

Title:

Identification of p38 beta as a therapeutic target for the treatment of Cutaneous T-Cell Lymphoma

Authors:

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Supplemental Figure Legends:**Supplemental Figure S1. Confirmation of cell death induced by small-molecule inhibitors.**

Hut78 cells were cultured with Enz, ARA, Enz+ARA, or DMSO and collected after 3 days. Data from four replicates were averaged. **(a)** Apoptosis measured by Annexin V staining and measured by flow cytometry. Positive stained cells quantified as percentage of total single cells. **(b)** Representative flow plots from **a**. **(c)** mRNA expression measured by qRT-PCR, normalized to house-keeping genes, and normalized to DMSO treatment. **(d)** Total β -catenin protein expression, normalized to β -actin, measured by immunoblot. **(e)** Quantification of **d**.

Supplemental Table S1. Small-molecule microarray GSEA pathways: statistical values, Figure 1 order.**Supplemental Figure S2. Pathways enriched and genes modulated by combined small-**

molecule treatment of Hut78 cells. Fold changes for each treatment (Enz, ARA, Enz+ARA) normalized to DMSO for common genes of GSEA significant pathway. **(a)** T-Cell Receptor signaling pathway genes modulated by combination treatment. **(b)** p38 α/β downstream signaling pathway genes modulated by Enz+ARA. **(a)** and **(b)** both pathways share MAPK11 (p38 β).

Supplemental Figure S3. Confirmation and validation of drug treatment microarray experiment. H9 and Hut78 cells were cultured with standard Enz+ARA drug treatment conditions. Data from three replicates were averaged. **(a)** PARP protein cleavage, normalized to α -tubulin, measured by immunoblot. Representative immunoblot images of three replicates. **(b)** Apoptosis measured by Annexin V staining and measured by flow cytometry. Positive stained cells quantified as percentage of total single cells. **(c)** Representative flow plots from **b**. **(d)** AXIN2, CD4, ICOS, and LAT mRNA expression measured by qRT-PCR, normalized to housekeeping genes, and normalized to DMSO treatment as described in materials and methods.

Supplemental Table S2. SS patient GSEA pathways: statistical values, Figure 2 order.

Supplemental Figure S4. Pathways enriched and genes modulated in SS patient samples. Fold changes for common genes of GSEA significant pathway. **(a)** T-Cell Receptor signaling pathway genes modulated in SS patients. **(b)** MAPK signaling pathway genes modulated in SS patients. **(a)** and **(b)** both pathways share MAPK11 (p38 β).

Supplemental Table S3. Negative correlation gene list: FC 89 genes up-regulated in SS patients and down-regulated Enz+ARA combined drug treatment Hut78 cells.

Supplemental Table S4. Negative correlation gene list: FC 34 genes down-regulated in SS patients and up-regulated Enz+ARA combined drug treatment Hut78 cells.

Supplemental Figure S5. Quantification of p38-isoform protein expression in SS cell lines after small-molecule inhibitor treatment and endogenous healthy volunteers and patient samples p38 isoform immunoblots. (a-d) H9 and Hut78 cells were treated with standard Enz+ARA treatment and collected. Data from three replicates were averaged. For graphic representation, p38 isoform expression was normalized to loading control (α -tubulin) expression and then normalized to DMSO control. (a) p38 α (b) p38 β (c) p38 γ (d) p38 δ . (e) p38 isoforms protein expression, normalized to α -tubulin, were measured by immunoblot. (Quantification, Figure 3d).

Supplemental Figure S6. Confirmation of cell death induced by p38 small-molecule inhibitors in SS cell lines. H9 and Hut78 cells were cultured with a dose range of either SB202, SB203, or BIRB. (a,c,e) PARP protein cleavage, normalized to α -tubulin, measured by immunoblot. Representative immunoblot images of three replicates. (b,d,f) Representative flow cytometry plots from Figure 4a. (a,b) SB202 (c,d) SB203 (e,f) BIRB.

Supplemental Figure S7. Example of primary patient sample flow cytometry gating for PBMC p38 drug treatment experiments. PBMCs were harvested, treated with increasing doses of SB202, SB203 or BIRB. Apoptosis was measured by Annexin V or Cleaved Caspase 3/7 staining and measured by flow cytometry. Positive stained cells quantified as percentage total PBMCs. (a) SB202 treatment (b) SB203 treatment (c) BIRB treatment.

