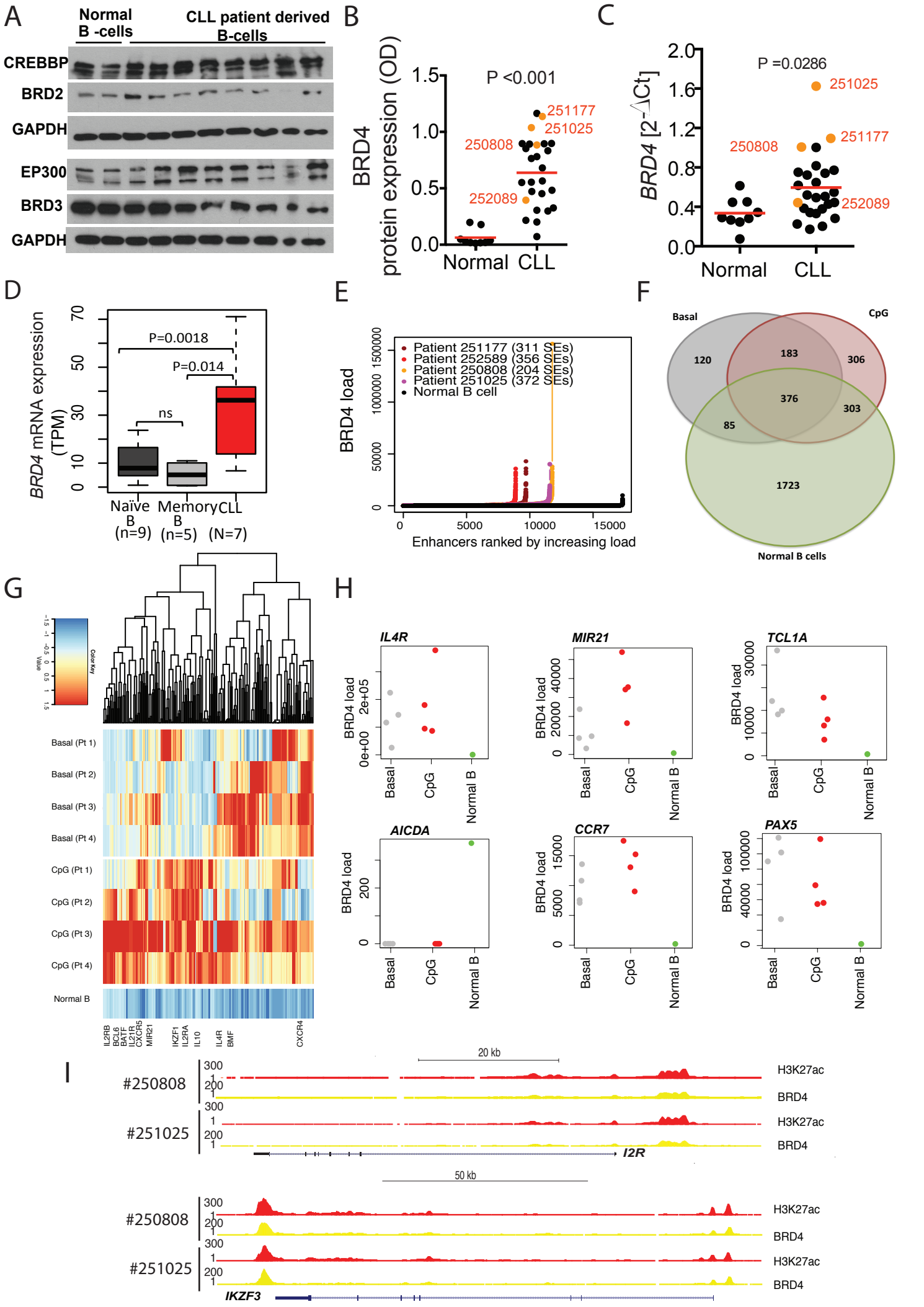
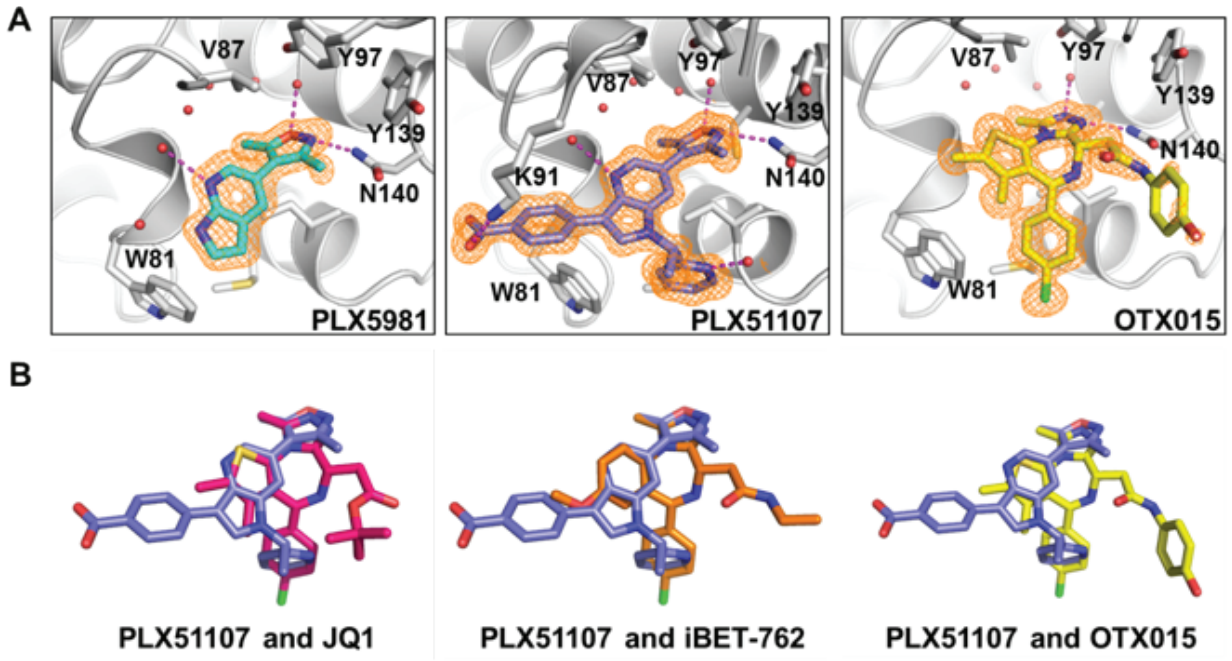
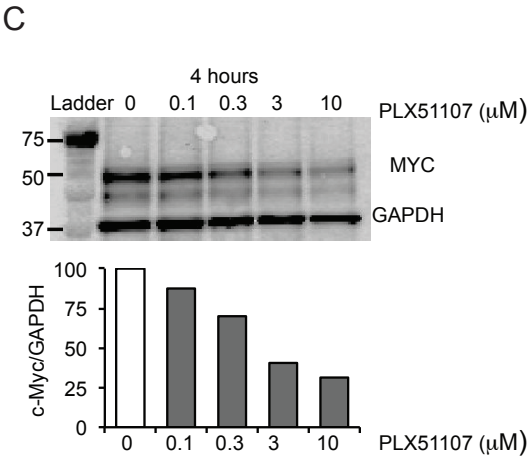
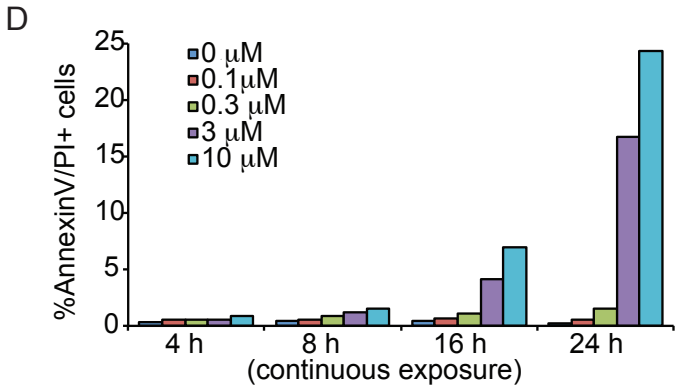

A
Normal B -cells
CLL patient derived B-cells
CREBBP
BRD2
GAPDH
EP300
BRD3
GAPDH
B
BRD4 protein expression (OD)
P <0.001
251177
251025
250808
252089
Normal
CLL
C
BRD4 [2-ΔCt]
P =0.0286
251025
251177
250808
252089
Normal
CLL
D
BRD4 mRNA expression (TPM)
P=0.0018
P=0.014
ns
Naïve B (n=9)
Memory B (n=5)
CLL (N=7)
E
BRD4 load
Patient 251177 (311 SEs)
Patient 252589 (356 SEs)
Patient 250808 (204 SEs)
Patient 251025 (372 SEs)
Normal B cell
Enhancers ranked by increasing load
F
Basal
CpG
Normal B cells
120
183
306
376
303
85
1723
G
Color key
Basal (Pt 1)
Basal (Pt 2)
Basal (Pt 3)
Basal (Pt 4)
CpG (Pt 1)
CpG (Pt 2)
CpG (Pt 3)
CpG (Pt 4)
Normal B
IL2RB
BCL6
BATF
IL21R
CXCR5
MIR21
IKZF1
IL2RA
IL10
IL4R
BMF
CXCR4
H
IL4R
MIR21
TCL1A
AICDA
CCR7
PAX5
BRD4 load
Basal
CpG
Normal B
I
20 kb
#250808
#251025
H3K27ac
BRD4
I2R
50 kb
IKZF3

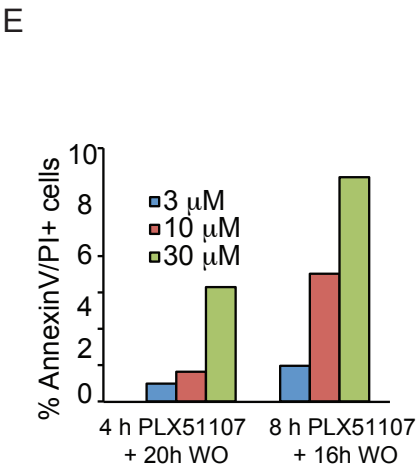
Figure S1

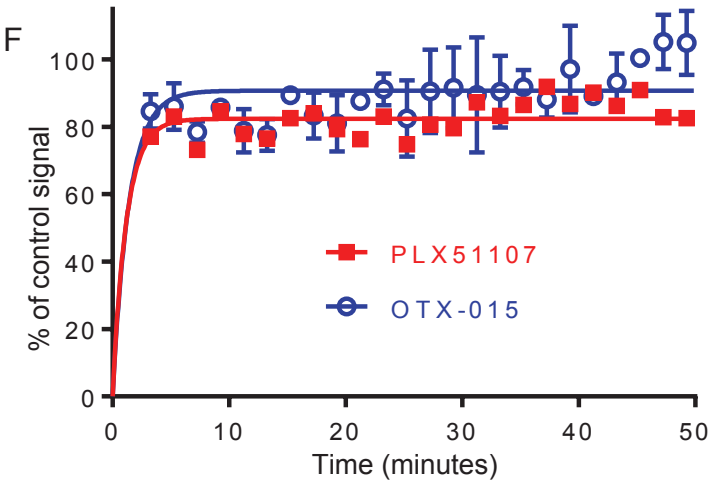
**Figure S1: A.** Representative immunoblot analysis of *CREBBP*, *BRD2*, *EP300*, *BRD3* and *GAPDH* in normal B-cells and CLL patient-derived B-cells. **B.** Protein expression quantification in B-cells isolated from normal donors (n=9) or CLL patients (n=26). Orange dots represent the four cases used or ChIP-seq studies; **C** *BRD4* transcript level in B-cells isolated from normal donors (n=9) or CLL patients (n=26), normalized to *GAPDH*. Red lines represent averages. Orange dots represents the four CLL cases used for ChIP-analysis; **D.** Boxplot showing the expression level distributions (transcript parts per million, TPM) of *BRD4* in patient's derived primary CLL cells and normal B cells (GEO study GSE42262, sample GSM1036401); **E.** Hockey stick plot for BRD4 load across enhancers of four CLL patient cells and a normal B cell line. SEs are defined as enhancers surpassing the inflection point; **F.** Venn diagram of SEs for primary CLL cells (basal and CpG stimulated conditions); **G.** Heatmap showing BRD4 load (total of reads per million per base pair) of SEs that are common for the four analyzed CLL samples (at least 3 out of 4) under basal or CpG stimulate conditions but not in normal B cell line; **H.** BRD4 load at super-enhancers of selected genes know to be either up-regulated (*IL4R*, *MIR21*, *TCL1A*, *CCR7*, and *PAX5*) or down-regulated (*AICDA*) in CLL compared to normal B cells with known prominent roles in tumor biology; **I.** Gene tracks of H3K27ac (red) and BRD4 (yellow) occupancy in primary CLL cells. The x-axis shows genomic position and y-axis shows signal of ChIP-seq occupancy in units of rpm/bp.




| | $t_{1/2}$(min) | Apparent $K_{off}$ ($min^{-1}$) |
|---|---|---|
| PLX51107 | < 3.25 | > 0.213 |
| OTX-015 | < 3.25 | > 0.213 |

Figure S2

**Figure S2: Co-structures with different BRD4 inhibitors. A.** A $F_O$-$F_C$ omit map contoured at +3σ level for PLX5981, PLX51107 and OTX015. The inhibitors and key residues at the active site are shown in stick model. Fo-Fc omit maps were calculated using the refined coordinates of the structures excluding the ligands; **B.** Overlay of PLX51107 (purple) with JQ1 (red; PDB: 3MXF), i-BET762 (orange; PDB: 3P5O) and OTX015 (yellow). (**C-F):** Effect of exposure time on PLX51107 pharmacodynamic markers and the determination of compound residence times. **C.** Short term (4 hours) PLX51107 treatment at 3 and 10 μM concentrations resulted in robust downregulation of c-Myc in MV4-11 cells (GAPDH was used as loading control). **D.** AnnexinV/PI flow cytometric analysis of MV4-11 cells treated with PLX51107 continuously for 4, 8, 16, and 24 hours. Significant apoptosis was observed at 3 and 10 μM only after prolonged incubation. **E.** AnnexinV/PI flow cytometric analysis of MV4-11 cells treated with PLX51107 for 2, 4 or 8 hours followed by a washout period of 22, 20, or 16 hours (i.e. cytometric analysis was conducted 24 hours after treatment initiation in all cases). Two representative dot plots are shown. **F**. Off-rate measurement of PLX51107 and OTX-015 using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. Compound incubations were performed with 0.3 μM GST-BRD4 (containing BD1 and BD2), 0.3 μM Eu-anti-GST antibody, and 1.5 μM of the test compounds.

