Classification: BIOLOGICAL SCIENCES: Immunology

Subtype Specific Addiction of the Activated B Cell Subset of Diffuse Large B Cell Lymphoma to FOXP1

Joseph D. Dekker[a], Daechan Park[a,b], Arthur L. Shaffer III[c], Holger Kohlhammer[c], Wei Deng[a], Bum-Kyu Lee[a], Gregory C. Ippolito[a,b], George Georgiou[a,b], Vishwanath R. Iyer[a], Louis M. Staudt[c], Haley O. Tucker[a1]

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Supplemental methods

shRNA knockdown

Sequences of the 21bp DNA stems of the shRNAs used were: #26 GGCGGTCCAACGGAGAGACGC, #36 GACCTCGCCCACGCCCAGCAG, and #42 GCAGCAACAGTGGCATCTCAT, or an ineffective non-specific control shRNA. Doxycycline (1-10 µg/mL) was applied for induction of shRNA expression in each experiment. Human FOXP1 primers were: F: 5'-AAAACATGCAGAGCAGCCAC-3', and R: 5'- TGGCTAAGTTGCCCAGAGTG-3'.

Flow cytometry

Anti-human antibodies used in this study were: Annexin V conjugated to PE (BD Biosciences, cat. #640908), pan-MHC class II antibody conjugated to AlexaFluor 647 (BioLegend, clone Tu39), and anti-IgM F(ab')2 antibody conjugated to R-PE (Invitrogen, cat. #H15104) were used.

Western blots

anti-FOXP1 Rabbit polyclonal antisera was kindly provided by Dr. Edward Morrisey (U. Penn), Anti-IKKβ and anti phospho-IKKα/β antibodies from Cell Signaling Technologies (clones D30C6 and 16A6) and IRAK 1 and 4 antibodies from Santa Cruz Biotechnology (Cat #'s sc-7883 and sc-374349).

Data analysis

Sequencing reads were trimmed to 35nt due to low base qualities, then the trimmed reads were mapped onto the hg19 reference genome using the Burrows-Wheeler Aligner (BWA, version 0.6.2)(1). Non-uniquely mapped reads were filtered out to eliminate bogus peaks on repeat regions. Then, a Parzen window density estimation algorithm was used to call peaks(2). For each peak site, a binomial P-value was calculated by comparing to the same locus in the corresponding input data. By applying FDR-corrected P value cutoff 0.001, the highest number of significant peaks among cell

lines was 5452 in TMD8. The same number of top peaks (5452) were considered FOXP1 targets in all cell lines. Assignment of peaks to target genes was performed using GREAT version 2.0.2(3). Genes qualifying in array and ChIP-seq analysis were considered direct targets. Gene expression signature enrichment was performed as described(4). GO terms were identified by DAVID analysis(5, 6).

Five gene lists (defined in Fig. 7B) of FOXP1 direct and/or indirect targets derived from GREAT analysis(3) of ChIP-seq data and/or from modulated microarray genes (log2 values of ± 0.3 change in at least 5 out of 12 KD samples) were pre-defined. Transcriptome RNA-seq of human primary DLBCL were obtained from the dbGaP database (accession number: phs000235). FPKM was calculated by using TopHat2 and Cufflinks(7, 8). Two subtypes, ABC (n=32) or GCB (n=53), were determined based on a previous study(9, 10), then the expression data were split by subtypes. For each subtype, Gene Set Enrichment Analysis (GSEA)(11) was used to rank genes by correlation with *FOXP1* expression and to evaluate the enrichment of the pre-defined five gene sets. The highly enriched (correlated) FOXP1 targets were further used for downstream analysis. Hierarchical clustering by Pearson correlation was performed on the genes enriched in either ABC or GCB subtypes, and heat maps were made with GENE-E(12).

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Table S1: GO Terms (27) of FOXP1 motif "TGTT" bound target genes.

ABC only

ABC significant GO terms	Count	%	p value
GO:0003714~transcription corepressor activity	17	3.03030303	1.40E-05
BP00152:B-cell- and antibody-mediated immunity	13	2.317290553	1.76E-05
GO:0006350~transcription	100	17.82531194	8.33E-05
GO:0010553~negative regulation of specific transcription from RNA polymerase II promoter	8	1.426024955	3.34E-04
MF00101:Guanyl-nucleotide exchange factor	13	2.317290553	6.47E-04
GO:0032582~negative regulation of gene-specific transcription	8	1.426024955	8.99E-04
GO:0035239~tube morphogenesis	13	2.317290553	9.55E-04
GO:0010551~regulation of specific transcription from RNA polymerase II promoter	11	1.960784314	0.001009536
GO:0046983~protein dimerization activity	32	5.704099822	0.001064851
GO:0003713~transcription coactivator activity	17	3.03030303	0.001297438
GO:0003677~DNA binding	99	17.64705882	0.001353452
GO:0006914~autophagy	7	1.247771836	0.001367184
GO:0040012~regulation of locomotion	16	2.852049911	0.001679807
GO:0046982~protein heterodimerization activity	16	2.852049911	0.002574275
MF00100:G-protein modulator	22	3.921568627	0.003227279
MF00039:Other transcription factor	21	3.743315508	0.003399324
P00057:Wnt signaling pathway	23	4.099821747	0.00410791
GO:0019898~extrinsic to membrane	27	4.812834225	0.004346414
GO:0032583~regulation of gene-specific transcription	12	2.139037433	0.004627434
GO:0008633~activation of pro-apoptotic gene products	5	0.8912655597	0.005234682
GO:0016585~chromatin remodeling complex	8	1.426024955	0.005482344
GO:0007264~small GTPase mediated signal transduction	20	3.565062389	0.00577331
GO:0008287~protein serine/threonine phosphatase complex	6	1.069518717	0.006751145
MF00275:Transcription cofactor	12	2.139037433	0.007082367
BP00040:mRNA transcription	72	12.8342246	0.007768854
GO:0007229~integrin-mediated signaling pathway	8	1.426024955	0.007907233
GO:0005955~calcineurin complex	3	0.534759358	0.008562244
hsa04310:Wnt signaling pathway	12	2.139037433	0.009103859
GO:0008283~cell proliferation	25	4.456327986	0.009244591

Common pathways

Overlap GO terms by p value	count	%	p value
GO:0010628~positive regulation of gene expression	47	7.605177994	7.82E-07
GO:0045941~positive regulation of transcription	45	7.281553398	2.04E-06
GO:0045893~positive regulation of transcription, DNA-dependent	40	6.472491909	2.57E-06
GO:0006357~regulation of transcription from RNA polymerase II promoter	53	8.57605178	3.08E-06
GO:0051254~positive regulation of RNA metabolic process	40	6.472491909	3.16E-06
GO:0051173~positive regulation of nitrogen compound metabolic process	48	7.766990291	5.67E-06
GO:0045935~positive regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	46	7.443365696	1.21E-05
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	32	5.177993528	1.84E-05
GO:0031328~positive regulation of cellular biosynthetic process	48	7.766990291	2.76E-05
BP00281:Oncogenesis	32	5.177993528	2.93E-05
GO:0010604~positive regulation of macromolecule metabolic process	56	9.061488673	3.72E-05
GO:0010557~positive regulation of macromolecule biosynthetic process	46	7.443365696	3.87E-05
GO:0009891~positive regulation of biosynthetic process	48	7.766990291	3.98E-05
GO:0010558~negative regulation of macromolecule biosynthetic process	39	6.310679612	1.29E-04
GO:0009890~negative regulation of biosynthetic process	40	6.472491909	1.60E-04
GO:0031327~negative regulation of cellular biosynthetic process	39	6.310679612	2.13E-04
BP00102:Signal transduction	143	23.13915858	2.23E-04
GO:0010605~negative regulation of macromolecule metabolic process	47	7.605177994	2.77E-04
GO:0006915~apoptosis	40	6.472491909	4.39E-04
GO:0010629~negative regulation of gene expression	35	5.663430421	4.90E-04
GO:0012501~programmed cell death	40	6.472491909	5.84E-04
GO:0045934~negative regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	35	5.663430421	6.53E-04
BP00111:Intracellular signaling cascade	47	7.605177994	6.96E-04
BP00207:Cell cycle control	27	4.368932039	7.65E-04
GO:0051172~negative regulation of nitrogen compound metabolic process	35	5.663430421	8.28E-04
GO:0016481~negative regulation of transcription	32	5.177993528	8.47E-04
GO:0045321~leukocyte activation	20	3.236245955	0.00157883
GO:0043087~regulation of GTPase activity	13	2.103559871	0.001917185
GO:0008219~cell death	43	6.957928803	0.002031497

GCB only

GCB GO terms by p value	Count	%	p value
GO:0042981~regulation of apoptosis	59	9.546925566	6.01E-07
GO:0043067~regulation of programmed cell death	59	9.546925566	8.37E-07
GO:0010941~regulation of cell death	59	9.546925566	9.42E-07
GO:0043066~negative regulation of apoptosis	31	5.01618123	1.91E-05
GO:0043069~negative regulation of programmed cell death	31	5.01618123	2.50E-05
GO:0060548~negative regulation of cell death	31	5.01618123	2.60E-05
GO:0006916~anti-apoptosis	21	3.398058252	7.47E-05
GO:0008289~lipid binding	32	5.177993528	4.96E-04
GO:0005543~phospholipid binding	17	2.750809061	7.34E-04
GO:0002252~immune effector process	14	2.265372168	0.001329072
GO:0030522~intracellular receptor-mediated signaling pathway	10	1.618122977	0.001674013
GO:0002444~myeloid leukocyte mediated immunity	5	0.809061489	0.00179167
GO:0042127~regulation of cell proliferation	46	7.443365696	0.002142707
GO:0006816~calcium ion transport	14	2.265372168	0.0022243082
GO:0007507~heart development	18	2.912621359	0.002533419
GO:0019899~enzyme binding	33	5.339805825	0.0028091
BP00121:Steroid hormone-mediated signaling	7	1.132686084	0.0028281 63
GO:0006974~response to DNA damage stimulus	26	4.207119741	0.002901731
GO:0006325~chromatin organization	26	4.207119741	0.003455069
GO:0048732~gland development	13	2.103559871	0.004151011
GO:0002443~leukocyte mediated immunity	10	1.618122977	0.0042 97797
MF00101:Guanyl-nucleotide exchange factor	12	1.941747573	0.004988963
GO:0045165~cell fate commitment	13	2.103559871	0.005244571
MF00100:G-protein modulator	23	3.721682848	0.005550641
GO:0015674~di-, tri-valent inorganic cation transport	15	2.427184466	0.005571491
MF00229:Extracellular matrix linker protein	5	0.809061489	0.005887274
BP00224:Cell proliferation and differentiation	48	7.766990291	0.006121618
GO:0045884~regulation of survival gene product expression	5	0.809061489	0.006595219
BP00273:Chromatin packaging and remodeling	14	2.265372168	0.006709616

