

**Figure S1, Related to Figure 1: Characterization and validation of genome-scale ORF and CRISPR BET inhibitor rescue screens.** **A.** Cumulative population doublings of SK-N-BE(2)-C cells treated with DMSO or the concentrations of IBET151 or JQ1 used in the ORF and CRISPR rescue screens shown in Figure 1. Both parental cells and cells infected with plx317-GFP to control for lentiviral infection effects were assayed. **B.** Scatter plots presenting the z-score for average  $\log_2(\text{FC})$  ORF representation for I-BET151 and JQ1 vs. ETP (y-axis) and for DMSO vs. ETP in SK-N-BE(2)-C (up) and LAN-1 (down) cells. Dotted gray lines at z-score = 2.5 on either axis demonstrate that the ORF hits are not scoring in the DMSO arm as promoting growth over time. Gene set enrichment analysis of ORF hits in SK-N-BE(2)-C (**C**) and LAN-1 (**D**) cells. The fraction overlap represents the fraction of ORF hits among the genes in each gene signature. **E.** Medium-throughput ORF validation screen with 150 ORFs corresponding to top hits from the genome-scale screen as well as negative and neutral control ORFs. ORF representation for JQ1 vs. ETP is shown for CHP-212 on the x-axis, and for LAN-1 cells on the y-axis. **F.** Long-term viability in SK-N-BE(2)-C cells lentivirally infected with either a non-targeting (NT) control sgRNA or an sgRNA directed against PTEN and treated with vehicle or 1  $\mu\text{M}$  JQ1. The experiment was conducted in biological duplicate. Data are shown as the percent of viable cells relative to the DMSO arm for each condition. Mean values of duplicate measurements are shown. **G.** Representative images of data presented in (F) demonstrating the ability of PTEN suppression to rescue the anti-viability effects of JQ1.

Table S1, Related to Figure 1. List of hits for the genome-wide ORF resistance screen in the SK-N-BE(2)-C cell line.

#	Construct ID	Gene [# ORF hits per gene/total # ORFs per gene]	Pathway	Hit specificity	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Av. z-scores I-BET151 and JQ1 vs. ETP	z-score DMSO vs. ETP	Validation screen
1	TRCN0000488343	KRAS [1/4]		SK-N-BE(2)-C specific hit	7.80	9.52	8.66	-2.48	1
2	TRCN0000488923	AKT1 [2/4]	PI3K/AKT	Core hit	8.85	8.04	8.45	-3.79	1
3	TRCN0000469233	TOX [1/1]		SK-N-BE(2)-C specific hit	9.66	7.06	8.36	1.64	1
4	TRCN0000492315	MTNR1A [2/2]		SK-N-BE(2)-C specific hit	8.59	7.35	7.97	-0.68	1
5	TRCN0000489962	AKT1 [2/4]	PI3K/AKT	Core hit	7.74	8.05	7.90	-1.37	1
6	TRCN0000488582	MTNR1A [2/2]		SK-N-BE(2)-C specific hit	8.23	7.36	7.80	-0.45	1
7	TRCN0000467249	S1PR1 [2/2]		SK-N-BE(2)-C specific hit	8.09	7.44	7.77	-1.47	1
8	TRCN0000492091	CNR2 [2/2]		SK-N-BE(2)-C specific hit	7.25	7.83	7.54	-1.74	1
9	TRCN0000489111	HTR1E [2/2]		SK-N-BE(2)-C specific hit	7.78	7.22	7.50	-1.93	1
10	TRCN0000487761	S1PR5 [5/5]		SK-N-BE(2)-C specific hit	7.90	6.67	7.29	-0.89	1
11	TRCN0000489463	GPR82 [2/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	6.74	7.67	7.21	-1.04	1
12	TRCN0000475926	HTR1E [2/2]		SK-N-BE(2)-C specific hit	6.70	7.48	7.09	-0.72	1
13	TRCN0000487935	S1PR5 [5/5]		SK-N-BE(2)-C specific hit	7.35	6.77	7.06	-0.65	1
14	TRCN0000489868	AKT2 [2/5]	PI3K/AKT	Core hit	6.59	7.41	7.00	0.50	1
15	TRCN0000488505	P2RY14 [2/2]		SK-N-BE(2)-C specific hit	6.61	7.32	6.97	-1.56	1