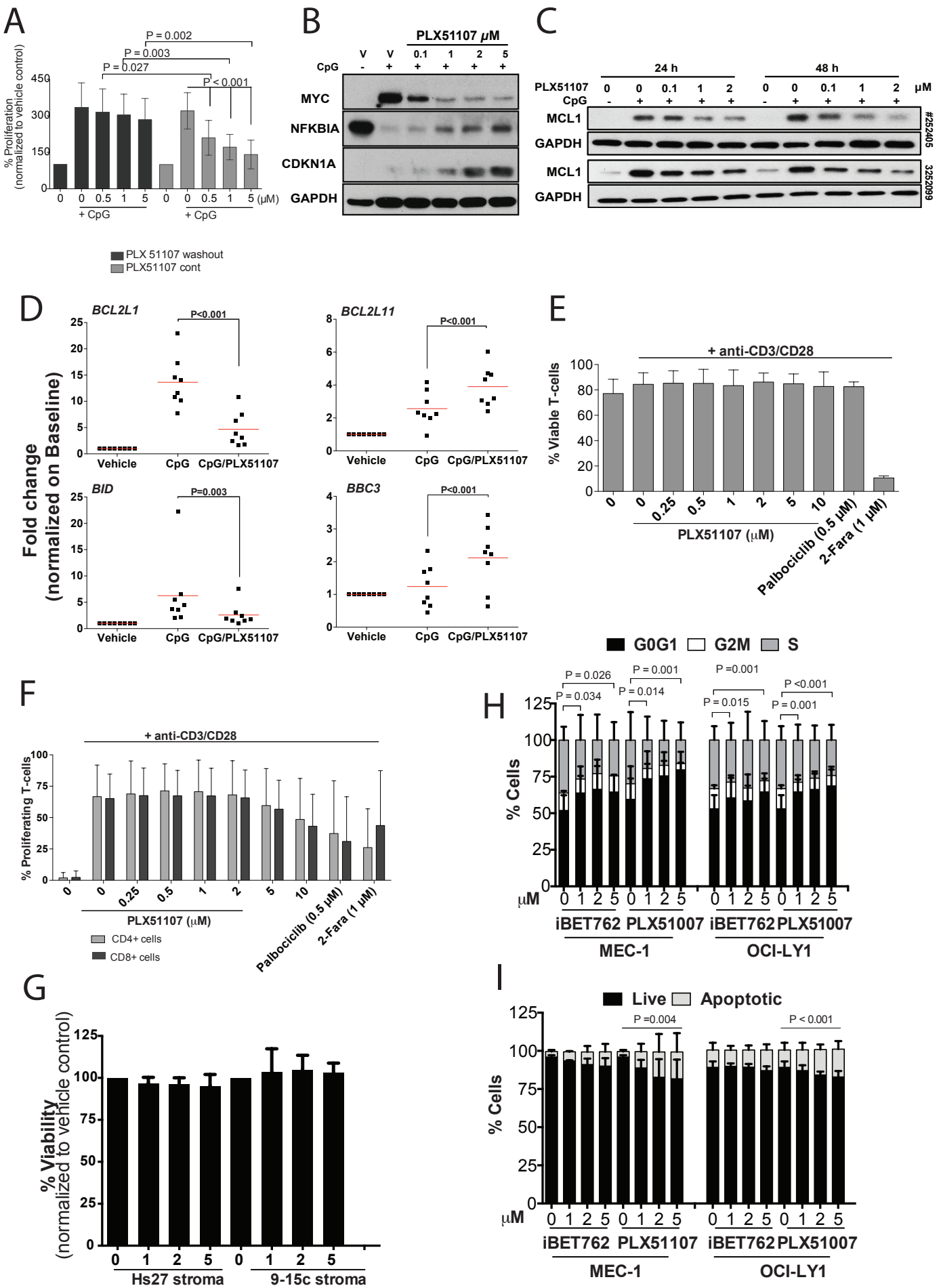

A
P = 0.002
P = 0.003
P = 0.027
P < 0.001
% Proliferation (normalized to vehicle control)
0 0 0.5 1 5 0 0 0.5 1 5 (μM)
+ CpG
+ CpG
PLX 51107 washout
PLX51107 cont
B
PLX51107 μM
V V 0.1 1 2 5
CpG - + + + + +
MYC
NFKBIA
CDKN1A
GAPDH
C
24 h
48 h
PLX51107 0 0 0.1 1 2 0 0 0.1 1 2 μM
CpG - + + + + - + + + +
MCL1
GAPDH
#2524052
MCL1
GAPDH
3252099
D
Fold change (normalized on Baseline)
BCL2L1
P<0.001
BCL2L11
P<0.001
BID
P=0.003
BBC3
P<0.001
Vehicle
CpG
CpG/PLX51107
E
+ anti-CD3/CD28
% Viable T-cells
0 0 0.25 0.5 1 2 5 10
PLX51107 (μM)
Palbociclib (0.5 μM)
2-Fara (1 μM)
F
+ anti-CD3/CD28
% Proliferating T-cells
0 0 0.25 0.5 1 2 5 10
PLX51107 (μM)
Palbociclib (0.5 μM)
2-Fara (1 μM)
CD4+ cells
CD8+ cells
G
% Viability (normalized to vehicle control)
0 1 2 5 0 1 2 5
Hs27 stroma
9-15c stroma
H
G0G1 G2M S
P = 0.026
P = 0.034
P = 0.001
P = 0.014
P =0.001
P = 0.015
P <0.001
P = 0.001
% Cells
μM 0 1 2 5 0 1 2 5 0 1 2 5 0 1 2 5
iBET762 PLX51007 iBET762 PLX51007
MEC-1
OCI-LY1
I
Live Apoptotic
P =0.004
P < 0.001
% Cells
μM 0 1 2 5 0 1 2 5 0 1 2 5 0 1 2 5
iBET762 PLX51107 iBET762 PLX51007
MEC-1
OCI-LY1

Figure S3

**Figure S3: BET inhibition attenuates CpG-induced survival effects in CLL. A.** Dose-dependent decrease of proliferation of CpG stimulated normal B cells upon BRD4 inhibition with increasing doses of PLX51107 for 4h followed by 44h washout or 48h continuously; (n=5); **B.** Representative immunoblot analysis of cMYC, IκBα, CDKN1A and GAPDH following PLX51107 treatment (0.1, 1, 2 or 5 μM) in CpG-stimulated CLL cells (4h, n=3); **C.** Representative immunoblot analyses of the antiapoptotic protein, MCL1 following PLX51107 treatment of CpG stimulated B-CLL cells (24 and 48h, n=5) GAPDH is used as loading control; **D.** Quantitative real time-PCR analysis of the indicated apoptosis-related genes in primary B-CLL cells following PLX51107 treatment (1μM, 4 h) under stimulated conditions with 3.2 μM CpG oligonucleotides (n=8). Red lines represent averages; **E-F.** Flow cytometric analysis of the effect of PLX51107 on T-cell viability and proliferation. Freshly isolated CD3 T-cells from healthy donors were stimulated by plate bound anti-CD3 and soluble anti-CD28 (+ anti-CD3/CD28) and treated with vehicle DMSO or increasing concentrations of PLX51107 as indicated. Palbociclib (0.5-1 μM) and Fludarabine (2-Fara, 1/5 μM) were used as control drugs to inhibit proliferation and viability, respectively. (E) T-cell viability was evaluated following a 4-day treatment using the LIVE/DEAD Fixable near-IR stain. Results are shown as Mean ± SD (n=3-7); (F) CD4 and CD8 T-cell were investigated for CFSE dilution resulting from proliferation at the indicated time points and treatment conditions. Gates were set on viable CD4 or CD8 T-cells that underwent at least 1 cellular division and results are shown as % proliferating T-cells (Mean +) **(F)**; **G.** Human Hs27 or murine 9-15c bone marrow-derived stroma cells were treated with increasing concentrations of PLX51107 for 72 h. Effects on proliferation were determined by MTS assay and represented as % of vehicle control. Results shown as mean ± SD of n=3 independent experiments per cell line; **H**. Cell cycle analysis demonstrates accumulation of cells in G0/G1 phase in malignant B-cell lines following treatment with iBET762 or PLX51107 (1, 2 or 5 μM) at 72h (n=3). Results shown as Mean ± SD (n=3-4); **I**. Annexin/PI flow cytometric analysis of malignant B-cell lines treated with BRD4i, iBET-762 or PLX51107 (1, 2 or 5 μM) at 72h (n=4).

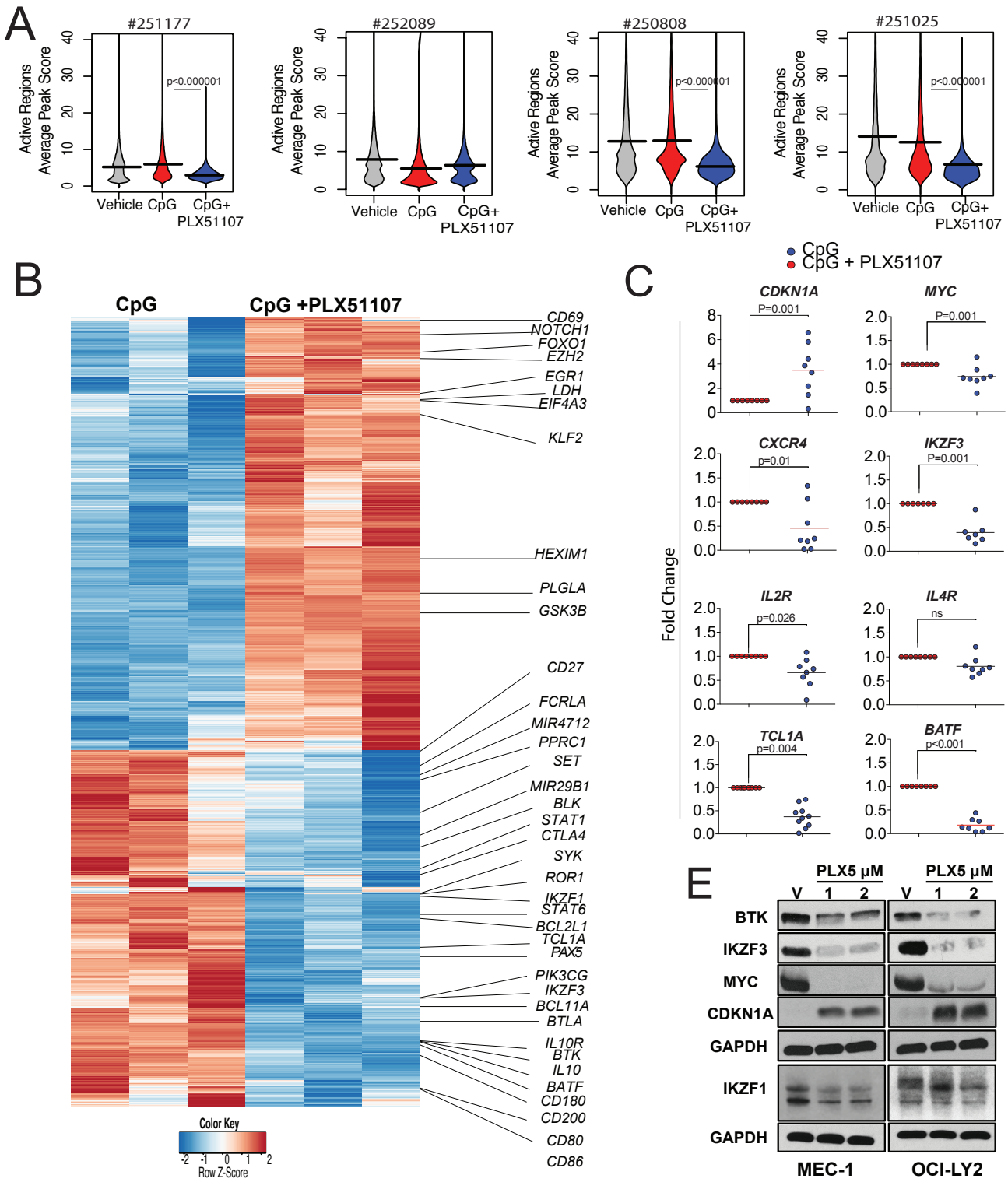

A
#251177
#252089
#250808
#251025
Active Regions
Average Peak Score
p<0.000001
Vehicle
CpG
CpG+
PLX51107
B
CpG
CpG +PLX51107
CD69
NOTCH1
FOXO1
EZH2
EGR1
LDH
EIF4A3
KLF2
HEXIM1
PLGLA
GSK3B
CD27
FCRLA
MIR4712
PPRC1
SET
MIR29B1
BLK
STAT1
CTLA4
SYK
ROR1
IKZF1
STAT6
BCL2L1
TCL1A
PAX5
PIK3CG
IKZF3
BCL11A
BTLA
IL10R
BTK
IL10
BATF
CD180
CD200
CD80
CD86
Color Key
Row Z-Score
C
CpG
CpG + PLX51107
CDKN1A
MYC
CXCR4
IKZF3
IL2R
IL4R
TCL1A
BATF
Fold Change
P=0.001
p=0.01
p=0.026
ns
p=0.004
p<0.001
D
#252436
#252108
24 h
48 h
PLX51107
CpG
μM
BATF
IL2R
GAPDH
IL21R
BCL6
GAPDH
E
PLX5 μM
V
1
2
BTK
IKZF3
MYC
CDKN1A
GAPDH
IKZF1
GAPDH
MEC-1
OCI-LY2

Figure S4

**Figure S4: A**. Bean plots showing global distribution of BRD4 peak scores at active regions following 4h treatment of primary CLL cells (a = vehicle, b = 3.2 μM CpG stimulation, c = CpG stimulation + PLX51107, horizontal bars mark the mean scores); **B.** Heatmap of 1361 differentially expressed genes (745 up and 616 down regulated) with absolute fold change of 2 or more and p-value less than 0.01 upon BRD4 inhibition in microarray data. Microarray analysis using GeneChip Human Transcriptome Array HTA 2.0 (Affymetrix®) was performed in patient-derived CLL cells stimulated with CpG oligonucleotides (3.2 μM) and treated with either vehicle (VEH/CpG) or 1 μM PLX51107 (PLX5/CpG) for 4 h. Experiments were performed as triplicates, each representing a pool of 2-3 CLL patient samples each; **C**. Quantitative real time-PCR analysis of the selected genes in PLX51107 treated CpG-stimulated CLL patient-derived B-cells (n=8-10). Red lines represent averages; **D.** of protein levels of BATF, IL2R, IL21R, BCL6, and GAPDH following PLX51107 treatment (0.1, 1, or 2 μM) in CpG-stimulated patient-derived CLL cells (24 and 48 h, n=5); **E.** Representative immunoblot analyses of relative protein levels of BTK, IKZF3, MYC, CDKN1A, IKZF1 and GAPDH following treatment with vehicle (V) or PLX51107 (PLX5: 1 or 2 μM, 72 h) in three B-cell malignant cell lines (MEC-1, OCI-LY1).

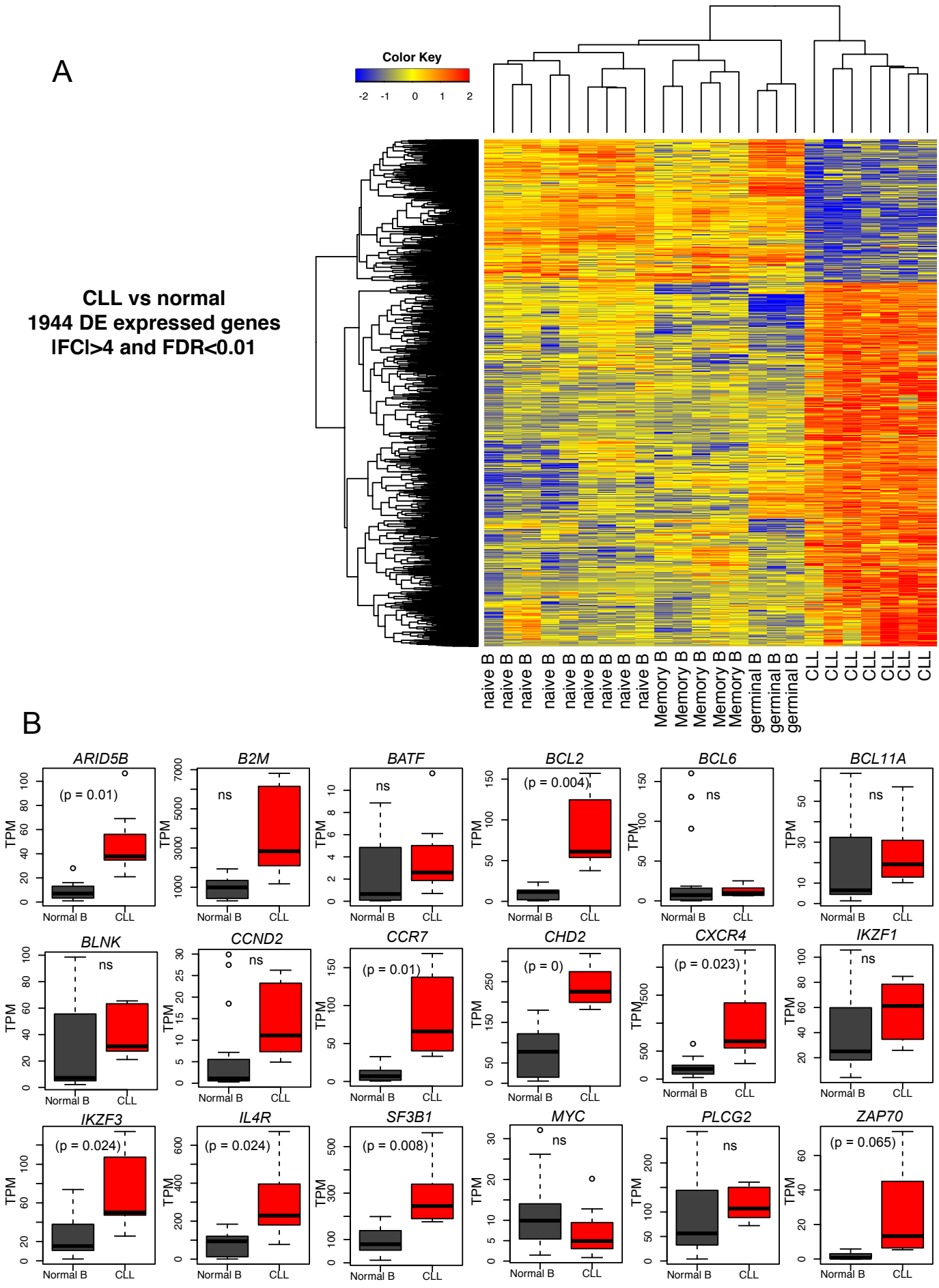

A
Color Key
-2 -1 0 1 2
CLL vs normal
1944 DE expressed genes
IFCI>4 and FDR<0.01
naive B
Memory B
germinal B
CLL
B
ARID5B
(p = 0.01)
B2M
ns
BATF
ns
BCL2
(p = 0.004)
BCL6
ns
BCL11A
ns
BLNK
ns
CCND2
ns
CCR7
(p = 0.01)
CHD2
(p = 0)
CXCR4
(p = 0.023)
IKZF1
ns
IKZF3
(p = 0.024)
IL4R
(p = 0.024)
SF3B1
(p = 0.008)
MYC
ns
PLCG2
ns
ZAP70
(p = 0.065)
TPM
Normal B
CLL

Figure S5

**Figure S5. A. Differential gene expression profile in CLL compared to normal B cells.** Heatmap of 1944 differentially expressed genes (with absolute fold change of 4 or more and p-value less than 0.01 in CLL compared to normal B cells in RNA-seq data; **B.** Boxplot showing the expression level distributions (transcript parts per million, TPM) for patients derived primary CLL cells and normal B cells for select genes.