		Signature	SIG.size	GENE list	List.size	Intersection	p value	Enrichment	Conf. Interval
DLBCL pathways modulated in ABC lines by FOXP1 loss	**Repressed**	MYD88Dn-1	279	HBL1.and.TMD8.GE_up	553	68	4.58E-44	8.609	6.456
		JAK2Dn-1	402	HBL1.and.TMD8.GE_up	553	49	5.67E-18	4.306	3.153
		GCBDLBCL-3	273	HBL1.and.TMD8.GE_up	553	35	7.99E-14	4.529	3.142
		BCL6-5	1163	HBL1.and.TMD8.GE_up	553	73	1.26E-10	2.217	1.720
		GCB-1	289	HBL1.and.TMD8.GE_up	553	31	2.21E-10	3.789	2.584
		GCB-6	210	HBL1.and.TMD8.GE_up	553	26	2.89E-10	4.373	2.874
		Module-3.4	280	HBL1.and.TMD8.GE_up	553	28	8.02E-09	3.532	2.368
		IL10Up-1	121	HBL1.and.TMD8.GE_up	553	18	8.87E-09	5.255	3.162
		MM-4	47	HBL1.and.TMD8.GE_up	553	11	5.86E-08	8.267	4.186
		IFN-3	304	HBL1.and.TMD8.GE_up	553	27	1.74E-07	3.137	2.093
	Activated	MYD88Up-1	271	HBL1.and.TMD8.GE_down	563	80	2.25E-58	10.242	7.771
		JAK2Up-1	945	HBL1.and.TMD8.GE_down	563	121	1.06E-45	4.443	3.591
		NFkB-10	206	HBL1.and.TMD8.GE_down	563	45	7.36E-27	7.579	5.385
		MYD88Up-2	91	HBL1.and.TMD8.GE_down	563	26	3.59E-19	9.913	6.240
		JAKUp-2	322	HBL1.and.TMD8.GE_down	563	36	3.75E-12	3.879	2.714
		MYD88Up-3	46	HBL1.and.TMD8.GE_down	563	14	2.39E-11	10.560	5.603
		NFkB-9	63	HBL1.and.TMD8.GE_down	563	14	2.37E-09	7.710	4.232
		IRF4Up-2	176	HBL1.and.TMD8.GE_down	563	18	3.52E-06	3.548	2.163
		ABCDLBCL-4	261	HBL1.and.TMD8.GE_down	563	22	7.47E-06	2.925	1.874
		Prolif-5	645	HBL1.and.TMD8.GE_down	563	39	1.87E-05	2.098	1.500
DLBCL pathways modulated And with ChIP-seq peaks	**Repressed**	BCL6-5	1163	HBL1.and.TMD8.GE.plus.peak_up	127	36	1.44E-15	4.761	3.222
		BCL6-6	4357	HBL1.and.TMD8.GE.plus.peak_up	127	68	2.61E-14	2.401	1.691
		MYD88Dn-1	279	HBL1.and.TMD8.GE.plus.peak_up	127	18	2.86E-13	9.923	5.939
		IL10Up-1	121	HBL1.and.TMD8.GE.plus.peak_up	127	10	6.49E-09	12.712	6.491
		GCB-6	210	HBL1.and.TMD8.GE.plus.peak_up	127	12	1.27E-08	8.789	4.772
		BCL6-4	2727	HBL1.and.TMD8.GE.plus.peak_up	127	43	1.53E-08	2.425	1.676
		GCB-1	289	HBL1.and.TMD8.GE.plus.peak_up	127	13	5.25E-08	6.919	3.851
		JAK2Dn-1	402	HBL1.and.TMD8.GE.plus.peak_up	127	15	5.56E-08	5.739	3.317
		GCBDLBCL-3	273	HBL1.and.TMD8.GE.plus.peak_up	127	12	2.25E-07	6.761	3.685
		GCB-3	50	HBL1.and.TMD8.GE.plus.peak_up	127	6	8.43E-07	18.457	7.721
	Activated	MYD88Up-1	271	HBL1.and.TMD8.GE.plus.peak_down	113	23	1.39E-20	14.671	9.126
		JAK2Up-1	945	HBL1.and.TMD8.GE.plus.peak_down	113	24	7.21E-10	4.390	2.784
		NFkB-10	206	HBL1.and.TMD8.GE.plus.peak_down	113	10	3.30E-07	8.392	4.319
		BCL6-5	1163	HBL1.and.TMD8.GE.plus.peak_down	113	22	7.32E-07	3.270	2.045
		OCT2Up-1	591	HBL1.and.TMD8.GE.plus.peak_down	113	12	0.00016	3.510	1.918

Table S2 DLBCL related signatures (10) were also analyzed under the same modulation criteria and by crossing with modulated genes that also had ChIP-seq peaks (bottom). Red text are signatures repressed by FOXP1 that went up upon loss, and Green text are activated signatures in which their encompassed genes went down upon FOXP1 loss. Signature size includes all of the genes in the signature, list size includes the total number of affected genes, and intersection are the number of affected genes that both qualify and are in the signature gene list. Standard statistical analysis was used for calculating p values, signature enrichment, and confidence intervals.

Table S3: Gene lists derived from enrichment of FOXP1 targets (Fig. 7B).

Genelist #1 unique vs ABC
MGEA5, LPP, TLE4, PNMA1, PLEKHG1, RUNX1, TOX2, DOCK10, NFATC1, PMFBP1, TBC1D22A, ZNF516, H3F3C, GPR52, MDFIC, IRS2, PRUNE2, BTAF1, KIF16B, TAB2, ARHGEF7, ZNF575, TGIF1, FOXK1, KLHL14, CTDP1, CACNG5, CBX7, BMPR2, BCOR, MYO1E, KLF9, MYADML, ST13P4, SLC38A4, SEMA3D, ADCY2, UST, LPIN1, LPCAT1, DTNBP1, DNAH17, GTSF1L, MATN1, ZMYND8, CCNL1, ZFHX3, ZBTB10, ST3GAL1, TRIO, NFATC2, RXRA, FUT8, AP1M1, ADARB2, DUSP5, RCOR1, MAP3K15, B3GALT2, ZNF608, IRF2BP2, HES1, TMEM131

Geneset #1 unique vs GCB
BCAS1, WNT7B, ZNF664, TOP1, NR3C2, KIAA0586, CPSF6, PPP3CA, CADM1, CUL1, TLE3, KIAA0020, CDCA7L, SLC14A2, ZNF804A, NFIA, DCLK3, RFC3, MYC, FER, LRIG1, RCBTB2, ALG1, BCAT1, BLM, SLC5A3, TNFSF8, TNPO1, MIS18BP1, ARHGAP20, MEF2C, LMBR1, NARS2, WDR12, TAB1, NBEA, RHOH, AGTPBP1, SGOL1, ZFAT, CUL3, POT1, PRKCA, RNF19B, ING1, PDE4B, ZNF250, PGAP1, MKLN1, ARL5B, PTK2, CHD1, USPL1, SYPL1, KIAA1217, LANCL2, BICD1, RANBP6, PARP8, ANO3, CPEB4, JPH3, CXXC5, MLANA, RBPJ, PCNX, TNS3, CHRNA9, GRID1, AK2, GOLIM4, STIM2, TGIF2, PLEKHA8, HMGB1, PCDH8, GJA10, GTDC1, NCOA2, MED25, TRPM1, TMEM170B, NLRP2, TPD52, SLC25A26, TNFAIP8

Geneset #2 unique vs ABC
STK10, CBFA2T3, ZNF394, RAC2, ZNF341, CD72, ZNF577, MEPCE, ARHGAP17, DGKG, SETX, YPEL1, IRF9, NAB2, NEK8, SMG6, CRYGS, ZBTB17, ARHGAP25, ATP9B, AKAP3, GH1, KDM5B, FCRL1, MAPK11, ACAD10, PLK3, TGFBR3, RNASEH1, MMP23B, CD82, PSD

Geneset #2 unique vs GCB
TNPO3, SBNO1, ERF, ANKRD17, NAA25, MED26, AICDA, EPC2, KCNN3, C11orf24, HNRNPL, FAM126B, LRRC34, EIF3G, DCAF10, DDX54, SMARCA5, ELK3, PIGK, DDX51, PUS1, NDUFAF1, RTTN, SETD8, TACC1, ANGPTL1, ERP29, RNASEH1, CD79B, ECT2, RAB3A, FAF2, DERL3, EIF2S1, DEPDC5, PRMT1, GAN, COPS2, ZC3H3, ENOX2, SBF1, FCRL2, CLPTM1L, ADA, DPF1, LRIF1, CCNJ

Geneset #3 unique vs ABC
KCNMB1, SESTD1, ARNTL, DIO2, ASPG, ADRA1D, MTRR, DSEL, ZNRF4, PITPNM3, SIRT6, FOSL2, CETN3, KCNH5, PM20D2, RBFOX1, CENPK, C9orf3, ABCA12, CLEC14A, SOX1, MANEA, SLITRK3, TRHR, GRIN2A, CYP2C19, NBPF14, IL13, ZIC3, PRELID2, SLC6A11, TSPAN32, BAZ2B, NKX2-2, FSHB, NRG2, MRPL46, RASL11A, TMEM232, KLHDC7A, COL11A1, ESRRB, BAHCC1, ABCA13, CACNA2D1, HGF, ZCWPW2, HK3, ARX, INSC, GNAI1, CNTN5, GPR128, PAX1, EPHA6, SLC30A8, RAD9B, NXPH1, BFSP1, TDRD9, SUSD2, IAH1, PPAP2B, SQRDL, VGLL2, CAMKK2, SGCD, C5orf38, FAM64A, ZBTB7C, AKAP7, CHAC1, HPSE2, BCAS2, GABRG2, TBK1, CDH8, DPYD, NAP1L1, NAT2, ACTN2, RSL24D1, DMXL2, PKHD1L1, SPTB, CDK1, ELFN2, MEGF9, MPPED2, MTFR1, ZP3, HAO1, FAM188A, RALYL, LAMB4, C10orf128, CSF3R, CCT2, ZNF334, ALK, GALC, MSR1, TMX4, ARL14, PRNP, C7orf66

Geneset #3 unique vs GCB
SLC25A15, TRIM32, SLC34A2, INADL, LGR5, SLMAP, CDH12, ASB7, TUSC3, C16orf62, INO80, PLCH1, MCCC2, BEND5, ATM, HIST1H3H, CAMSAP3, ZNF606, ROBO1, ANKS1B, TRIM14, ABAT, WAPAL, ZNF780A, PKP1, SLITRK6, YTHDC2, DIAPH3, BCKDHB, LIX1L, NOVA1, ZNF804B, SALL3, TMEM114, BRE, SAFB2, CYP11B2, NTRK3, GTF2F2, CPXCR1, DYM, PSAPL1, TPGS2, EBF2, IPO8, GABRA1, SAP30L, NRSN1, ZSCAN1, SLC12A2, FAAH, TPPP3, ACAA2, IRX5, ADAM17, KY, ABCA7, USP40, ADCYAP1R1, ZNF638, CSNK1A1L

Genelist #4 DN vs ABC
MTMR14, LIMD1, CHMP4B, ZNF395, TOX2, GTPBP1, PPFIA3, TNFRSF13B, CD22, NLRC5, TMEM44, TUB, JAK3, DTX3, POU5F1P4, ARHGAP27, DAG1, SNRNP70, CLDN15, TBC1D17, ROGDI, BIN1, GPDD3, MAB21L2, TRAF3IP3, ECE1, POU3F1, RHOT2, LAT2, CD2BP2, HECTD3, ERBB2, HEMK1, CLIP3, RNF112, ANO9, ANKS3, RAI1, RASSF1, RXRB, VASH2, MICALL1, WFIKKN1, BAX, EGR1, SH2B1, MLLT6, TNXB, CC2D1A, ZC3HAV1L, ZDHHC22, NAGPA, TXNRD2, SPEG, ARL10, ABCA7, PKD1P1, CDK10, MAN2B1, BHLHE40, TSR2, PQLC1, AXIN1, PHLDA3, SAMD4B, CCR7, CRY2, IGHMBP2, MFSD10, TNF, PPOX, AP1B1, NCKIPSD, VPS53, GADD45B, PTK2B, ARFGAP1, SSBP4, DHRS13, VPS37D, MLLT1, CPSF7, CDIPT, PFKL, TRIM65, PLD4, COTL1, GAK, ELMO2, RANGAP1, TP53I11, LIMS3, COASY, ABCB6, AKT1, CLSTN3, DDX19A, EML3, LZTR1, PLEKHM2, RAB40C, KCTD17, C17orf70, GGT3P, CDC42BPB, MVD, NCAN, CNP, SH3BP2, STARD3, ZNF598, CALML6, TP53I13, NOC2L, B4GALT2, KIF5A, BCL2L1, FA2H

