CHOLESTEROL_BIOSYNTHESIS	-0.667	-1.881	0.002	0.009
REACTOME_HOST_INTERACTIONS_OF_HIV_FACTORS	-0.479	-1.874	0.000	0.009
REACTOME_CDT1_ASSOCIATION_WITH_THE_CDC6_ORC_ORIGIN_COMPLEX	-0.534	-1.869	0.000	0.009
REACTOME_CELL_CYCLE_MITOTIC	-0.419	-1.862	0.000	0.010
KEGG_MISMATCH_REPAIR	-0.651	-1.852	0.000	0.023
REACTOME_NEP_NS2_INTERACTS_WITH_THE_CELLULAR_EXPORT_MACHINERY	-0.623	-1.845	0.002	0.012
REACTOME_ORC1_REMOVAL_FROM_CHROMATIN	-0.515	-1.840	0.000	0.013
REACTOME_CYCLIN_E_ASSOCIATED_EVENTS_DURING_G1_S_TRANSITION_	-0.518	-1.839	0.000	0.013
REACTOME_PROCESSING_OF_CAPPED_INTRON_CONTAINING_PRE_MRNA	-0.458	-1.824	0.000	0.015
KEGG_DNA_REPLICATION	-0.584	-1.823	0.002	0.023
REACTOME_PLC_BETA_MEDIATED_EVENTS	-0.554	-1.821	0.002	0.015
REACTOME_CYTOSOLIC_TRNA_AMINOACYLATION	-0.635	-1.820	0.002	0.014
REACTOME_EXTENSION_OF_TELOMERES	-0.597	-1.820	0.006	0.014
REACTOME_DESTABILIZATION_OF_MRNA_BY_AUF1_HNRNP_D0	-0.533	-1.814	0.000	0.015
REACTOME_POST_TRANSLATIONAL_PROTEIN_MODIFICATION	-0.431	-1.808	0.000	0.015
REACTOME_METABOLISM_OF_NON_CODING_RNA	-0.539	-1.796	0.004	0.017
REACTOME_G1_S_SPECIFIC_TRANSCRIPTION	-0.680	-1.792	0.002	0.018
REACTOME_DNA_STRAND_ELONGATION	-0.585	-1.783	0.004	0.019
REACTOME_P53_DEPENDENT_G1_DNA_DAMAGE_RESPONSE	-0.509	-1.774	0.004	0.021
REACTOME_REGULATION_OF_MRNA_STABILITY_BY_PROTEINS_THAT_BIND_AU_RICH_ELEMENTS	-0.481	-1.774	0.000	0.021
REACTOME_REGULATION_OF_GLUCOKINASE_BY_GLUCOKINASE_REGULATORY_PROTEIN	-0.595	-1.773	0.000	0.020
REACTOME_TRANSPORT_OF_MATURE_MRNA_DERIVED_FROM_AN_INTRONLESS_TRANSCRIPT	-0.570	-1.768	0.006	0.021
REACTOME_DNA_REPAIR	-0.456	-1.767	0.002	0.021
REACTOME_P53_INDEPENDENT_G1_S_DNA_DAMAGE_CHECKPOINT	-0.518	-1.764	0.000	0.021
REACTOME_CA_DEPENDENT_EVENTS	-0.585	-1.763	0.006	0.021

REACTOME_METABOLISM_OF_RNA	-0.404	-1.760	0.000	0.021
REACTOME_CDK_MEDIATED_PHOSPHORYLATION_AND_REMOVAL_OF_CDC6	-0.531	-1.760	0.002	0.021
REACTOME_REGULATION_OF_MITOTIC_CELL_CYCLE	-0.474	-1.752	0.000	0.022
REACTOME_DAG_AND_IP3_SIGNALING	-0.576	-1.751	0.002	0.022
REACTOME_MITOCHONDRIAL_PROTEIN_IMPORT	-0.514	-1.743	0.000	0.024
REACTOME_CITRIC_ACID_CYCLE_TCA_CYCLE	-0.632	-1.738	0.004	0.025
REACTOME_CELL_CYCLE	-0.379	-1.734	0.000	0.026
REACTOME_AUTODEGRADATION_OF_CDH1_BY_CDH1_APC_C	-0.488	-1.721	0.007	0.029
KEGG_CITRATE_CYCLE_TCA_CYCLE	-0.564	-1.721	0.008	0.068
REACTOME_GABA_B_RECEPTOR_ACTIVATION	-0.546	-1.720	0.002	0.028
REACTOME_G_ALPHA_Z_SIGNALLING_EVENTS	-0.520	-1.717	0.004	0.029
REACTOME_PRE_NOTCH_TRANSCRIPTION_AND_TRANSLATION	-0.574	-1.714	0.008	0.030
REACTOME_SCFSKP2_MEDIATED_DEGRADATION_OF_P27_P21	-0.504	-1.711	0.004	0.030
REACTOME_SCF_BETA_TRCP_MEDIATED_DEGRADATION_OF_EMI1	-0.511	-1.710	0.006	0.030
REACTOME_DARPP_32_EVENTS	-0.587	-1.704	0.016	0.031
REACTOME_METABOLISM_OF_PROTEINS	-0.375	-1.703	0.000	0.031
REACTOME_GLUCOSE_TRANSPORT	-0.532	-1.702	0.004	0.030
REACTOME_OPIOID_SIGNALLING	-0.462	-1.700	0.002	0.030
REACTOME_AUTODEGRADATION_OF_THE_E3_UBIQUITIN_LIGASE_COP1	-0.501	-1.700	0.004	0.030
REACTOME_NOTCH1_INTRACELLULAR_DOMAIN_REGULATES_TRANSCRIPTION	-0.514	-1.698	0.008	0.030
KEGG_VIBRIO_CHOLERAE_INFECTION	-0.493	-1.688	0.006	0.076
REACTOME_DESTABILIZATION_OF_MRNA_BY_KSRP	-0.638	-1.685	0.012	0.033
REACTOME_SIGNALING_BY_ERBB2	-0.439	-1.683	0.000	0.034
REACTOME_REGULATION_OF_ORNITHINE_DECARBOXYLASE_ODC	-0.492	-1.682	0.002	0.033
REACTOME_CIRCADIAN_REPRESSION_OF_EXPRESSION_BY_REV_ERBA	-0.592	-1.680	0.010	0.033
KEGG_ONE_CARBON_POOL_BY_FOLATE	-0.633	-1.680	0.017	0.069
REACTOME_CLEAVAGE_OF_GROWING_TRANSCRIPT_IN_THE_TERMINATION_REGION_	-0.508	-1.677	0.006	0.034
REACTOME_TRNA_AMINOACYLATION	-0.509	-1.676	0.004	0.034
REACTOME_DEADENYLATION_OF_MRNA	-0.625	-1.676	0.012	0.033
REACTOME_PROLONGED_ERK_ACTIVATION_EVENTS	-0.611	-1.675	0.010	0.033
KEGG_PROTEASOME	-0.510	-1.669	0.000	0.068
KEGG_CELL_CYCLE	-0.422	-1.667	0.002	0.060
REACTOME_ACTIVATION_OF_NF_KAPPAB_IN_B_CELLS	-0.467	-1.661	0.006	0.038
REACTOME_APC_C_CDC20_MEDIATED_DEGRADATION_OF_MITOTIC_PROTEINS	-0.468	-1.657	0.004	0.039
REACTOME_A_TETRASACCHARIDE_LINKER_SEQUENCE_IS_REQUIRED_FOR_GAG_SYNTHESIS	-0.563	-1.656	0.010	0.039
KEGG_PURINE_METABOLISM	-0.399	-1.647	0.000	0.066
REACTOME_PERK_REGULATED_GENE_EXPRESSION	-0.548	-1.643	0.016	0.043
REACTOME_RORA_ACTIVATES_CIRCADIAN_EXPRESSION	-0.576	-1.642	0.027	0.043
REACTOME_AQUAPORIN_MEDIATED_TRANSPORT	-0.487	-1.641	0.002	0.042
REACTOME_VIF_MEDIATED_DEGRADATION_OF_APOBEC3G	-0.489	-1.639	0.004	0.043
REACTOME_SIGNALING_BY_EGFR_IN_CANCER	-0.418	-1.639	0.005	0.043
KEGG_N_GLYCAN_BIOSYNTHESIS	-0.489	-1.638	0.002	0.064
REACTOME_UNFOLDED_PROTEIN_RESPONSE	-0.449	-1.633	0.000	0.044
REACTOME_DOWNSTREAM_SIGNAL_TRANSDUCTION	-0.434	-1.633	0.000	0.044
REACTOME_TRIGLYCERIDE_BIOSYNTHESIS	-0.509	-1.631	0.002	0.044
REACTOME_SIGNALING_BY_THE_B_CELL_RECEPTOR_BCR	-0.411	-1.623	0.000	0.047
KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	-0.432	-1.623	0.000	0.069