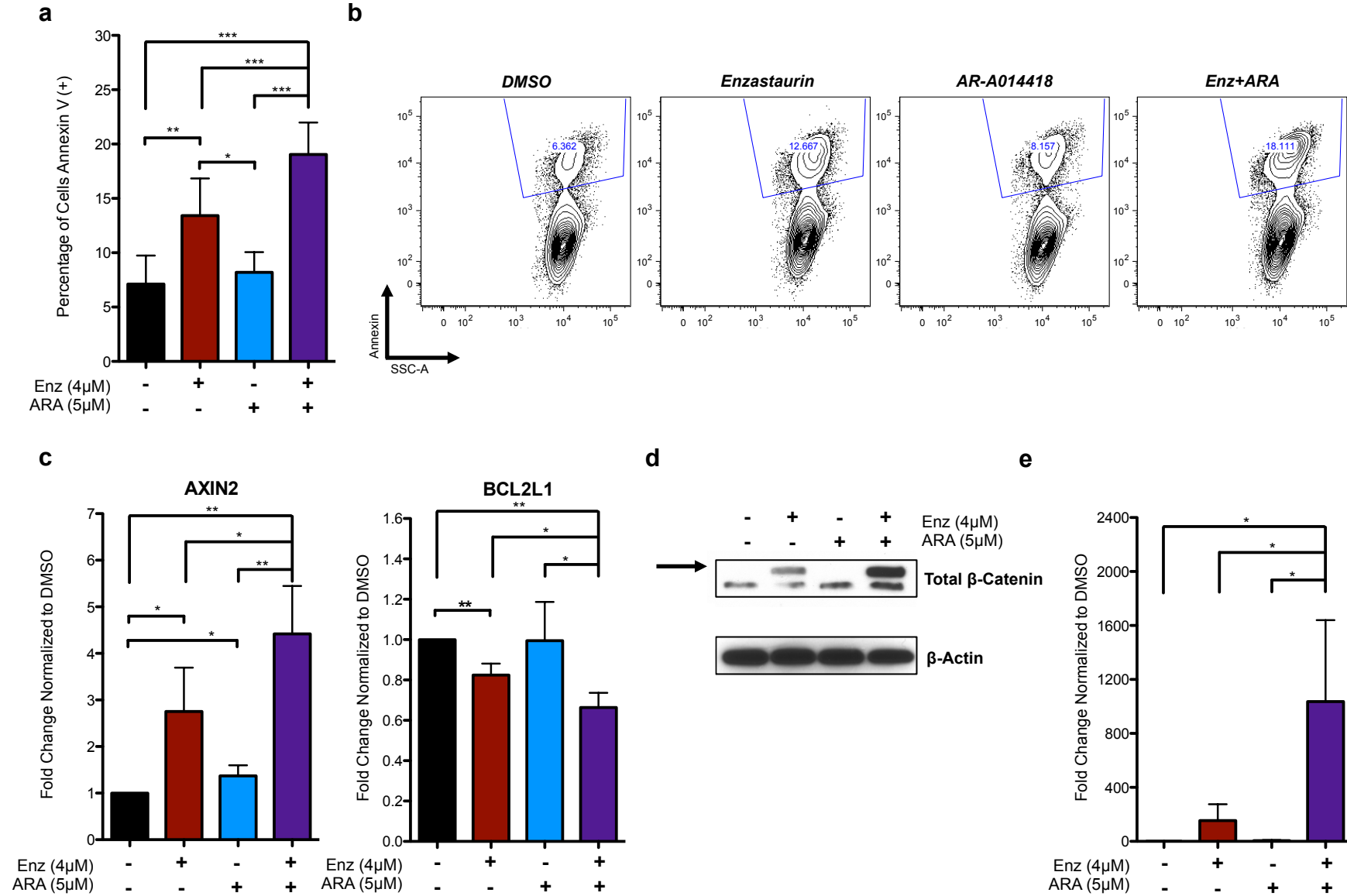
Supplemental Figure S8. Importance of p38 signaling in primary SS patient samples, confirmation of cell death by Cleaved Caspase 3/7 staining. (a-c) PBMCs were harvested from SS patients (n=3) and healthy volunteers (n=5) and treated with increasing concentrations of SB202, SB203, or BIRB. Apoptosis measured by Cleaved Caspase 3/7 staining and

measured by flow cytometry. Positive stained cells quantified as percentage of total PBMCs.

Example of PBMC gating schematics for Cleaved Caspase 3/7 over p38 dose concentrations

can be seen in Supplemental Figure 7, online. **(a)** SB202 **(b)** SB203 **(c)** BIRB.

Supplemental Figure 1: Confirmation of cell death induced by small-molecule inhibitors.

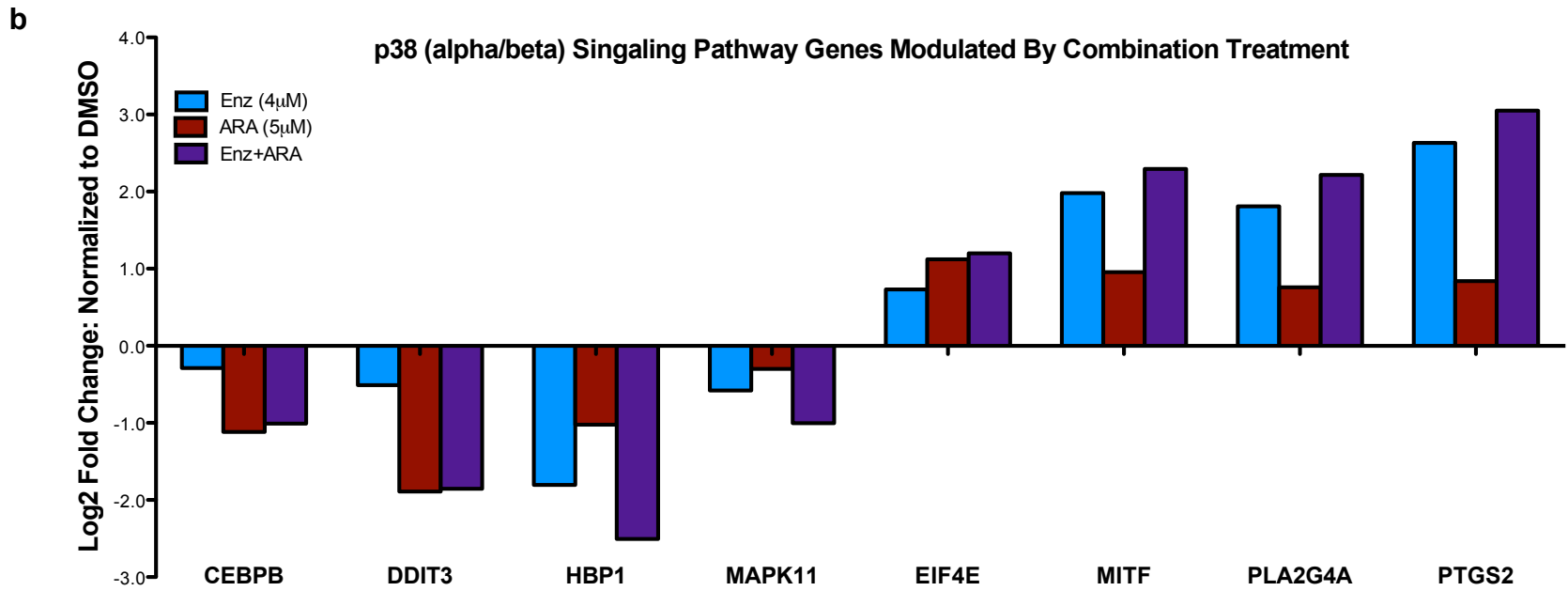
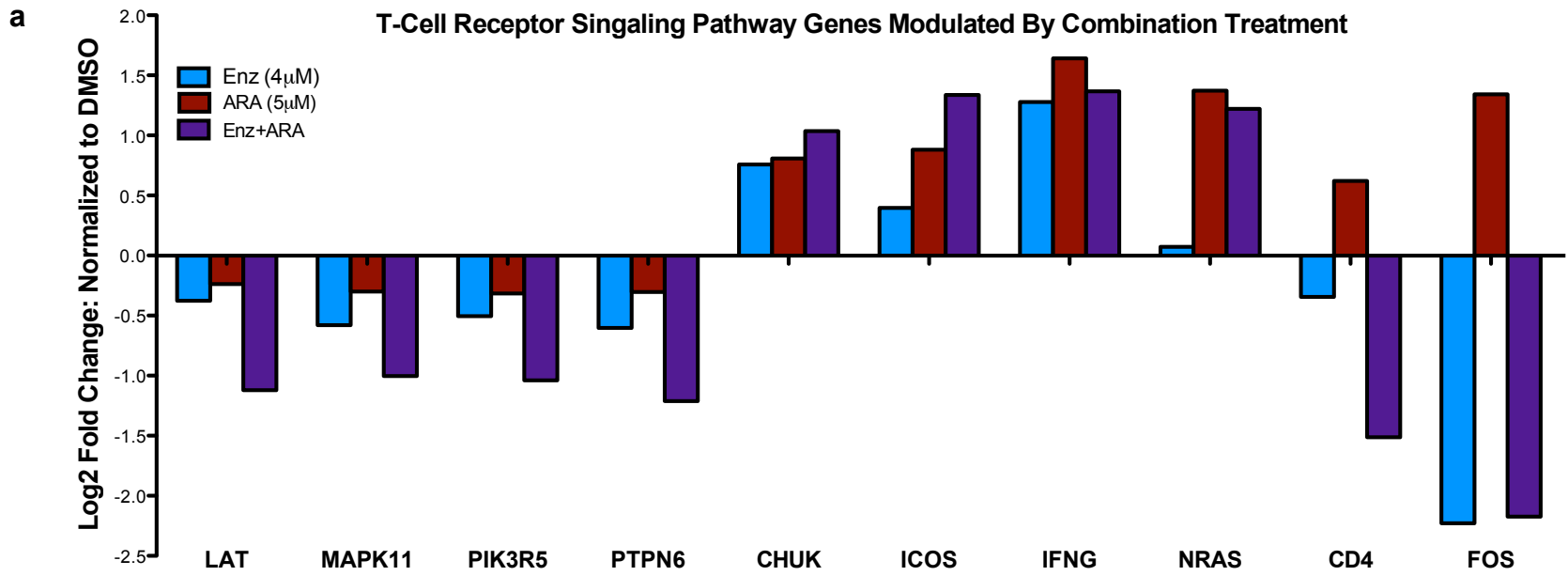