Genelist #4 DN vs GCB
SBNO1, POLD2, HIST1H2AL, ATOH7, NOC2L, TLE3, TRIM28, SFN, ANKLE1, ELOVL6, PRR7, RCAN2, MAPK12, FKBP4, SLC38A5, GTF3C2, DLG3, SLC1A5, PKMYT1, TNNT1, UBE2S, DYRK3, TRIM14, USP5, GRAP, ICAM5, NUDC, ATAD3B, CTU1, FA2H, TUBB3, YARS, GANAB, CCDC86, FUT10, CEND1, ANXA6, MLEC, ADAM15, PRPS1, B4GALT2, HIST1H1B, FAM27E3, ERP29, TNXB, OGG1, ITGA2B, DERL3, APH1A, ARF3, ZDHHC21, SNRPF, YKT6, CAMP, HMBS, UBE2M, MLST8, SCARB1, SMARCB1, PRRG2, KHSRP, STK35, TIMM13

Genelist #4 UP Unique vs ABC
LRCH3, MPHOSPH8, TMEM145, TLE4, RBM5, SIDT1, MED23, DIDO1, FMNL3, WIPF2, ZNF185, KIAA2018, LRCH1, KIF16B, IRF8, PCMTD2, IRF9, RNU12, ZBTB20, NCOA1, WWP2, FMO4, SH3KBP1, TAS2R19, B3GAT2, CPT1A, NEIL1, NEDD4L, ANKRD20A1, SPATA2, LCK, VIPR2, KLHDC1, DLGAP4, RPS27, DAAM2, ATP11A, ZNF608, TCFL5, PIK3CG, PDK4, MLLT1, PPP1R12B, RNF113B, DUSP8, HP, SPG11, ANO7, FOXF1, IGF2, ZFX, LCOR, ZNF425

Genelist #4 UP vs GCB
KIAA1377, GPT2, PCDH9, PHF20L1, WDR19, KLHL5, DKKL1, CUL4B, HNRNPR, FAM98A, ZNF804A, BPTF, EPS15, SMC2, WDR78, CASC4, AICDA, IL6, MFHAS1, GPR37, TXLNB, CA13, CNGB1, ZNF484, MBNL2, YME1L1, EPC1, TRIM37, RNF144B, AHI1, MAP3K1, RPL28, SAMD9, OR6N1, IREB2, SUSD3, CLIC4, ZZZ3, SLC10A7, MEF2C, TCF15, KIF20B, MYSM1, MAGED1, BANK1, CEP97, APC, C4orf32, TMEM123, PRPF4B, CNOT6L, ARL5B, SESN1, PTK2, ZFR, KPNA5, TTC3, PARP8, CPEB4, RPS6KA3, C12orf42, DET1, ODF4, AP1AR, CHURC1, UBA6, TNS3, OR7E91P, DEPDC5, BNIP2, PELI1, STIM2, SLC41A1, KIF21A, ZNF708, DHTKD1, IRS1, RALGPS2, FILIP1L, HIF1A, FCRL3, MBNL1, BRMS1L, PPP1R12A, FAS, SPOPL, TMED9, TPD52, NDFIP2, AGGF1, ZNF615, GPATCH2, DPF3, GAL3ST1, SEC23A, CSNK1A1L, STXBP3, HBS1L, UBA2, PELI2, ZNF451, USP3, ADAM10, RPS26

Genelist #5 DN v ABC
MTMR14, LIMD1, ZNF395, TRIM28, TOX2, PPFIA3, TNFRSF13B, CD22, ECE1, MLLT6, ABCA7, BHLHE40, PQLC1, SAMD4B, CCR7, JMJD8, DHRS13, MLLT1, TRIM65, COTL1, RANGAP1, TP53I11, COASY, EML3

Genelist #5 DN vs GCB
POLD1, NOC2L, TLE3, TRIM28, ELOVL6, ZBTB20, C3orf58, FUZ, GTF3C2, SLC1A5, UBE2S, CTU1, CCDC86, ANXA6, HIST1H1B, ERP29, DERL3, CKAP2

Genelist #5 UP vs ABC
KIAA0226, TLE4, FMNL3, KIF16B, ZBTB20, NCOA1, FMO4, SH3KBP1, CPT1A, NEDD4L, ATP11A, ZNF608, NACC1, NR4A2, PPP1R12B

Genelist #5 UP vs GCB
GPT2, KLHL5, BPTF, CASC4, TXLNB, TRIM37, KIAA0226, ZZZ3, NIPBL, MEF2C, BANK1, PTK2, PARP8, TNS3, DEPDC5, PELI1, STIM2, DHTKD1, RALGPS2, FILIP1L, HIF1A, MBNL1, USP3, ADAM10, RASSF6, OXR1, NLN, CD69, COL9A3, BACH1, OSR2, NEDD9

Signature	Signature size	Genelist and DLBCL Correlation	Genelist size	Intersection	p value	Enrichment	Conf Interval
BCL6-5	1174	Genelist 1 vs. ABC	63	11	4.33E-06	5.4922663	2.85840814
BCL6-6	4445	Genelist 1 vs. ABC	63	24	1.10E-07	3.16494724	1.901567968
CLLmut-1	17	Genelist 1 vs. ABC	63	2	0.0003832	68.961718	15.43936022
MycCHIP-2	3084	Genelist 1 vs. ABC	63	17	1.09E-05	3.23118296	1.850237814
BCL6-4	2786	Genelist 1 vs. GCB	86	23	6.23E-08	3.54499658	2.195647848
BCL6-6	4445	Genelist 1 vs. GCB	86	37	5.70E-13	3.57436629	2.32974133
MycCHIP-2	3084	Genelist 1 vs. GCB	86	24	9.03E-08	3.34168854	2.083055683
Prolif-6	3	Genelist 1 vs. GCB	86	1	0.0069703	143.135659	12.8574088
BAnergyUp-1	17	Genelist 2 vs. ABC	31	2	9.20E-05	140.148008	30.66217215
BCL6-6	4445	Genelist 2 vs. ABC	31	14	4.68E-06	3.7519939	1.848235443
PitLung-1	6	Genelist 2 vs. ABC	31	1	0.0050265	198.543011	22.51841047
BCL6-6	4445	Genelist 2 vs. GCB	48	26	2.16E-12	4.50015936	2.548426213
MycCHIP-2	3084	Genelist 2 vs. GCB	48	13	0.0001111	3.24306231	1.714038931
FDC-1	3	Genelist 3 vs. ABC	106	1	0.0085867	116.128931	10.45013722
MycCHIP-2	3084	Genelist 3 vs. ABC	106	19	0.0012726	2.14635183	1.30482771
BCL6-4	2786	Genelist 3 vs. GCB	61	13	0.0005286	2.82487967	1.528737129
MycCHIP-2	3084	Genelist 3 vs. GCB	61	17	6.76E-06	3.33712339	1.904427015
BCL6-5	1174	Genelist..4.DN.vs.ABC	119	17	2.38E-07	4.49367243	2.680207597
BCL6-6	4445	Genelist..4.DN.vs.ABC	119	33	3.05E-06	2.30389542	1.540378394
Heme-2	17	Genelist..4.DN.vs.ABC	119	2	1.36E-03	36.5091448	8.256784774
JAK2Up-1	952	Genelist..4.DN.vs.ABC	119	26	4.34E-17	8.47533719	5.460226096
JAKUp-2	325	Genelist..4.DN.vs.ABC	119	11	9.39E-09	10.5034001	5.592995937
MYD88Up-1	273	Genelist..4.DN.vs.ABC	119	15	1.52E-14	17.0509742	9.788457563
NFkB-10	208	Genelist..4.DN.vs.ABC	119	11	8.60E-11	16.4115627	8.689050982
NFkB-2	39	Genelist..4.DN.vs.ABC	119	4	7.73E-06	31.8284852	11.13200299
BCL6-4	2786	Genelist..4.DN.vs.GCB	67	18	1.54E-06	3.56109974	2.071942485
BCL6-6	4445	Genelist..4.DN.vs.GCB	67	27	4.29E-09	3.34799456	2.052744943
JAK2Up-1	952	Genelist..4.DN.vs.GCB	67	21	1.48E-17	12.1583626	7.226522857
MYD88Up-1	273	Genelist..4.DN.vs.GCB	67	14	7.18E-17	28.2655951	15.48917366
BCL6-4	2786	Genelist..4.UP.Unique.vs.ABC	60	20	7.33E-09	4.41840153	2.579570537
BCL6-5	1174	Genelist..4.UP.Unique.vs.ABC	60	15	4.37E-10	7.86392675	4.371109776
BCL6-6	4445	Genelist..4.UP.Unique.vs.ABC	60	28	3.43E-11	3.87706037	2.332440698
BCL6-4	2786	Genelist..4.UP.vs.GCB	104	23	2.40E-06	2.93143948	1.84188782
BCL6-5	1174	Genelist..4.UP.vs.GCB	104	11	0.000481	3.32704593	1.776132332
BCL6-6	4445	Genelist..4.UP.vs.GCB	104	48	6.55E-18	3.83445531	2.604445948
CLLmut-1	17	Genelist..4.UP.vs.GCB	104	2	1.04E-03	41.7748869	9.432344689
GCBDLBCL-3	284	Genelist..4.UP.vs.GCB	104	10	8.53E-09	12.5030471	6.444956518
JAK2Dn-1	409	Genelist..4.UP.vs.GCB	104	13	1.54E-10	11.2863692	6.259436729
MycCHIP-2	3084	Genelist..4.UP.vs.GCB	104	19	0.0010425	2.18762783	1.328534646
MYD88Dn-1	283	Genelist..4.UP.vs.GCB	104	11	5.23E-10	13.8019503	7.305330197
BCL6-6	4445	Genelist..5.DN.v.ABC	25	10	0.00037	3.3231946	1.492062896
BCL6-4	2786	Genelist..5.UP.vs.GCB	32	13	2.21E-07	5.38492687	2.656685542
BCL6-5	1174	Genelist..5.UP.vs.GCB	32	10	3.46E-08	9.82990843	4.644356082
BCL6-6	4445	Genelist..5.UP.vs.GCB	32	19	2.37E-10	4.93286699	2.434540706

Table S4: Significant signatures (10, 51) from indicated enriched FOXP1 target GSEA gene lists (Fig 7B).

Table S5: GO and KEGG Terms (27) of GSEA enriched FOXP1 target genes from combined genelists (Fig 7B)