REACTOME_ARMS_MEDIATED_ACTIVATION	-0.602	-1.622	0.014	0.047
KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS	-0.631	-1.621	0.023	0.064
KEGG_NUCLEOTIDE_EXCISION_REPAIR	-0.501	-1.617	0.008	0.061
REACTOME_METABOLISM_OF_MRNA	-0.380	-1.616	0.000	0.049
REACTOME_SIGNALING_BY_FGFR	-0.417	-1.616	0.000	0.049
REACTOME_MRNA_SPLICING	-0.415	-1.615	0.000	0.048
REACTOME_APC_C_CDH1_MEDIATED_DEGRADATION_OF_CDC20_AND_OTHER_APC_C_CDH1_TARGETED_PROTEINS_IN_LATE_MITOSIS_EARLY_G1	-0.454	-1.609	0.004	0.050
REACTOME_REGULATION_OF_WATER_BALANCE_BY_RENAL_AQUAPORINS	-0.487	-1.603	0.010	0.053
KEGG_GLYCOSYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS	-0.550	-1.600	0.024	0.065
REACTOME_POST_TRANSLATIONAL_MODIFICATION_SYNTHESIS_OF_GPI_ANCHORED_PROTEINS	-0.544	-1.600	0.016	0.054
REACTOME_METABOLISM_OF_CARBOHYDRATES	-0.369	-1.598	0.000	0.054
REACTOME_SIGNALING_BY_CONSTITUTIVELY_ACTIVE_EGFR	-0.597	-1.591	0.022	0.057
REACTOME_GLOBAL_GENOMIC_NER_GG_NER	-0.531	-1.588	0.015	0.058
KEGG_COLORECTAL_CANCER	-0.445	-1.585	0.017	0.070
REACTOME_SIGNALING_BY_FGFR_IN_DISEASE	-0.397	-1.584	0.000	0.059
REACTOME_G0_AND_EARLY_G1	-0.547	-1.583	0.024	0.058
REACTOME_HIV_INFECTION	-0.380	-1.582	0.000	0.059
REACTOME_BIOSYNTHESIS_OF_THE_N_GLYCAN_PRECURSOR_DOLICHOL_LIPID_LINKED_OLIGOSACCHARIDE_LLO_AND_TRANSFER_TO_A_NASCENT_PROTEIN	-0.533	-1.581	0.011	0.058
REACTOME_CHONDROITIN_SULFATE_DERMATAN_SULFATE_METABOLISM	-0.477	-1.578	0.008	0.060
REACTOME_GLUCAGON_SIGNALING_IN_METABOLIC_REGULATION	-0.506	-1.577	0.015	0.060
KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	-0.485	-1.575	0.016	0.071
REACTOME_DEADENYLATION_DEPENDENT_MRNA_DECAY	-0.478	-1.573	0.016	0.061
REACTOME_DOWNSTREAM_SIGNALING_EVENTS_OF_B_CELL_RECEPTOR_BCR	-0.407	-1.572	0.002	0.061
REACTOME_REGULATION_OF_INSULIN_SECRETION_BY_GLUCAGON_LIKE_PEPTIDE1	-0.477	-1.565	0.013	0.064
REACTOME_DOWNSTREAM_SIGNALING_OF_ACTIVATED_FGFR	-0.411	-1.564	0.002	0.064
REACTOME_ACTIVATION_OF_GENES_BY_ATF4	-0.540	-1.562	0.023	0.064
REACTOME_NUCLEOTIDE_EXCISION_REPAIR	-0.463	-1.560	0.015	0.064
REACTOME_INSULIN_SYNTHESIS_AND_PROCESSING	-0.560	-1.553	0.031	0.068
REACTOME_SIGNALING_BY_WNT	-0.440	-1.552	0.020	0.068
KEGG_RNA_DEGRADATION	-0.447	-1.544	0.009	0.088
REACTOME_RNA_POL_I_TRANSCRIPTION_INITIATION	-0.536	-1.540	0.041	0.074
REACTOME_PYRUVATE_METABOLISM_AND_CITRIC_ACID_TCA_CYCLE	-0.468	-1.534	0.017	0.077
REACTOME_ZINC_TRANSPORTERS	-0.587	-1.531	0.056	0.078
REACTOME_GLUCOSE_METABOLISM	-0.423	-1.523	0.015	0.082
REACTOME_PHOSPHOLIPASE_C_MEDIATED_CASCADE	-0.444	-1.522	0.010	0.083
REACTOME_REGULATION_OF_APOPTOSIS	-0.437	-1.522	0.008	0.082
REACTOME_LAGGING_STRAND_SYNTHESIS	-0.560	-1.521	0.043	0.081
REACTOME_GLYCOLYSIS	-0.513	-1.521	0.033	0.081
REACTOME_METAL_ION_SLC_TRANSPORTERS	-0.550	-1.520	0.037	0.081
KEGG_O_GLYCAN_BIOSYNTHESIS	-0.496	-1.519	0.026	0.105
REACTOME_SIGNALLING_TO_P38_VIA_RIT_AND_RIN	-0.593	-1.514	0.048	0.084
KEGG_LYSINE_DEGRADATION	-0.455	-1.509	0.021	0.108
REACTOME_INTRINSIC_PATHWAY_FOR_APOPTOSIS	-0.497	-1.509	0.037	0.086
REACTOME_AMINO_ACID_SYNTHESIS_AND_INTERCONVERSION_TRANSAMINATION	-0.579	-1.508	0.057	0.086
REACTOME_TRANSCRIPTION_COUPLED_NER_TC_NER	-0.461	-1.501	0.030	0.090