Supplemental Table S1. Small-molecule microarray GSEA pathways: statistical values, Figure 1 order.

Gene Set Name and Description	p-value	FDR	# Genes in Gene Set (K)	# Genes in Overlap (k)	k/K
REACTOME_IMMUNE_SYSTEM <i>Genes involved in Immune System</i>	4.55E-11	6.61E-08	933	70	0.0750
REACTOME_ADAPTIVE_IMMUNE_SYSTEM <i>Genes involved in Adaptive Immune System</i>	3.24E-07	0.00005	539	41	0.0761
REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM <i>Genes involved in Cytokine Signaling in Immune system</i>	2.11E-06	0.00020	270	25	0.0926
REACTOME_INNATE_IMMUNE_SYSTEM <i>Genes involved in Innate Immune System</i>	0.00164	0.03270	279	19	0.0681
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY <i>Toll-like receptor signaling pathway</i>	0.00002	0.00112	102	13	0.1275
REACTOME_MHC_CLASS_II_ANTIGEN_PRESENTATION <i>Genes involved in MHC class II antigen presentation</i>	0.00001	0.00037	91	13	0.1429
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION <i>Antigen processing and presentation</i>	4.74E-06	0.00031	89	13	0.1461
REACTOME_COSTIMULATION_BY_THE_CD28_FAMILY <i>Genes involved in Costimulation by the CD28 family</i>	4.31E-06	0.00030	63	11	0.1746
KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY <i>T-cell receptor signaling pathway</i>	0.00235	0.04160	108	10	0.0926
PID_IL2_1PATHWAY <i>IL2-mediated signaling events</i>	0.00033	0.01080	55	8	0.1455
BIOCARTA_NKT_PATHWAY <i>Selective expression of chemokine receptors during T-cell polarization</i>	0.00202	0.03710	29	5	0.1724
REACTOME_INTERFERON_SIGNALING <i>Genes involved in Interferon Signaling</i>	8.14E-07	0.00008	159	19	0.1195
REACTOME_INTERFERON_GAMMA_SIGNALING <i>Genes involved in Interferon gamma signaling</i>	6.00E-07	0.00007	63	12	0.1905
PID_IL12_2PATHWAY <i>IL12-mediated signaling events</i>	4.31E-06	0.00030	63	11	0.1746
REACTOME_INTERFERON_ALPHA_BETA_SIGNALING <i>Genes involved in Interferon alpha/beta signaling</i>	0.00003	0.00156	64	10	0.1562
PID_IFNGPATHWAY <i>IFN-gamma pathway</i>	0.00154	0.03160	40	6	0.1500
KEGG_PATHWAYS_IN_CANCER <i>Pathways in cancer</i>	2.64E-06	0.00023	328	28	0.0854