16	TRCN0000488729	CNR2 [2/2]		SK-N-BE(2)-C specific hit	6.83	7.06	6.95	-0.97	1
17	TRCN0000487993	P2RY14 [2/2]		SK-N-BE(2)-C specific hit	6.24	7.40	6.82	-0.96	1
18	TRCN0000489826	GPR34 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	6.75	6.88	6.82	-0.25	1
19	TRCN0000487973	S1PR5 [5/5]		SK-N-BE(2)-C specific hit	7.20	6.42	6.81	-0.66	1
20	TRCN0000488625	ADORA1 [1/3]		SK-N-BE(2)-C specific hit	6.49	7.11	6.80	-1.08	1
21	TRCN0000488236	S1PR5 [5/5]		SK-N-BE(2)-C specific hit	7.09	6.36	6.73	-1.40	1
22	TRCN0000489149	S1PR4 [3/3]		SK-N-BE(2)-C specific hit	6.40	6.97	6.69	-0.69	1
23	TRCN0000487798	S1PR1 [2/2]		SK-N-BE(2)-C specific hit	6.52	6.84	6.68	-2.10	1
24	TRCN0000487714	PIK3CA [8/11]	PI3K/AKT	Core hit	5.69	7.40	6.55	-0.25	1
25	TRCN0000470181	CCND3 [1/1]	Cell cycle	Core hit	6.56	6.42	6.49	1.07	1
26	TRCN0000488708	GPR22 [2/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	5.81	6.95	6.38	-0.97	1
27	TRCN0000489040	PIK3CA [8/11]	PI3K/AKT	Core hit	6.32	6.43	6.38	-0.39	1
28	TRCN0000469954	GPR22 [2/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	6.40	6.25	6.33	-1.28	1
29	TRCN0000466710	S1PR5 [5/5]		SK-N-BE(2)-C specific hit	6.78	5.85	6.32	-1.46	1
30	TRCN0000488655	S1PR4 [3/3]		SK-N-BE(2)-C specific hit	6.35	6.22	6.29	-0.57	1
31	TRCN0000488331	CDK6 [3/3]	Cell cycle	Core hit	6.92	5.42	6.17	2.40	1
32	TRCN0000488076	HCAR2 [2/2]		SK-N-BE(2)-C specific hit	5.70	6.64	6.17	-1.40	1
33	TRCN0000472965	GPR34 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	5.91	6.27	6.09	-1.26	1
34	TRCN0000489344	HCAR2 [2/2]		SK-N-BE(2)-C specific hit	5.80	6.34	6.07	-2.80	1
35	TRCN0000489648	PIK3CA [8/11]	PI3K/AKT	Core hit	5.24	6.45	5.85	-1.73	1
36	TRCN0000474343	CCNE2 [1/2]	Cell cycle	Core hit	5.81	5.84	5.83	1.36	1
37	TRCN0000487730	PIK3CA [8/11]	PI3K/AKT	Core hit	5.27	6.29	5.78	-2.03	1
38	TRCN0000489611	HTR1F [2/2]		SK-N-BE(2)-C specific hit	5.94	5.61	5.78	-1.93	1
39	TRCN0000488074	GPR20 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	5.93	5.55	5.74	-1.84	1
40	TRCN0000489708	HCAR1 [2/2]		SK-N-BE(2)-C specific hit	5.48	5.98	5.73	-0.99	1
41	TRCN0000489472	SUCNR1 [1/2]		SK-N-BE(2)-C specific hit	5.31	5.98	5.65	0.16	1
42	TRCN0000488224	HTR1B [3/3]		SK-N-BE(2)-C specific hit	5.54	5.68	5.61	-2.93	1
43	TRCN0000491310	GPR20 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	5.64	5.50	5.57	-1.48	1
44	TRCN0000489793	HTR1F [2/2]		SK-N-BE(2)-C specific hit	5.33	5.81	5.57	-0.99	1
45	TRCN0000492042	GPR34 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	5.84	5.28	5.56	1.13	1
46	TRCN0000489451	HTR1B [3/3]		SK-N-BE(2)-C specific hit	5.38	5.71	5.55	-2.01	1
47	TRCN0000466228	HTR1D [3/3]		SK-N-BE(2)-C specific hit	5.40	5.66	5.53	-3.15	1
48	TRCN0000488528	CXCR1 [3/3]		SK-N-BE(2)-C specific hit	5.43	5.59	5.51	-0.16	1
49	TRCN0000487810	HTR1D [3/3]		SK-N-BE(2)-C specific hit	5.03	5.85	5.44	-2.31	1
50	TRCN0000492093	PIK3CA [8/11]	PI3K/AKT	Core hit	4.80	5.98	5.39	-0.58	1
51	TRCN0000489036	HTR1D [3/3]		SK-N-BE(2)-C specific hit	5.14	5.63	5.39	-2.68	1
52	TRCN0000471924	HTR1B [3/3]		SK-N-BE(2)-C specific hit	5.25	5.48	5.37	-1.45	1
53	TRCN0000491318	PIK3CA [8/11]	PI3K/AKT	Core hit	4.90	5.78	5.34	1.08	1
54	TRCN0000465402	FGFR2 [1/7]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	4.54	6.12	5.33	-1.17	1