REACTOME_NGF_SIGNALLING_VIA_TRKA_FROM_THE_PLASMA_MEMBRANE	-0.371	-1.498	0.005	0.091
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_CHONDROITIN_SULFATE	-0.533	-1.498	0.034	0.113
REACTOME_FATTY_ACID_TRIACYLGLYCEROL_AND_KETONE_BODY_METABOLISM	-0.362	-1.493	0.002	0.094
REACTOME_PRE_NOTCH_EXPRESSION_AND_PROCESSING	-0.461	-1.492	0.035	0.094
REACTOME_PKB_MEDIATED_EVENTS	-0.505	-1.487	0.052	0.097
REACTOME_PI_METABOLISM	-0.442	-1.483	0.030	0.099
KEGG_LONG_TERM_DEPRESSION	-0.404	-1.483	0.014	0.123
REACTOME_MITOTIC_PROMETAPHASE	-0.394	-1.481	0.013	0.100
REACTOME_SIGNALING_BY_ERBB4	-0.397	-1.480	0.013	0.099
REACTOME_SIGNALING_BY_NOTCH	-0.381	-1.478	0.004	0.100
REACTOME_PROCESSING_OF_CAPPED_INTRONLESS_PRE_MRNA	-0.522	-1.471	0.041	0.104
REACTOME_APOPTOSIS	-0.365	-1.464	0.010	0.109
REACTOME_PLATELET_SENSITIZATION_BY_LDL	-0.562	-1.464	0.066	0.108
REACTOME_JNK_C_JUN_KINASES_PHOSPHORYLATION_AND_ACTIVATION_MEDIATED_BY_ACTIVATED_HUMAN_TAK1	-0.562	-1.460	0.062	0.110
REACTOME_RNA_POL_II_TRANSCRIPTION	-0.378	-1.452	0.004	0.116
REACTOME_GLUCONEOGENESIS	-0.472	-1.451	0.043	0.116
REACTOME_ANTIGEN_PROCESSING_UBIQUITINATION_PROTEASOME_DEGRADATION	-0.344	-1.447	0.000	0.118
REACTOME_SIGNALING_BY_PDGF	-0.370	-1.438	0.011	0.125
REACTOME_INTEGRATION_OF_ENERGY_METABOLISM	-0.361	-1.431	0.011	0.129
REACTOME_MAP_KINASE_ACTIVATION_IN_TLR_CASCADE	-0.430	-1.430	0.038	0.130
KEGG_GAP_JUNCTION	-0.383	-1.425	0.024	0.185
REACTOME_TRANSPORT_OF_VITAMINS_NUCLEOSIDES_AND_RELATED_MOLECULES	-0.464	-1.416	0.063	0.142
KEGG_INOSITOL_PHOSPHATE_METABOLISM	-0.414	-1.416	0.035	0.190
REACTOME_SIGNALLING_TO_ERKS	-0.446	-1.416	0.033	0.141
REACTOME_ACTIVATED_AMPK_STIMULATES_FATTY_ACID_OXIDATION_IN_MUSCLE	-0.531	-1.416	0.064	0.140
REACTOME_TRANSPORT_TO_THE_GOLGI_AND_SUBSEQUENT_MODIFICATION	-0.462	-1.416	0.052	0.139
REACTOME_CHROMOSOME_MAINTENANCE	-0.361	-1.415	0.020	0.139
REACTOME_SIGNALING_BY_NODAL	-0.518	-1.415	0.077	0.138
REACTOME_SIGNALLING_BY_NGF	-0.331	-1.413	0.005	0.138
REACTOME_ACTIVATION_OF_CHAPERONE_GENES_BY_XBP1S	-0.425	-1.411	0.057	0.139
REACTOME_THROMBIN_SIGNALLING_THROUGH_PROTEINASE_ACTIVATED_RECEPTORS_PARS	-0.452	-1.407	0.059	0.141
REACTOME_TELOMERE_MAINTENANCE	-0.389	-1.405	0.031	0.142
REACTOME_TRANSLATION	-0.348	-1.404	0.013	0.142
REACTOME_TRANSMEMBRANE_TRANSPORT_OF_SMALL_MOLECULES	-0.307	-1.403	0.000	0.142
KEGG_PYRIMIDINE_METABOLISM	-0.372	-1.399	0.039	0.205
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_KERATAN_SULFATE	-0.537	-1.396	0.083	0.201
REACTOME_PPARA_ACTIVATES_GENE_EXPRESSION	-0.365	-1.392	0.027	0.152
REACTOME_APOPTOTIC_CLEAVAGE_OF_CELLULAR_PROTEINS	-0.438	-1.390	0.063	0.153
REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS	-0.301	-1.387	0.000	0.155
REACTOME_GENERIC_TRANSCRIPTION_PATHWAY	-0.310	-1.385	0.000	0.156
REACTOME_SYNTHESIS_OF_PIPS_AT_THE_GOLGI_MEMBRANE	-0.518	-1.377	0.107	0.163
REACTOME_RNA_POL_I_TRANSCRIPTION_TERMINATION	-0.509	-1.376	0.094	0.163
REACTOME_SIGNALING_BY_INSULIN_RECEPTOR	-0.357	-1.373	0.031	0.165
KEGG_WNT_SIGNALING_PATHWAY	-0.336	-1.373	0.020	0.228
REACTOME_ION_TRANSPORT_BY_P_TYPE_ATPASES	-0.448	-1.372	0.074	0.165
KEGG_ADHERENS_JUNCTION	-0.382	-1.372	0.046	0.221
KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	-0.346	-1.368	0.028	0.219