KEGG_MAPK_SIGNALING_PATHWAY <i>MAPK signaling pathway</i>	0.00239	0.04190	267	18	0.0674
KEGG_CHEMOKINE_SIGNALING_PATHWAY <i>Chemokine signaling pathway</i>	0.00117	0.02660	190	15	0.0789
KEGG_JAK_STAT_SIGNALING_PATHWAY <i>Jak-STAT signaling pathway</i>	0.00045	0.01340	155	14	0.0903
REACTOME_SIGNALING_BY_INSULIN_RECEPTOR <i>Genes involved in Signaling by Insulin receptor</i>	0.00017	0.00647	108	12	0.1111
REACTOME_DOWNSTREAM_SIGNALING_OF_ACTIVATED_FGFR <i>Genes involved in Downstream signaling of activated FGFR</i>	0.00132	0.02940	100	10	0.1000
PID_BETACATENIN_NUC_PATHWAY <i>Regulation of nuclear beta catenin signaling and target gene transcription</i>	0.00022	0.00803	80	10	0.1250
REACTOME_INSULIN_RECEPTOR_SIGNALLING_CASCADE <i>Genes involved in Insulin receptor signalling cascade</i>	0.00178	0.03390	87	9	0.1034
KEGG_TGF_BETA_SIGNALING_PATHWAY <i>TGF-beta signaling pathway</i>	0.00165	0.03270	86	9	0.1047
KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY <i>B cell receptor signaling pathway</i>	0.00061	0.01650	75	9	0.1200
PID_P38ALPHABETADOWNSTREAMPATHWAY <i>Signaling mediated by p38-alpha and p38-beta</i>	0.00002	0.00112	38	8	0.2105
REACTOME_PI3K_CASCADE <i>Genes involved in PI3K Cascade</i>	0.00183	0.03410	71	8	0.1127
PID_SHP2_PATHWAY <i>SHP2 signaling</i>	0.00235	0.04160	58	7	0.1207
REACTOME_PD1_SIGNALING <i>Genes involved in PD-1 signaling</i>	0.00019	0.00724	18	5	0.2778

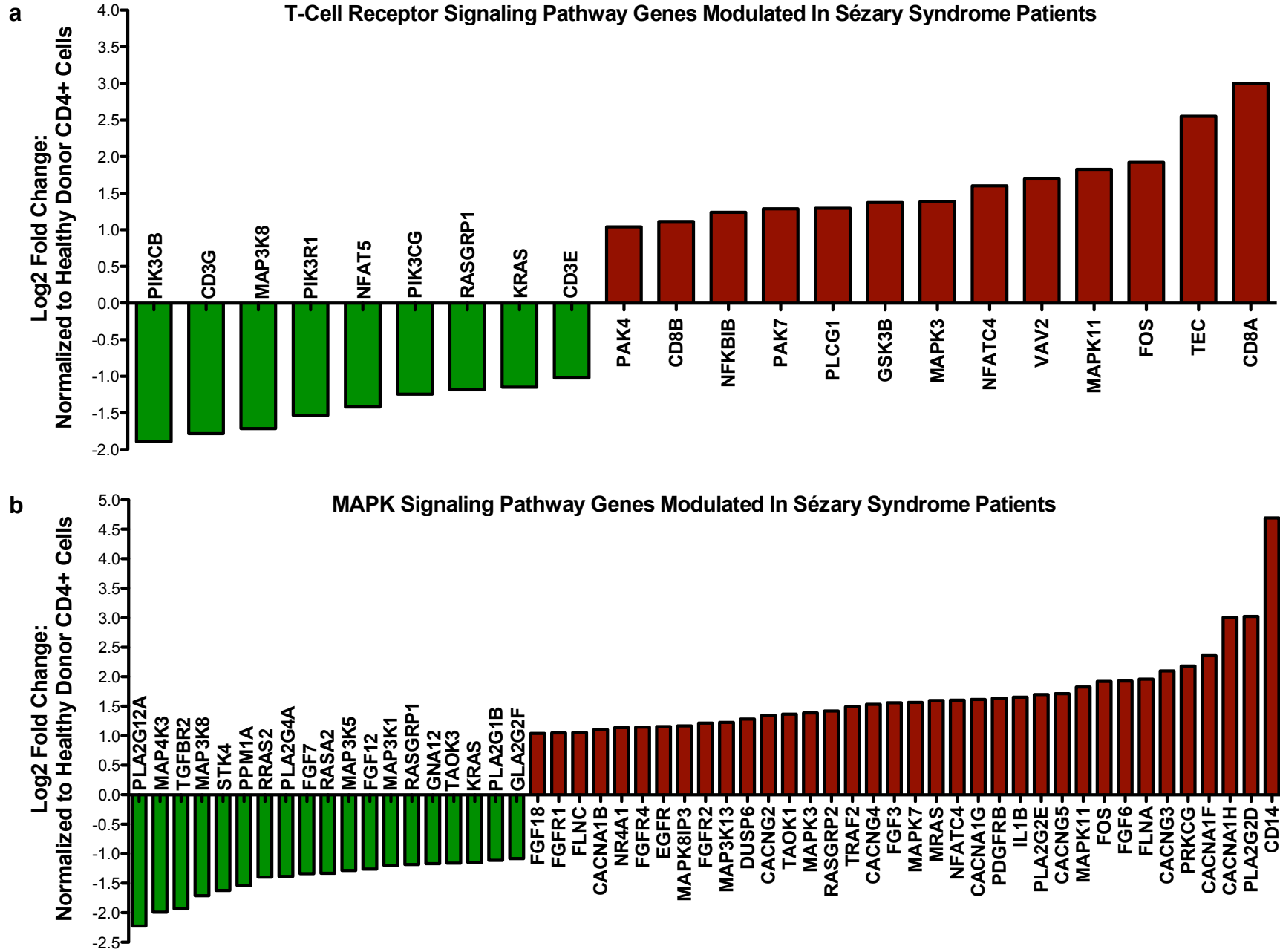
Supplemental Figure 2. Pathways enriched and genes modulated by combined small-molecule treatment of Hut78 cells.



Supplemental Table S2. SS patient GSEA pathways: statistical values, Figure 2 order.