55	TRCN0000468617	NFIB [1/1]		SK-N-BE(2)-C specific hit	5.17	4.75	5.21	1.17	1
56	TRCN0000488434	DRD3 [1/3]		SK-N-BE(2)-C specific hit	5.20	5.12	5.16	-0.09	1
57	TRCN0000489478	NTRK3 [2/6]		SK-N-BE(2)-C specific hit	4.88	5.40	5.14	0.00	1
58	TRCN0000481165	CDK6 [3/3]	Cell cycle	Core hit	5.60	4.64	5.12	2.19	1
59	TRCN0000492137	GRM8 [5/5]		SK-N-BE(2)-C specific hit	4.77	5.44	5.11	-0.66	1
60	TRCN0000473906	S1PR4 [3/3]		SK-N-BE(2)-C specific hit	4.83	5.21	5.02	-1.54	1
61	TRCN0000491586	STK40 [4/5]		SK-N-BE(2)-C specific hit	5.62	4.42	5.02	-1.69	1
62	TRCN0000472445	NFIC [1/1]		SK-N-BE(2)-C specific hit	4.72	5.23	4.98	-0.56	1
63	TRCN0000489632	RASGRP1 [1/1]		SK-N-BE(2)-C specific hit	4.73	5.20	4.97	0.09	1
64	TRCN0000491475	PDGFRA [2/4]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	4.45	5.33	4.89	1.30	1
65	TRCN0000467546	CDK6 [3/3]	Cell cycle	Core hit	5.16	4.41	4.79	2.16	1
66	TRCN0000487905	GPR183 [2/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	4.69	4.86	4.78	-1.18	1
67	TRCN0000489482	HCAR3 [2/3]		SK-N-BE(2)-C specific hit	4.54	5.00	4.77	-0.79	1
68	TRCN0000488432	MTNR1B [1/1]		SK-N-BE(2)-C specific hit	4.56	4.96	4.76	0.67	1
69	TRCN0000489225	GRM8 [5/5]		SK-N-BE(2)-C specific hit	4.92	4.57	4.75	-2.82	1
70	TRCN0000488502	ADORA3 [2/3]		SK-N-BE(2)-C specific hit	5.27	4.17	4.72	-0.88	1
71	TRCN0000466042	P2RY13 [1/4]		SK-N-BE(2)-C specific hit	4.30	5.14	4.72	-0.83	1
72	TRCN0000489920	BCL2L1 [2/2]	Apoptosis	Core hit	3.74	5.66	4.70	0.84	1
73	TRCN0000489020	CXCR1 [3/3]		SK-N-BE(2)-C specific hit	4.39	4.89	4.64	-0.77	1
74	TRCN0000487954	GRM8 [5/5]		SK-N-BE(2)-C specific hit	4.13	5.07	4.60	-2.62	1
75	TRCN0000489394	PIK3CA [8/11]	PI3K/AKT	Core hit	4.13	5.04	4.59	0.26	1
76	TRCN0000488896	LTB4R [1/3]		SK-N-BE(2)-C specific hit	5.29	3.88	4.59	-1.14	1
77	TRCN0000472603	BCL2L1 [2/2]	Apoptosis	Core hit	4.00	5.10	4.55	0.72	1
78	TRCN0000467216	CCND1 [1/1]	Cell cycle	Core hit	4.64	4.33	4.49	1.98	1
79	TRCN0000488235	GPR82 [2/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	4.05	4.91	4.48	-0.75	1

#	Construct ID	Gene [# ORF hits per gene/total # ORFs per gene]	Pathway	Hit specificity	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Av. z-scores I-BET151 and JQ1 vs. ETP	z-score DMSO vs. ETP	Validation n screen
80	TRCN0000478486	GPR20 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	4.50	4.45	4.48	-0.87	1
81	TRCN0000491535	NTRK3 [2/6]		SK-N-BE(2)-C specific hit	4.04	4.85	4.45	-0.08	1
82	TRCN0000487741	GRM3 [2/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	4.03	4.85	4.44	-1.64	1
83	TRCN0000479853	GPR183 [2/2]		SK-N-BE(2)-C specific hit	4.61	4.05	4.33	-0.23	1
84	TRCN0000466719	PIK3CA [8/11]	PI3K/AKT	Core hit	3.84	4.71	4.28	2.36	1
85	TRCN0000474663	FGF6 [1/1]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	4.21	4.23	4.22	-2.65	1
86	TRCN0000492155	HCAR3 [2/3]	PI3K/AKT	SK-N-BE(2)-C specific hit	4.12	4.27	4.20	-0.76	1
87	TRCN0000488553	AKT2 [2/5]		Core hit	3.65	4.65	4.15	-3.27	1
88	TRCN0000488711	FFAR4 [3/4]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.48	4.77	4.13	-2.33	1
89	TRCN0000489086	STK40 [4/5]		SK-N-BE(2)-C specific hit	4.65	3.59	4.12	-0.46	1
90	TRCN0000471007	SPATS2L [1/1]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	4.12	4.08	4.10	2.39	1