KEGG_NICOTINATE_AND_NICOTINAMIDE_METABOLISM	-0.475	-1.368	0.088	0.212
REACTOME_CROSS_PRESENTATION_OF_SOLUBLE_EXOGENOUS_ANTIGENS_ENDOSOMES	-0.415	-1.365	0.061	0.171
REACTOME_METABOLISM_OF_POLYAMINES	-0.539	-1.364	0.117	0.171
REACTOME_HEPARAN_SULFATE_HEPARIN_HS_GAG_METABOLISM	-0.401	-1.361	0.062	0.174
KEGG_BASE_EXCISION_REPAIR	-0.440	-1.360	0.083	0.215
KEGG_ACUTE_MYELOID_LEUKEMIA	-0.387	-1.356	0.068	0.214
REACTOME_DOUBLE_STRAND_BREAK_REPAIR	-0.475	-1.354	0.115	0.180
KEGG_THYROID_CANCER	-0.446	-1.352	0.084	0.213
KEGG_APOPTOSIS	-0.357	-1.350	0.037	0.209
KEGG_EPITHELIAL_CELL_SIGNALING_IN_HELICOBACTER_PYLORI_INFECTION	-0.380	-1.349	0.072	0.205
REACTOME_NFKB_AND_MAP_KINASES_ACTIVATION_MEDIATED_BY_TLR4_SIGNALING_REPERTOIRE	-0.370	-1.345	0.062	0.189
REACTOME_REGULATION_OF_INSULIN_SECRETION	-0.357	-1.336	0.044	0.199
REACTOME_HOMOLOGOUS_RECOMBINATION_REPAIR_OF_REPLICATION_INDEPENDENT_DOUBLE_STRAND_BREAKS	-0.507	-1.331	0.118	0.204
REACTOME_SYNTHESIS_OF_PIPS_AT_THE_PLASMA_MEMBRANE	-0.434	-1.329	0.099	0.205
REACTOME_INSULIN_RECEPTOR_SIGNALLING_CASCADE	-0.360	-1.328	0.067	0.205
REACTOME_NCAM_SIGNALING_FOR_NEURITE_OUT_GROWTH	-0.371	-1.326	0.068	0.207
REACTOME_MITOTIC_G2_G2_M_PHASES	-0.368	-1.325	0.065	0.206
KEGG_PROTEIN_EXPORT	-0.454	-1.325	0.106	0.233
REACTOME_TGF_BETA_RECEPTOR_SIGNALING_ACTIVATES_SMADS	-0.453	-1.324	0.122	0.206
REACTOME_SYNTHESIS_OF_GLYCOSYLPHOSPHATIDYLINOSITOL_GPI	-0.498	-1.324	0.142	0.205
REACTOME_KERATAN_SULFATE_KERATIN_METABOLISM	-0.444	-1.321	0.110	0.207
REACTOME_SIGNAL_AMPLIFICATION	-0.432	-1.321	0.100	0.207
REACTOME_REGULATION_OF_KIT_SIGNALING	-0.510	-1.320	0.113	0.206
KEGG_UBIQUITIN_MEDIATED_PROTEOLYSIS	-0.331	-1.318	0.034	0.237
REACTOME_SIGNALING_BY_NOTCH1	-0.370	-1.317	0.075	0.208
KEGG_STEROID_BIOSYNTHESIS	-0.499	-1.316	0.142	0.234
REACTOME_NUCLEAR_SIGNALING_BY_ERBB4	-0.403	-1.315	0.128	0.210
REACTOME_LYSOSOME_VESICLE_BIOGENESIS	-0.460	-1.314	0.135	0.210
REACTOME_GLYCOSAMINOGLYCAN_METABOLISM	-0.339	-1.313	0.052	0.210
REACTOME_HIV_LIFE_CYCLE	-0.343	-1.313	0.033	0.209
REACTOME_MRNA_3_END_PROCESSING	-0.415	-1.311	0.110	0.211
REACTOME_APC_CDC20_MEDIATED_DEGRADATION_OF_NEK2A	-0.464	-1.311	0.136	0.210
REACTOME_GABA_RECEPTOR_ACTIVATION	-0.387	-1.310	0.084	0.210
KEGG_CHRONIC_MYELOID_LEUKEMIA	-0.364	-1.308	0.077	0.239
REACTOME_SYNTHESIS_AND_INTERCONVERSION_OF_NUCLEOTIDE_DI_AND_TRIPHOSPHATES	-0.482	-1.306	0.130	0.214
REACTOME_TRANSCRIPTION	-0.307	-1.298	0.027	0.222
REACTOME_LATE_PHASE_OF_HIV_LIFE_CYCLE	-0.332	-1.297	0.076	0.223
REACTOME_INHIBITION_OF_VOLTAGE_GATED_CA2_CHANNELS_VIA_GBETA_GAMMA_SUBUNITS	-0.443	-1.286	0.144	0.236
REACTOME_YAP1_AND_WWTR1_TAZ_STIMULATED_GENE_EXPRESSION	-0.446	-1.283	0.140	0.238
REACTOME_FANCONI_ANEMIA_PATHWAY	-0.457	-1.278	0.139	0.243
REACTOME_APOPTOTIC_EXECUTION_PHASE	-0.374	-1.278	0.088	0.242
REACTOME_CLASS_I_MHC_MEDIATED_ANTIGEN_PROCESSING_PRESENTATION	-0.296	-1.274	0.027	0.246
REACTOME_SHC_RELATED_EVENTS	-0.473	-1.274	0.169	0.245
REACTOME_ACTIVATION_OF_THE_MRNA_UPON_BINDING_OF_THE_CAP_BINDING_COMPLEX_AND_EIFS_AND_SUBSEQUENT_BINDING_TO_43S	-0.366	-1.270	0.105	0.250
REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS	-0.427	-1.269	0.166	0.249
KEGG_ARACHIDONIC_ACID_METABOLISM	0.448	1.474	0.033	0.200