GSEA listed GO terms

Category	Term	Count	%	PValue
GOTERM_BP_FAT	GO:0016265~death	52	7.1922545	9.76E-05
GOTERM_BP_FAT	GO:0008219~cell death	50	6.9156293	2.94E-04
GOTERM_BP_FAT	GO:0008284~positive regulation of cell proliferation	31	4.2876902	0.00173
GOTERM_BP_FAT	GO:0042127~regulation of cell proliferation	49	6.7773167	0.00346
GOTERM_BP_FAT	GO:0012501~programmed cell death	40	5.5325035	0.0039
GOTERM_BP_FAT	GO:0006915~apoptosis	39	5.3941909	0.0052
GOTERM_BP_FAT	GO:0008629~induction of apoptosis by intracellular signals	8	1.1065007	0.00614
GOTERM_BP_FAT	GO:0070227~lymphocyte apoptosis	4	0.5532503	0.00657
GOTERM_BP_FAT	GO:0070265~necrotic cell death	3	0.4149378	0.01536
GOTERM_BP_FAT	GO:0043068~positive regulation of programmed cell death	28	3.8727524	0.01935
GOTERM_BP_FAT	GO:0010942~positive regulation of cell death	28	3.8727524	0.02037
GOTERM_BP_FAT	GO:0008283~cell proliferation	27	3.7344398	0.034
GOTERM_BP_FAT	GO:0046649~lymphocyte activation	15	2.0746888	0.03403
GOTERM_BP_FAT	GO:0016477~cell migration	19	2.6279391	0.03437
GOTERM_BP_FAT	GO:0002902~regulation of B cell apoptosis	3	0.4149378	0.03965
GOTERM_BP_FAT	GO:0045321~leukocyte activation	17	2.351314	0.03992
GOTERM_BP_FAT	GO:0012502~induction of programmed cell death	21	2.9045643	0.04023
GOTERM_BP_FAT	GO:0001775~cell activation	19	2.6279391	0.0473
GOTERM_BP_FAT	GO:0043067~regulation of programmed cell death	44	6.0857538	0.04781
KEGG_PATHWAY	hsa05200:Pathways in cancer	24	3.3195021	0.01608
KEGG_PATHWAY	hsa04662:B cell receptor signaling pathway	9	1.2448133	0.01618
KEGG_PATHWAY	hsa04115:p53 signaling pathway	8	1.1065007	0.02837
KEGG_PATHWAY	hsa04310:Wnt signaling pathway	13	1.7980636	0.0324
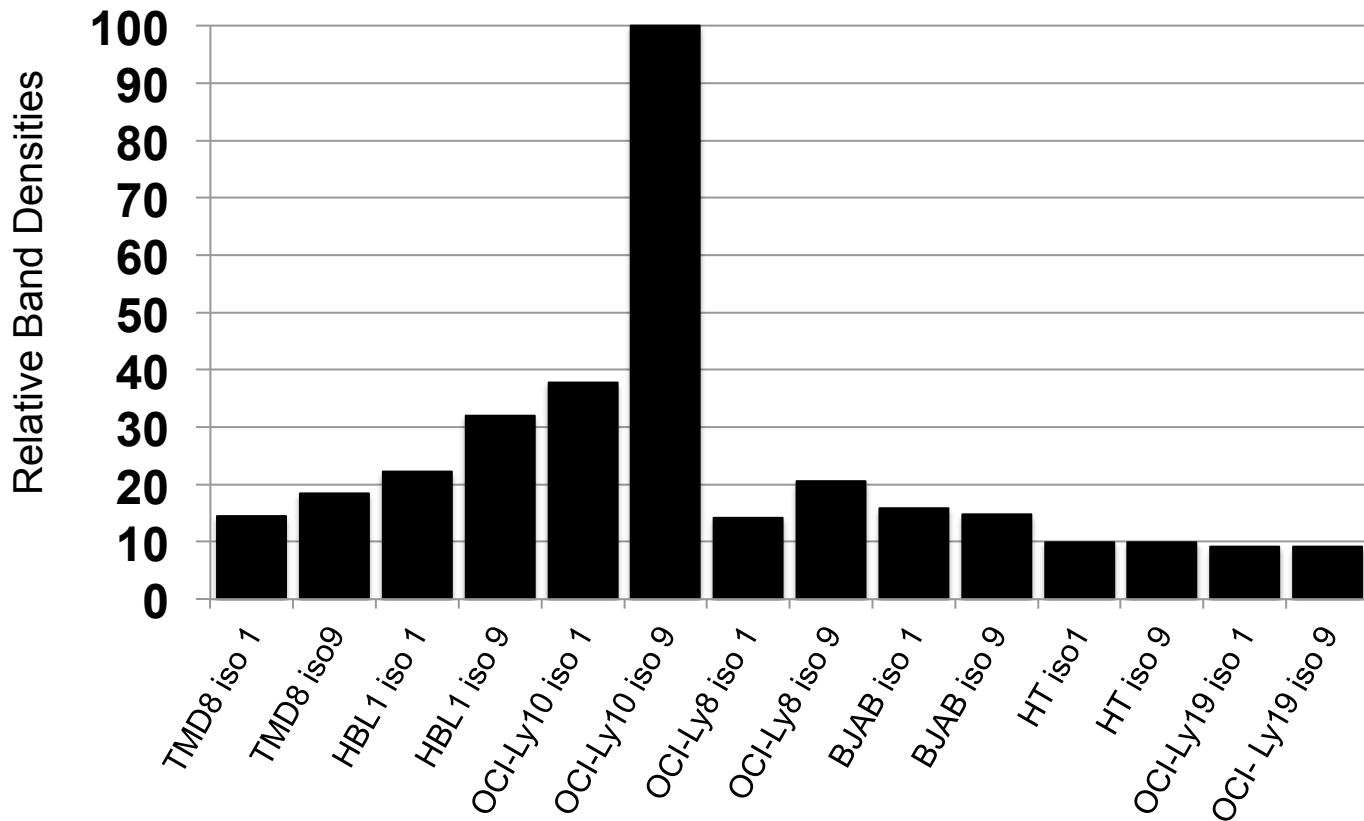
Figure S1. Band densities from western blot of FOXP1 in all lines tested days of elevated FOXP1 protein level in ABC lines compared to GCB lines. Bar graphs are normalized to GAPDH. The quantitative analyses confirms that the GCB-line OCI-Ly8 shows similar FOXP1 expression to an ABC line (TMD8), and exhibits an ABC-DLBCL like ratio of isoform 9 to isoform 1 expression. Our FOXP1 ChIP-seq binding analysis, however, identified FOXP1 direct targets for OCI-Ly8 as intermediate between ABC and GCB, but somewhat closer to GCB-DLBCL. This indicates that not only FOXP1 expression but also its functional promoter/enhancer binding to control gene expression plays an important role in potential diagnosis (analyzed in Fig. 7). This trend is also observed in additional GCB lines (eg, OCI-Ly1 and Karpas_422) which express FOXP1 at higher levels (Figure 3A).
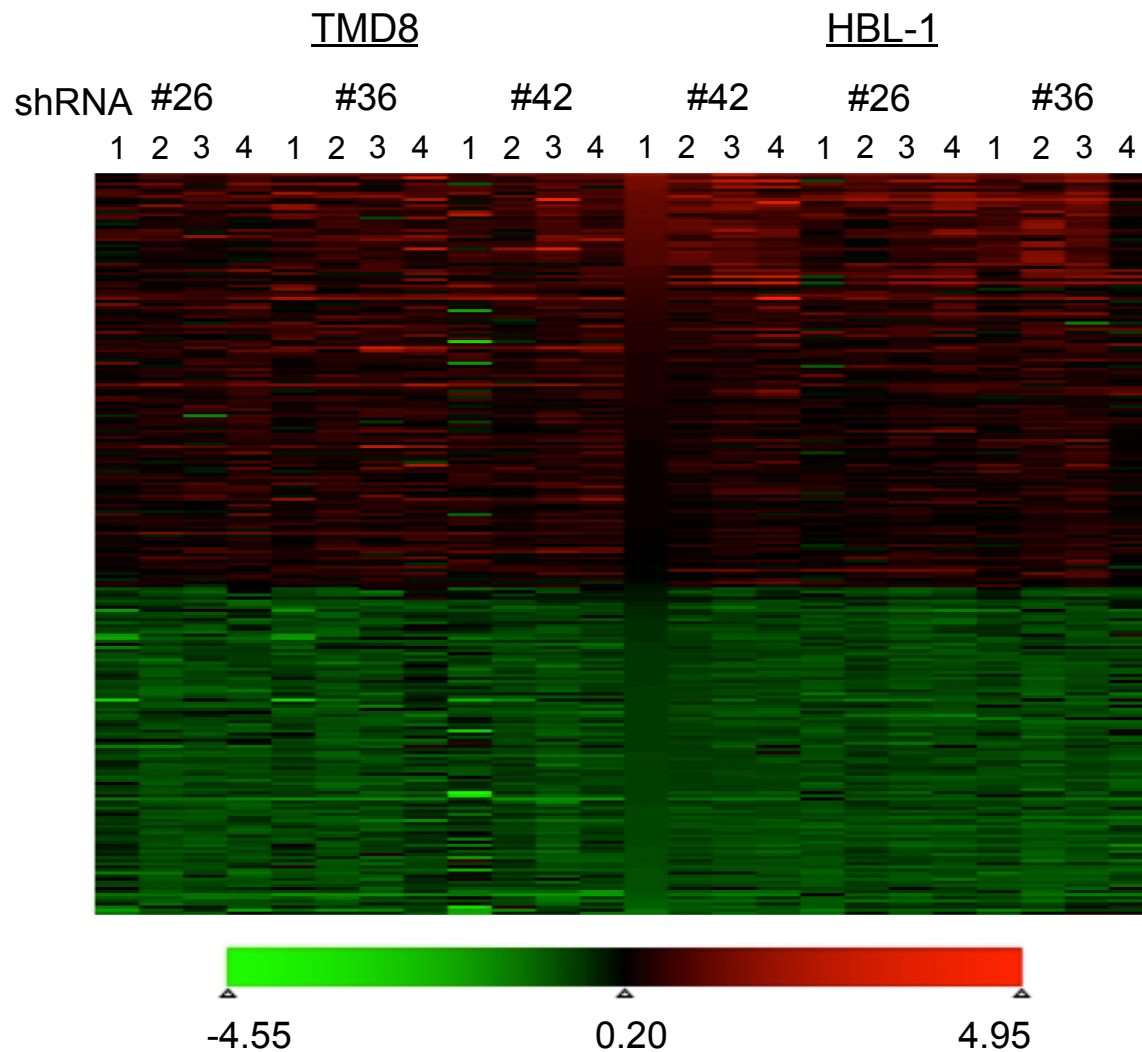
Figure S2. ABC-DLBCL lines TMD8 and HBL-1 were each transformed with pRSMX vector containing one of three different FOXP1 targeted shRNAs. After doxycycline induction, RNA was collected at multiple timepoints as indicated for Agilent microarray analysis. The representative heat map indicates strong correlation both between cell lines and modulation of targets compared to scrambled shRNA controls.
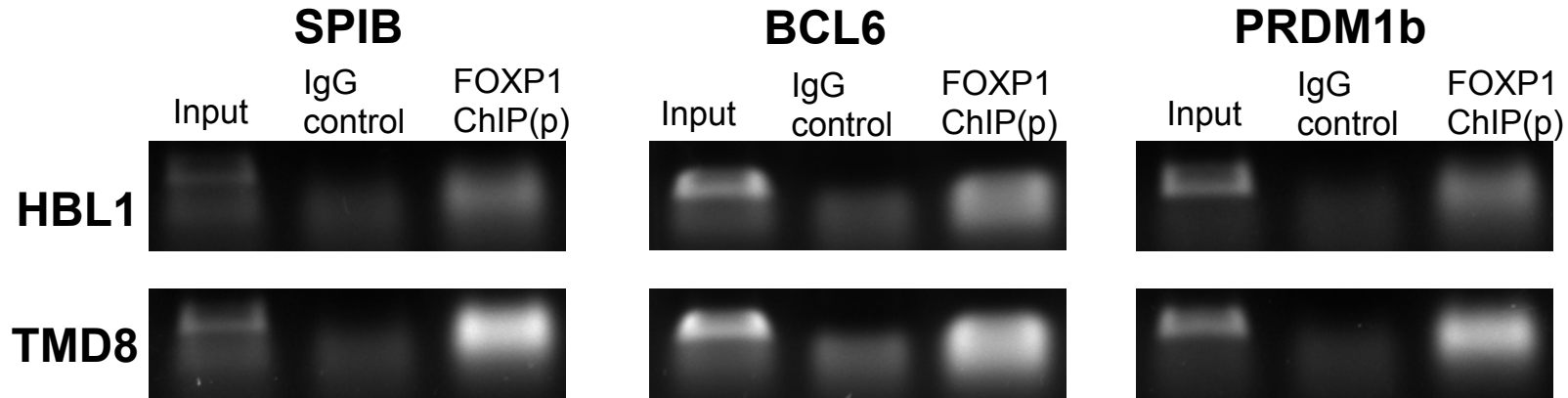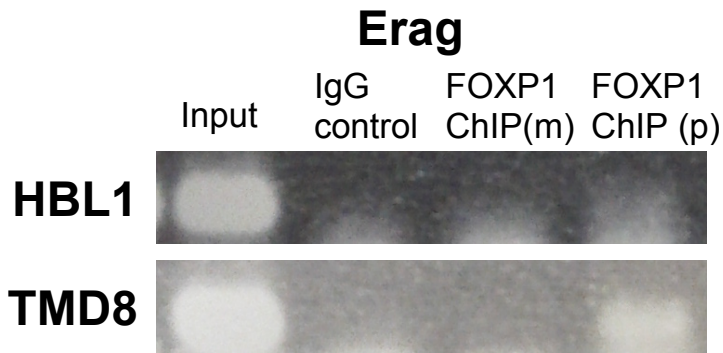
Figure S3: Endpoint RT-qPCR confirmation of FOXP1 targets established by ChIP-seq.
Top: Establishing endpoint ChIP-PCR conditions. Specificity of initial ChIP conditions with monoclonal or polyclonal FOXP1 antibodies were confirmed by employing a previously determined FOXP1 binding site, the enhancer of RAG (Erag) (54). Polyclonal anti-FOXP1 proved superior, and we proceeded with these conditions.
Bottom: Endpoint ChIP-PCR of FOXP1-bound target genes identified in our ChIP-seq dataset.
Primers designed for spanning peaks were:
SPIB F: AGGTGCTGACCTGTTTCCTCC, R: GGATAGAGATGGGAGTCGCTG;
BCL6 F: CTGGTGTCCGGCCTTTCCTA, R: GCAGTAAAAATCTCGGAGAGCTG;
PRDM1b F: CCGCCTGTGTTAAAGGGACA , R: AAGGCACTGTTCGTAGCAGG