91	TRCN0000489686	HTR5A [1/4]		SK-N-BE(2)-C specific hit	4.55	3.63	4.09	0.12	1
92	TRCN0000488761	CNR1 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.83	4.22	4.03	-0.42	1
93	TRCN0000489575	BRAF [2/5]		SK-N-BE(2)-C specific hit	4.25	3.72	3.99	-2.07	1
94	TRCN0000488215	GRM2 [2/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.79	4.10	3.95	-1.97	1
95	TRCN0000472203	FFAR4 [3/4]		SK-N-BE(2)-C specific hit	3.68	4.17	3.93	-0.94	1
96	TRCN0000477307	GRM8 [5/5]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.30	4.53	3.92	-0.57	1
97	TRCN0000467576	DEPDC7 [1/1]		SK-N-BE(2)-C specific hit	3.49	4.29	3.89	-0.78	1
98	TRCN0000491982	P2RY12 [2/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.35	4.36	3.86	-1.29	1
99	TRCN0000492109	PPF1A1 [1/1]		SK-N-BE(2)-C specific hit	3.36	4.27	3.82	0.12	1
100	TRCN0000474946	RAF1 [1/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.20	4.28	3.74	-2.32	1
101	TRCN0000489865	GRM3 [2/2]		SK-N-BE(2)-C specific hit	3.26	4.21	3.74	-0.49	1
102	TRCN0000489666	GRM8 [5/5]	Apoptosis	SK-N-BE(2)-C specific hit	3.29	4.02	3.66	-0.46	1
103	TRCN0000466971	BCL2L2 [1/1]		Core hit	3.07	4.23	3.65	0.48	1
104	TRCN0000477891	ZBTB39 [1/1]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.76	3.52	3.64	-2.94	1
105	TRCN0000489033	GRM2 [2/3]		SK-N-BE(2)-C specific hit	3.01	4.23	3.62	-2.05	1
106	TRCN0000491613	RXFP4 [2/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.48	3.73	3.61	0.54	1
107	TRCN0000472808	GDNF [1/1]		SK-N-BE(2)-C specific hit	3.46	3.71	3.59	0.32	1
108	TRCN0000489538	FFAR4 [3/4]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.04	4.03	3.54	-2.53	1
109	TRCN0000474239	ADORA3 [2/3]		SK-N-BE(2)-C specific hit	4.46	2.60	3.53	-0.25	1
110	TRCN0000480740	STK40 [4/5]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.73	3.29	3.51	-1.83	1
111	TRCN0000488765	ROS1 [1/1]		SK-N-BE(2)-C specific hit	2.80	4.20	3.50	-1.67	1
112	TRCN0000489590	EGFR [2/12]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.42	4.49	3.46	-0.79	1
113	TRCN0000470229	THRB [1/2]		SK-N-BE(2)-C specific hit	3.33	3.57	3.45	0.88	1
114	TRCN0000476850	ZBTB20 [1/1]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.19	3.69	3.44	0.74	1
115	TRCN0000476022	FGF5 [1/1]		SK-N-BE(2)-C specific hit	3.70	3.13	3.42	0.50	1
116	TRCN0000487732	P2RY12 [2/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.78	4.04	3.41	-0.27	1
117	TRCN0000489911	CNSK1A1L [1/4]		SK-N-BE(2)-C specific hit	3.74	3.06	3.40	1.24	1
118	TRCN0000470239	FFAR3 [2/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.05	3.67	3.36	-0.30	1
119	TRCN0000488834	PTGER3 [2/6]		SK-N-BE(2)-C specific hit	2.91	3.77	3.34	-0.76	1
120	TRCN0000491390	EGFR [2/12]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.97	3.66	3.32	-3.21	1
121	TRCN0000479087	ETS2 [1/2]		SK-N-BE(2)-C specific hit	3.06	3.41	3.24	-0.55	1
122	TRCN0000480161	STK40 [4/5]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.43	2.96	3.20	-0.94	1
123	TRCN0000465444	FLT3 [1/8]		SK-N-BE(2)-C specific hit	2.56	3.82	3.19	1.07	1
124	TRCN0000491640	CXCR1 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.19	3.17	3.18	0.19	1
125	TRCN0000489021	RXFP4 [2/3]		SK-N-BE(2)-C specific hit	3.03	3.33	3.18	0.76	1
126	TRCN0000488387	FFAR3 [2/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.72	3.55	3.14	-1.01	1