KEGG_RIG_I_LIKE_RECEPTOR_SIGNALING_PATHWAY	0.441	1.481	0.045	0.204
KEGG_ECM_RECEPTOR_INTERACTION	0.430	1.512	0.026	0.177
REACTOME_NEGATIVE_REGULATORS_OF_RIG_I_MDA5_SIGNALING	0.540	1.535	0.045	0.225
REACTOME_STEROID_HORMONES	0.540	1.567	0.034	0.191
REACTOME_CHYLOMICRON_MEDIATED_LIPID_TRANSPORT	0.619	1.578	0.032	0.187
KEGG_DRUG_METABOLISM_OTHER_ENZYMES	0.519	1.579	0.027	0.118
REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL	0.472	1.582	0.031	0.192
REACTOME_HDL_MEDIATED_LIPID_TRANSPORT	0.658	1.613	0.036	0.161
REACTOME_POST_CHAPERONIN_TUBULIN_FOLDING_PATHWAY	0.660	1.619	0.037	0.163
KEGG_STEROID_HORMONE_BIOSYNTHESIS	0.518	1.619	0.016	0.093
KEGG_RETINOL_METABOLISM	0.493	1.620	0.018	0.100
KEGG_ASCORBATE_AND_ALDARATE_METABOLISM	0.665	1.627	0.025	0.104
REACTOME_PHASE_II_CONJUGATION	0.495	1.627	0.012	0.165
KEGG_PENTOSE_AND_GLUCURONATE_INTERCONVERSIONS	0.626	1.629	0.031	0.113
REACTOME_EICOSANOID_LIGAND_BINDING_RECEPTORS	0.658	1.632	0.031	0.170
REACTOME_TRAF6_MEDIATED_IRF7_ACTIVATION	0.587	1.638	0.021	0.176
REACTOME_BIOLOGICAL_OXIDATIONS	0.441	1.644	0.002	0.181
REACTOME_SMOOTH_MUSCLE_CONTRACTION	0.595	1.646	0.030	0.195
REACTOME_PD1_SIGNALING	0.643	1.672	0.012	0.177
KEGG_GLUTATHIONE_METABOLISM	0.529	1.682	0.009	0.082
KEGG_STARCH_AND_SUCROSE_METABOLISM	0.557	1.692	0.011	0.086
REACTOME_TERMINATION_OF_O_GLYCAN_BIOSYNTHESIS	0.635	1.692	0.012	0.168
REACTOME_RIG_I_MDA5_MEDIATED_INDUCTION_OF_IFN_ALPHA_BETA_PATHWAYS	0.502	1.720	0.002	0.150
KEGG_AUTOIMMUNE_THYROID_DISEASE	0.574	1.815	0.002	0.032
KEGG_TYPE_I_DIABETES_MELLITUS	0.572	1.832	0.010	0.032
REACTOME_STRIATED_MUSCLE_CONTRACTION	0.662	1.873	0.002	0.036
KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0.568	1.891	0.000	0.018
KEGG_GRAFT_VERSUS_HOST_DISEASE	0.629	1.939	0.000	0.016
KEGG_ALLOGRAFT_REJECTION	0.639	1.957	0.000	0.018
REACTOME_MUSCLE_CONTRACTION	0.633	1.989	0.000	0.010
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	0.612	2.002	0.000	0.020
REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM	0.504	2.060	0.000	0.004
REACTOME_REGULATION_OF_INSULIN_LIKE_GROWTH_FACTOR_IGF_ACTIVITY_BY_INSULIN_LIKE_GROWTH_FACTOR_BINDING_PROTEINS_IGFBPS	0.839	2.095	0.000	0.003
REACTOME_INTERFERON_GAMMA_SIGNALING	0.674	2.219	0.000	0.001
REACTOME_INTERFERON_SIGNALING	0.601	2.317	0.000	0.000
REACTOME_INTERFERON_ALPHA_BETA_SIGNALING	0.839	2.811	0.000	0.000

Table S1C: Top up and down regulated GSEA REACTOME and KEGG pathways by 5-AZA treatment in H23 cells. GSEA pathway cut-off of FDR ≤0.250 was used to delineate pathways with significant enrichment by 5-AZA. ES=Enrichment Score, NES=Normalized Enrichment Score, NOM p-Value= Nominal p Value, FDR q Value= False Discover Rate q Value.

H1299 5-AZA Enriched Pathways	**ES**	**NES**	**NOM p-val**	**FDR q-val**
KEGG_AMINOACYL_TRNA_BIOSYNTHESIS	-0.641	-2.148	0.000	0.000
REACTOME_TRNA_AMINOACYLATION	-0.647	-2.139	0.000	0.001
REACTOME_CYTOSOLIC_TRNA_AMINOACYLATION	-0.722	-2.115	0.000	0.001
REACTOME_GENERIC_TRANSCRIPTION_PATHWAY	-0.463	-2.097	0.000	0.001
REACTOME_CHOLESTEROL_BIOSYNTHESIS	-0.673	-1.914	0.000	0.022
REACTOME_AMINO_ACID_TRANSPORT_ACROSS_THE_PLASMA_MEMBRANE	-0.608	-1.883	0.000	0.028
KEGG_MISMATCH_REPAIR	-0.639	-1.839	0.002	0.027
REACTOME_ASPARAGINE_N_LINKED_GLYCOSYLATION	-0.494	-1.831	0.000	0.044
REACTOME_UNFOLDED_PROTEIN_RESPONSE	-0.494	-1.814	0.000	0.048
REACTOME_INSULIN_SYNTHESIS_AND_PROCESSING	-0.629	-1.806	0.002	0.046
KEGG_TERPENOID_BACKBONE_BIOSYNTHESIS	-0.689	-1.774	0.006	0.040
REACTOME_TRANSPORT_TO_THE_GOLGI_AND_SUBSEQUENT_MODIFICATION	-0.563	-1.763	0.004	0.076
REACTOME_SYNTHESIS_OF_PIPS_AT_THE_GOLGI_MEMBRANE	-0.639	-1.722	0.008	0.114
REACTOME_GABA_SYNTHESIS_RELEASE_REUPTAKE_AND_DEGRADATION	-0.642	-1.698	0.009	0.133
REACTOME_DIABETES_PATHWAYS	-0.416	-1.663	0.000	0.171
KEGG_N_GLYCAN_BIOSYNTHESIS	-0.500	-1.663	0.010	0.107
REACTOME_FATTY_ACYL_COA_BIOSYNTHESIS	-0.606	-1.647	0.018	0.187
REACTOME_PI3K_CASCADE	-0.447	-1.645	0.002	0.178
REACTOME_NEUROTRANSMITTER_RELEASE_CYCLE	-0.516	-1.626	0.011	0.197
REACTOME_AMINO_ACID_AND_OLIGOPEPTIDE_SLC_TRANSPORTERS	-0.473	-1.618	0.010	0.198
REACTOME_ACTIVATION_OF_CHAPERONE_GENES_BY_XBP1S	-0.477	-1.613	0.008	0.196
KEGG_GLYOXYLATE_AND_DICARBOXYLATE_METABOLISM	-0.602	-1.611	0.036	0.145
REACTOME_CD28_DEPENDENT_PI3K_AKT_SIGNALING	-0.564	-1.609	0.030	0.193
REACTOME_NETRIN1_SIGNALING	-0.492	-1.608	0.014	0.184
KEGG_SELENOAMINO_ACID_METABOLISM	-0.539	-1.606	0.015	0.125
REACTOME_TRIGLYCERIDE_BIOSYNTHESIS	-0.495	-1.600	0.006	0.188
KEGG_SMALL_CELL_LUNG_CANCER	-0.423	-1.599	0.002	0.113
REACTOME_TGF_BETA_RECEPTOR_SIGNALING_ACTIVATES_SMADS	-0.537	-1.594	0.013	0.188
REACTOME_PERK_REGULATED_GENE_EXPRESSION	-0.541	-1.584	0.018	0.196
REACTOME_MITOTIC_PROMETAPHASE	-0.411	-1.581	0.000	0.192
REACTOME_INSULIN_RECEPTOR_SIGNALLING_CASCADE	-0.416	-1.572	0.006	0.198
KEGG_LYSINE_DEGRADATION	-0.467	-1.569	0.002	0.127
KEGG_STEROID_BIOSYNTHESIS	-0.587	-1.559	0.021	0.124
REACTOME_POST_TRANSLATIONAL_PROTEIN_MODIFICATION	-0.368	-1.552	0.000	0.224
REACTOME_METAL_ION_SLC_TRANSPORTERS	-0.544	-1.550	0.020	0.218
REACTOME_FATTY_ACID_TRIACYLGLYCEROL_AND_KETONE_BODY_METABOLISM	-0.368	-1.548	0.000	0.214
REACTOME_AMINO_ACID_SYNTHESIS_AND_INTERCONVERSION_TRANSAMINATION	-0.580	-1.544	0.037	0.213
REACTOME_GLUTAMATE_NEUROTRANSMITTER_RELEASE_CYCLE	-0.597	-1.533	0.030	0.226
REACTOME_ACTIVATION_OF_GENES_BY_ATF4	-0.522	-1.530	0.030	0.224
REACTOME_GLOBAL_GENOMIC_NER_GG_NER	-0.489	-1.520	0.028	0.235
REACTOME_DEADENYLATION_OF_MRNA	-0.548	-1.518	0.043	0.232
REACTOME_TRANSPORT_OF_RIBONUCLEOPROTEINS_INTO_THE_HOST_NUCLEUS	-0.504	-1.514	0.038	0.232
REACTOME_CELL_CYCLE_MITOTIC	-0.336	-1.514	0.000	0.226
KEGG_ONE_CARBON_POOL_BY_FOLATE	-0.574	-1.508	0.026	0.177
REACTOME_PKB_MEDIATED_EVENTS	-0.502	-1.505	0.031	0.234