Black box (top left):
ERP29 TRIM65 DUSP1 ARFGAP2
TPRA1 EML3 RPS6KB2 JMJD8
NOC2L UBE2J2 COMTD1 OGDH
COASY CCDC86 NACC1 C7orf50
TRMT2A SLC1A5 OAZ1 CTU1
GIT1 PQLC1 UBE2S NCAPH2
RANGAP1 SMPD4 POLD1 TRIM28
SNRNP70 SAMD4B GLTSCR1

Yellow box (top middle):
DDAH1 CD80 NEDD9 NCOA1
FMNL3 NEDD4L ARIH2 FOXP1
GBA2 PPFIA3 CABLES1 CPT1A
TLE3 TNS3 SYK KIF16B CALML6
OSR2 TMEM52 RGS1 RCAN2
SERP1 CUEDC2 MKNK2

Dark red box (top right):
GAS5 PARP8 IKZF2 ZCCHC7
TIFA PRRT2 TRIM41 SNX29
LOC147727 HIST1H1B LPP
FMO4 RRAGA BAG1 EMP3
CPEB3 BPTF USP6NL ZBTB20
ERP44 STIM2 CBLB ELOVL6
CNOT2 KLHL5 SLC25A11 CD69
TRIM22 TRANK1 RASSF6
TXLNB PLEKHH3 VPS13B
RALGPS2 PELI1 NCOA3
RALGPS1 FCRL4 KLF6 P2RX5
MTPN

Blue box (middle left):
ATP11A DGKZ C9orf139 AKT1S1
SBNO2 TBC1D17 TMC1 KLHL17
MFAP5 PLAC8 PRICKLE1
MTMR14 TLE4 ANXA6 ECE1
AHNAK ABCA7 DNASE1L3
ADAP1 IL4I1 PTPN1 BZRAP1
DUSP5P SLC12A7 CLCN5
BHLHE40 CCR7 NR4A2 PARVB
TTC28 LIMD1 GAB1 CASK
SH3PXD2A TNFRSF13B ARID5B
PRDM1 DMD RBM47 COL9A3
TOX2 CEP68 TP53I11 BANK1
FAM43A KMO JAZF1

Orange box (middle center):
RAP1GAP2 SCD SH3KBP1 GPER
LRRC32 DERL3 SEC14L1 FUZ
SIPA1L3 LIMK1 KIAA0226
AKAP13 CD22 PTK2 COTL1
POU2F2 SLC46A3 CD19 ST6GAL1
ZNF608 TIAM1 ZNF395

Cyan box (bottom center):
IL28RA DNAJB6 STK35 AGPAT6
RNF122 SNRPD3 MCM7
C14ORF93 SMARCB1 RBM38
STX10 ATF4 GPT2 LARP1
DEPDC5 MLLT6 SYNE2 RALGDS
MAF1 MXI1

Purple box (bottom right):
ZNF238 CSNK1G3 PPP1R12B
PJA2 USP3 FCHO2 PDE4DIP
VPS13D DHTKD1 DHTKD1
MBNL1 MEF2C PIK3R1 CCDC6
C3ORF26 NLN FILIP1L CKAP2
HSPD1 MDM2 SEPSECS OXR1
HIF1A NFE2L2 BACH1 FNDC3A
RANBP2 ADAM10 NIPBL PHIP
CHD9 LCOR C3ORF58 UBE2G1
TRIM37 ZZZ3 PCMTD2 CCPG1
NEK7 DDHD1 C15ORF29 CASC4
PTEN OTUD1

Black box (bottom left):
ABI1 FADD PGK1 C15orf39
DHRS13 TIGD6 GTF3C2 CNP

Figure S4. Genes listed in heatmap for Figure 3A (color code is on right side of heatmap). **RED** are genes that went DOWN after FOXP1 KD, and are directly upregulated by FOXP1 and **GREEN** are genes that went UP after FOXP1 KD and are directly repressed.
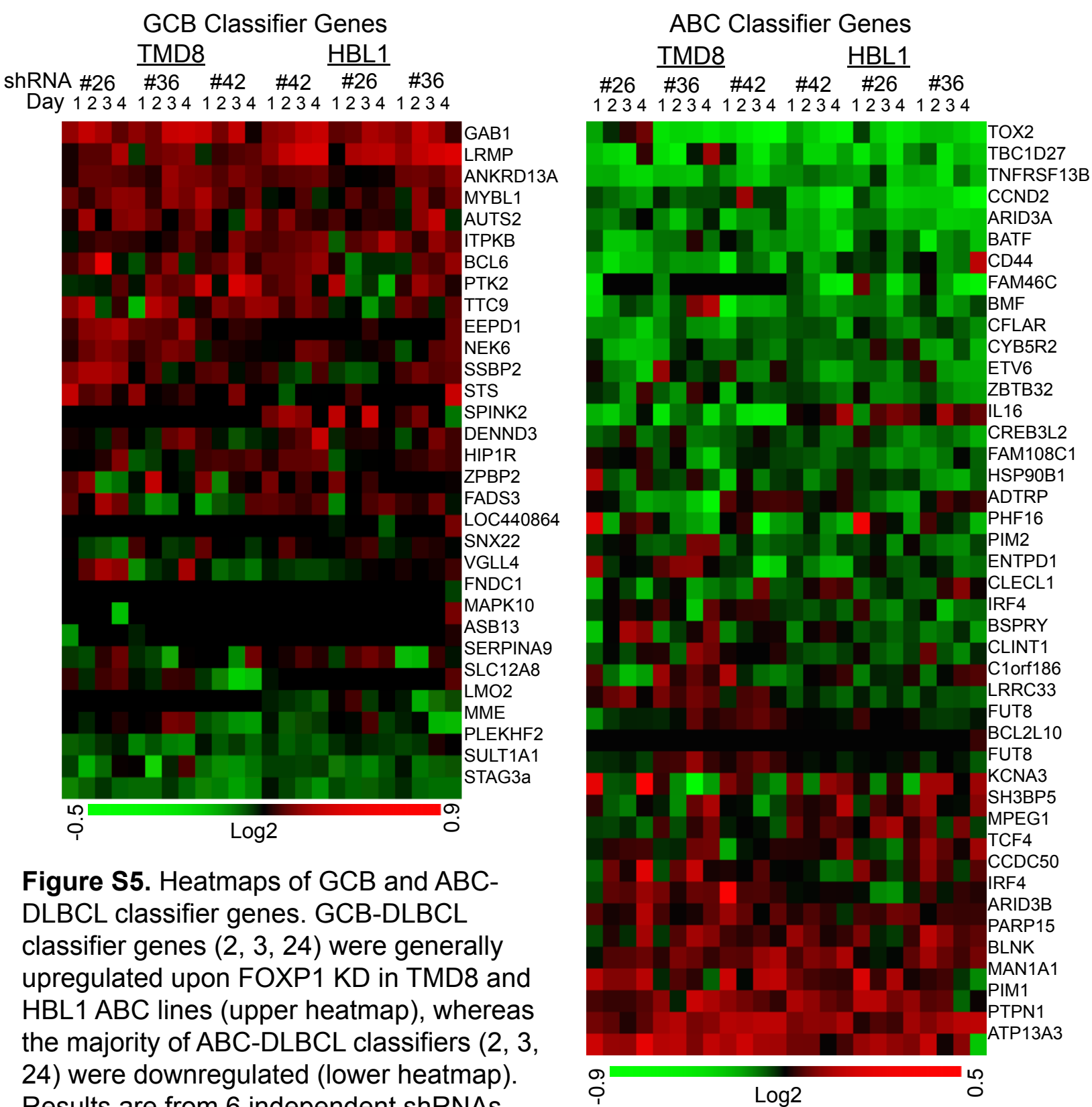
Figure S5. Heatmaps of GCB and ABC-DLBCL classifier genes. GCB-DLBCL classifier genes (2, 3, 24) were generally upregulated upon FOXP1 KD in TMD8 and HBL1 ABC lines (upper heatmap), whereas the majority of ABC-DLBCL classifiers (2, 3, 24) were downregulated (lower heatmap). Results are from 6 independent shRNAs (#'s indicated) following induction for indicated times (days).

Gene Ontology Analysis

p value (log10)	Gene #	Pathway
	103	Cell activation
	45	Leukocyte activation
	49	Lymphocyte activation
	25	Positive regulation of cell death
	74	Positive regulation of apoptosis
	70	B cell activation
	21	Positive regulation of programmed cell death
	70	Regulation of phosphorylation
	71	Regulation of Ras GTPase activity
	42	Cell migration
	51	Regulation of protein kinase cascade
	59	Death