127	TRCN0000473856	ARL4C [1/1]		SK-N-BE(2)-C specific hit	3.24	2.98	3.11	0.47	1
128	TRCN0000479725	CNR1 [3/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	3.13	3.06	3.10	-0.35	1
129	TRCN0000468563	ARL4D [1/1]		SK-N-BE(2)-C specific hit	3.22	2.92	3.07	1.05	1
130	TRCN0000474390	SSBP2 [1/1]	Cell cycle	Core hit	3.32	2.80	3.06	-1.43	1
131	TRCN0000467811	CCND2 [1/1]		Core hit	2.96	3.14	3.05	0.63	1
132	TRCN0000489453	CYSLTR1 [1/4]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.75	3.30	3.03	0.27	1
133	TRCN0000477429	HCAR1 [2/2]		SK-N-BE(2)-C specific hit	2.74	3.29	3.02	-1.22	1
134	TRCN0000492361	DRD2 [2/4]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.98	3.01	3.00	-0.21	1
135	TRCN0000468660	YES1 [1/2]		SK-N-BE(2)-C specific hit	3.19	2.80	3.00	0.02	1
136	TRCN0000472927	PDGFRA [2/4]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.64	3.34	2.99	-0.38	1
137	TRCN0000488960	GAB2 [1/2]		SK-N-BE(2)-C specific hit	2.58	3.37	2.98	-1.08	1
138	TRCN0000489177	GRM7 [2/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.94	3.01	2.98	-0.88	0
139	TRCN0000467360	C1orf111 [1/1]		SK-N-BE(2)-C specific hit	2.81	3.10	2.96	-0.15	1
140	TRCN0000489494	BRAF [2/5]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.52	3.37	2.95	-3.42	0
141	TRCN0000467736	MCL1 [1/1]		SK-N-BE(2)-C specific hit	2.65	3.22	2.94	0.44	1
142	TRCN0000492171	CHRM2 [1/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.76	3.11	2.94	0.40	0
143	TRCN0000489523	AGTR2 [1/2]		SK-N-BE(2)-C specific hit	2.99	2.87	2.93	-0.07	1
144	TRCN0000489148	GRM7 [2/3]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.60	3.25	2.93	-0.74	0
145	TRCN0000469846	CYYR1 [1/1]		SK-N-BE(2)-C specific hit	2.72	3.07	2.90	0.94	1
146	TRCN0000487757	PTGER3 [2/6]	Cell cycle	SK-N-BE(2)-C specific hit	2.92	2.85	2.89	-0.68	1
147	TRCN0000491742	CDK4 [1/3]		Core hit	2.91	2.80	2.86	1.31	0
148	TRCN0000489434	CXCR2 [1/2]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.60	3.08	2.84	-1.16	1
149	TRCN0000488636	CNR1 [3/3]		SK-N-BE(2)-C specific hit	2.40	3.27	2.84	-0.35	1
150	TRCN0000488273	DRD2 [2/4]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.42	3.02	2.72	-1.69	0
151	TRCN0000466384	NFYB [1/1]		SK-N-BE(2)-C specific hit	2.66	2.68	2.67	-0.44	1
152	TRCN0000489184	IL10RB [1/2]	Growth factors/RTKs	Core hit	2.62	2.68	2.65	1.31	0
153	TRCN0000491439	CCR3 [1/3]		SK-N-BE(2)-C specific hit	2.51	2.72	2.62	0.69	1
154	TRCN0000491939	KIT [1/7]	Growth factors/RTKs	SK-N-BE(2)-C specific hit	2.57	2.66	2.62	-3.63	0

Table S2, Related to Figure 1. List of hits for the genome-wide ORF resistance screen in the LAN-1 cell line.

#	Construct ID	Gene [# ORF hits per gene/total # ORFs per gene]	Pathway	Hit specificity	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Av. z-scores I-BET151 and JQ1 vs. ETP	z-score DMSO vs. ETP	Validation screen
1	TRCN0000480014	AXL [2/3]		LAN-1 specific hit	5.85	7.49	6.67	1.98	1
2	TRCN0000470181	CCND3 [1/1]	Cell cycle	Core hit	5.51	7.28	6.40	1.29	1
3	TRCN0000488331	CDK6 [3/3]	Cell cycle	Core hit	6.22	5.92	6.07	2.50	1
4	TRCN0000489649	AXL [2/3]		LAN-1 specific hit	4.23	6.54	5.39	1.01	1
5	TRCN0000474343	CCNE2 [1/2]	Cell cycle	Core hit	4.89	5.57	5.23	0.72	1
6	TRCN0000491742	CDK4 [2/3]	Cell cycle	Core hit	5.14	4.58	4.86	1.46	1
7	TRCN0000488281	PIM3 [3/3]		LAN-1 specific hit	4.44	5.04	4.74	2.92	1