REACTOME_DNA_REPLICATION	-0.356	-1.502	0.002	0.233
REACTOME_ACTIVATED_POINT_MUTANTS_OF_FGFR2	-0.574	-1.502	0.047	0.227
REACTOME_MITOTIC_M_M_G1_PHASES	-0.357	-1.493	0.000	0.236
REACTOME_INTERACTIONS_OF_VPR_WITH_HOST_CELLULAR_PROTEINS	-0.480	-1.490	0.038	0.237
REACTOME_DOUBLE_STRAND_BREAK_REPAIR	-0.515	-1.488	0.051	0.234
REACTOME_PI_3K_CASCADE	-0.423	-1.484	0.033	0.234
REACTOME_FGFR_LIGAND_BINDING_AND_ACTIVATION	-0.520	-1.483	0.044	0.230
KEGG_GLYCEROLIPID_METABOLISM	-0.438	-1.483	0.026	0.196
REACTOME_ACTIVATION_OF_THE_PRE_REPLICATIVE_COMPLEX	-0.479	-1.482	0.033	0.226
KEGG_ERBB_SIGNALING_PATHWAY	-0.391	-1.473	0.008	0.192
REACTOME_LOSS_OF_NLP_FROM_MITOTIC_CENTROSOMES	-0.421	-1.471	0.028	0.239
REACTOME_ACTIVATION_OF_ATR_IN_RESPONSE_TO_REPLICATION_STRESS	-0.452	-1.471	0.047	0.235
KEGG_BUTANOATE_METABOLISM	-0.475	-1.469	0.034	0.183
REACTOME_NEGATIVE_REGULATION_OF_FGFR_SIGNALING	-0.461	-1.467	0.024	0.237
REACTOME_NEP_NS2_INTERACTS_WITH_THE_CELLULAR_EXPORT_MACHINERY	-0.488	-1.465	0.049	0.235
KEGG_PROTEIN_EXPORT	-0.508	-1.464	0.031	0.177
KEGG_PROPANOATE_METABOLISM	-0.468	-1.461	0.034	0.170
REACTOME_FORMATION_OF_INCISION_COMPLEX_IN_GG_NER	-0.540	-1.460	0.055	0.238
REACTOME_BOTULINUM_NEUROTOXICITY	-0.527	-1.451	0.063	0.248
KEGG_SPLICEOSOME	-0.358	-1.445	0.020	0.182
KEGG_P53_SIGNALING_PATHWAY	-0.399	-1.437	0.021	0.182
KEGG_PYRIMIDINE_METABOLISM	-0.368	-1.416	0.020	0.203
KEGG_THYROID_CANCER	-0.454	-1.390	0.082	0.233
KEGG_BETA_ALANINE_METABOLISM	-0.482	-1.378	0.093	0.242
REACTOME_TIGHT_JUNCTION_INTERACTIONS	0.563	1.650	0.010	0.174
REACTOME_TAK1_ACTIVATES_NFKB_BY_PHOSPHORYLATION_AND_ACTIVATION_OF_IKKS_COMPLEX	0.579	1.663	0.026	0.169
REACTOME_REGULATION_OF_INSULIN_LIKE_GROWTH_FACTOR_IGF_ACTIVITY_BY_INSULIN_LIKE_GROWTH_FACTOR_BINDING_PROTEINS_IGFBPS	0.636	1.663	0.026	0.180
REACTOME_LATENT_INFECTION_OF_HOMO_SAPIENS_WITH_MYCOBACTERIUM_TUBERCULOSIS	0.568	1.667	0.016	0.188
REACTOME_RIP_MEDIATED_NFKB_ACTIVATION_VIA_DAI	0.629	1.687	0.020	0.173
REACTOME_RIG_I_MDA5_MEDIATED_INDUCTION_OF_IFN_ALPHA_BETA_PATHWAYS	0.481	1.699	0.002	0.167
REACTOME_MEIOTIC_RECOMBINATION	0.465	1.704	0.006	0.178
REACTOME_INTEGRIN_CELL_SURFACE_INTERACTIONS	0.483	1.751	0.000	0.129
REACTOME_TRAF6_MEDIATED_NFKB_ACTIVATION	0.628	1.756	0.006	0.138
REACTOME_POST_CHAPERONIN_TUBULIN_FOLDING_PATHWAY	0.700	1.782	0.004	0.123
REACTOME_HDL_MEDIATED_LIPID_TRANSPORT	0.724	1.827	0.004	0.094
REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL	0.537	1.850	0.000	0.089
REACTOME_RNA_POL_I_PROMOTER_OPENING	0.605	2.028	0.000	0.010
REACTOME_PACKAGING_OF_TELOMERE_ENDS	0.615	2.040	0.000	0.011
REACTOME_AMYLOIDS	0.581	2.088	0.000	0.009
REACTOME_INTERFERON_ALPHA_BETA_SIGNALING	0.623	2.144	0.000	0.007

Table S1D: Top up and down regulated GSEA REACTOME and KEGG pathways by 5-AZA treatment in H1299 cells. GSEA pathway cut-off of FDR ≤0.250 was used to delineate pathways with significant enrichment by 5-AZA. ES=Enrichment Score, NES=Normalized Enrichment Score, NOM p-Value= Nominal p Value, FDR q Value= False Discover Rate q Value.