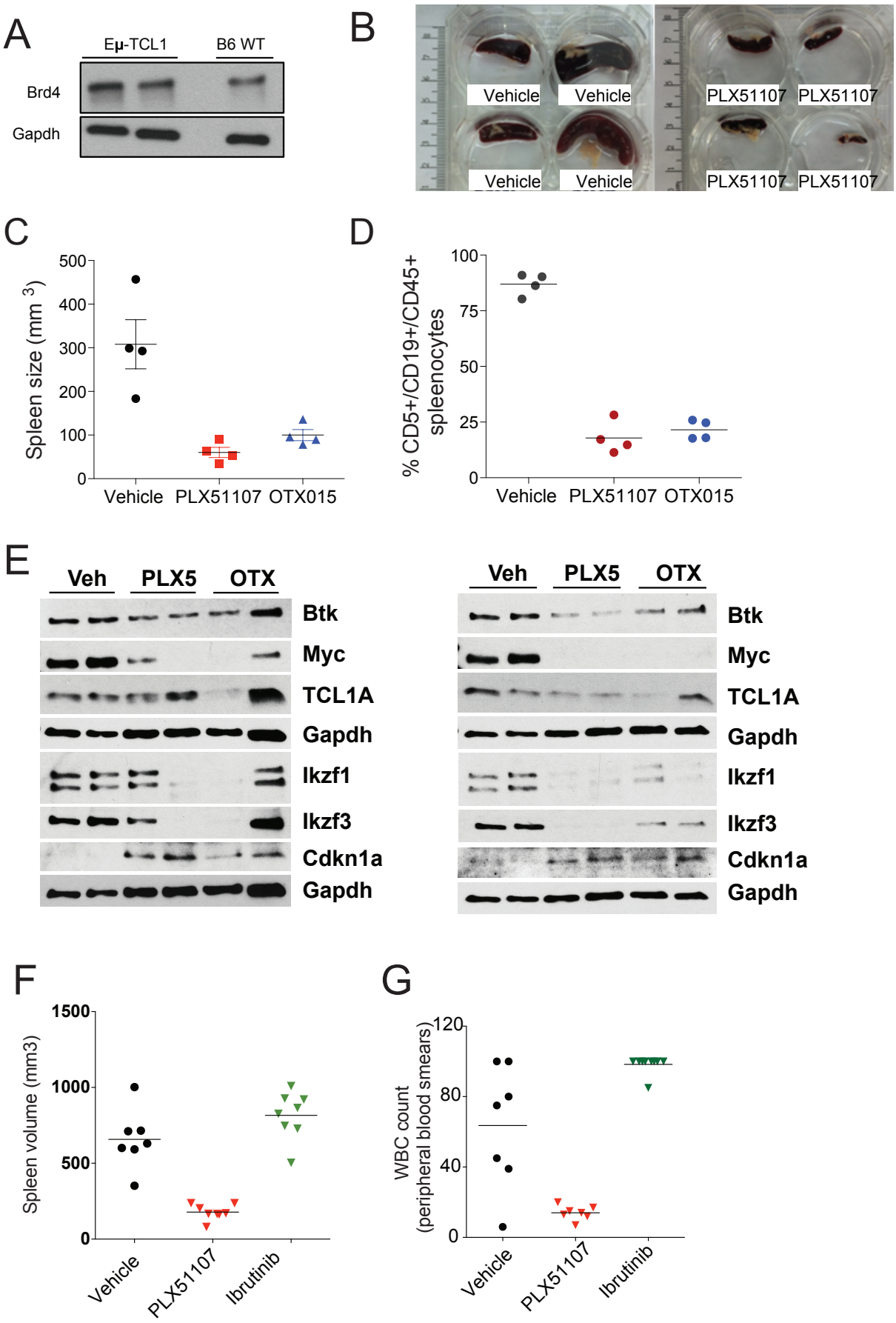

A
Eμ-TCL1
B6 WT
Brd4
Gapdh
B
Vehicle
Vehicle
PLX51107
PLX51107
Vehicle
Vehicle
PLX51107
PLX51107
C
Spleen size (mm 3)
500
400
300
200
100
0
Vehicle
PLX51107
OTX015
D
% CD5+/CD19+/CD45+ spleenocytes
100
75
50
25
0
Vehicle
PLX51107
OTX015
E
Veh
PLX5
OTX
Btk
Myc
TCL1A
Gapdh
Ikzf1
Ikzf3
Cdkn1a
Gapdh
Veh
PLX5
OTX
Btk
Myc
TCL1A
Gapdh
Ikzf1
Ikzf3
Cdkn1a
Gapdh
F
Spleen volume (mm3)
1500
1000
500
0
Vehicle
PLX51107
Ibrutinib
G
WBC count (peripheral blood smears)
120
80
40
0
Vehicle
PLX51107
Ibrutinib

Figure S6

**Figure S6: Targeting BRD4 in transgenic mouse models of B-cell malignancies. A.** Immunoblot analysis of BRD4 expression in CD19 positive B-cells isolated from spleens of leukemic Eμ-TCL1A mice and C56BL/6 wild type mouse (WT, 12 mo); GAPDH is used as loading control**. B.** Splenocytes derived from Eμ-TCL1A mice were cultured in vitro with or without increasing concentration of PLX51107 for 48h. Effects on proliferation were determined by MTS assay and represented as % of vehicle control. Results shown as mean ± SD of n=3 independent experiments; **C.** Splenocytes derived from Eμ-TCL1A mice were cultured in vitro with or without increasing concentration of PLX51107 for 8h. *TCL1* mRNA transcript derived from the Eμ-TCL1 transgene, *Hexim1* and *Myc* were assessed using qRT-PCR. Endogenous *Tcl1* expression (not shown) was also measured and was undetermined as previously described in this model; **D.** Decreased spleen size of PLX51107-treated Eμ-TCL1 mice *vs.* vehicle control following an 8 day treatment (PLX51107: 20 mg/kg, qd, oral gavage); **E.** Caliper-derived spleen volumes of mice treated with PLX51107 (20 mg/kg, qd, oral gavage), OTX015 (50 mg/kg, qd, oral gavage) or vehicle control for 30 days. Spleen volumes were measured at time of death using a manual caliper (with 1mm error). Splenic volume was then calculated using the standard clinical ellipsoid equation of length × width × thickness × 0.523; **F.** Flow cytometry analysis of CD19/CD5/CD45 positive peripheral blood cells of mice treated for 30 days with PLX51107, OTX15 or vehicle control BL; **G.** Representative immunoblot analysis of relative protein levels of Btk, Myc, TCL1A, Ikzf1, Ikzf3, and Cdkn1a in splenocytes derived from mice treated with PLX51107, OTX15 or vehicle control for 30 days; **H-I**. Using an adoptive transfer model of Eμ-TCL1, recipient wild type mice were randomized to receive vehicle Ibrutinib or PLX51107 (20 mg/kg, qd, oral gavage) at leukemia onset. Disease progression was measured by flow cytometry as % CD19/CD5/CD45 positive PBL: PLX51107 reduced spleen mass (F), and decreased % of circulating leukemic PBL as measured at time of death (G).

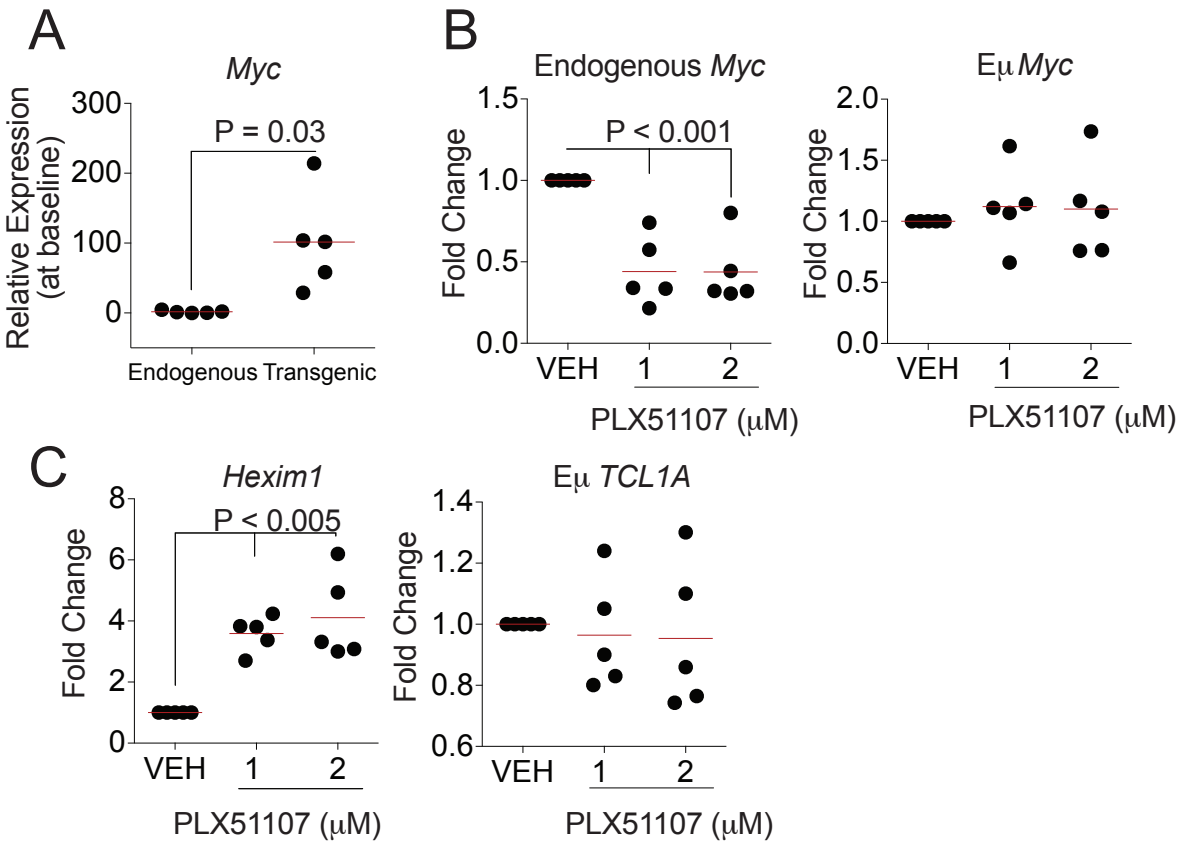



Figure S7

**Figure S7: BRD4 target modulation in a disease model of aggressive CLL and Richter's Transformation: A-C)** Splenocytes derived from E*μ*-Myc/TCL1 mice were cultured in vitro. *Myc* mRNA transcript derived from the E*μ-Myc* transgene or the endogenous *Myc* locus was assessed using qRT-PCR at baseline (A) or following 8h exposure to either DMSO (vehicle) or PLX51107 (B) Transcript levels of Hexim1 and E*μ*-TCL1 transgene following 8h exposure to either DMSO (vehicle) or PLX51107.

## SUPPLEMENTARY TABLES

### Table S1. Characteristic of patients used for the in vitro studies.

| Fig. 1A | IgVH mutational status (%) | Karyotype | Cytogenetics | | | | Treatment Status |
|---|---|---|---|---|---|---|---|
| | | | 17p | 11q | 13q | 12q | |
| **250672** | U (0) | 49,XY,+X,add(1)(q21),dic(1;17)(p12;p11.2),t(2;14)(p13;q32.3),+4,add(4)(p12)x2,+6,add(6)(p21),psu dic(8;6)(q24;q12),der(9)t(1;9)(p22;p13),+11,+12,t(19;22)(q13.3;q11.2)[cp25]/50,sl,+15[5].ish add(6)(D6Z1+,SEC63+),dic(8;6)(D6Z1+,SEC63-) | pos | pos | neg | pos | T |
| **251161** | M (10) | 46,XX,t(7;8)(p15;q24.1),del(13)(q12q14)[9]/47,XX,+X[2]/46,XX[7]/nonclonal[1] | neg | neg | pos | neg | T |
| **251806** | U (0) | 46,XX,del(11)(q21q23)[3]/46,XX[16]/nonclonal[1] | neg | pos | pos | neg | T |
| **251868** | U (0) | 43-46,XX,del(11)(q14q23),del(13)(q12q14)[cp2]/46,XX[12]/nonclonal[1] | neg | post | pos | neg | T |
| **250782** | U (2.2) | 46,XX,add(10)(q24),add(19)(p13.3)[cp3]/45,sl,-X[cp8]/46,X,del(X)(q22)[cp2]/46,XX,del(13)(q22q34)[cp2]/46,XX[2]/nonclonal[3] | pos | neg | pos | neg | T |
| **250547** | M (8.9) | 46,XX(19)/nonclonal(1) | pos | neg | pos | neg | Unt |

| Fig. S1A | IgVH mutational status (%) | Karyotype | Cytogenetics | | | | Treatment Status |
|---|---|---|---|---|---|---|---|
| | | | 17p | 11q | 13q | 12q | |
| **250751** | M (*) | 46,XX[19]/nonclonal[1] | neg | neg | pos | neg | T |
| **251600** | U (0) | 46,XY[20] | neg | pos | pos | neg | T |
| **251308** | M (7.8) | 46,XY[20] | neg | neg | pos | neg | Unt |
| **250872** | M (4.1) | 46,XX[20] | neg | neg | pos | neg | Unt |
| **250622** | M (4.4) | 46,XX[19]/nonclonal[1] | | | | | Unt |
| **250789** | U (0) | 48,XX,dup(1)(q12q32),inv(7)(p13q22),t(14;19)(q32;q13.3),+15,+21[17]/nonclonal with clonal abnormalities[3].ish t(14;19)(3 (sq) IGH+;3 (sq) IGH+,5 (sq) IGH+) | neg | neg | neg | neg | T |
| **250749** | U (0) | 44,XY,add(3)(p26),der(11)t(11;15)(q21;q13),del(12)(q22),-15,dic(17;18)(p11.2;p11.2)[cp10]/46,XY[9]/nonclonal[1]Previously described as: 44,XY,add(3)(p26),der(11)t(11;15)(q21;q13),del(12)(q22),-15,der(17;18)(q10;q10)[cp10]/46,XY[9]/nonclonal[1] | pos | pos | pos | neg | T |
| **250967** | U (*) | 38-41,XX,ider(2)(p10)add(2)(p23),add(3)(p21),-4[8],del(4)(q13)[5],add(7)(q36),-8,-9,der(11)add(11)(p15)add(11)(q21),-13,- | pot | pos | pos | neg | T |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 13,-14,-15,-17,der(19)t(13;19)(q14;p13.3),-21,-22,-22,+mar1-12,inc[cp19, one is 4n]/46,XX[1] | | | | | |