8	TRCN0000489868	AKT2 [1/5]	PI3K/AKT	Core hit	3.63	5.76	4.70	4.66	1
9	TRCN0000489876	TYRO3 [2/4]		LAN-1 specific hit	3.53	5.66	4.60	0.38	1
10	TRCN0000489909	PIM1 [3/3]		LAN-1 specific hit	3.99	4.96	4.48	3.91	0
11	TRCN0000467546	CDK6 [3/3]	Cell cycle	Core hit	4.30	4.52	4.41	1.87	1
12	TRCN0000479963	TYRO3 [2/4]		LAN-1 specific hit	3.24	5.08	4.16	0.54	1
13	TRCN0000481165	CDK6 [3/3]	Cell cycle	Core hit	4.06	4.01	4.04	1.40	1
14	TRCN0000466006	PIM1 [3/3]		LAN-1 specific hit	3.46	4.10	3.78	2.81	0
15	TRCN0000489631	PIM2 [2/3]		LAN-1 specific hit	3.39	4.13	3.76	3.31	0
16	TRCN0000467216	CCND1 [1/1]	Cell cycle	Core hit	3.01	4.46	3.74	0.50	1
17	TRCN0000488146	PIM3 [3/3]		LAN-1 specific hit	3.16	4.23	3.70	2.32	1
18	TRCN0000472603	BCL2L1 [2/2]	Apoptosis	Core hit	3.67	3.56	3.62	0.40	1
19	TRCN0000474390	SSBP2 [1/1]		Core hit	3.23	3.74	3.49	0.83	1
20	TRCN0000480123	CDK4 [2/3]	Cell cycle	Core hit	3.81	3.09	3.45	0.47	1
21	TRCN0000481389	PIM1 [3/3]		LAN-1 specific hit	2.88	3.83	3.36	2.78	0
22	TRCN0000489184	IL10RB [2/2]		Core hit	3.13	3.55	3.34	1.82	1
23	TRCN0000489920	BCL2L1 [2/2]	Apoptosis	Core hit	3.06	3.50	3.28	0.36	1
24	TRCN0000487677	AKT3 [1/5]	PI3K/AKT	LAN-1 specific hit	3.03	3.40	3.22	1.25	1
25	TRCN0000491449	MAP3K8 [1/3]		LAN-1 specific hit	2.78	3.39	3.09	0.47	1
26	TRCN0000475569	PIM3 [3/3]		LAN-1 specific hit	2.84	3.31	3.08	1.82	1
27	TRCN0000466971	BCL2L2 [1/1]	Apoptosis	Core hit	2.90	3.10	3.00	0.29	1
28	TRCN0000466782	TGIF2 [1/1]		LAN-1 specific hit	2.56	3.4	2.98	0.36	1
29	TRCN0000491814	AKT1 [1/4]	PI3K/AKT	Core hit	2.69	3.27	2.98	1.99	1
30	TRCN0000487730	PIK3CA [1/11]	PI3K/AKT	Core hit	2.75	3.16	2.96	-0.24	1
31	TRCN0000478988	TGIF1 [1/2]		LAN-1 specific hit	2.70	3.12	2.91	0.13	1
32	TRCN0000488585	PIM2 [2/3]		LAN-1 specific hit	2.56	3.21	2.89	2.61	0
33	TRCN0000491760	IL10RB [2/2]		Core hit	2.74	3.00	2.87	1.84	1
34	TRCN0000467811	CCND2 [1/1]	Cell cycle	Core hit	2.52	2.87	2.70	0.11	1

**Table S3, Related to Figure 1. Results of the mini-ORF rescue screen in LAN-1 and CHP-212 cells.**

#	Category	Gene symbol	Pathway	Genome-wide ORF screen: SK-N-BE(2)-C			Genome-wide ORF screen: LAN-1				Validation ORF screen: LAN-1			CHP-212	Validation screen hit
				Construct ID	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Genome-wide screen hit	Construct ID	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Genome-wide screen hit	Construct ID	z-score JQ1 vs. ETP		
1	Hit	CCND3	Cell cycle	TRCN0000470181	6.56	6.42	1	TRCN0000470181	5.51	7.28	1	TRCN0000470181	6.46	-0.45	0
2	Hit	AXL	LAN-1 specific hit	TRCN0000480014	1.43	1.9	0	TRCN0000480014	5.85	7.49	1	TRCN0000480014	6.06	0.17	0
3	Hit	TYRO3	LAN-1 specific hit	TRCN0000479963	0.47	0.63	0	TRCN0000489876	3.53	5.66	1	TRCN0000489876	5.62	-4.09	0
4	Hit	CCNE2	Cell cycle	TRCN0000474343	5.81	5.84	1	TRCN0000474343	4.89	5.57	1	TRCN0000474343	5.24	0.38	0
5	Hit	CCND1	Cell cycle	TRCN0000467216	4.64	4.33	1	TRCN0000467216	3.01	4.46	1	TRCN0000467216	4.32	2.08	1
6	Hit	CDK6	Cell cycle	TRCN0000488331	6.92	5.42	1	TRCN0000488331	6.22	5.92	1	TRCN0000488331	4.04	-0.05	0
7	Hit	CDK4	Cell cycle	TRCN0000491742	2.91	2.8	1	TRCN0000491742	5.14	4.58	1	TRCN0000491742	3.61	-0.27	0
8	Hit	BCL2L1	Apoptosis	TRCN0000489920	3.74	5.66	1	TRCN0000472603	3.67	3.56	1	TRCN0000489920	3.49	-0.53	0