Figure S6: Genes qualified as modulated when 5/12 samples (See Fig S1 for the 12 samples and their timepoints) reached a log2 +/- 0.3 value change for either the HBL1 or TMD8 cell lines after shRNA interference of FOXP1 expression. For Gene Ontology analysis, the top half of qualified activated and repressed genes were analyzed by DAVID analysis (49,50) using GO_TERM_BP_FAT functional annotation. Gene # are the number of modulated genes intersecting with the indicated pathway.
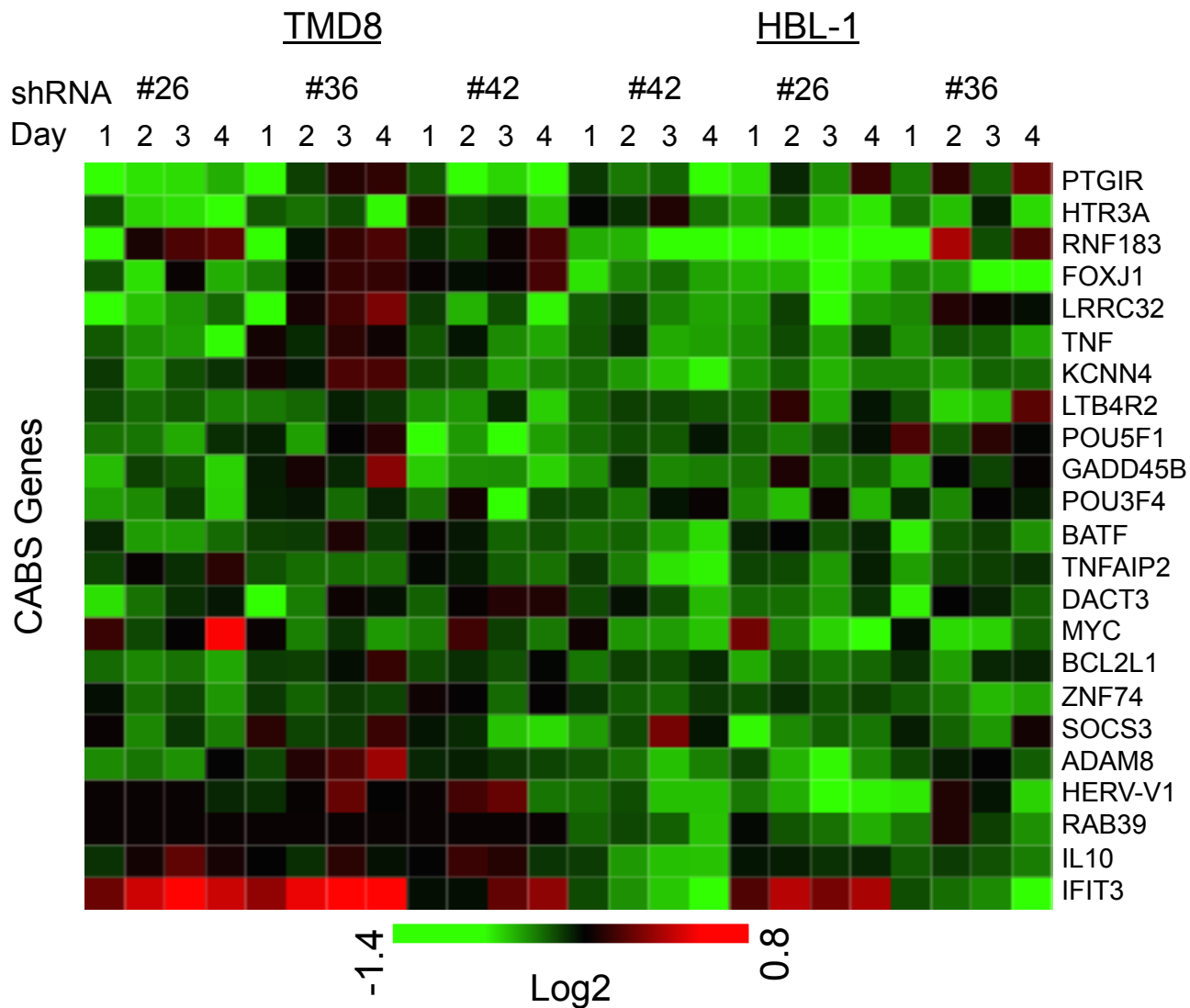
Figure S7. Heatmap of modulated genes from a hallmark of ABC-DLBCL, chronic activation of BCR signaling (8), are nearly all upregulated by FOXP1.
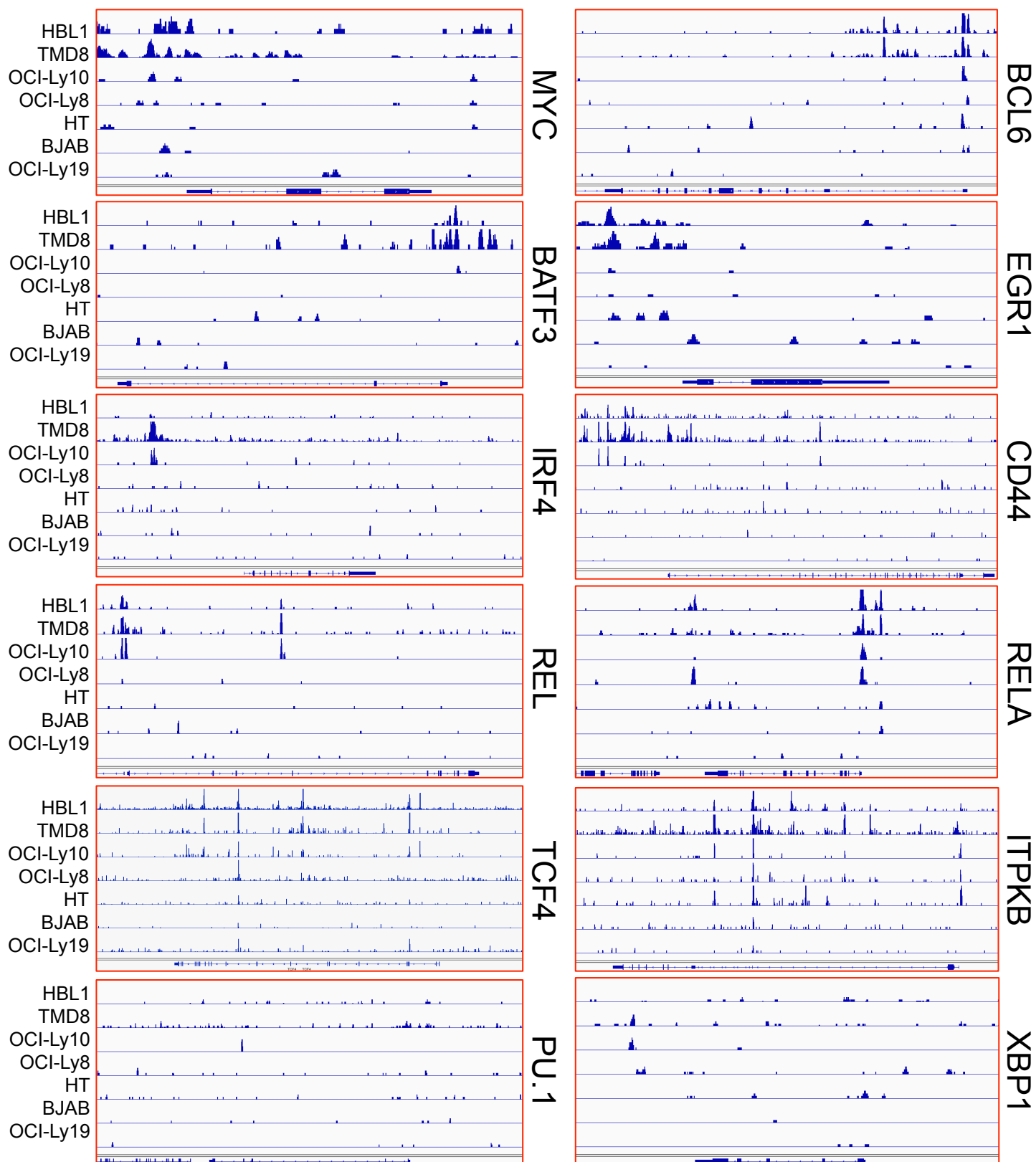
Figure S8. Examples of peak mapping along the loci of select genes relevant to B cell identity (BCL6), cell survival/proliferation (MYC, EGR1), NF-κB (REL, RELA) plasmacytic differentiation (IRF4, BATF3) and ABC (CD44, TCF4, MYC) or GCB-DLBCL(ITPKB). ChIP-seq peaks from seven DLBCL cell lines were determined and aligned. In general, many loci had aligned peaks across all seven lines while many had aligned peaks only in ABC-lines, indicating different binding patterns between the two DLBCL types. Still other relevant loci that were or were not modulated had no aligned peaks, as with PU.1 (not modulated) and XBP1 (activated by FOXP1, Fig.4A,6A).

FOXP1 bound genes, this study

ABC-lines 2836 | 6380 | GCB-lines 3486

FOXP1 in ABC-lines 7512 | 1705 | BCL6 1495

FOXP1 in GCB-lines 8378 | 1488 | BCL6 1712
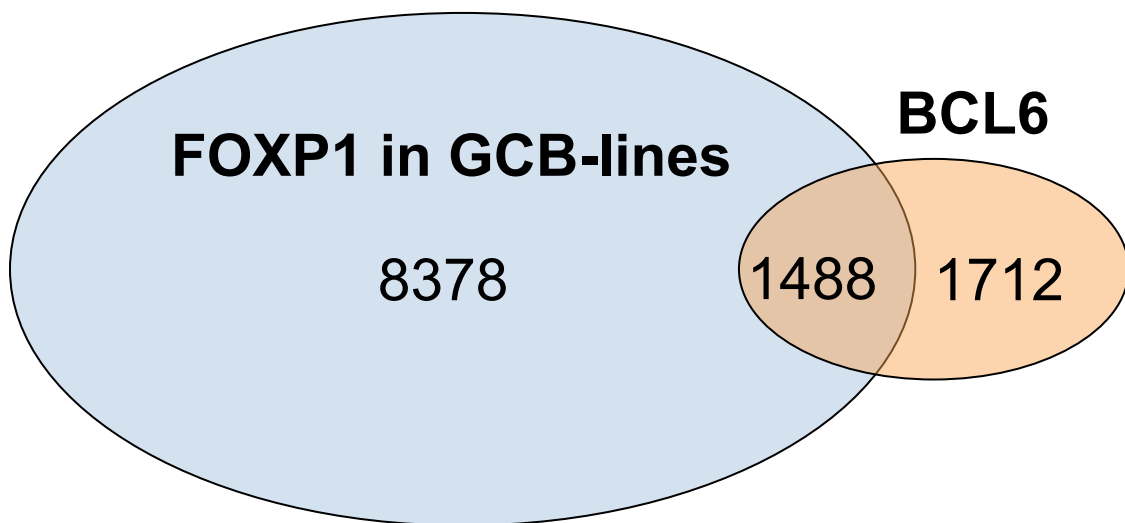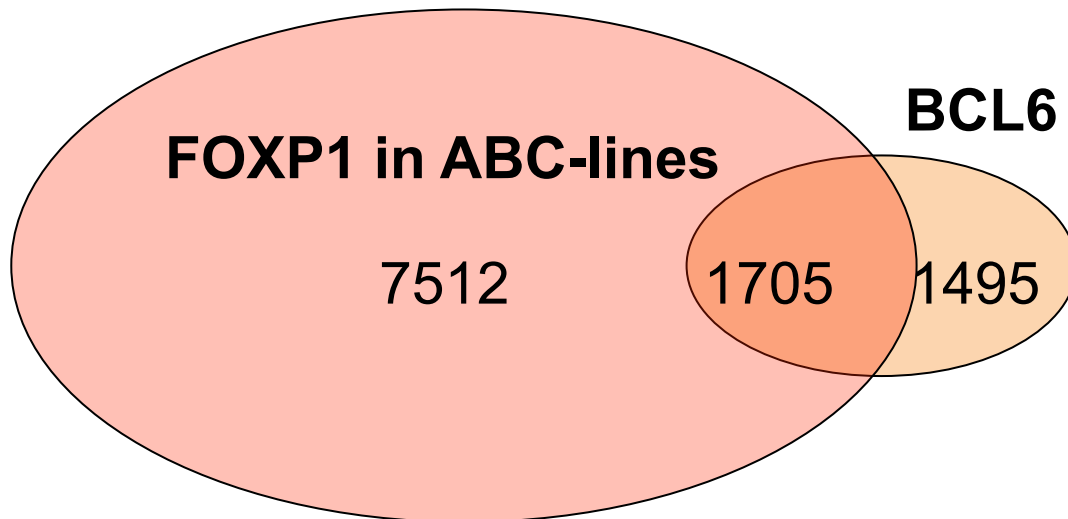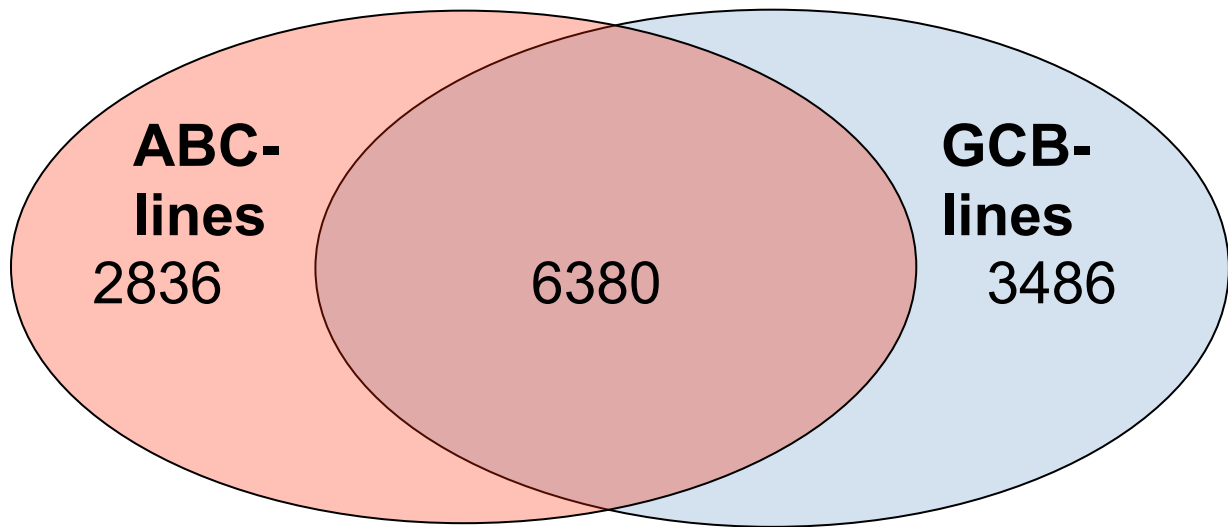
FOXP1 bound genes in ABC-lines
FOXP1 bound genes in GCB-lines
BCL6 bound genes Ci et. al.