REACTOME DNA Repair Gene List Z Score

Gene	H460 5-AZA	H23 5-AZA	H1299 5-AZA	A549 5-AZA
REV1	-1.496149171	0.432746556	0.598242704	0.465159912
OGG1	-1.455102828	0.174217176	0.513971272	0.76691438
CCNH	-1.440099005	0.756866979	0.096805645	0.586426381
GTF2H3	-1.436385387	0.874488566	0.196678758	0.365218063
TDP1	-1.42323755	0.813936573	0.55592553	0.053375447
NBN	-1.413214734	0.218113277	0.944766057	0.250335399
POLR2H	-1.38565279	-0.074806784	0.667383916	0.793075658
RPS27A	-1.364856644	-0.095127208	0.906543237	0.553440616
XRCC4	-1.36442525	0.62036627	0.860229011	-0.116170031
APEX1	-1.358881319	0.810319819	0.690431859	-0.141870359
RFC4	-1.339044684	0.484179197	0.978401136	-0.12353565
FANCL	-1.327935415	0.705619544	0.83319724	-0.210881368
CDK7	-1.315823996	1.098675873	-0.029160982	0.246309105
XPA	-1.298348689	1.028699187	0.466271005	-0.196621503
RAD52	-1.296887535	1.013608146	-0.212307789	0.495587178
USP1	-1.295963169	-0.007642825	1.136945634	0.16666036
RPA3	-1.247912554	1.199308463	0.06425382	-0.01564973
FANCB	-1.228006258	1.221315103	0.016904032	-0.010212877
ERCC8	-1.212551698	-0.308498046	1.13318502	0.387864724
FANCE	-1.202437507	-0.305833848	0.352160269	1.156111086
MDC1	-1.186685983	-0.456428524	0.951049992	0.692064515
ATR	-1.101213868	1.196584808	-0.466591788	0.371220848
MRE11A	-1.089456669	1.31916053	0.037656646	-0.267360507
POLD1	-1.072120904	0.034255104	1.328500885	-0.290635085
FANCC	-1.047533051	0.563991058	-0.614874252	1.098416245
MNAT1	-1.029019367	-0.669123887	1.009613069	0.688530185
LIG4	-1.01597088	-0.185016221	-0.178090793	1.379077894
ALKBH3	-0.981121562	0.667027627	-0.721345634	1.035439569
GTF2H1	-0.97163782	-0.21739586	-0.21225402	1.4012877
PALB2	-0.939691445	0.100790703	1.356185124	-0.517284382
POLB	-0.930013091	-0.691577747	1.22432743	0.397263408
UBA52	-0.925618931	-0.52302974	1.364784326	0.083864344
MGMT	-0.916829935	1.199688293	0.441737369	-0.724595726
FANCG	-0.913964393	1.224614504	0.399984164	-0.710634275
UBE2T	-0.871260019	0.582788556	1.108511519	-0.820040055
MUTYH	-0.83848357	1.360655658	0.132124865	-0.654296954
BRCA1	-0.78776264	-0.018177938	1.41646165	-0.610521072
RAD23B	-0.761683423	-0.164292217	-0.528004357	1.453979996
XAB2	-0.743159391	-0.356929907	1.476116171	-0.376026873
TCEA1	-0.663757699	1.489451144	-0.419018155	-0.406675291
POLE2	-0.650460534	-0.310109437	1.485119772	-0.524549801
RFC2	-0.612320444	-0.551692431	1.488437943	-0.324425068

NTHL1	-0.587845402	0.621022475	1.048357122	-1.081534194
FANCF	-0.574695962	1.079787759	-1.08207109	0.576979293
POLD3	-0.57382279	0.528761569	1.115719376	-1.070658154
PRKDC	-0.464975788	0.047790231	-0.952116427	1.369301983
MPG	-0.451592787	-0.468649695	1.497668422	-0.57742594
POLR2K	-0.390293346	-0.376425012	1.481550145	-0.714831787
RFC3	-0.370782847	-0.817341856	1.456805713	-0.268681011
XRCC5	-0.29109715	1.296194587	-1.106714098	0.101616661
POLR2E	-0.244484909	0.259552435	1.190954065	-1.206021591
MAD2L2	-0.174813904	-0.216300265	1.38848817	-0.997374
C19orf40	-0.131547947	0.347889416	1.083103011	-1.299444481
POLR2I	-0.061299996	0.473790356	0.952782615	-1.365272975
POLE	-0.048649403	0.827430104	0.613042432	-1.391823133
TDG	-0.018855971	-1.39226021	0.52440688	0.886709301
LIG1	0.022802935	0.965038475	0.394973395	-1.382814805
POLR2J	0.037117852	0.245438144	1.062562406	-1.345118402
POLD2	0.126157552	-0.120235095	1.215564573	-1.22148703
ATM	0.178186168	1.151674679	-1.280409988	-0.049450859
RPA2	0.209345051	1.327797295	-0.692001935	-0.845140411
RFC5	0.223531045	-0.398389129	1.265570014	-1.09071193
LIG3	0.236260472	-1.283523131	-0.088075227	1.135337886
CCNO	0.258631867	-1.432585881	0.896592282	0.277361732
XRCC1	0.263155393	0.873101252	0.304483808	-1.440740453
BRCA2	0.267881764	0.59847498	0.614385482	-1.480742226
ALKBH2	0.313885978	0.083922049	-1.385349771	0.987541744
REV3L	0.319514923	1.1634735	-1.212987742	-0.270000681
FANCM	0.337220105	-1.131944857	1.200229029	-0.405504277
POLR2G	0.344759209	0.446353219	0.692786667	-1.483899095
C17orf70	0.35936559	0.262892478	-1.453088176	0.830830109
POLR2L	0.508183797	-0.16820854	0.982328198	-1.322303455
RAD50	0.542608875	0.689888807	0.24110283	-1.473600512
DDB1	0.595712272	0.754339799	-1.438170209	0.088118138
ERCC1	0.624779178	0.539142999	0.324024118	-1.487946295
SMUG1	0.649026609	-1.483069558	0.291611492	0.542431457
ERCC5	0.682839136	0.45193191	-1.485436611	0.350665564
RAD51	0.705497373	-0.309190219	0.880768381	-1.277075536
H2AFX	0.748618197	-1.048715829	0.954640828	-0.654543196
POLR2C	0.768394528	-0.146440334	0.736570412	-1.358524606
POLR2F	0.773902341	-1.266291652	0.827725825	-0.335336514
POLD4	0.885525918	0.82800889	-0.680494382	-1.033040426
DDB2	0.917698049	0.307291818	0.197783395	-1.422773263
FANCA	0.984272729	-0.721236214	0.727676545	-0.990713059
POLR2B	1.006097642	-0.895730349	-0.823084749	0.712717456
GTF2H4	1.010479066	-0.701682157	-1.002601391	0.693804482
XPC	1.017582089	0.695895302	-0.935013962	-0.778463429