| Fig. S4A | IgVH mutational status | Karyotype | Cytogenetics | | | | Treatment Status* |
|---|---|---|---|---|---|---|---|
| | | | 17p | 11q | 13q | 12q | |
| **250486** | M (5) | 46,XX,der(13)t(13;17)(q14;q11.2)ins(13;?)(q14;?),der(17t(13;17)(q14;q11.2)[20] | neg | neg | neg | neg | T |
| **250510** | M (11.53) | 46,XY[20] | neg | neg | pos | neg | Unt |
| **251186** | U (0.3) | 46,XY,t(1;3)(p34;q12)[2]/46,XY[18] | neg | neg | pos | neg | Unt |
| **251847** | U (1.4) | 48,XY,+7,add(7)(q22),+12[20] | neg | neg | neg | pos | Unt |
| **251900** | U (0) | 45,XX,dic(4;18)(p12;p11.3),del(11)(q13.3q23.3)[cp2]/45,sl,add(12)(q24.3)[9]/45,sdl1,add(15)(q26)[2]/45,sdl2,+12,-add(12)[5]/45,sdl3,add(5)(q35)[cp2] | neg | pos | pos | neg | Unt |
| **250236** | U (0) | 46,XY,dic(11;17)(p11.2;p11.2),+mar1[4]/46,sl,-dic(11;17),+11[cp3]/46,XY[10]/nonclonal[3] | pos | neg | pos | neg | T |
| **250547** | U (*)_ | 46,XX[19]/nonclonal[1] | pos | neg | pos | neg | Unt |
| **250720** | M (7.14) | 46,XY,t(13;17)(q14;p13)[cp6,one is 4n]/46,sl,add(9)(q34)[cp3]/46,XY,der(17)t(2;17)(p11.2;p11.2)[cp5]/45,XY,t(3;4)(q21;q35),del(11)(q21),-17[3]/46,XY[1]/nonclonal[2] | pos | pos | neg | neg | Unt |
| **251608** | M (5.1) | 46,X,t(X;8)(q28;q22),del(6)(q15q21),inv(11)(p15q23)[6]/nonclonal w/clonal abnormalities[2]/46,XX[11]/nonclonal[1] | neg | neg | pos | neg | T |
| **252097** | M (6.1) | 45,X,-Y,del(21)(q21.1q22)[17]/nonclonal w/clonal abnormalities[2]/46,XY[1] | neg | neg | pos | neg | Unt |

| Fig 4G and S3D | IgVH mutational status | Karyotype | Cytogenetics | | | | Treatment Status* |
|---|---|---|---|---|---|---|---|
| | | | 17p | 11q | 13q | 12q | |
| **251032** | U (0.3) | 45,XX,dic(4;17)(p11;p11.2)[12]/46,XX,t(13;16)(q14;q24)[2]/46,XX[6] | pos | neg | pos | neg | T |
| **251201** | U (0) | 46,XY,add(11)(q22)[6]/46,XY[13]/4n[1] | neg | pos | neg | neg | Unt |
| **251495** | M (8) | 46,XX[20] | neg | neg | pos | neg | Unt |
| **251725** | U (0) | 46,XY[20] | neg | neg | neg | neg | Unt |
| **252026** | M (3) | 44-76,XY,-15,der(17)t(15;17)(q12;p12)[cp5,one is 4n]/40-45,XY,der(3)t(2;3)(p13;p21),-6,add(17)(p13)[cp5]/46,XY[4]nonclonal[1].ish der(3)t(2;3)(REL+),nuc ish(D4Z1x2,D6Z1x1)[40/210] | pos | pos | pos | neg | Unt |
| **251045** | U (*)_ | 46,XY[19]/nonclonal[1] | neg | neg | pos | neg | T |
| **251180** | M (4.8) | 46,XY[19]/nonclonal[1] | neg | neg | pos | neg | Unt |
| **251749** | U (0) | Insufficient Metaphases (46,XY[3]/nonclonal[1]) | neg | neg | pos | neg | T |
| **252502** | M (6.1) | 46,XX[18]/nonclonal[2] | neg | neg | pos | neg | Unt |
| **250810** | U (0) | 46,XX,del(10)(q23q25)[3]/45,X,-X[cp4]/46,XX[13] | neg | neg | neg | neg | T |

| ChIP-seq and ATAC-seq | IgVH mutational status | Karyotype | Cytogenetics | | | | Treatment Status* |
|---|---|---|---|---|---|---|---|
| | | | 17p | 11q | 13q | 12q | |
| **251177** | U (0) | 46,XY,del(11)(q14q23)[11]/nonclonal w/clonal abnormalities[6]/46,XY[2]/nonclonal[1] | neg | pos | neg | neg | T |
| **252089** | U (0.8) | 47,XX,+12[20] | neg | neg | neg | pos | Unt |
| **250808** | U (*) | 46,XX[20] | neg | neg | pos | neg | Unt |
| **251025** | U (*)_ | 46,XY[30] | neg | neg | pos | neg | Unt |

| Fig 4G, S3C, and S4C | IgVH mutational status | Karyotype | Cytogenetics | | | | Treatment Status* |
|---|---|---|---|---|---|---|---|
| | | | 17p | 11q | 13q | 12q | |
| **252405** | U (0) | 45,XX,dic(17;18)(p11.2;p11.2)[5]/46,XX[15]/nonclonal[2] | pos | neg | neg | neg | T |
| **252099** | M (11.1) | 46,XX,del(13)(q12q14)[4]/46,XX[15]/nonclonal[1] | neg | neg | pos | neg | Unt |
| **251692** | U (*)_ | 46,XY[20] | neg | neg | pos | neg | T |
| **252436** | U (0) | 46,XX[21] | neg | pos | neg | neg | Unt |
| **252108** | M (4.7) | 45,X,-X[10]/45,sl,t(10;13)(q22;q14)[2]/46,XX[8] | neg | neg | pos | neg | Unt |

| Fig 3C | IgVH mutational status | Karyotype | Cytogenetics | | | | Treatment Status* |
|---|---|---|---|---|---|---|---|
| | | | 17p | 11q | 13q | 12q | |
| **250468** | U (*)_ | 45,X,-Y,t(11;14)(q13;q32.3)[18]/46,XY[2] | neg | pos | neg | neg | Unt |
| **251915** | U (1.4) | 46,XY,del(11)(q21q23)[16]/nonclonal w/del(11q)[1]/46,XY[2]/nonclonal[1] | neg | pos | pos | neg | Unt |
| **252087** | U (0) | 47,XX,+12[19]/46,XX[1] | neg | pos | pos | pos | Unt |
| **250169** | U (*)_ | 47,XY,+12[12]/nonclonal w/ clonal abnormalities[1]/46,XY[6]/nonclonal[1] | neg | pos | pos | pos | T |
| **250236** | U (0) | 46,XY,dic(11;17)(p11.2;p11.2),+mar1[6]/43-45,sl,-dic(11;17),+11[cp2]/46,sdl,-mar1,+mar2[2]/46,XY[10]/nonclonal[8] | pos | neg | pos | neg | T |
| **250529** | U (2.36) | 46,XY[29]/nonclonal[1] | neg | neg | pos | pos | Unt |
| **250955** | M (6) | 46,XY[20] | neg | neg | pos | pos | Unt |
| **251013** | U (0.7) | 47,XX,+12[10]/47,sl,del(6)(q13q25)[6]/nonclonal w/ clonal abnormalities[1]/46,XX[3] | neg | neg | neg | pos | Unt |
| **251383** | U (*)_ | 47,XY,+12[1]/45-46,sl,dic(8;17)(p11.2;p11.2)[14]/nonclonal w/clonal abnormalities[1]/46,XY[4] | pos | neg | neg | pos | Unt |
| **251606** | U (0.3) | 46,XX,i(17)(q10)[cp1]/45,sl,-9,-10,+mar1[cp1]/46,XX,-14,add(17)(p11.2),-18,-21,+r,+mar2,+mar3[cp18, one is 4n]/46,XX[7]/nonclonal[2] | pos | neg | pos | neg | Unt |
| **251725** | U (0) | 46,XY[20] | neg | neg | neg | neg | Unt |
| **251975** | M (4.8) | 47,XY,+12[3]/46,XY[17] | neg | neg | pos | pos | Unt |
| **252099** | M (11.1) | 46,XX,del(13)(q12q14)[4]/46,XX[15]/nonclonal[1] | neg | neg | pos | neg | Unt |

| Fig S3A, and | IgVH | Karyotype | Cytogenetics | Treatment |
|---|---|---|---|---|

| S3B | mutational status | | 17p | 11q | 13q | 12q | Status |
|---|---|---|---|---|---|---|---|
| 250262 | U (0.3) | 46,XY[19]/nonclonal[1] | neg | neg | pos | neg | T |
| 250776 | U (0) | 46,XY,del(11)(q21q23)[2]/46,XY,dic(8;12)(p11.2;p11.2),+12[cp2]/46,XY[15]/nonclonal[1] | neg | pos | pos | pos | T |
| 251161 | M (10.9) | 46,XX,t(7;8)(p15;q24.1),del(13)(q12q14)[12] | neg | neg | pos | neg | Unt |
| 251606 | U (0.3) | 46,XX,i(17)(q10)[2]/45,sl,-9,-10,+mar[12]/90,sdlx2[3]/nonclonal w/clonal abnormalities[1]/nonclonal[2] | pos | neg | pos | neg | Unt |

| Fig 3A, and 3B | IgVH mutational status | Karyotype | Cytogenetics | | | | Treatment Status |
|---|---|---|---|---|---|---|---|
| | | | 17p | 11q | 13q | 12q | |
| 251476 | U (1) | N/A | neg | neg | pos | neg | Unt |
| 251751 | U (1) | N/A | neg | neg | pos | neg | Unt |
| 252535 | U (*) | 47,XY,+2,del(2)(q31q35),del(11)(q13q23)[2,one w/nonclonal abnormalities]/46,sl,-del(2),add(2)(p23),del(13)(q12q14)[5,two w/nonclonal abnormalities]/46,XY[12]/nonclonal[1] | neg | pos | pos | neg | Unt |
| 252053 | U (*) | 46,XY,del(13)(q12q14)[10]/46,sl,del(11)(q21q23)[3]/46,sdl1,t(5;19)(q11.2;q12)[2]/46,sl,add(17)(q25)[2]/46,XY[3]Previously reported as:46,XY,del(13)(q12q14)[10]/46,sl,del(11)(q13q23)[3]/46,sdl1,t(5;19)(q11.2;q12)[2]/46,sl,add(17)(q25)[2]/46,XY[3] | neg | pos | pos | neg | Unt |
| 251843 | U (0.3) | 46,XX,t(9;13)(q33;q12)[2]/46,sl,der(11)inv(11)(p15q13)del(11)(q22q23)[5]/46,XX,del(13)(q14.1q14.3)[3]/46,XX[10] | neg | pos | pos | neg | T |

* Test for IgVH mutational status was preformed but no % was documented; U (unmutated IgVH mutational status); M (mutated IgVH mutational status); pos (positive); neg (negative); T (treated patient); Unt (Untreated patient); NA (information not available).

**Table S2.** Top functional annotations of 764 genes common to super-enhancers (SEs) of at least three out of four samples by DAVID Functional Annotation Tool.

| Annotation Term | Genes | p-value | FDR |
|---|---|---|---|
| **GO Biological Process Enrichment** | | | |
| B cell receptor signaling pathway | IGHG2, PTPN6, IGLC7, BLK, IGLC6, TRDC, IGHM, IGHD, BCL2, IGHE, IGHA1, IGHA2, IGKC | 4.01E-10 | 6.78E-07 |
| Positive regulation of B cell activation | IGHG2, IGLC7, IGHD, IGHE, IGLC6, IGHA1, IGHA2, TRDC, IGKC, IGHM | 8.43E-10 | 1.42E-06 |
| Phagocytosis, recognition | IGHG2, IGLC7, IGHD, IGHE, IGLC6, IGHA1, IGHA2, TRDC, IGKC, IGHM | 1.80E-09 | 3.04E-06 |
| Immune response | TNF, IL19, TNFRSF8, TNFSF13, TNFSF12, HLA-DMA, TNFRSF4, IL10, CHIT1, B2M, TNFRSF1B, CXCR5, IL4R, TNFRSF18, IGHA1, NRROS, IGHA2, IGKC, LTB, LTA, CIITA, IL2RA, IL24, HLA-DQA1, SERPINB9, CCR7, IGHD, IRF8, IGHE, TNFSF12-TNFSF13 | 4.04E-09 | 6.82E-06 |
| Phagocytosis, | IGHG2, IGLC7, IGHD, IGHE, IGLC6, | 1.63E- | 2.76E-05 |

| | | | |
|---|---|---|---|
| engulfment | IGHA1, IGHA2, TRDC, IGKC, IGHM | 08 | |
| Negative regulation of transcription from RNA polymerase II promoter | TNF, USP3, SPI1, PAX5, CBX7, NR1H2, HEXIM2, ATN1, HEXIM1, BCL11A, SOX15, BCL6, SUPT4H1, TCF4, ETV6, BCOR, CIITA, ZFP36, ZBTB20, IKZF1, ARID5B, KLF16, SPEN, TMPRSS6, JUNB, FOXP1, PLK3, BTG2, IRF8, JAZF1, TGIF1, PAF1, ZFPM1, ID3 | 4.75E-06 | 0.00803 |
| Negative regulation of transposition | APOBEC3G, APOBEC3H, APOBEC3F, APOBEC3C, APOBEC3D | 9.29E-06 | 0.0157 |
| **GO Molecular Function Enrichment** | | | |
| Immunoglobulin receptor binding | IGHG2, IGLC7, IGHD, IGHE, IGLC6, IGHA1, IGHA2, TRDC, IGKC, IGHM | 9.44E-10 | 1.37E-06 |
| Protein binding | 212 Genes | 1.66E-05 | 0.0241 |
| Tumor necrosis factor receptor binding | TRAF1, TNF, TNFSF13, TNFSF12, LTB, LTA, TRAF4 | 1.82E-05 | 0.02643 |
| Antigen binding | IGHG2, IGLC7, IGHD, IGHE, IGLC6, IGHA1, IGHA2, FCGRT, TRDC, IGKC, IGHM | 3.63E-05 | 0.05255 |
| Hydrolase activity, acting on carbon-nitrogen bonds, in cyclic amidines | APOBEC3G, APOBEC3H, APOBEC3F, APOBEC3C, APOBEC3D | 4.40E-05 | 0.06374 |
| **GO Cellular Component Enrichment** | | | |
| External side of plasma membrane | IGHG2, IL2RB, TNF, IL2RA, IGLC7, IGLC6, TNFRSF13C, TRDC, IGHM, PDCD1, B2M, CD83, CCR7, ECE1, CXCR5, IGHD, IGHE, IGHA1, IGHA2, IGKC | 2.75E-08 | 3.72E-05 |
| Immunoglobulin complex, circulating | IGHG2, IGLC7, IGHD, IGHE, IGLC6, TRDC, IGKC | 1.00E-06 | 0.00136 |
| Cytoplasmic mRNA processing body | ZFP36, ZFP36L1, PATL2, APOBEC3G, LSM2, APOBEC3H, APOBEC3F, ZC3H12D, APOBEC3D, SAMD4B, DDX6 | 2.20E-06 | 0.00297 |
| Blood microparticle | IGHG2, IGLC7, IGLC6, HSPA1A, HSPA1B, TRDC, IGHM, HSPA1L, PFN1, IGHD, IGHE, IGHA1, IGHA2, IGKC | 7.01E-06 | 0.00949 |
| **KEGG Pathway Enrichment** | | | |
| Cytokine-cytokine receptor interaction | IL2RB, TNF, IL2RA, IL21R, TNFRSF13C, TNFRSF8, TNFSF13, TNFSF12, TNFRSF4, IL10, FLT3LG, TNFRSF1B, CCR7, CXCR5, CXCR4, IL10RA, IL4R, TNFRSF18, LTB, LTA | 1.66E-06 | 0.00207 |

**Table S3: Crystallography data collection and refinement statistics**

| | BRD4-PLX5981 (PDB: 5WMA) | BRD4$^{D96A}$-PLX51107 (PDB: 5WMG) | BRD4$^{D96A}$-OTX015 (PDB: 5WMD) |
|---|---|---|---|
| **Data collection** | | | |
| Space group | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ |

| | | | |
|---|---|---|---|
| Cell dimensions | | | |
| *a*, *b*, *c* (Å) | 39.2, 44.5, 78.3 | 38.8, 42.2, 92.4 | 36.9, 44.6, 77.8 |
| Resolution (Å)[a] | 78.6-1.40 (1.45-1.40) | 24.9-1.15 (1.19-1.15) | 21.2-1.18 (1.22-1.18) |
| $R_{sym}$ or $R_{merge}$ | 0.111 (0.558) | 0.04 (0.486) | 0.037 (0.239) |
| $I/\sigma I$ | 9.8 (3.3) | 20.8 (2.5) | 25.5 (6.7) |
| Completeness (%) | 99.9 (100.0) | 94.3 (70.3) | 93.6 (79.8) |
| Redundancy | 5.6 (5.6) | 5.7 (4.0) | 5.9 (5.5) |
| **Refinement** | | | |
| Resolution (Å) | 38.7-1.40 | 24.1-1.19 | 21.2-1.27 |
| No. reflections | 26,187 | 48,029 | 33,012 |
| $R_{work}$/ $R_{free}$ | 0.146/0.176 | 0.130/0.146 | 0.145/0.170 |
| R.m.s deviations | | | |
| Bond lengths (Å) | 0.004 | 0.004 | 0.012 |
| Bond angles (°) | 1.0 | 1.0 | 1.5 |
| Most favored region (%)[b] | 99.2 | 98.3 | 96.7 |
| Additional allowed region | 0.8 | 1.7 | 3.3 |
| Disallowed region (%)[b] | 0.0 | 0.0 | 0.0 |

[a]Highest resolution shell is shown in parenthesis.