Figure S9: Venn diagrams of: Top) FOXP1 gene targets shared by in ABC vs. GCB-lines, middle) BCL6 gene targets from Ci et. al. 2012 (31) shared by FOXP1 ABC-line gene targets, or (bottom) The same BCL6 gene targets shared by FOXP1 GCB-line gene targets. All FOXP1 gene targets were determined by GREAT analysis (35).
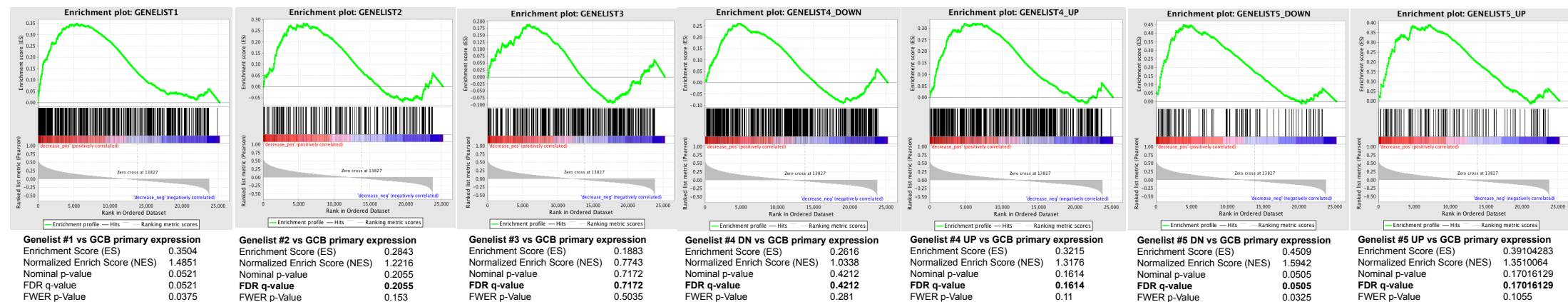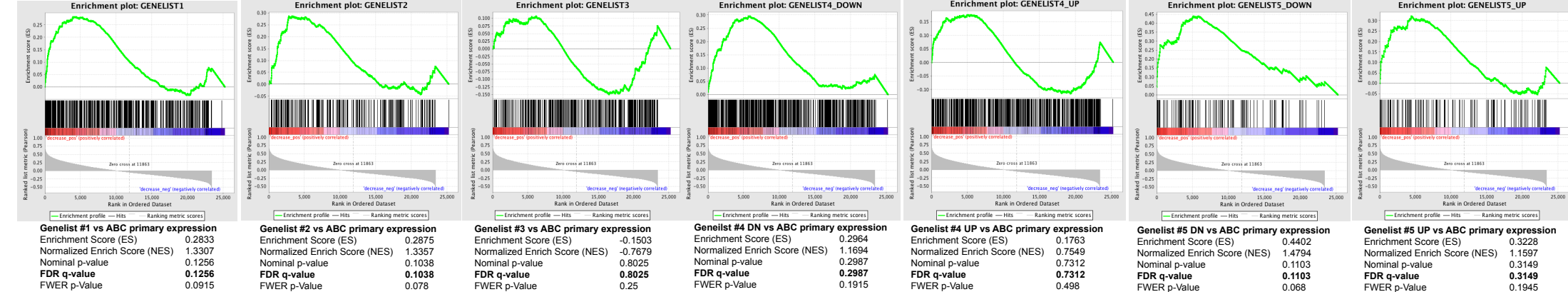
Figure S10: Gene Set Enrichment Analysis (GSEA) of defined genelists (Fig 7B, Table S3). Each list was correlated with FOXP1 gene expression in ABC or GCB primary RNA-seq data from the dbGenotypes and Phenotypes database (dbGaP; accession number: phs00235)

Below: Enriched Gene set #1 compared with ABC primary DLBCL expression
Right: Enriched Gene set #1 compared with GCB primary DLBCL expression
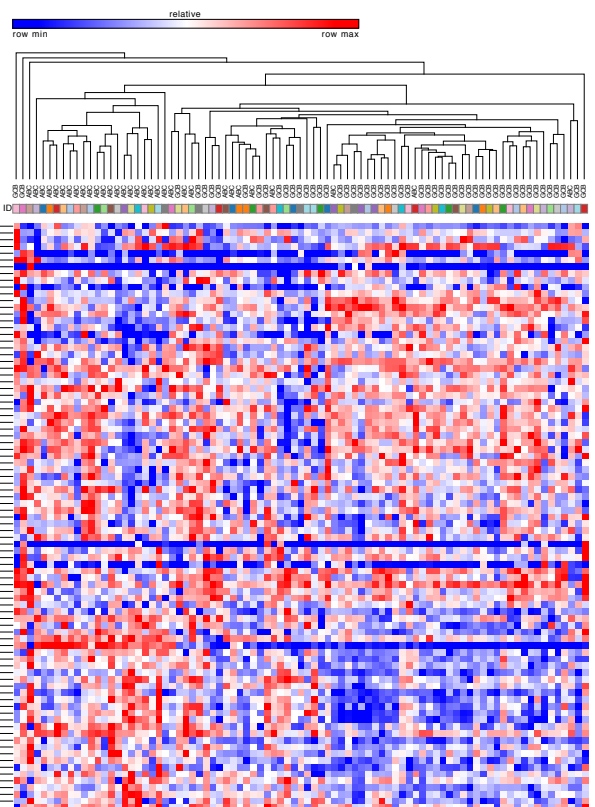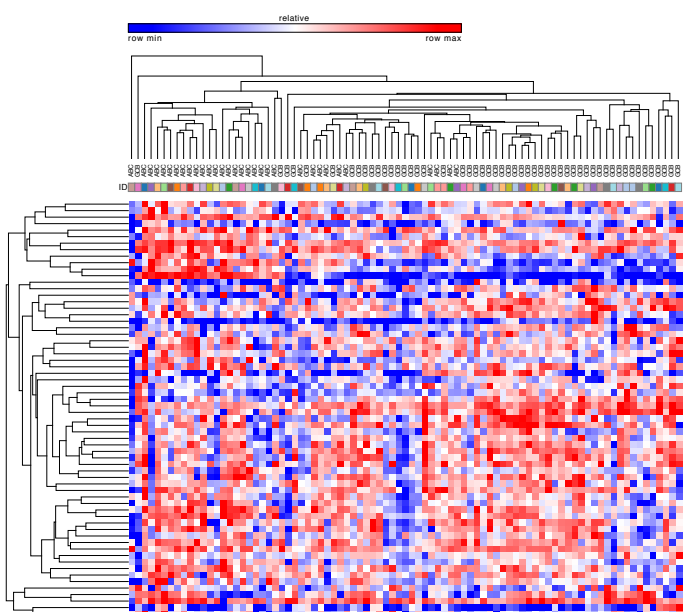
Below: Enriched Gene set #2 compared with ABC primary DLBCL expression
Right: Enriched Gene set #2 compared with GCB primary DLBCL expression
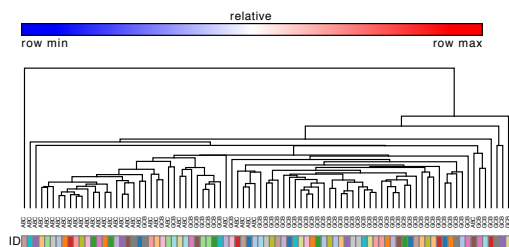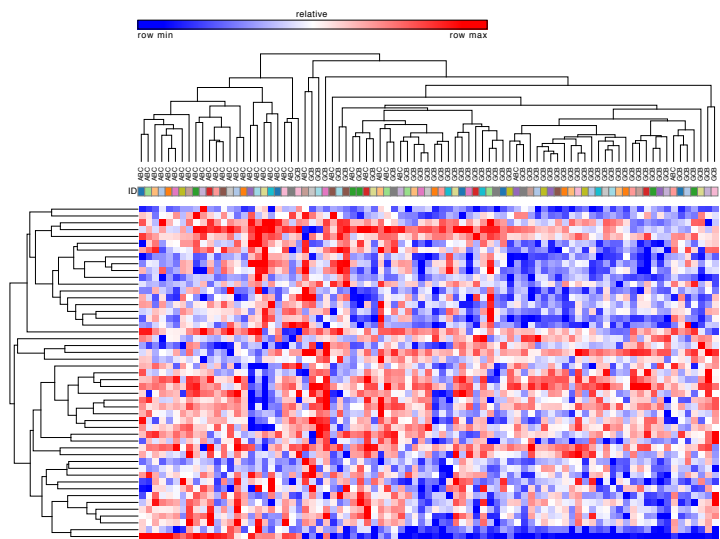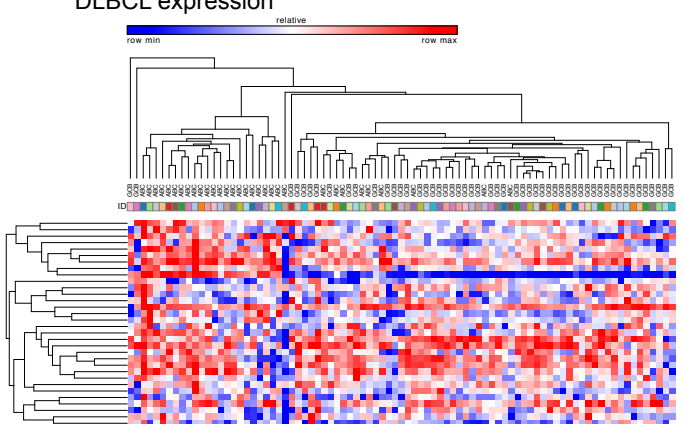
Below: Enriched Gene set #3 compared with GCB primary DLBCL expression
Left: Enriched Gene set #3 compared with ABC primary DLBCL expression
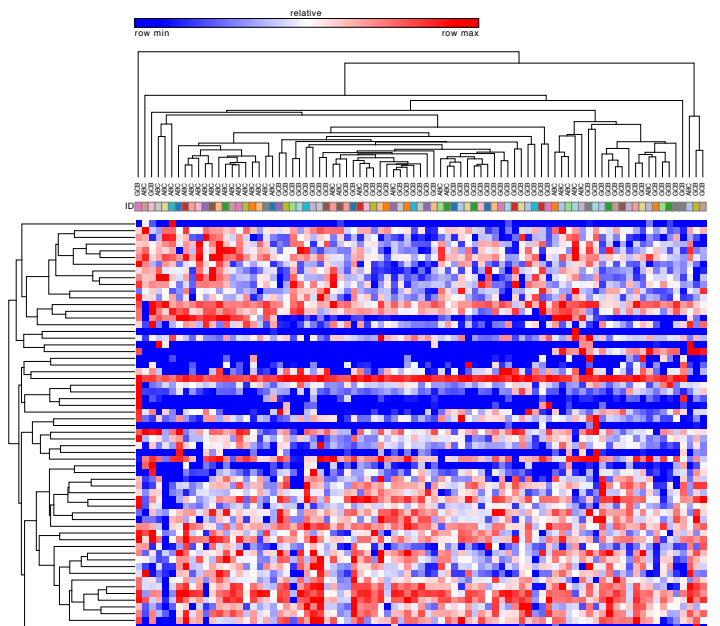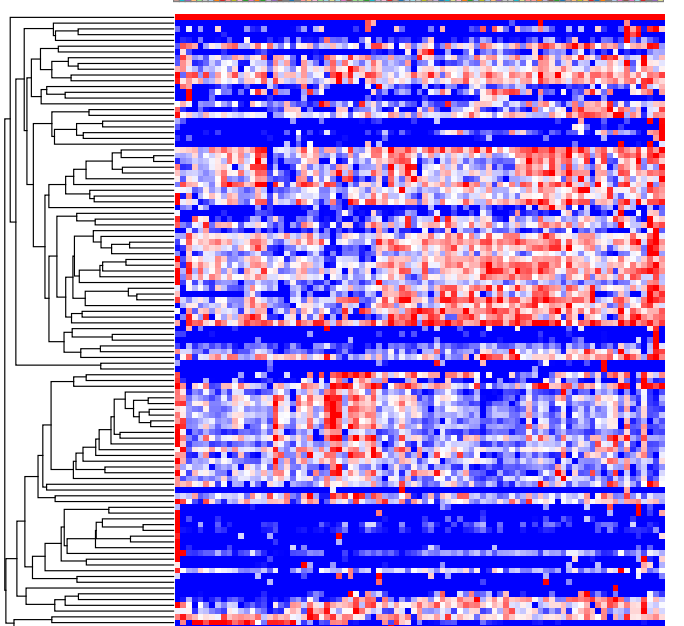
Figure S11: Primary DLBCL expression for each gene form GSEA derived gene lists (Fig. 7B) were compared to ABC or GCB primary expression (dbGaP: accession number: phs000235) and then hierarchically clustered by expression to determine the ability of each FOXP1 target gene set to segregate ABC from GCB subtypes. Genes were also hierarchically clustered along the x axis. Gene lists are zoomable or available in Table S3.
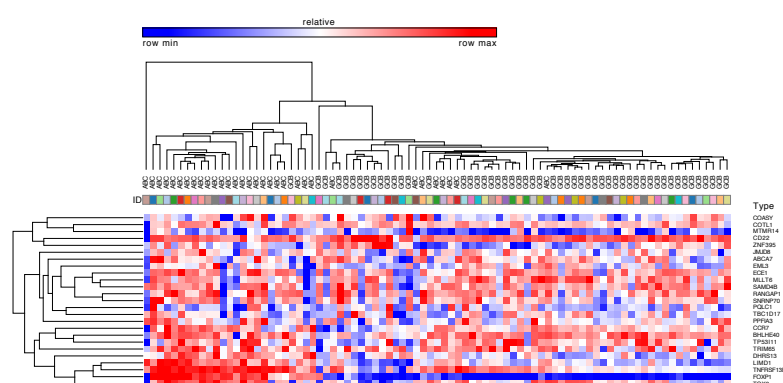
Below: Enriched Gene set #4 Downregulated genes compared with GCB primary DLBCL expression
Left: Enriched Gene set #4 Downregulated genes compared with ABC primary DLBCL expression