9	Hit	TGIF2	LAN-1 specific hit	TRCN0000466782	-0.59	-2.63	0	TRCN0000466782	2.56	3.40	1	TRCN0000466782	3.38	-0.02	0
10	Hit	SSBP2	LAN-1 specific hit	TRCN0000474390	3.32	2.8	1	TRCN0000474390	3.23	3.74	1	TRCN0000474390	3.31	-0.72	0
11	Hit	TGIF1	LAN-1 specific hit	TRCN0000475377	-0.47	-0.57	0	TRCN0000478988	2.70	3.12	1	TRCN0000478988	3.31	-1.36	0
12	Hit	MAP3K8	LAN-1 specific hit	TRCN0000491449	1.96	2.87	0	TRCN0000491449	2.78	3.39	1	TRCN0000491449	3.27	0.04	0
13	Hit	BCL2L2	Apoptosis	TRCN0000466971	3.07	4.23	1	TRCN0000466971	2.90	3.10	1	TRCN0000466971	3.14	0.45	0
14	Hit	CCND2	Cell cycle	TRCN0000467811	2.96	3.14	1	TRCN0000467811	2.52	2.87	1	TRCN0000467811	3.07	0.08	0
15	Hit	PIK3CA	PI3K/AKT	TRCN0000487714	5.69	7.4	1	TRCN0000487730	2.75	3.16	1	TRCN0000487714	2.95	2.01	1
16	Hit	AKT1	PI3K/AKT	TRCN0000488923	8.85	8.04	1	TRCN0000489962	2.06	5.13	1	TRCN0000488923	2.82	0.97	1
17	Hit	AKT3	PI3K/AKT	TRCN0000489669	2.48	2.12	0	TRCN0000487677	3.03	3.40	1	TRCN0000487677	2.61	0.35	0
18	Hit	PIM3	LAN-1 specific hit	TRCN0000475569	1.59	1.35	0	TRCN0000488281	4.44	5.04	1	TRCN0000488146	2.51	-1.28	0
19	Hit	IL10RB	LAN-1 specific hit	TRCN0000489184	2.62	2.68	1	TRCN0000489184	3.13	3.55	1	TRCN0000489184	2.26	0.24	0
20	Hit	AKT2	PI3K/AKT	TRCN0000489868	6.59	7.41	1	TRCN0000489868	3.63	5.76	1	TRCN0000489868	2.00	0.19	0
21	Hit	PDGFRA	Growth factors/RTKs	TRCN0000491475	4.45	5.33	1	TRCN0000489486	1.89	2.73	0	TRCN0000491475	3.68	0.31	0
22	Hit	KIT	SK-N-BE(2)-C specific hit	TRCN0000491939	2.57	2.66	1	TRCN0000491939	0.48	1.75	0	TRCN0000491939	3.25	1.67	1
23	Hit	NTRK3	SK-N-BE(2)-C specific hit	TRCN0000489478	4.88	5.4	1	TRCN0000489478	1.62	1.61	0	TRCN0000489478	2.13	-0.08	0
24	Hit	KRAS	SK-N-BE(2)-C specific hit	TRCN0000488343	7.8	9.52	1	TRCN0000488343	1.96	1.94	0	TRCN0000488343	1.75	-0.03	0
25	Hit	GAB2	SK-N-BE(2)-C specific hit	TRCN0000488960	2.58	3.37	1	TRCN0000488960	0.99	1.04	0	TRCN0000488960	1.67	0.21	0
26	Hit	FGFR2	Growth factors/RTKs	TRCN0000465402	4.54	6.12	1	TRCN0000492076	0.60	1.45	0	TRCN0000465402	1.61	0.48	0
27	Hit	EGFR	Growth factors/RTKs	TRCN0000489590	2.42	4.49	1	TRCN0000488104	0.02	0.12	0	TRCN0000491390	1.40	1.00	0
28	Hit	TOX	SK-N-BE(2)-C specific hit	TRCN0000469233	9.66	7.06	1	TRCN0000469233	1.15	1.12	0	TRCN0000469233	1.26	-0.18	0
29	Hit	LTB4R	SK-N-BE(2)-C specific hit	TRCN0000488896	5.29	3.88	1	TRCN0000491676	-0.22	-0.22	0	TRCN0000488896	1.25	0.16	0
30	Hit	GDNF	SK-N-BE(2)-C specific hit	TRCN0000472808	3.46	3.71	1	TRCN0000472808	0.84	1.33	0	TRCN0000472808	1.12	0.42	0
31	Hit	THRB	SK-N-BE(2)-C specific hit	TRCN0000470229	3.33	3.57	1	TRCN0000470229	0.62	0.60	0	TRCN0000470229	1.08	0.12	0
32	Hit	ROS1	SK-N-BE(2)-C specific hit	TRCN0000488765	2.8	4.2	1	TRCN0000488765	0.97	0.97	0	TRCN0000488765	1.08	-3.69	0
33	Hit	ARL4C	SK-N-BE(2)-C specific hit	TRCN0000473856	3.24	2.98	1	TRCN0000473856	0.96	0.73	0	TRCN0000473856	0.95	0.13	0
34	Hit	SPATS2L	SK-N-BE(2)-C specific hit	TRCN0000471007	4.12	4.08	1	TRCN0000471007	0.67	0.58	0	TRCN0000471007	0.94	0.08	0
35	Hit	ZBTB39	SK-N-BE(2)-C specific hit	TRCN0000477891	3.76	3.52	1	TRCN0000477891	0.32	0.23	0	TRCN0000477891	0.94	0.51	0
36	Hit	FGF5	Growth factors/RTKs	TRCN0000476022	3.7	3.13	1	TRCN0000476022	0.83	1.17	0	TRCN0000476022	0.88	0.61	0