Gene Set Name and Description	p-value	FDR	# Genes in Gene Set (K)	# Genes in Overlap (k)	k/K
KEGG_PATHWAYS_IN_CANCER <i>Pathways in cancer</i>	0.000E+00	0.000E+00	328	83	0.2530
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION <i>Cytokine-cytokine receptor interaction</i>	0.000E+00	0.000E+00	267	74	0.2772
KEGG_MAPK_SIGNALING_PATHWAY <i>MAPK signaling pathway</i>	6.660E-16	2.480E-14	267	55	0.2060
KEGG_CHEMOKINE_SIGNALING_PATHWAY <i>Chemokine signaling pathway</i>	1.330E-15	4.130E-14	190	45	0.2368
KEGG_JAK_STAT_SIGNALING_PATHWAY <i>Jak-STAT signaling pathway</i>	3.660E-11	5.230E-10	155	34	0.2194
KEGG_ENDOCYTOSIS <i>Endocytosis</i>	4.790E-08	3.180E-07	183	32	0.1749
KEGG_HEMATOPOIETIC_CELL_LINEAGE <i>Hematopoietic cell lineage</i>	1.490E-14	3.950E-13	88	29	0.3295
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY <i>Toll-like receptor signaling pathway</i>	1.190E-09	1.300E-08	102	25	0.2451
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION <i>Antigen processing and presentation</i>	1.780E-09	1.740E-08	89	23	0.2584
KEGG_CELL_ADHESION_MOLECULES_CAMS <i>Cell adhesion molecules CAMS</i>	4.840E-06	1.700E-05	134	23	0.1716
KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY <i>T-cell receptor signaling pathway</i>	3.900E-07	1.860E-06	108	22	0.2037
KEGG_TGF_BETA_SIGNALING_PATHWAY <i>TGF-beta signaling pathway</i>	2.880E-06	1.070E-05	86	18	0.2093
KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY <i>B cell receptor signaling pathway</i>	3.350E-05	1.000E-04	75	15	0.2000
KEGG_ARGININE_AND_PROLINE_METABOLISM <i>Arginine and proline metabolism</i>	1.380E-05	4.340E-05	54	13	0.2407
KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM <i>Glycine, serine and threonine metabolism</i>	8.200E-06	2.830E-05	31	10	0.3226
KEGG_ABC_TRANSPORTERS <i>ABC transporters</i>	1.040E-03	2.190E-03	44	9	0.2045
KEGG_PRIMARY_IMMUNODEFICIENCY <i>Primary immunodeficiency</i>	1.680E-04	4.540E-04	35	9	0.2571

Supplemental Figure 4. Pathways enriched and genes modulated in SS patient samples.



Supplemental Table S3. Negative correlation gene list: FC 89 genes up-regulated in SS patients cells and down-regulated Enz+ARA combined drug treatment Hut78

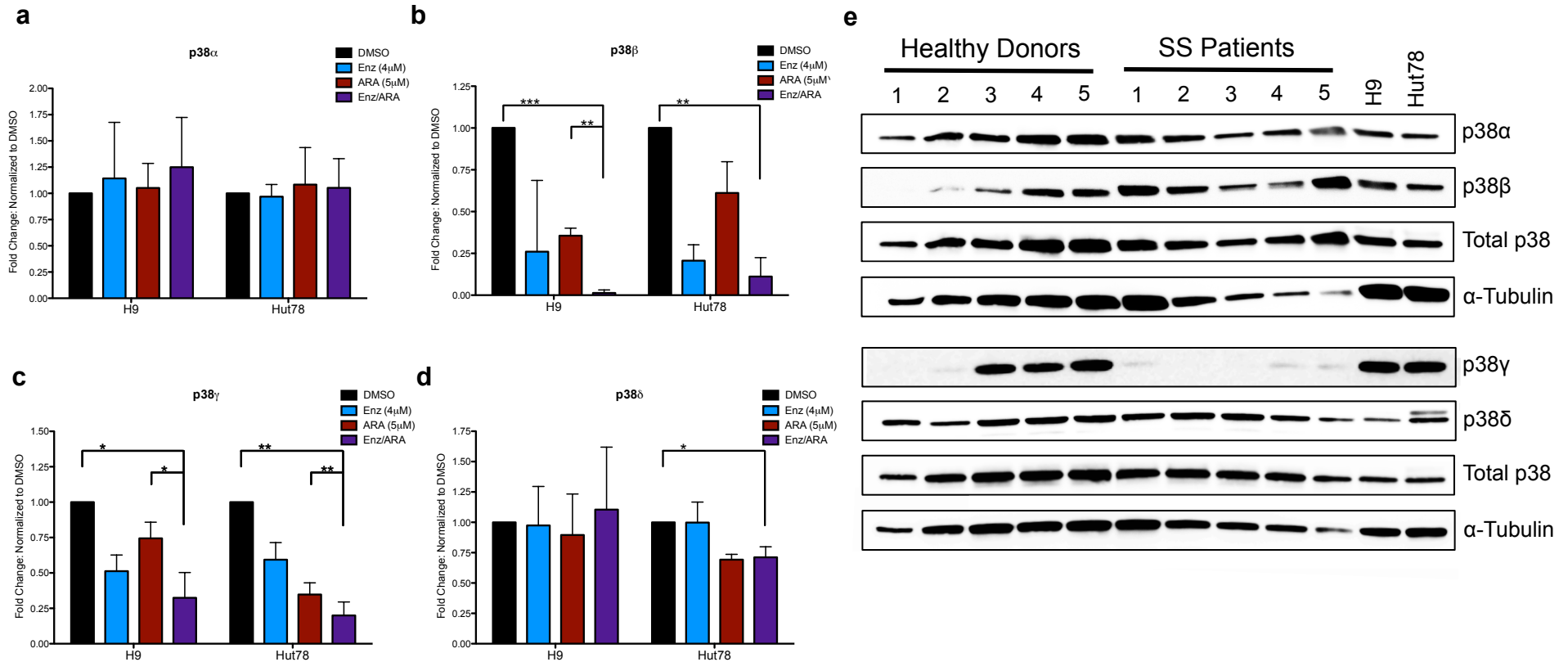
Gene	Description	CTCL Up	Enz+ARA Down
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	5.0994	0.1844
ABCB6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	2.2680	0.4117
ADAM29	ADAM metallopeptidase domain 29	2.2867	0.1437
ADM2	adrenomedullin 2	2.8672	0.4541
AIF1	allograft inflammatory factor 1	3.2304	0.3072
AMHR2	anti-Mullerian hormone receptor, type II	6.6147	0.4746
ANXA9	annexin A9	2.3876	0.1968
BLVRB	biliverdin reductase B (flavin reductase (NADPH))	3.5992	0.4940
BPHL	biphenyl hydrolase-like (serine hydrolase; breast epithelial mucin-associated antigen)	2.3609	0.4410
C19orf73	chromosome 19 open reading frame 73	2.4600	0.3028
C8G	complement component 8, gamma polypeptide	2.6734	0.2845
C9orf53	chromosome 9 open reading frame 53	2.4874	0.3162
CACNA1H	calcium channel, voltage-dependent, alpha 1H subunit	8.0428	0.3014
CCR8	chemokine (C-C motif) receptor 8	2.4857	0.1795
CCRL2	chemokine (C-C motif) receptor-like 2	2.3735	0.2394
CD40	CD40 molecule, TNF receptor superfamily member 5	2.0031	0.2080
CDKN1A	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	5.1118	0.4981
CDKN2D	cyclin-dependent kinase inhibitor 2D (p19, inhibits CDK4)	4.0748	0.3879
CHMP1B	chromatin modifying protein 1B	2.1019	0.3897
CPNE6	copine VI (neuronal)	3.7185	0.1423
CUL7	cullin 7	2.6682	0.4515
CX3CR1	chemokine (C-X3-C motif) receptor 1	2.3245	0.1962
CYBRD1	cytochrome b reductase 1	4.2082	0.3603
CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	9.0889	0.4897
DAPK2	death-associated protein kinase 2	2.0204	0.2088
DDAH2	dimethylarginine dimethylaminohydrolase 2	2.3856	0.4360
DHX58	DEAH (Asp-Glu-Ala-His) box polypeptide 58	2.5131	0.4522
DNAJB5	DnaJ (Hsp40) homolog, subfamily B, member 5	2.0755	0.4413
EMID1	EMI domain containing 1	2.9442	0.4945
FAM127B	family with sequence similarity 127B	2.1067	0.2436
FHOD3	formin homology 2 domain containing 3	2.3699	0.1168
FOS	v-fos FBJ murine osteosarcoma viral oncogene homolog	3.7904	0.2217
GNA14	guanine nucleotide binding protein (G protein), alpha 14	2.6283	0.3153
GPR132	G protein-coupled receptor 132	7.7095	0.3790
GPR19	G protein-coupled receptor 19	3.2232	0.0719
GRP	gastrin-releasing peptide	2.1925	0.2257
HDAC6	histone deacetylase 6	2.1014	0.4477
IQSEC3	IQ motif and Sec7 domain 3	2.8492	0.2456
JUP	junction plakoglobin	3.0046	0.3455
KCND1	potassium voltage-gated channel, Shal-related subfamily, member 1	2.0569	0.3107
KCNN4	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4	3.6160	0.3627
KCNQ1DN	KCNQ1 downstream neighbor	2.3728	0.2578
KRT81	keratin 81	4.2320	0.1818
LAMA3	laminin, alpha 3	3.3160	0.2728
LAT2	linker for activation of T cells family, member 2	2.2018	0.2957