[b]In the Ramachandran plot

**Table S4: Single concentration binding assays and $K_d$ measurements for PLX51107 against 32 bromodomains.**

| Domain [a] | Bromodomain Protein Name | %Inhibition at 1 µM | $K_d$ (nM) |
|---|---|---|---|
| BRD2(1) | bromodomain-containing protein 2, bromodomain 1 | 100 | 1.6 |
| BRD2(2) | bromodomain-containing protein 2, bromodomain 2 | 100 | 5.9 |
| BRD3(1) | bromodomain-containing protein 3, bromodomain 1 | 100 | 2.1 |
| BRD3(2) | bromodomain-containing protein 3, bromodomain 2 | 100 | 6.2 |
| BRD4(1) | bromodomain-containing protein 4, bromodomain 1 | 100 | 1.7 |
| BRD4(2) | bromodomain-containing protein 4, bromodomain 2 | 100 | 6.1 |
| BRDT(1) | bromodomain testis-specific protein, bromodomain 1 | 90 | 5.0 |
| BRDT(2) | bromodomain testis-specific protein, bromodomain 2 | 97 | 120 |
| CREBBP | CREB binding protein | 100 | 110 |
| EP300 | E1A binding protein p300 | 100 | 130 |
| TAF1(2) | TATA box binding protein (TBP)-associated factor 1, bromodomain 2 | 48 | 2,200 |
| SMARCA4 | SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 | 60 | >10,000 |
| CECR2 | cat eye syndrome chromosome region, candidate 2 | 37 | NA |

| Domain [a] | Bromodomain Protein Name | %Inhibition at 1 μM | $K_d$ (nM) |
|---|---|---|---|
| WDR9(2) | bromodomain and WD repeat domain containing 1, bromodomain 2 | 36 | NA |
| GCN5L2 | GCN5 like 2 or K(lysine) acetyltransferase 2A (KAT2A) | 30 | NA |
| BAZ2A | bromodomain adjacent to zinc finger domain, 2A | 29 | NA |
| BRD9 | bromodomain-containing protein 9 | 28 | NA |
| PBRM1(5) | polybromo 1, bromodomain 5 | 25 | NA |
| TRIM24 | tripartite motif containing 24 (PHD+bromodomain) | 23 | NA |
| BAZ2B | bromodomain adjacent to zinc finger domain, 2B | 23 | NA |
| TRIM33 | tripartite motif containing 33 (PHD+bromodomain) | 15 | NA |
| SMARCA2 | SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2 | 11 | NA |
| BRPF3 | bromodomain and PHD finger containing, 3 | 10 | NA |
| BRD7 | bromodomain containing 7 | 10 | NA |
| PCAF | P300/CBP-associated factor or K(lysine) acetyltransferase 2B (KAT2B) | 6 | NA |
| PBRM1(2) | polybromo 1, bromodomain 2 | 0 | NA |
| ATAD2A | ATPase family AAA domain containing 2 | 0 | NA |
| ATAD2B | ATPase family AAA domain containing 2B | 0 | NA |
| BRD1 | bromodomain-containing protein 1 | 0 | NA |
| BRPF1 | bromodomain and PHD finger containing, 1 | 0 | NA |
| BPTF | bromodomain PHD finger transcription factor, also known as FALZ | 0 | NA |
| TAF1L(2) | TATA box binding protein (TBP)-associated factor 1L, bromodomain 2 | 0 | NA |

[a] Each assay used a truncated protein that includes a single bromodomain (value in parentheses indicates which bromodomain is used when the full length protein contains two bromodomains; 1 stands for BD1 and 2 stands for BD2). [b] Single concentration (at 1 μM) primary screening data for all 32 bromodomains are presented as percentage of inhibition. [c] Kd values for 12 bromodomains that exhibited >50% inhibition in the primary screen. Assays that showed <50% inhibition at 1 μM were not pursued for Kd determination (NA)

**Table S5:** Profiling PLX51107 in Genscript Leukemia and Lymphoma panel reveals broad activity in various malignant cell lines.

| Cell Line | Histologic Type | $IC_{50}$ (μM) | 95% CI (μM) |
|---|---|---|---|
| CCRF-CEM | Leukemia, acute lymphoblastic | 0.020 | 0.015 - 0.027 |
| RPMI 8226 | Myeloma, plasmacytoma | 0.020 | 0.015 - 0.027 |
| MV4-11 | Leukemia, biphenotypic B myelomonocytic | 0.031 | 0.029 - 0.032 |
| 8E5 | Leukemia, acute lymphoblastic | 0.051 | 0.032 - 0.081 |
| SC | Monocyte/Macrophage | 0.056 | 0.036 - 0.088 |
| KE-37 | Leukemia, T cell | 0.067 | 0.054 - 0.083 |
| HuT 78 | Lymphoma | 0.067 | 0.050 - 0.090 |
| Loucy | Leukemia, acute lymphoblastic t(16;20) | 0.084 | 0.067 - 0.11 |

| Cell Line | Histologic Type | $IC_{50}$ (μM) | 95% CI (μM) |
|---|---|---|---|
| | translocation | | |
| BDCM | Leukemia, acute myelogenous | 0.084 | 0.055 - 0.13 |
| RL | Lymphoma, non-Hodgkin's | 0.091 | 0.071 - 0.12 |
| J.RT3-T3.5 | Leukemia, acute T cell | 0.10 | 0.081 - 0.13 |
| CA46 | Lymphoma, Burkitt's | 0.11 | 0.076 - 0.16 |
| BC-1 | Lymphoma, EBV and KSHV positive | 0.11 | 0.068 - 0.19 |
| DOHH2 | Lymphoma | 0.12 | 0.096 - 0.14 |
| EOL-1 | Lymphoma | 0.12 | 0.092 - 0.16 |
| CEM/C2 | Leukemia, acute lymphoblastic | 0.14 | 0.11 - 0.18 |
| K562 | Leukemia, myelogenous | 0.15 | 0.10 - 0.23 |
| MOLT-4 | Leukemia, acute lymphoblastic | 0.16 | 0.089 - 0.27 |
| P3HR-1 | Lymphoma, Burkitt's | 0.16 | 0.13 - 0.21 |
| Kasumi-1 | Leukemia, acute myeloblastic | 0.18 | 0.14 - 0.23 |
| MPC-11 | Myeloma, Mouse | 0.19 | 0.14 - 0.26 |
| H9 | Lymphoma, cutaneous | 0.22 | 0.20 - 0.24 |
| Mo | Leukemia, hairy cell | 0.23 | 0.16 - 0.32 |
| CEM/C3 | Leukemia, acute lymphoblastic | 0.24 | 0.18 - 0.31 |
| MJ | Lymphoma, cutaneous T cell, mycosis fungoides | 0.24 | 0.18 - 0.32 |
| JVM-2 | Leukemia | 0.24 | 0.15 - 0.40 |
| HH | Lymphoma, cutaneous T cell | 0.25 | 0.15 - 0.39 |
| TF-1 | Erythroleukemia | 0.26 | 0.16 - 0.43 |
| KU812 | Leukemia, chronic myelogenous | 0.27 | 0.19 - 0.36 |
| AHH-1 | Lymphoblastoid | 0.30 | 0.22 - 0.41 |
| GDM-1 | Leukemia, myelomonoblastic | 0.34 | 0.23 - 0.48 |
| MOLT-3 | Leukemia, acute lymphoblastic | 0.39 | 0.21 - 0.73 |
| KG-1 | Leukemia, acute lymphoblastic | 0.39 | 0.22 - 0.70 |
| RPMI 7666 | Lymphoblast | 0.43 | 0.25 - 0.74 |
| Daudi | Lymphoma, Burkitt's | 0.45 | 0.37 - 0.54 |
| CESS | Leukemia, myelomonocytic | 0.49 | 0.29 - 0.84 |
| HL-60 clone15 | Leukemia, Acute promyelocytic | 0.49 | 0.43 - 0.57 |
| GK-5 | B lymphoblast; Epstein-Barr virus (EBV) transformed | 0.53 | 0.30 - 0.91 |
| ARH-77 | Leukemia, plasma cell | 0.57 | 0.27 - 1.20 |

| Cell Line | Histologic Type | $IC_{50}$ (μM) | 95% CI (μM) |
|---|---|---|---|
| CEM/C1 | Leukemia, acute lymphoblastic | 0.58 | 0.39 - 0.84 |
| HL-60 | Leukemia, promyelocytic | 0.61 | 0.54 - 0.68 |
| D1.1 | Leukemia, acute T cell, CD4 negative | 0.62 | 0.25 - 1.52 |
| P116 | Leukemia, acute T cell | 0.62 | 0.37 - 1.03 |
| SUP-B15 | Leukemia, acute lymphoblastic | 0.63 | 0.38 - 1.04 |
| Jurkat | Leukemia, acute T cell | 0.67 | 0.42 - 1.08 |
| KU 812 E | Leukemia, chronic myelogenous | 0.73 | 0.63 - 0.84 |
| CCRF-HSB-2 | Leukemia, acute lymphoblastic | 0.82 | 0.52 - 1.28 |
| WIL2-S | B lymphoblast, hereditary spherocytosis, spleen | 0.93 | 0.63 - 1.39 |
| MC116 | Lymphoma, undifferentiated | 0.95 | 0.48 - 1.88 |
| J45.01 | Leukemia, acute T cell, CD45 deficient | 0.99 | 0.70 - 1.40 |
| P116.cl39 | Leukemia, acute T cell | 1.88 | 0.80 - 4.41 |
| Ramos.2G6.4C10 | Lymphoma, Burkitt's | 1.91 | 0.96 - 3.83 |
| RS4;11 | Leukemia, acute lymphoblastic, t(4;11) translocation | 2.13 | 0.73 - 6.16 |
| CML-T1 | Leukemia, T-lymphocyte, chronic myelogenous | ~2.5 [a] | NA |
| SU-DHL-6 | Lymphoblast-like, peritoneal effusion | 2.86 | 0.86 - 9.46 |
| I 9.2 | Leukemia, acute T cell | 2.88 | 0.94 - 8.77 |
| TALL-1 | Lymphoma, T cell | 3.30 | 1.60 - 6.84 |
| SUP-T1 | Leukemia, lymphoblastic | 3.70 | 1.60 - 8.56 |
| Raji | Lymphoma, Burkitt's | 4.00 | 2.45 - 6.51 |
| ST486 | Lymphoma, Burkitt's | 5.19 | 3.00 - 8.99 |
| U266B1 | Myeloma; plasmacytoma | 6.59 | 3.56 - 12.20 |
| U-937 | Lymphoma, histiocytic | 7.58 | 5.42 - 10.62 |
| AML-193 | Leukemia, Acute monocytic | 8.21 | 4.84 - 13.94 |
| Toledo | Lymphoma, diffuse large cell, non-Hodgkin's B cell | 12.06 | 2.25 - 64.51 |
| NAMALWA | Lymphoblastoid | 13.57 | 9.47 - 19.44 |
| EB-1 | Lymphoma, Burkitt's | >20 | NA |
| EB-2 | Lymphoma, Burkitt's | >20 | NA |
| GA-10 | Lymphoma, Burkitt's | >20 | NA |
| NCI-H929 | Myeloma, plasmacytoma | >20 | NA |

[a] Estimated value from incomplete curve.

**Table S6A.** The top 20 canonical pathways identified by IPA for 1361 differentially expressed genes upon BRD4 inhibition in microarray data of CpG-stimulated B-CLL cells (fold change > 2 and $p < 0.01$).