RPA1	1.03362759	0.107613293	0.225877521	-1.367118404
ERCC4	1.171475497	0.441592449	-1.063095047	-0.549972899
FEN1	1.218688892	-1.210067326	0.154587429	-0.163208995
ERCC6	1.227925037	-1.103823481	-0.426792625	0.302691069
POLR2D	1.256746032	-0.185416993	0.101648981	-1.17297802
PCNA	1.266675021	-0.960855661	0.308353829	-0.614173189
BRIP1	1.280005966	0.266128693	-0.554556397	-0.991578262
POLH	1.285966395	-1.039287841	0.219987141	-0.466665695
MBD4	1.324143561	0.069935836	-0.329599823	-1.064479574
ZBTB32	1.391460618	0.034069043	-0.865423345	-0.560106315
ERCC3	1.419640405	-0.019775844	-0.746941008	-0.652923553
TP53BP1	1.424582256	-0.78465943	-0.04598663	-0.593936197
ERCC2	1.442633707	-0.109627804	-0.762256181	-0.570749722
XRCC6	1.463798622	-0.681280999	-0.182712798	-0.599804825
POLR2A	1.481730098	-0.527955733	-0.665163428	-0.288610937
FANCD2	1.484043313	-0.36171501	-0.697118713	-0.42520959

Table S2A: Z score table of REACTOME DNA Repair Pathway gene expression. Z score table based on Log2 fold change of gene expression by 5-AZA treatment..

Fanconi Anemia Combined Gene List Z Score

Gene	H460 5-AZA	H23 5-AZA	H1299 5-AZA	A549 5-AZA
NBN	-1.413214734	0.218113277	0.944766057	0.250335399
RPS27A	-1.364856644	-0.095127208	0.906543237	0.553440616
RAD1	-1.347802176	0.392423585	1.012973753	-0.057595162
RFC4	-1.339044684	0.484179197	0.978401136	-0.12353565
FANCL	-1.327935415	0.705619544	0.83319724	-0.210881368
USP1	-1.295963169	-0.007642825	1.136945634	0.16666036
FANCB	-1.228006258	1.221315103	0.016904032	-0.010212877
FANCE	-1.202437507	-0.305833848	0.352160269	1.156111086
ATR	-1.101213868	1.196584808	-0.466591788	0.371220848
MRE11A	-1.089456669	1.31916053	0.037656646	-0.267360507
FANCC	-1.047533051	0.563991058	-0.614874252	1.098416245
PALB2	-0.939691445	0.100790703	1.356185124	-0.517284382
UBA52	-0.925618931	-0.52302974	1.364784326	0.083864344
FANCG	-0.913964393	1.224614504	0.399984164	-0.710634275
UBE2T	-0.871260019	0.582788556	1.108511519	-0.820040055
BLM	-0.864822786	0.341642224	1.261216008	-0.738035447
APITD1	-0.859711026	-0.249523251	1.444402157	-0.335167879
BRCA1	-0.78776264	-0.018177938	1.41646165	-0.610521072
SSPO	-0.739004691	0.199977832	1.334550038	-0.795523179
RFC2	-0.612320444	-0.551692431	1.488437943	-0.324425068
FANCF	-0.574695962	1.079787759	-1.08207109	0.576979293
WDR48	-0.513619469	1.115093393	-1.110637056	0.509163132
FAN1	-0.469815255	-0.070016055	-0.876527204	1.416358514
RMI1	-0.469358107	-0.645438961	1.490598744	-0.375801676
RFC3	-0.370782847	-0.817341856	1.456805713	-0.268681011
FANCI	-0.353012532	1.18419286	0.335289004	-1.166469333
HES1	-0.28620914	-1.278404343	0.955163604	0.609449878
TOPBP1	-0.234199422	-1.318449991	0.749120388	0.803529026
C19orf40	-0.131547947	0.347889416	1.083103011	-1.299444481
RAD17	-0.123204512	0.02374947	1.270241953	-1.170786911
TOP3A	-0.054847413	0.06565313	1.217835272	-1.228640988
ATM	0.178186168	1.151674679	-1.280409988	-0.049450859
RPA2	0.209345051	1.327797295	-0.692001935	-0.845140411
RFC5	0.223531045	-0.398389129	1.265570014	-1.09071193
BRCA2	0.267881764	0.59847498	0.614385482	-1.480742226
FANCM	0.337220105	-1.131944857	1.200229029	-0.405504277
C17orf70	0.35936559	0.262892478	-1.453088176	0.830830109
RAD50	0.542608875	0.689888807	0.24110283	-1.473600512
RAD9A	0.550626468	-0.067958463	0.893502536	-1.376170541
H2AFX	0.748618197	-1.048715829	0.954640828	-0.654543196
FANCA	0.984272729	-0.721236214	0.727676545	-0.990713059
RPA1	1.03362759	0.107613293	0.225877521	-1.367118404

CHEK1	1.152507659	-0.69818544	0.508045953	-0.962368171
XRCC3	1.235625267	0.033439107	-1.211961764	-0.057102611
BRIP1	1.280005966	0.266128693	-0.554556397	-0.991578262
ZBTB32	1.391460618	0.034069043	-0.865423345	-0.560106315
FBXW11	1.398393816	-0.062829227	-0.3951279	-0.940436689
HUS1	1.430949219	-0.142171695	-0.418891768	-0.869885756
ATRIP	1.441872844	-0.630672762	-0.093965815	-0.717234268
FANCD2	1.484043313	-0.36171501	-0.697118713	-0.42520959

Table S2B: Z score table of REACTOME Combined Fanconi Anemia Pathway gene expression. Z score table based on Log2 fold change of gene expression by 5-AZA treatment. See methods for description of combined Fanconi Anemia gene set.