LST1	leukocyte specific transcript 1	2.0606	0.3961
LTBP4	latent transforming growth factor beta binding protein 4	2.9161	0.4356
MAPK11	mitogen-activated protein kinase 11	3.5473	0.4991
MAST1	microtubule associated serine/threonine kinase 1	3.5092	0.2175
MCPH1	microcephaly, primary autosomal recessive 1	2.8295	0.3642
MEGF6	multiple EGF-like-domains 6	2.0582	0.1381
MGAT2	mannosyl (alpha-1,6-)-glycoprotein beta-1,2-N-acetylglucosaminyltransferase	2.0672	0.4173
MLXIPL	MLX interacting protein-like	2.2621	0.1719
MTHFR	5,10-methylenetetrahydrofolate reductase (NADPH)	2.0385	0.1724
MXD3	MAX dimerization protein 3	4.2940	0.1540
NOL3	nucleolar protein 3 (apoptosis repressor with CARD domain)	2.0210	0.2145
NQO2	NAD(P)H dehydrogenase, quinone 2	2.0148	0.4817
NRGN	neurogranin (protein kinase C substrate, RC3)	5.9865	0.4038
NXF3	nuclear RNA export factor 3	2.0864	0.2840
PDE1B	phosphodiesterase 1B, calmodulin-dependent	5.3156	0.1038
PDE6G	phosphodiesterase 6G, cGMP-specific, rod, gamma	4.7937	0.3603
PFKFB4	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4	2.7001	0.1095
PLEKHH3	pleckstrin homology domain containing, family H (with MyTH4 domain) member 3	2.0466	0.4773
PLTP	phospholipid transfer protein	2.2266	0.3077
PPIL6	peptidylprolyl isomerase (cyclophilin)-like 6	5.6507	0.2460
PPP2R5B	protein phosphatase 2, regulatory subunit B (B56), beta isoform	2.5129	0.4495
RAB38	RAB38, member RAS oncogene family	2.0891	0.2254
RASSF4	Ras association (RalGDS/AF-6) domain family 4	2.0719	0.3488
REEP2	receptor accessory protein 2	12.5296	0.2951
REN	renin	5.8544	0.3539
RHBDL1	rhomboid, veinlet-like 1 (Drosophila)	2.9405	0.4618
RNF125	ring finger protein 125	2.6728	0.4308
S100A9	S100 calcium binding protein A9	17.0737	0.3809
SCD	stearoyl-CoA desaturase (delta-9-desaturase)	3.6654	0.4964
SEMA6C	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	4.2191	0.4660
SEZ6L2	seizure related 6 homolog (mouse)-like 2	2.0840	0.3858
SGCA	sarcoglycan, alpha (50kDa dystrophin-associated glycoprotein)	2.7166	0.2940
SLC37A1	solute carrier family 37 (glycerol-3-phosphate transporter), member 1	2.1674	0.4756
SOAT2	sterol O-acyltransferase 2	2.2380	0.3850
STOML1	stomatolipin (EPB72)-like 1	2.0203	0.3205
TGM1	transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase)	2.2206	0.2185
TIMP2	TIMP metalloproteinase inhibitor 2	5.9325	0.3384
UNC93B1	unc-93 homolog B1 (C. elegans)	3.1656	0.4755
ZCWPW1	zinc finger, CW type with PWWP domain 1	4.7215	0.4432
ZDHHC11	zinc finger, DHHC-type containing 11	2.4290	0.3403
ZDHHC14	zinc finger, DHHC-type containing 14	3.8468	0.3937
ZNF219	zinc finger protein 219	2.5816	0.2999
ZNF264	zinc finger protein 264	2.6317	0.2708
ZNF446	zinc finger protein 446	3.5138	0.1587