Below: Enriched Gene set #4 Upregulated genes compared with ABC primary DLBCL expression
Right: Enriched Gene set #4 Upregulated genes compared with GCB primary DLBCL expression
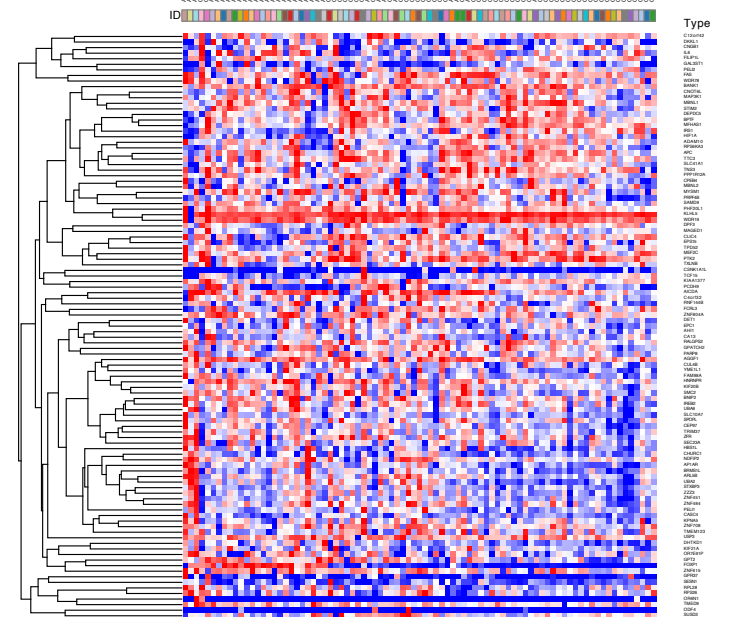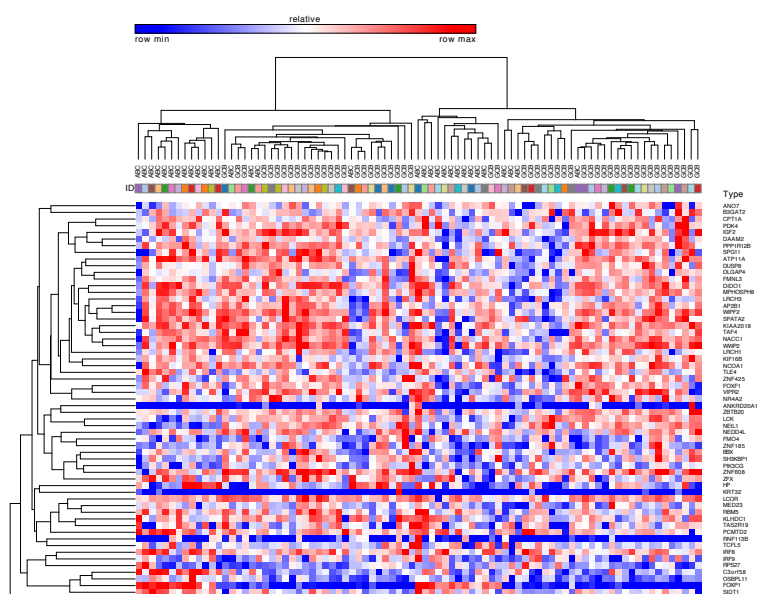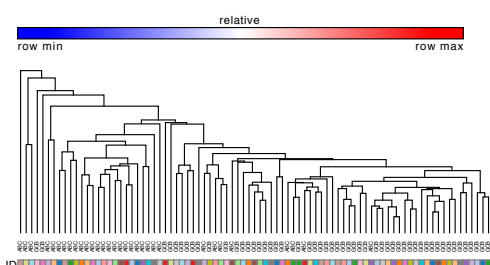
Below: Enriched Gene set #5 Downregulated genes compared with GCB primary DLBCL expression
Left: Enriched Gene set #5 Downregulated genes compared with ABC primary DLBCL expression

Below: Enriched Gene set #5 Upregulated genes compared with ABC primary DLBCL expression
Right: Enriched Gene set #5 Upregulated genes compared with GCB primary DLBCL expression
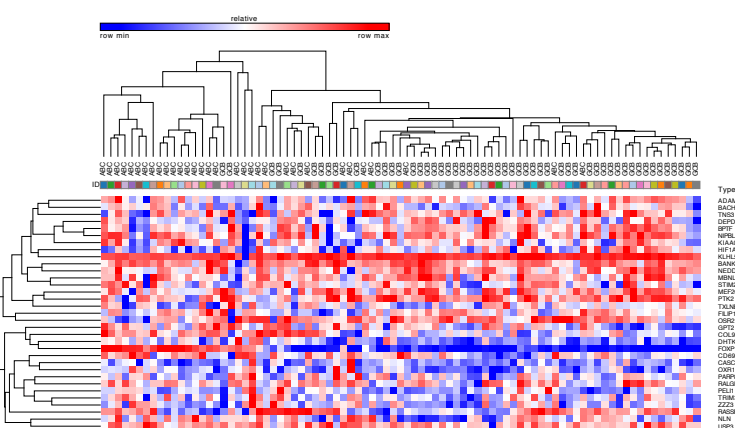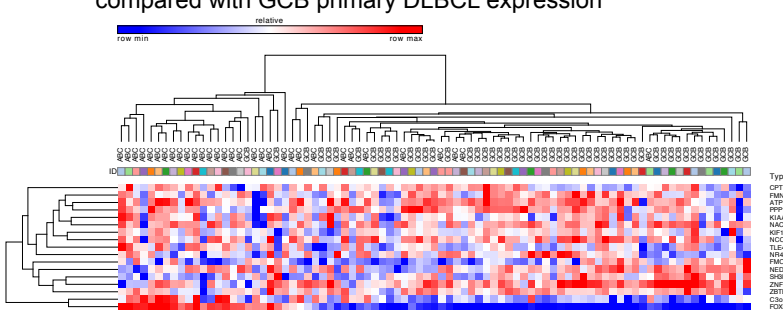
Figure S11 (cont): Primary DLBCL expression for each gene form GSEA derived gene lists (Fig. 7B) were compared to ABC or GCB primary expression (dbGaP: accession number: phs000235) and then hierarchically clustered by expression to determine the ability of each FOXP1 target gene set to segregate ABC from GCB subtypes. Genes were also hierarchically clustered along the x axis. Gene lists are zoomable or available in Table S3.

NF-κB

ARF3 BAX BCL2L1
CASC4 CCNL1 CCR7 CD22
CD69 CDCA7L CTU1
ECE1 FCRL2 GADD45B IL6
JMJD8 LAT2 MAN2B1
MCCC2 MEPCE MYC
NAGPA NAP1L1 NFATC2
NOVA1 PLK3 PRMT1 RAC2
SCARB1 SLC38A5 SPATA2
STK35 STXBP3 TNF
TRAF3IP3 TSR2 VPS53
YME1L1 ZNF395

JAK-STAT

ACAD10 ADAM15 AKT1 ANKLE1
AP1B1 APH1A ARFGAP1 ATAD3B
ATM BAX BCL2L1 CAMKK2
CCDC86 CD22 CHMP4B CNOT6L
CNP CTU1 DCAF10 DDX54 DIAPH3
ECE1 EIF2S1 ERF FAM126B
FAM98A FKBP4 FOSL2 FOXK1
FUT8 GADD45B GANAB GGT3P
GPT2 GRAP HES1 HMBS
IGHMBP2 IRF2BP2 KCTD17 KHSRP
KIAA0020 LAT2 LIMD1 LPP LZTR1
MAN2B1 MAPK12 MBNL1 MICALL1
MPHOSPH8 MYC NAA25 NEDD9
NLN NLRC5 NOC2L PHLDA3
PKMYT1 PM20D2 POLD2 PQLC1
PRELID2 PRNP PRPS1 PRR7
PUS1 RANGAP1 RXRA RXRA
SBNO1 SCARB1 SH2B1 SH3BP2
SIRT6 SLC1A5 SLC38A5 SLC5A3
SLMAP SNRNP70 SSBP4 STK35
TACC1 TBC1D17 TLE4 TMED9
TMEM44 TNF TNPO1 TOX2
TP53I13 TRIM14 TRIM28 TSR2
TTC3 UBA6 VASH2 WDR12
ZMYND8

MYD88

ARFGAP1 CCDC86 CCR7
CD22 CD69 CTU1 FKBP4
GADD45B HMBS IL6 JAK3
KCTD17 LAT2 NOC2L
PLK3 POLD1 PRR7 PRRG2
RAI1 RUNX1 SCARB1
SLC1A5 SLC1A5 SNRNP70
SNRPF TIMM13 TLE3 TNF
TNFRSF13B TRIM65 TSR2
TUB UBE2S

Figure S12. Genes contained within GSEA derived gene lists were identified in NFκB, MYD88, and JAK-STAT gene signatures (10).