| Ingenuity Canonical Pathways | p-value | Molecules |
|---|---|---|
| B Cell Receptor Signaling | 6.30957E-12 | MAP2K6, RAP2B, RAP2A, POU2F2, NFATC3, PIK3R1, SOS2, PDPK1, PTPRC, PAX5, IKBKB, PIK3CG, CD22, IRS2, RASSF5, GSK3B, MAP2K1, PPP3CA, MAP3K9, MAP3K14, NRAS, CSK, FGFR1, EGR1, MAPK8, IKBKE, MALT1, BCL2L1, CALM1, SYNJ1, FOXO1, SYK, VAV3, IGHG4, MEF2C, MAP2K3, MAP3K3 |
| CD28 Signaling in T Helper Cells | 5.24807E-08 | FYN, NFATC3, CSK, FGFR1, PIK3R1, CHP1, MAPK8, PDPK1, IKBKE, HLA-DQB1, MALT1, ITPR1, CTLA4, PTPRC, IKBKB, CALM1, CD80, PIK3CG, SYK, HLA-DMB, HLA-DOB, CD86, IRS2, MAP2K1, PPP3CA |
| T Cell Receptor Signaling | 1.34896E-07 | FYN, NRAS, NFATC3, CSK, FGFR1, PIK3R1, SOS2, MAPK8, IKBKE, MALT1, CTLA4, PTPRC, TEC, CALM1, IKBKB, TXK, VAV3, RASGRP1, PIK3CG, IRS2, MAP2K1, PPP3CA |
| PKCθ Signaling in T Lymphocytes | 8.31764E-07 | FYN, MAP3K14, MAP3K9, NRAS, NFATC3, FGFR1, PIK3R1, SOS2, CHP1, MAPK8, IKBKE, MALT1, HLA-DQB1, IKBKB, CD80, VAV3, PIK3CG, HLA-DMB, CD86, HLA-DOB, IRS2, MAP3K3, PPP3CA |
| PI3K Signaling in B Lymphocytes | 2.0893E-06 | CD81, FYN, NRAS, NFATC3, PIK3R1, CHP1, PDPK1, IKBKE, ITPR1, MALT1, PTPRC, BLK, CALM1, IKBKB, CD180, VAV3, PIK3CG, SYK, FOXO3, IRS2, MAP2K1, PPP3CA |
| Th1 and Th2 Activation Pathway | 2.13796E-06 | MAP2K6, TNFSF4, ICAM1, NFATC3, CHD4, PIK3R1, HLA-DQB1, NFIL3, NOTCH2, TGFB1, PIK3CG, HLA-DMB, IRS2, STAT1, STAT6, IL10, mir-29, IKZF1, FGFR1, CD80, LTA, IL10RA, S1PR1, CD86, HLA-DOB, JAK3, NOTCH1 |
| CD27 Signaling in Lymphocytes | 2.39883E-06 | MAP2K6, MAP3K14, MAP3K9, APAF1, MAPK8, IKBKE, IKBKB, BCL2L1, BID, MAP2K3, CD27, MAP2K1, MAP3K3 |
| Regulation of IL-2 Expression in Activated and Anergic T Lymphocytes | 4.89779E-06 | FYN, IKBKB, CALM1, NRAS, CD80, NFATC3, TGFB1, VAV3, CHP1, SOS2, MAPK8, TOB1, IKBKE, MALT1, MAP2K1, PPP3CA |
| Th1 Pathway | 1.07152E-05 | MAP2K6, ICAM1, IL10, mir-29, NFATC3, FGFR1, PIK3R1, HLA-DQB1, NFIL3, NOTCH2, CD80, LTA, PIK3CG, HLA-DMB, IL10RA, CD86, HLA-DOB, IRS2, STAT1, JAK3, NOTCH1 |
| CD40 Signaling | 1.34896E-05 | MAP2K6, MAP3K14, ICAM1, FGFR1, PIK3R1, MAPK8, IKBKE, IKBKB, LTA, PIK3CG, IRS2, MAP2K3, JAK3, MAP2K1, FCER2 |
| Germ Cell-Sertoli Cell Junction Signaling | 2.23872E-05 | MAP2K6, TUBA1B, MAP3K14, MAP3K9, NRAS, TUBB4B, FGFR1, PIK3R1, TUBB2A, MAPK8, TUBA4A, PDPK1, TUBA1A, SORBS1, TGFB1, PIK3CG, MAP2K3, IRS2, MTMR2, ACTN4, VCL, MAP3K3, ACTG1, MAP2K1 |
| Death Receptor Signaling | 2.63027E-05 | MAP3K14, MAPK8, APAF1, ZC3HAV1, PARP8, IKBKE, PARP9, IKBKB, PARP15, TIPARP, BID, SPTAN1, CFLAR, MAP4K4, ACTG1, PARP14 |
| NRF2-mediated Oxidative Stress Response | 3.71535E-05 | MAP2K6, NRAS, FGFR1, NQO2, PIK3R1, MAPK8, DNAJC3, GCLC, DNAJC1, SOD1, CLPP, FTL, PIK3CG, VCP, CAT, IRS2, MAP2K3, JUND, DNAJB1, GSK3B, FKBP5, MAP2K1, ENC1, ACTG1, DNAJC7 |
| Docosahexaenoic Acid (DHA) Signaling | 4.57088E-05 | BCL2L1, FOXO1, PIK3CG, PIK3R1, FGFR1, APAF1, BID, PDPK1, IRS2, GSK3B, PNPLA2, |

| | | |
|---|---|---|
| | | APP |
| Granzyme A Signaling | 5.01187E-05 | SET, ANP32A, HIST1H1C, NME1, HIST1H1E, H1FX, HMGB2 |
| Altered T Cell and B Cell Signaling in Rheumatoid Arthritis | 7.76247E-05 | MAP3K14, SLAMF1, IL10, LTB, HLA-DQB1, TLR10, CD80, TGFB1, LTA, TLR1, HLA-DMB, TLR6, CD86, HLA-DOB, TNFRSF13B |
| Role of NFAT in Regulation of the Immune Response | 8.51138E-05 | FYN, NRAS, NFATC3, FGFR1, PIK3R1, SOS2, CHP1, IKBKE, ITPR1, HLA-DQB1, GNAI2, CALM1, IKBKB, CD80, SYK, PIK3CG, HLA-DMB, CD86, HLA-DOB, MEF2C, IRS2, GSK3B, MAP2K1, PPP3CA |
| IL-4 Signaling | 8.91251E-05 | STAT6, NRAS, IL13RA1, NFATC3, FGFR1, PIK3R1, SOS2, HLA-DQB1, SYNJ1, PIK3CG, HLA-DMB, HLA-DOB, IRS2, JAK3, FCER2 |
| Glucocorticoid Receptor Signaling | 0.000102329 | ICAM1, POU2F2, NFATC3, PIK3R1, HSPA1A/HSPA1B, SOS2, GTF2A1, IKBKB, GTF2B, POLR2A, TGFB1, PIK3CG, FOXO3, IRS2, FKBP5, STAT1, MAP2K1, POLR2L, PPP3CA, MAP3K14, NRAS, IL10, FGFR1, CHP1, MAPK8, IKBKE, BCL2L1, TAF5, SMARCA2, PRKACA, JAK3, HLTF |
| UVA-Induced MAPK Signaling | 0.000109648 | NRAS, FGFR1, PIK3R1, MAPK8, ZC3HAV1, PARP8, SMPD1, RPS6KA5, PARP9, BCL2L1, PARP15, TIPARP, PIK3CG, IRS2, STAT1, PARP14 |

**Table S6B.** The top 20 upstream regulators predicted by IPA to be inhibited or activated for 1361 differentially expressed genes upon BRD4 inhibition in microarray data of CpG-stimulated B-CLL cells (fold change > 2 and $p < 0.01$).

| Upstream Regulator | Molecule Type | Predicted Activation State | Activation z-score | p-value of overlap | Target molecules in dataset |
|---|---|---|---|---|---|
| IFNG | cytokine | Inhibited | -5.484 | 0.0000114 | ABCB1, ABCD3, ALOX5AP, APOL6, APP, ARL6IP5, ATP1A1, BCL2L1, BID, BST2, CASP4, CAT, CCL4, CD200, CD80, CD86, CERS6, CFLAR, CIRBP, CLEC2D, CSK, DDIAS, DTX3L, EGR1, EIF2AK2, ERAP2, ERCC8, FCER2, FKBP5, FOXO1, FTL, GART, GBP3, GBP4, GCH1, GLIPR2, GLS, GLUL, GNAI2, HDAC9, HERC6, HLA-DMB, HLA-DOB, HLA-DQB1, HSPA1A/HSPA1B, ICAM1, IER3, IFI16, IFI30, IFIH1, IFIT5, IFITM2, IKBKE, IL10, IL10RA, IRF2, IRF5, IRF7, IRS2, ISG20, ITGAL, ITPR1, JAK3, JUND, KARS, KLF2, KMO, KYNU, LAT2, LPL, LTA, LTB, MAN2A1, MAP2K1, MARCKSL1, MNDA, NCF2, NF1, NMI, NOD2, NOTCH1, OAS2, OAS3, OPN3, P2RY14, PARP9, PECAM1, PLEK, RAD18, RAP2B, RFX5, RTP4, SAMD9, SAMHD1, SELL, SELP, SLAMF1, SLC11A2, SLC12A2, SP110, STAT1, STAT6, TGFB1, TLR1, TLR6, TMEM50B, TRIM21, TXK, WARS, ZFP36 |

| | | | | | |
|---|---|---|---|---|---|
| IFNA2 | cytokine | Inhibited | -3.899 | 0.000000866 | APOL6, BST2, CCDC92, CD69, CD86, DDX60, EIF2AK2, FAM65B, GBP4, HERC6, HSH2D, IFI16, IFIH1, IFIT5, IFITM2, IL10, IRF5, IRF7, ISG20, LILRB2, LILRB4, MAP2K1, OAS2, OAS3, PARP9, SAMD9, SAMHD1, SP110, STAT1, TNFRSF10D, TRIM21, XAF1, ZC3HAV1 |
| IFNL1 | cytokine | Inhibited | -3.628 | 0.00000059 | APOL6, BST2, CD80, DDX60, EIF2AK2, HERC6, IFIH1, IFIT5, IL10, ISG20, OAS2, OAS3, SAMD9, SP110, STAT1, TMEM140, ZC3HAV1 |
| IFNB1 | cytokine | Inhibited | -3.486 | 0.00697 | ANXA5, BCL2L1, BST2, BTN3A3, CCL4, CD80, CD86, EIF2AK2, GBP3, GBP4, HMGB2, IFI16, IFIH1, IL10, IRF7, ISG20, NMI, NOD2, NOTCH1, OAS2, RNASEL, STAT1, TNFSF4, TRIM21, VCL, XAF1 |
| TNF | cytokine | Inhibited | -3.412 | 0.00000104 | ABCD2, ACOX1, AIMP1, ALCAM, ALOX5AP, APAF1, APP, ARID5B, ARL6IP5, ARRDC3, ATP1A1, ATP2B4, BCKDHB, BCL2L1, BID, BST2, BTN3A3, CALR, CASP4, CAT, CCL4, CD5, CD69, CD80, CD86, CERS6, CFLAR, CNR2, COTL1, CPT1A, CRY1, CTLA4, DAG1, DDIAS, DENND2D, DGAT1, DUSP14, DUSP16, EGLN1, EGR1, EIF2AK2, ELK3, ETV5, ETV6, FCER2, FGFR1, FYN, GADD45A, GADD45B, GBP3, GCH1, GCLC, GKAP1, GLS, GM2A, GNAI2, GPX4, GSK3B, HDAC9, HERC1, HEXB, HIVEP1, HSPA1A/HSPA1B, ICAM1, IER3, IFI16, IFIH1, IFIT5, IKBKE, IL10, IL10RA, IRF5, IRF7, IRS2, ITGAL, ITPR1, JUND, KLF2, KMO, KYNU, L3MBTL3, LDHA, LFNG, LPL, LSS, LTB, MAP2K3, MAP2K6, MAP3K14, MAP4K4, MARCKSL1, MEF2C, MPC1, NCF2, NME1, NOD2, NOTCH1, NR4A3, NRARP, NRROS, OAS2, OAS3, PARP14, PCNA, PDE7B, PDIA4, PECAM1, PIK3CG, PILRB, PLK2, PTPRC, QKI, RANBP9, RAPGEF5, RFTN1, RFX5, RGS2, RND1, SAMD9, SAT1, SCD, SELL, SELP, SIRT1, SKI, SLC11A2, SLC35B2, SLC7A1, SMPD1, SOD1, SORBS1, ST3GAL5, ST6GAL1, ST8SIA4, STAT1, STMN1, TERF2IP, TGFB1, TNFRSF10D, TNFSF9, TP53INP1, TSHZ1, UCP2, VAV3, VCL, VIM, WNT10A, ZFP36 |
| IRF7 | transcription regulator | Inhibited | -3.297 | 0.0000139 | BCL2L1, CASP4, CD69, CD80, CTLA4, GBP3, GBP4, IFI16, IFIH1, IFITM2, IRF7, ISG20, NMI, OAS2, OAS3, PARP14, PLAC8, RTP4, SAMD9L, SAP30, STAT1, TRIM21, XAF1, ZC3HAV1 |
| BRD4 | kinase | Inhibited | -3.202 | 0.000111 | ACSL5, ACSM3, ADAT2, BCL2L1, DCPS, DCTPP1, GTF3C6, KCNA3, MTHFD1L, MTMR2, NME1, RRS1, SFXN4, TTC27, ZNF485 |