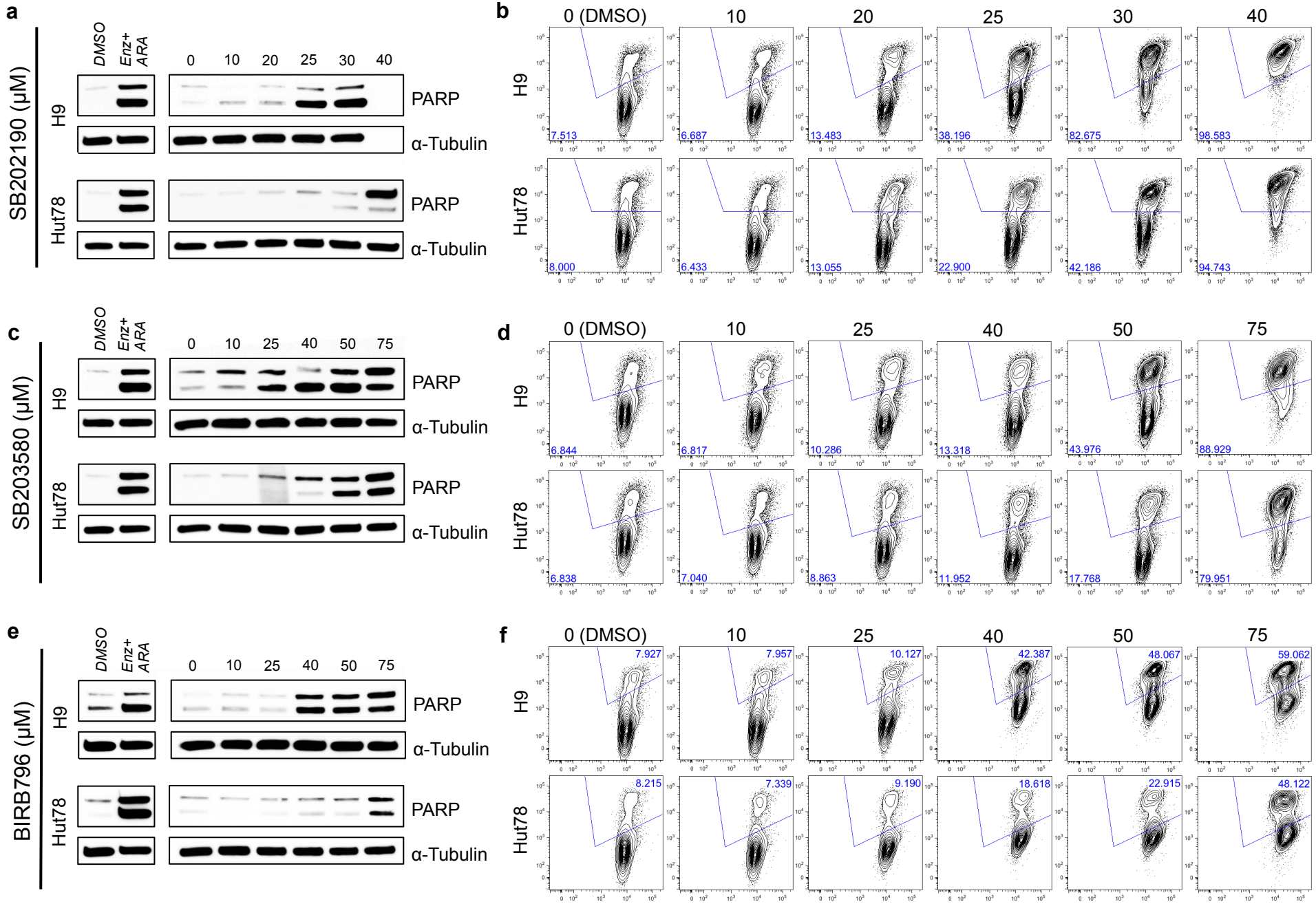
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Gene	Description	CTCL Down	Enz+ARA Up
ANKRD36	ankyrin repeat domain 36	0.1253	5.7521
ANKRD36B	ankyrin repeat domain 36B	0.0950	3.7497
ANKRD55	ankyrin repeat domain 55	0.1743	10.3316
BMP2K	BMP2 inducible kinase	0.4311	4.5525
CCNJ	cyclin J	0.2646	3.7396
DHODH	dihydroorotate dehydrogenase	0.4895	2.3574
ETNK1	ethanolamine kinase 1	0.4125	3.1431
FERMT2	fermitin family member 2	0.4675	4.4257
GAN	giant axonal neuropathy (gigaxonin)	0.4362	2.5266
HSPA4L	heat shock 70kDa protein 4-like	0.3260	2.0060
IGJ	immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	0.0912	4.5941
IL18RAP	interleukin 18 receptor accessory protein	0.4415	4.1317
KLF5	Kruppel-like factor 5 (intestinal)	0.4183	4.2300
MDM1	Mdm4, transformed 3T3 cell double minute 1, p53 binding protein (mouse)	0.3446	3.1613
MREG	melanoregulin	0.2452	2.1818
NRIP1	nuclear receptor interacting protein 1	0.1992	3.9799
PAK1IP1	PAK1 interacting protein 1	0.3373	2.2436
PLA2G4A	phospholipase A2, group IVA (cytosolic, calcium-dependent)	0.3832	4.6492
POLR3G	polymerase (RNA) III (DNA directed) polypeptide G (32kD)	0.3564	2.8058
RND3	Rho family GTPase 3	0.3808	5.1408
RORA	RAR-related orphan receptor A	0.2033	2.9089
RRAGD	Ras-related GTP binding D	0.4574	2.2481
RRP15	ribosomal RNA processing 15 homolog (<i>S. cerevisiae</i>)	0.4211	3.1997
SLC12A6	solute carrier family 12 (potassium/chloride transporters), member 6	0.4259	4.5719
SOAT1	sterol O-acyltransferase (acyl-Coenzyme A: cholesterol acyltransferase) 1	0.4738	2.0171
SPATA5L1	spermatogenesis associated 5-like 1	0.4646	2.0218
TAF1A	TATA box binding protein (TBP)-associated factor, RNA polymerase I, A, 48kDa	0.3519	2.1219
TRAF3IP1	TNF receptor-associated factor 3 interacting protein 1	0.3578	2.1714
TRPC3	transient receptor potential cation channel, subfamily C, member 3	0.3425	6.4208
VPS53	vacuolar protein sorting 53 (<i>S. cerevisiae</i>)	0.4826	6.9288
YARS2	tyrosyl-tRNA synthetase 2 (mitochondrial)	0.4212	2.2284
ZMYM5	zinc finger, MYM-type 5	0.2170	2.2931
ZNF280D	zinc finger protein 280D	0.3360	3.3529
ZNF292	zinc finger protein 292	0.4644	7.3191

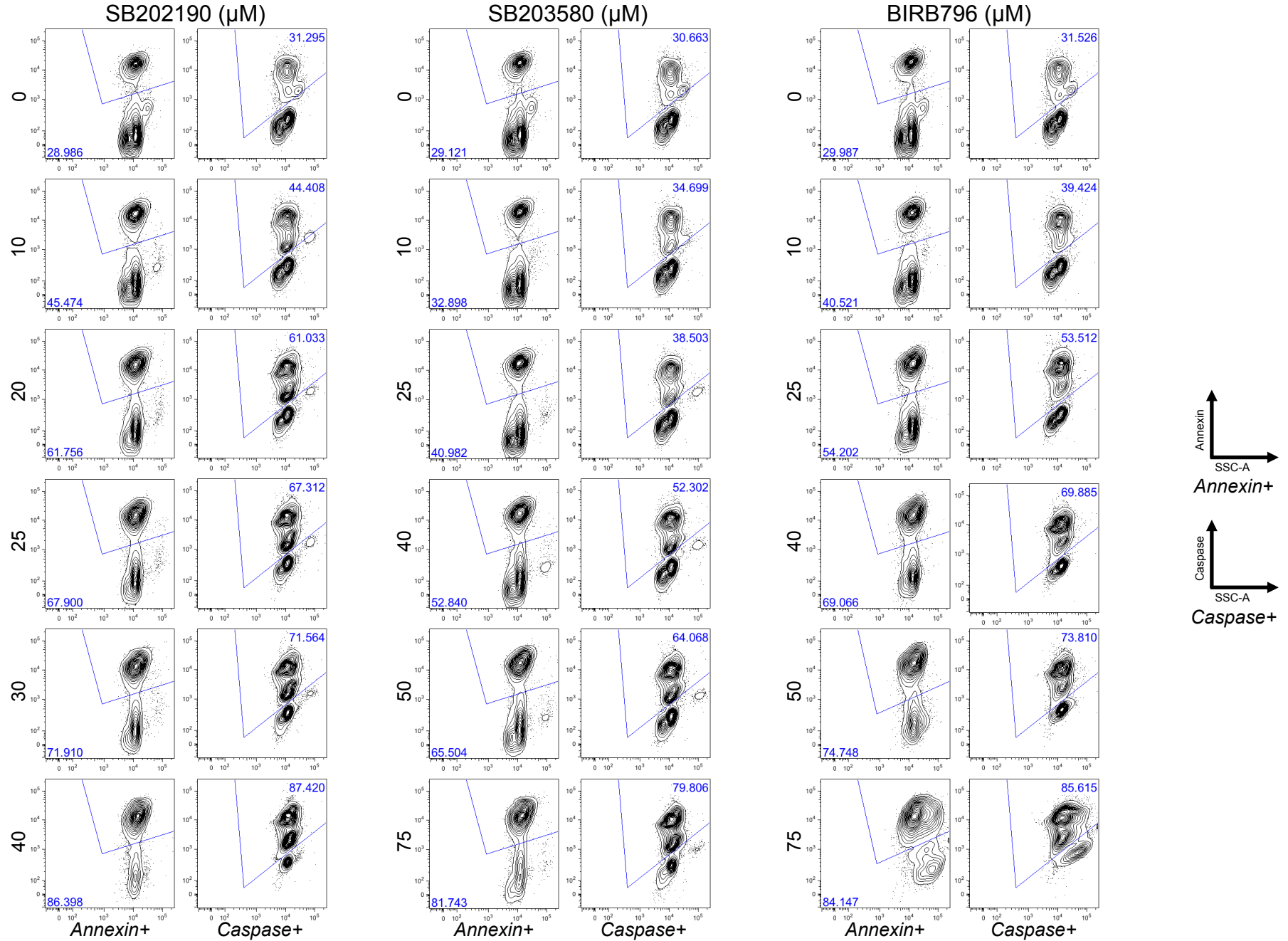
Supplemental Figure 5. Quantification of p38-isoform protein expression in SS cell lines after small-molecule inhibitor treatment and endogenous healthy volunteers and patient samples p38 immunoblot.



Supplemental Figure 6. Confirmation of cell death induced by p38 small-molecule inhibitors in SS cell lines.



Supplemental Figure S7. Example of primary patient sample flow cytometry gating for PBMC p38 drug treatment experiments.



Supplemental Figure S8. Importance of p38 signaling in primary SS patient samples, confirmation of cell death by Cleaved Caspase 3/7 staining.