| | | | | | |
|---|---|---|---|---|---|
| Interferon alpha | group | Inhibited | -3.097 | 0.000406 | ANXA5, APOL3, BCL2L1, BST2, CD69, CD80, CD81, CD86, DAG1, EIF2AK2, GBP3, GLS, ICAM1, IFI16, IFIH1, IFITM2, IFNLR1, IKBKE, IL10, IL10RA, IRF5, IRF7, ISG20, LILRB4, mir-29, MNDA, NFIL3, NMI, OAS2, PNPT1, PRKACA, RNASEL, STAT1, TGFB1, TLR1, TRIM21, WARS, ZC3HAV1 |
| EGLN | group | Inhibited | -3.039 | 0.00254 | ALDOC, APAF1, BNIP3, EGLN1, FAM117B, FTL, FYN, GAPDH, GYS1, LDHA, SAP30, TPI1, ZNF337 |
| CD2 | transmembrane receptor | Inhibited | -2.975 | 0.000508 | CD48, CD80, CD86, ICAM1, IL10, ITGAL, PTPRC, SELL, STAT1 |
| Ifn | group | Inhibited | -2.934 | 0.000143 | CD69, CD80, CD86, EIF2AK2, ICAM1, IFI16, IFIH1, IL10, IL10RA, IRF7, ISG20, OAS2, OAS3, PECAM1, RNASEL, STAT1, TLR1, TRIM21 |
| STAT1 | transcription regulator | Inhibited | -2.884 | 0.085 | APOL6, BCL2L1, CASP4, CCL4, CD86, EGR1, EIF2AK2, FOXO1, GBP3, HERC6, ICAM1, IFI16, IFITM2, IL10, IRF5, IRF7, OAS2, PARP9, PECAM1, SAMHD1, SP110, STAT1, WARS |
| CD40LG | cytokine | Inhibited | -2.812 | 0.000000694 | ALCAM, ALG3, BATF, BCL2L1, BNIP3, CCL4, CD27, CD69, CD80, CD86, CELF2, CFLAR, EGR1, EIF2AK2, GADD45A, GCH1, GPR183, HDDC2, HLA-DQB1, HSPA1A/HSPA1B, ICAM1, IL10, IL10RA, IL13RA1, IL1RAP, IPO8, IRF2, JUND, LTA, LTB, MAP2K3, MARCKSL1, MPHOSPH9, NR4A3, PLEK, RAD50, RGS2, SELL, SELP, SLAMF1, STAT1, TM7SF2, TNFRSF13B, TNFSF4, TNFSF9, TNPO1, ZFP36L1 |
| MGEA5 | enzyme | Inhibited | -2.785 | 0.025 | ACTG1, ACTN4, ALDOC, ALOX5AP, BCL2L1, CD48, CD86, CDCA7L, CREB3L2, FGFR1, FLNA, FLNB, G6PD, GADD45A, GLUL, GTF3A, HSDL1, LSS, MAP3K3, NOTCH2, OGDH, PIK3R1, RAP2A, SORBS1, STAT1, TGFB1, TSPAN5, TUBA1A, TUBA4A, VIM |
| FLT3LG | cytokine | Inhibited | -2.773 | 0.00861 | ADGRE5, CD80, CD86, ICAM1, IL10, PAX5, PTPRC, TCF4 |
| Ifnar | group | Inhibited | -2.64 | 0.00346 | CD86, EIF2AK2, IFI16, IFIH1, IRF7, ISG20, OAS2, PNPT1, STAT1, TRIM21, UNC93B1, XAF1 |
| RBL2 | other | Inhibited | -2.598 | 0.11 | CASP4, CCNF, CHKA, GSK3B, KPNA2, MAP2K3, MAP3K14, PCNA, STMN1 |
| EBI3 | cytokine | Inhibited | -2.596 | 0.0163 | CD80, CD86, HLA-DMB, HLA-DOB, ICAM1, IL10, STAT1 |
| IL12 (complex) | complex | Inhibited | -2.589 | 0.0248 | BCL2L1, CCL4, CD69, CD86, GADD45B, GCNT2, ICAM1, IFIH1, IL10, ISG20, ITGAL, LTA, LTB, PLAC8, SELL, SELP, SET, TGFB1, TXK |
| IRF3 | transcription regulator | Inhibited | -2.534 | 0.000648 | B4GALT5, BTLA, CCL4, CD69, CD86, DDX60, EIF2AK2, IFI16, IFIH1, IL10, IRF5, IRF7, ISG20, |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | OAS2, OAS3, PARP14, PLAC8, PNP, SAMD9L, SAP30, STAT1, TNFSF4, VIM |
| IL5 | cytokine | Activated | 2.453 | 0.000000184 | ALDOC, ANXA2, BCL2L1, BNIP3, BNIP3L, CASP4, CD69, CYSLTR1, DDX21, EAF2, EGLN1, EGR1, ELL2, FAM65B, GADD45A, GBP4, GLIPR2, HSPH1, ICAM1, IER3, IFI30, IL13RA1, IRF7, LFNG, LTA, LTB, NABP1, NDRG1, NFIL3, P4HA1, PAX5, PTPRC, QSOX1, SAP30, TGFB1, TLR1, TPI1, VIM, ZNF443 |
| FOXM1 | transcription regulator | Activated | 2.477 | 0.143 | CCNE2, CCNF, CDKN3, HIST1H2BG, LDHA, MAPK8, PCNA, PECAM1, STMN1, VIM |
| Nr1h | group | Activated | 2.517 | 0.00957 | ABCD2, ERCC8, HLA-DOB, IFIH1, IL10, ITGAL, ITPR1, LAT2, LPL, LTB, MARCKSL1, MYLIP, NPC1, SCD, SELP, SP110 |
| EGR2 | transcription regulator | Activated | 2.534 | 0.0446 | BNIP3L, CHKA, EGR1, FCER2, GOLGB1, GTF2A1, HOMER1, IL10, MAP2, NOTCH1, RALGAPA1, SCD, SLC12A2, SLC16A1 |
| ARNT | transcription regulator | Activated | 2.538 | 0.00063 | ALDOC, BNIP3, CD81, G6PD, GAPDH, IL10, IRS2, LDHA, MYO1C, OAZ1, PDPK1, PGM2, S1PR1, SELL, TPI1, TUBA4A, VIM |
| SMAD4 | transcription regulator | Activated | 2.597 | 0.519 | CELF2, GADD45A, GADD45B, ICAM1, IER3, IL10, PTPRC, SCD, SERTAD1, SLC25A4, TGFB1, VIM, ZFP36 |
| TRIM24 | transcription regulator | Activated | 2.685 | 0.000297 | DDX60, EPSTI1, GBP3, GBP4, GLUL, HERC6, HNF1B, IFIH1, IRF7, NMI, PLAC8, RTP4, SAMD9L, SAMHD1, STAT1 |
| CREM | transcription regulator | Activated | 2.724 | 0.0467 | CD86, DUSP14, EGR1, GADD45B, IRS2, LSS, MEST, MIDN, MKNK2, NFIL3, NOTCH1, SERTAD1, SLC16A1, TIPARP |
| ERBB2 | kinase | Activated | 2.802 | 0.00104 | ABHD5, ALDOC, ANXA2, APLP2, ATP1B3, BAG2, BCKDHB, BCL2L1, BNIP3, CCL4, CCNE2, CDCA7L, CDKN3, CHD4, DAAM1, DAG1, DDX10, DGAT1, DTX1, EGR1, ELK3, ELL2, EPSTI1, ETV5, ETV6, FOXO1, G3BP1, GART, GLS, GSK3B, GTF3A, HIST1H4C, HMGB2, HSPA1A/HSPA1B, IGF2R, IKBKB, LPCAT1, MAN1A1, MAP2K3, MGAT5, MKNK2, MLXIP, MPHOSPH9, NDRG1, NOTCH1, PCNA, PDIA4, PDPK1, PFKFB3, PLAC8, POLE, POLK, POLR1B, POLR2A, POLR2L, QKI, SIRPA, SLC4A7, SORBS1, TUBA1A, VCL, VIM, WSB2 |
| E2F1 | transcription regulator | Activated | 2.842 | 1.08E-08 | ABCB1, ACSL5, APAF1, ATAD2, BCL2L1, BID, BNIP3, CALM1 (includes others), CALR, CCNE2, CCNF, CFLAR, CWC27, EGR1, EIF2AK2, EXOSC9, EZH2, FANCD2, FGFR1, FOXO1, FOXO3, GM2A, HIST1H2AC, HIST1H2AE, HIST1H2BJ, HIST1H4H, |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | HIST2H2AA3/HIST2H2AA4, HLTF, HMGB2, HN1, ICAM1, IRS2, KCNA3, LTA4H, MAP3K14, MGEA5, mir-223, MTHFD1, NMI, NUSAP1, PCNA, PIK3R1, PKNOX1, PLK2, PPP1R13B, QKI, RCOR1, RYBP, SERTAD2, STMN1, TGFB1, TNFSF9, TP53INP1, TRIM28, TRMT13, UCP2, VCP, VIM, YARS, ZFP36 |
| XBP1 | transcription regulator | Activated | 2.852 | 0.181 | APP, CALR, CAT, CRK, DNAJC1, DNAJC3, ERO1B, GOLGB1, ICAM1, MAP1LC3B, P3H1, PDIA4, S1PR1, SOD1, STARD5 |
| MKNK1 | kinase | Activated | 2.887 | 0.0112 | ANXA2, ANXA5, FLNA, FLNB, IFRD1, KIF1B, MAN2A1, NR4A3, PDLIM5, STXBP1, TTC3, VIM |
| NFE2L2 | transcription regulator | Activated | 2.899 | 0.000941 | ABCB4, ACSL5, ACTG1, ARHGEF3, ATP1A1, BCL2L1, BNIP3, CAT, CD86, CLPP, CREG1, DNAJC3, DYNLL1, ESD, ETV6, FKBP5, FOXO3, FTL, G6PD, GCLC, GNAI2, IFRD1, IL10, LPL, MAP1LC3B, MEF2C, NCF2, OAT, PDIA4, PGD, PKIA, PTPRO, RRS1, SAT1, SLC30A4, SOD1, TGFB1, TPI1, VCP |
| ESRRA | ligand-dependent nuclear receptor | Activated | 2.941 | 0.189 | ACOX1, ALDOC, ASAH1, CHKA, FAM102A, GAPDH, IKZF3, LDHA, LPL, MED24, PDP1, SIRT1, TPI1 |
| GH1 | growth factor | Activated | 3.077 | 0.387 | CAT, EGR1, GADD45A, GCLC, LPL, NRAS, PCNA, SIRT1, SKI, SOD1, TUBA1A, VIM, XRCC1, ZFP36 |
| IL1RN | cytokine | Activated | 3.2 | 0.0174 | ERAP2, HDAC9, HERC6, HLA-DQB1, ICAM1, IFIH1, IFIT5, IL10, IRF7, ISG20, OAS2, OAS3, RTP4, SAMD9 |
| PPARG | ligand-dependent nuclear receptor | Activated | 3.209 | 0.0592 | ACOX1, ACSL5, APAF1, APP, ASAP1, BCL2L1, CAT, CPT1A, DGAT1, EGLN1, GAPDH, ICAM1, IL10, IRS2, LPL, MANBA, MAP2, MKNK2, MRTO4, NDRG1, PCNA, PECAM1, PFKFB3, RAPGEF1, SAT1, SCD, SLC44A1, SLC9A1, SOD1, SORBS1, TCF4, UCP2, VIM, WIPF1, XYLT1 |
| CD38 | enzyme | Activated | 3.229 | 0.0000025 | ALDOC, ANXA2, BNIP3, BNIP3L, CD86, EAF2, EGLN1, ELL2, GBP4, GLIPR2, ICAM1, IFI30, LFNG, LTA, NABP1, NDRG1, NFIL3, P4HA1, PAX5, PPP3CA, SAP30, SELL, TPI1, VIM, ZNF443 |
| PPARGC1A | transcription regulator | Activated | 3.608 | 0.276 | ACOX1, BNIP3, CALM1 (includes others), CAT, CPT1A, DGAT1, GSK3B, IL10, IRS2, LDHA, LPL, NRF1, PNPLA2, SCD, SOD1, UCP2 |
| FOXO3 | transcription regulator | Activated | 3.684 | 0.000000703 | APAF1, BNIP3, BNIP3L, CASP4, CAT, CCNE2, CDKN3, CFLAR, CPT1A, EGR1, FOXO1, FOXO3, GADD45A, GADD45B, GCLC, GLUL, IARS, IER3, IFIH1, IL10, IMPDH2, IRS2, LARS, MEF2C, MXD1, PCNA, PPRC1, RTN3, RTN4, SESN1, SLC7A1, SOD1, TGFB1, TP53INP1, |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | UCP2, VIM |

**Table S7A.** The top 20 canonical pathways identified by IPA for 142 genes contained within SEs that are ranked lower in 3 out of 4 CLL patient samples after *ex-vivo* PLX51107 treatment.

| Ingenuity Canonical Pathways | p-value | Molecules |
|---|---|---|
| Th1 and Th2 Activation Pathway | 6.30957E-07 | IL10, IKZF1, IL10RA, HLA-DQA1, IL2RA, SPI1, IL24, mir-21, IL2RB |
| Th2 Pathway | 1.31826E-06 | IL10, IKZF1, HLA-DQA1, IL2RA, SPI1, IL24, mir-21, IL2RB |
| T Helper Cell Differentiation | 4.46684E-05 | IL10, IL10RA, HLA-DQA1, IL2RA, BCL6 |
| Molecular Mechanisms of Cancer | 0.00019 | ZBTB17, RAC2, RAPGEF1, PMAIP1, TCF4, CCND2, PRKAR1B, RHOH, BCL2 |
| Antigen Presentation Pathway | 0.00105 | B2M, NLRC5, HLA-DQA1 |
| Leukocyte Extravasation Signaling | 0.00575 | RAC2, CD44, RASSF5, RHOH, SELPLG |
| Th1 Pathway | 0.00589 | IL10, IL10RA, HLA-DQA1, mir-21 |
| Ovarian Cancer Signaling | 0.00741 | TCF4, CD44, PRKAR1B, BCL2 |
| Allograft Rejection Signaling | 0.01023 | B2M, IL10, HLA-DQA1 |
| OX40 Signaling Pathway | 0.01175 | B2M, HLA-DQA1, BCL2 |
| Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells | 0.01230 | B2M, BCL2 |
| Death Receptor Signaling | 0.01259 | PARP15, PARP9, BCL2 |
| Hepatic Fibrosis / Hepatic Stellate Cell Activation | 0.01738 | IL10, IL10RA, ECE1, BCL2 |
| Protein Kinase A Signaling | 0.01995 | TCF4, PTPRJ, PTPN1, PRKAR1B, UBASH3B, PDE4B |
| p53 Signaling | 0.02089 | PMAIP1, CCND2, BCL2 |
| IL-8 Signaling | 0.02188 | RAC2, CCND2, RHOH, BCL2 |
| Netrin Signaling | 0.02239 | RAC2, PRKAR1B |
| Neuroprotective Role of THOP1 in Alzheimer's Disease | 0.02455 | PRKAR1B, ECE1 |
| Autoimmune Thyroid Disease Signaling | 0.02754 | IL10, HLA-DQA1 |
| iCOS-iCOSL Signaling in T Helper Cells | 0.02951 | HLA-DQA1, IL2RA, IL2RB |

**Table S7B.** The top upstream regulators (activation z-score>2) predicted by IPA for 142 genes contained within SEs that are ranked lower in 3 out of 4 CLL patient samples after *ex-vivo* PLX51107 treatment

| Upstream Regulator | Molecule Type | Predicted Activation State | Activation z-score | p-value of overlap | Target molecules in dataset |
|---|---|---|---|---|---|
| STAT3 | transcription regulator | Inhibited | -2.047 | 0.0000002 | BATF, BCL2, BCL6, BMF, CCND2, HLA-DQA1, IKZF3, IL10, IL2RA, IL2RB, mir-21, PMAIP1, SERPINB1, SERPINB9, TCF4 |
| CD3 | complex | Activated | 2.097 | 0.0000003 | BATF, BCL2, BCL6, CCND2, CD44, CKS2, DAD1, IL10, IL2RA, IL2RB, PDE4B, PTPRJ, RAC2, RHOH, SELPLG, SRP14 |
| BCL6 | transcription regulator | Activated | 2.308 | 0.0000016 | BCL2, BCL6, CCND2, CD44, IL10, IL24, IL2RA, IL2RB, LPP |
| IL21 | cytokine | Inhibited | -2.574 | 0.0000043 | BATF, BCL2, BCL6, CCND2, IL10, IL2RA, IL2RB, mir-21 |
| IL4 | cytokine | Inhibited | -2.111 | 0.0000338 | BCL11A, BCL2, BCL6, CCND2, CD44, IL10, IL10RA, IL24, IL2RA, IL2RB, mir-21, PDE4B, PIGR, SELPLG, ST6GAL1 |
| CSF2 | cytokine | Inhibited | -2.941 | 0.000222 | BCL2, IL10, IL24, IL2RA, mir-21, PDE4B, RHOH, SERPINB9, SPI1, TCF4 |
| STAT5B | transcription regulator | Inhibited | -2.191 | 0.000275 | BCL2, BCL6, CCND2, IL24, IL2RA, IL2RB |

| | | | | | |
|---|---|---|---|---|---|
| CBFB | transcription regulator | Activated | 2 | 0.000675 | IKZF3, IL2RA, IL2RB, SLC25A19 |
| Nr1h | group | Activated | 2 | 0.00871 | BCL2, CCND2, ECE1, IL10 |
| IL1 | group | Inhibited | -2.412 | 0.0115 | BCL2, IL10, IL2RA, IL2RB, mir-21, PIGR |
| ERBB2 | kinase | Inhibited | -2.371 | 0.021 | BCL2, BTG2, CCND2, CDC42EP3, CKS2, ETV6, LPCAT1, mir-21, PTPN1 |
| Creb | group | Inhibited | -2.195 | 0.024 | BCL2, DDX6, IL10, mir-21, PDE4B |
| MGEA5 | enzyme | Inhibited | -2 | 0.137 | BCL2, CD44, PRKAR1B, SERPINB9 |
| NUPR1 | transcription regulator | Activated | 2 | 0.286 | ETV6, JADE2, PARP9, PTPRJ |

**Table S7C.** The top bio-functions (activation z-score >2) predicted by IPA for 142 genes contained within SEs that are ranked lower in 3 out of 4 CLL patient samples after *ex-vivo* PLX51107 treatment.

| Diseases or Functions Annotation | Predicted Activation State | Activation z-score | p-Value | Molecules |
|---|---|---|---|---|
| leukopoiesis | Decreased | -2.964 | 7.25E-14 | ARID5B, B2M, BATF, BCL11A, BCL2, BCL6, CCND2, CD44, EIF2AK4, ETV6, HLA-DQA1, IGKC, IKZF1, IKZF3, IL10, IL10RA, IL2RA, IL2RB, LAIR1, MAPKAPK2, mir-21, PTPRJ, RAC2, RASSF5, RHOH, SLAMF6, SMARCE1, SPEN, SPI1, TCF4, ZBTB17 |
| hematopoiesis of mononuclear leukocytes | Decreased | -2.576 | 3.94E-13 | ARID5B, B2M, BATF, BCL11A, BCL2, BCL6, CCND2, CD44, EIF2AK4, ETV6, HLA-DQA1, IGKC, IKZF1, IKZF3, IL10, IL10RA, IL2RA, IL2RB, LAIR1, PTPRJ, RASSF5, RHOH, SLAMF6, SMARCE1, SPEN, SPI1, TCF4, ZBTB17 |
| lymphopoiesis | Decreased | -2.744 | 6.21E-13 | ARID5B, B2M, BATF, BCL11A, BCL2, BCL6, CCND2, CD44, EIF2AK4, ETV6, HLA-DQA1, IGKC, IKZF1, IKZF3, IL10, IL10RA, IL2RA, IL2RB, PTPRJ, RASSF5, RHOH, SLAMF6, SMARCE1, SPEN, SPI1, TCF4, ZBTB17 |
| dendropoiesis | Decreased | -2.007 | 1.05E-09 | BATF, BCL11A, BCL6, EIF2AK4, IKZF1, IL10, IL2RA, IL2RB, LAIR1, mir-21, SPI1 |
| development of antigen presenting cells | Decreased | -2.378 | 1.2E-09 | BATF, BCL11A, BCL6, EIF2AK4, IKZF1, IL10, IL2RA, IL2RB, LAIR1, MAPKAPK2, mir-21, SPI1 |
| homeostasis of leukocytes | Decreased | -3.057 | 2.01E-09 | B2M, BATF, BCL11A, BCL2, BCL6, BMF, EIF2AK4, HLA-DQA1, IGKC, IKZF1, IL10, IL10RA, IL2RA, IL2RB, PDE4B, RHOH, SLAMF6, SMARCE1, SPI1, TCF4, ZBTB17 |
| differentiation of T lymphocytes | Decreased | -3.169 | 2.35E-09 | B2M, BATF, BCL11A, BCL2, BCL6, EIF2AK4, HLA-DQA1, IKZF1, IL10, IL2RA, IL2RB, RHOH, SLAMF6, SMARCE1, SPI1, TCF4, ZBTB17 |
| T cell homeostasis | Decreased | -2.784 | 3.88E-09 | B2M, BATF, BCL11A, BCL2, BCL6, BMF, EIF2AK4, HLA-DQA1, IGKC, IKZF1, IL10, IL10RA, IL2RA, IL2RB, RHOH, SLAMF6, SMARCE1, SPI1, TCF4, ZBTB17 |
| development of phagocytes | Decreased | -2.706 | 7.34E-09 | BATF, BCL11A, BCL2, BCL6, EIF2AK4, IKZF1, IL10, IL2RA, IL2RB, LAIR1, MAPKAPK2, mir-21, SPI1 |
| hematopoiesis of phagocytes | Decreased | -2.378 | 8.56E-09 | BATF, BCL11A, BCL2, BCL6, EIF2AK4, IKZF1, IL10, IL2RA, IL2RB, LAIR1, mir-21, SPI1 |
| T cell development | Decreased | -2.598 | 1.59E-08 | B2M, BATF, BCL11A, BCL2, BCL6, EIF2AK4, HLA-DQA1, IGKC, IKZF1, IL10, IL10RA, IL2RA, IL2RB, RHOH, SLAMF6, SMARCE1, SPI1, TCF4, ZBTB17 |
| differentiation of antigen | Decreased | -2.033 | 1.93E-08 | BATF, BCL11A, BCL2, BCL6, EIF2AK4, IKZF1, |

| | | | | |
|---|---|---|---|---|
| presenting cells | | | | IL10, IL2RA, IL2RB, LAIR1, mir-21, SPI1 |
| cell proliferation of T lymphocytes | Increased | 3.125 | 2.59E-08 | ADORA2A, B2M, BATF, BCL2, CD44, HLA-DQA1, IKZF1, IKZF3, IL10, IL2RA, IL2RB, LAIR1, PTPRJ, RAC2, RASSF5, RHOH, SERPINB9, SPI1, TIGIT, ZC3H12D |
| anemia | Increased | 2.188 | 0.00000018 | ADORA2A, BCL2, CCND2, CDC42EP3, DAD1, GRHPR, HLA-DQA1, IKZF1, IL10, IL2RA, IL2RB, PTPRJ, RAC2, SLC25A19, SPI1 |
| hypoplasia of lymphoid organ | Increased | 2.949 | 0.00000048 | ARID5B, BCL11A, BCL6, IGKC, IKZF1, IL10, IL2RB, RASSF5, RHOH |
| abdominal neoplasm | Increased | 2.126 | 0.00000212 | ADORA2A, APOBEC3D, APOBEC3F, APOBEC3H, ARID5B, B2M, BATF, BCL11A, BCL2, BCL6, BTG2, C1orf186, C1QTNF6, CBX7, CCND2, CD44, CDC42EP3, CHIT1, CKS2, CORO1C, CYTOR, DAD1, DDX6, DTX3L, ECE1, EIF2AK4, EIF2D, ETV6, FAM167A, FAM53B, FAM60A, FGD2, GPR107, GRHPR, HERPUD1, HLA-DQA1, IGHA2, IGKC, IKZF1, IL10, IL10RA, IL24, IL2RA, IL2RB, JAZF1, KLHDC7B, LDLRAD4, LILRA4, LILRA5, LPCAT1, LPP, MAPKAPK2, MCTP2, MIF4GD, mir-21, MSI2, MTSS1, NLRC5, NSMCE1, NUBP1, PARP15, PATL2, PDE4B, PIGR, PLEKHG1, PMAIP1, PPP1R16B, PRKAR1B, PTPN1, PTPRJ, RAD51B, RAPGEF1, RASSF5, RBM17, RHOH, SECISBP2, SELPLG, SERPINB1, SERPINB9, SLAMF6, SLC39A13, SMAP2, SPEN, SPI1, SSTR3, ST6GAL1, SUSD1, TAGAP, TCF4, TCTN1, TIGIT, TRIM69, TVP23A, UBASH3B, USP3, VMP1, VOPP1, XXYLT1, ZBTB17, ZBTB20, ZC3H12D, ZCCHC7, ZMYND8 |
| hypoplasia of organ | Increased | 3.216 | 0.00000247 | ARID5B, BCL11A, BCL2, BCL6, CCND2, ECE1, IGKC, IKZF1, IL10, IL2RB, PTPRJ, RASSF5, RHOH, SPEN |
| morbidity or mortality | Increased | 3.531 | 0.0000037 | ADORA2A, ARID5B, B2M, BCL11A, BCL2, BCL6, BMF, CCND2, CD44, CKS2, DAD1, ECE1, EIF2AK4, ETV6, FCMR, GPR107, IKZF3, IL10, IL2RA, IL2RB, MAPKAPK2, mir-21, MTSS1, NUBP1, PDE4B, PTPN1, PTPRJ, RAC2, RAD51B, RAPGEF1, RASSF5, SECISBP2, SERPINB1, SLAMF6, SLC25A19, SPEN, SPI1, TCF4, ZBTB17, ZBTB20 |
| cellular homeostasis | Decreased | -2.981 | 0.00000421 | ADORA2A, B2M, BATF, BCL11A, BCL2, BCL6, BMF, EIF2AK4, HERPUD1, HLA-DQA1, IGKC, IKZF1, IL10, IL10RA, IL24, IL2RA, IL2RB, NUBP1, PDE4B, PMAIP1, PTPRJ, RAC2, RHOH, SLAMF6, SLC39A13, SMARCE1, SPI1, TCF4, UBASH3B, VMP1, ZBTB17 |
| quantity of plasma cells | Increased | 2.219 | 0.0000257 | FCMR, IL10, IL2RB, RAC2, RASSF5 |

**Table S8A.** The top 20 canonical pathways identified by IPA for 106 genes that are directly regulated by BRD4.

| **Ingenuity Canonical Pathways** | **p-value** | **Molecules** |
|---|---|---|
| tRNA Charging | 0.00047 | LARS, GARS, LARS2, IARS |
| Th2 Pathway | 0.00052 | STAT6, IKZF1, HLA-DQB1, JAK3, mir-21 |
| IL-4 Signaling | 0.00069 | STAT6, NRAS, HLA-DQB1, JAK3 |
| Th1 and Th2 Activation Pathway | 0.00138 | STAT6, IKZF1, HLA-DQB1, JAK3, mir-21 |

| | | |
|---|---|---|
| Role of JAK1 and JAK3 in γc Cytokine Signaling | 0.00372 | STAT6, NRAS, JAK3 |
| TREM1 Signaling | 0.00457 | TLR6, TLR1, CCL3 |
| IL-15 Signaling | 0.00468 | STAT6, NRAS, JAK3 |
| Colorectal Cancer Metastasis Signaling | 0.00501 | NRAS, GRK3, TLR6, TLR1, JAK3 |
| JAK/Stat Signaling | 0.00575 | STAT6, NRAS, JAK3 |
| Communication between Innate and Adaptive Immune Cells | 0.00724 | TLR6, TLR1, CCL3 |
| Altered T Cell and B Cell Signaling in Rheumatoid Arthritis | 0.00724 | TLR6, TLR1, HLA-DQB1 |
| Oncostatin M Signaling | 0.00977 | NRAS, JAK3 |
| UVA-Induced MAPK Signaling | 0.01047 | NRAS, PARP15, PARP9 |
| Primary Immunodeficiency Signaling | 0.01862 | RFX5, JAK3 |
| Th1 Pathway | 0.02188 | HLA-DQB1, JAK3, mir-21 |
| Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses | 0.02239 | OAS2, TLR6, TLR1 |
| Pyrimidine Ribonucleotides Interconversion | 0.02344 | NME1, CTPS2 |
| Retinoic acid Mediated Apoptosis Signaling | 0.03236 | PARP15, PARP9 |
| IL-2 Signaling | 0.03388 | NRAS, JAK3 |
| Pyrimidine Ribonucleotides De Novo Biosynthesis | 0.03467 | NME1, CTPS2 |

**Table S8B.** The top upstream regulators (activation z-score >2) predicted by IPA for 106 genes that are directly regulated by BRD4.

| Upstream Regulator | Molecule Type | Predicted Activation State | Activation z-score | p-value of overlap | Target molecules in dataset |
|---|---|---|---|---|---|
| Interferon alpha | group | Inhibited | -2.513 | 0.000379 | CCL3, CCND2, IFI16, LILRB4, mir-21, MX2, OAS2, TLR1 |
| IFN Beta | group | Inhibited | -2.164 | 0.000398 | CCL3, IFI16, MX2, OAS2, XAF1 |
| BCR (complex) | complex | Inhibited | -2.18 | 0.00044 | CCL3, CCND2, CLEC2D, FCMR, KCNN4 |
| STAT1 | transcription regulator | Inhibited | -2.433 | 0.00008 | APOL6, CCL3, CCND2, HERC6, IFI16, OAS2, PARP9, SP110 |
| PRL | cytokine | Inhibited | -2.828 | 0.0000485 | DTX3L, EPSTI1, HERC6, MX2, OAS2, SP110, TMEM140, XAF1 |
| VEGFA | growth factor | Inhibited | -2.186 | 0.0101 | BATF, CTLA4, MRPL3, NME1, TLR1 |
| IFNL1 | cytokine | Inhibited | -2.449 | 0.00000125 | APOL6, DDX60, HERC6, OAS2, SP110, TMEM140 |
| IL21 | cytokine | Inhibited | -2.414 | 0.000147 | BATF, CCND2, HERC6, IFI16, mir-21, OAS2 |
| CSF2 | cytokine | Inhibited | -2.771 | 0.00145 | CCL3, CD180, CTLA4, GRK3, HLA-DQB1, mir-21, TIFA, TLR1 |
| TNF | cytokine | Inhibited | -2.761 | 0.00797 | AIMP1, ARID5B, BTN3A3, CCL3, CCND2, CTLA4, DENND2D, ELK3, ETV6, IFI16, mir-21, NCF2, NME1, OAS2, RFX5, TIFA |
| TGM2 | enzyme | Inhibited | -2.607 | 0.0000901 | CCL3, DDX60, NCF2, OAS2, PARP9, SP110, XAF1 |
| IRF7 | transcription regulator | Inhibited | -2.2 | 0.00096 | CTLA4, IFI16, MX2, OAS2, XAF1 |
| MSC | transcription regulator | Inhibited | -2 | 0.000137 | DDX60, EPSTI1, PAX5, XAF1 |
| ATF4 | transcription regulator | Inhibited | -2.236 | 0.000767 | ARHGAP24, BCAT1, GARS, IARS, LARS |
| IFNB1 | cytokine | Inhibited | -2.401 | 0.00179 | BTN3A3, CCL3, IFI16, mir-21, OAS2, XAF1 |
| IFNG | cytokine | Inhibited | -3.874 | 0.00000733 | APOL6, CCL3, CCND2, CLEC2D, DTX3L, ERCC8, HERC6, HLA-DQB1, IFI16, JAK3, MX2, NCF2, OAS2, PARP9, RFX5, SP110, STAT6, TLR1, TLR6 |
| IFNA2 | cytokine | Inhibited | -3.231 | 1.06E-08 | APOL6, CCL3, DDX60, HERC6, IFI16, |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | LILRB4, MX2, OAS2, PARP9, SP110, XAF1 |
| MYC | transcription regulator | Inhibited | -2.329 | 0.0117 | ABCE1, BCAT1, CCND2, CD48, DDX21, IFI16, IKZF1, NME1, PAX5, PNO1, TMEM126A |
| CD3 | complex | Activated | 3.031 | 0.000173 | AIMP1, BATF, CCL3, CCND2, CTLA4, ELK3, HLA-DQB1, JAK3, KCNN4, NME1, XAF1 |
| NUPR1 | transcription regulator | Activated | 2.449 | 0.0288 | CTPS2, ETV6, LARS2, MX2, PARP9, RFX5 |
| SOCS1 | other | Activated | 2 | 0.00257 | CCL3, IFI16, OAS2, STAT6 |
| NKX2-3 | transcription regulator | Activated | 2 | 0.0181 | DDX60, PARP9, SP110, XAF1 |
| IL1RN | cytokine | Activated | 2 | 0.00339 | HERC6, HLA-DQB1, MX2, OAS2 |

**Table S8C.** The top bio-functions (activation z-score >2) predicted by IPA for 106 genes that are directly regulated by BRD4.

| Diseases or Functions Annotation | Predicted Activation State | Activation z-score | p-Value | Molecules |
|---|---|---|---|---|
| cell survival | Decreased | -3.891 | 0.000161 | ACSL5, AIMP1, ALKBH8, AMIGO2, CCL3, CD48, CTLA4, ERCC8, ETV6, FANCF, FCMR, JAK3, mir-21, NCF2, NME1, NRAS, PAX5, PFDN1, STAT6, UPF2, UTP15, XRCC4 |
| cell viability | Decreased | -3.75 | 0.000171 | ACSL5, AIMP1, ALKBH8, AMIGO2, CCL3, CD48, CTLA4, ERCC8, ETV6, FANCF, FCMR, JAK3, mir-21, NCF2, NME1, NRAS, PAX5, PFDN1, UPF2, UTP15, XRCC4 |
| migration of cells | Decreased | -2.468 | 0.00946 | AIMP1, ARHGAP24, ARID5B, BATF, BCAT1, CCL3, CD48, CTLA4, DOCK10, ELK3, ETV6, IKZF1, JAK3, KCNN4, mir-21, NCF2, NME1, NRAS, PARP9, PAX5, SH2D3C, STAT6 |
| leukopoiesis | Decreased | -2.439 | 0.000000196 | ARID5B, BATF, CCL3, CCND2, CTLA4, ETV6, HLA-DQB1, IFI16, IKZF1, IKZF3, JAK3, LILRB1, LILRB4, mir-21, PAX5, SLAMF6, STAT6, TLR1, TLR6, XRCC4 |
| Lymphocyte migration | Decreased | -2.333 | 0.00128 | BATF, CCL3, CD48, CTLA4, ETV6, JAK3, KCNN4, SH2D3C |
| hematopoiesis of mononuclear leukocytes | Decreased | -2.291 | 8.12E-08 | ARID5B, BATF, CCL3, CCND2, CTLA4, ETV6, HLA-DQB1, IFI16, IKZF1, IKZF3, JAK3, LILRB1, LILRB4, PAX5, SLAMF6, STAT6, TLR1, TLR6, XRCC4 |
| cell proliferation of tumor cell lines | Decreased | -2.222 | 0.00602 | ACSL5, CCL3, CCND2, CTLA4, CWC27, DDX21, ETV6, IFI16, IKZF1, JAK3, KCNN4, LILRB1, mir-21, NAT10, NME1, NRAS, PAX5, PPIL1, SH2D3C, SP110 |
| tumorigenesis of tissue | Decreased | -2.204 | 0.00122 | ABCE1, ALKBH8, AMIGO2, ARHGAP24, ARID5B, BATF, BCAT1, BTN3A3, C3orf38, CCND2, CD180, CD48, CLEC2D, CTLA4, CTPS2, CWC27, DDX21, DDX60, DENND2D, DOCK10, DTX3L, ELK3, EPSTI1, ERCC8, ETV6, FANCF, FCRLA, FYCO1, GARS, GPATCH4, GTF3C6, HERC6, HLA-DQB1, IARS, IFI16, IKZF1, JAK3, KCNN4, KIAA0391, LARS, LARS2, LILRA4, LILRB1, LILRB4, LRRC32, MCTP2, METTL3, mir-21, MTX3, MX2, NAT10, NCF2, NME1, NRAS, NUP205, OAS2, PARP15, PFDN1, PIGK, PPIL1, PYROXD1, RFX5, SH2D3C, SLAMF6, SLC43A3, SMYD5, SNX11, SP110, STAT6, TIFA, TIGIT, TLR1, TLR6, |

| | | | | |
|---|---|---|---|---|
| | | | | TMEM126A, TMEM140, TRIT1, TXLNB, UPF2, XAF1, ZC3H12D, ZC3H7A, ZNF484 |
| Bacterial Infections | Increased | 2 | 0.00453 | AIMP1, CCL3, FCMR, SLAMF6, SP110, STAT6, TLR1, TLR6 |
| hypoplasia of lymphoid organ | Increased | 2.165 | 0.00118 | ARID5B, CTLA4, IKZF1, JAK3, XRCC4 |