37	Hit	RAF1	SK-N-BE(2)-C specific hit	TRCN0000474946	3.2	4.28	1	TRCN0000474946	0.67	0.40	0	TRCN0000474946	0.84	0.10	0
38	Hit	YES1	SK-N-BE(2)-C specific hit	TRCN0000468660	3.19	2.8	1	TRCN0000468660	0.84	0.50	0	TRCN0000468660	0.83	-0.08	0
39	Hit	ARL4D	SK-N-BE(2)-C specific hit	TRCN0000468563	3.22	2.92	1	TRCN0000468563	0.97	0.94	0	TRCN0000468563	0.83	0.19	0
40	Hit	FGF6	SK-N-BE(2)-C specific hit	TRCN0000474663	4.21	4.23	1	TRCN0000474663	-2.85	-1.31	0	TRCN0000474663	0.82	-1.83	0
41	Hit	BRAF	SK-N-BE(2)-C specific hit	TRCN0000489575	4.25	3.72	1	TRCN0000489575	1.07	0.44	0	TRCN0000489575	0.76	-0.20	0
42	Hit	DEPDC7	SK-N-BE(2)-C specific hit	TRCN0000467576	3.49	4.29	1	TRCN0000467576	0.31	0.41	0	TRCN0000467576	0.75	0.20	0
43	Hit	HCAR3	SK-N-BE(2)-C specific hit	TRCN0000489482	4.54	5	1	TRCN0000491859	0.34	0.31	0	TRCN0000489482	0.57	0.07	0
44	Hit	GPR183	Growth factors/RTKs	TRCN0000487905	4.69	4.86	1	TRCN0000479853	1.71	1.40	0	TRCN0000487905	0.52	0.19	0
45	Hit	FLT3	SK-N-BE(2)-C specific hit	TRCN0000465444	2.56	3.82	1	TRCN0000488186	-0.25	1.28	0	TRCN0000465444	0.46	0.22	0
46	Hit	CNR1	SK-N-BE(2)-C specific hit	TRCN0000488761	3.83	4.22	1	TRCN0000488761	0.63	0.47	0	TRCN0000488761	0.45	0.98	0
47	Hit	SUCNR1	SK-N-BE(2)-C specific hit	TRCN0000489472	5.31	5.98	1	TRCN0000489472	0.71	0.61	0	TRCN0000489472	0.45	0.19	0
48	Hit	CHRM2	SK-N-BE(2)-C specific hit	TRCN0000492171	2.76	3.11	1	TRCN0000492120	0.52	0.19	0	TRCN0000492171	0.42	-0.69	0
49	Hit	HTR1D	SK-N-BE(2)-C specific hit	TRCN0000466228	5.4	5.66	1	TRCN0000487810	0.25	0.25	0	TRCN0000466228	0.42	0.01	0
50	Hit	STK40	SK-N-BE(2)-C specific hit	TRCN0000491586	5.62	4.42	1	TRCN0000478606	0.55	0.45	0	TRCN0000491586	0.37	0.11	0
51	Hit	ETS2	SK-N-BE(2)-C specific hit	TRCN0000479087	3.06	3.41	1	TRCN0000479087	0.01	0.20	0	TRCN0000479087	0.37	0.37	0
52	Hit	CYSLTR1	SK-N-BE(2)-C specific hit	TRCN0000489453	2.75	3.3	1	TRCN0000489453	0.32	0.40	0	TRCN0000489453	0.34	1.35	0
53	Hit	ZBTB20	SK-N-BE(2)-C specific hit	TRCN0000476850	3.19	3.69	1	TRCN0000476850	0.78	1.39	0	TRCN0000476850	0.34	0.19	0
54	Hit	HTR1F	SK-N-BE(2)-C specific hit	TRCN0000489611	5.94	5.61	1	TRCN0000489793	0.93	0.84	0	TRCN0000489611	0.33	0.49	0
55	Hit	DRD2	SK-N-BE(2)-C specific hit	TRCN0000492361	2.98	3.01	1	TRCN0000492361	0.15	0.16	0	TRCN0000492361	0.30	-0.29	0
56	Hit	RASGRP1	SK-N-BE(2)-C specific hit	TRCN0000489632	4.73	5.2	1	TRCN0000489632	0.07	0.21	0	TRCN0000489632	0.23	0.18	0
57	Hit	HCAR2	SK-N-BE(2)-C specific hit	TRCN0000488076	5.7	6.64	1	TRCN0000488076	0.51	0.15	0	TRCN0000488076	0.23	-0.08	0

#	Category	Gene symbol	Pathway	Genome-wide ORF screen: SK-N-BE(2)-C			Genome-wide ORF screen: LAN-1				Validation ORF screen: LAN-1		CHP-212	Validation screen hit	
				Construct ID	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Genome-wide screen hit	Construct ID	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Genome-wide screen hit	Construct ID	z-score JQ1 vs. ETP		z-score JQ1 vs. ETP
58	Hit	FFAR3	SK-N-BE(2)-C specific hit	TRCN0000470239	3.05	3.67	1	TRCN0000488387	0.36	0.11	0	TRCN0000470239	0.22	0.06	0
59	Hit	ADORA1	SK-N-BE(2)-C specific hit	TRCN0000488625	6.49	7.11	1	TRCN0000470054	0.23	0.33	0	TRCN0000488625	0.22	0.11	0
60	Hit	GRM7	SK-N-BE(2)-C specific hit	TRCN0000489177	2.94	3.01	1	TRCN0000489177	-0.47	-0.46	0	TRCN0000489177	0.17	0.25	0
61	Hit	MTNR1B	SK-N-BE(2)-C specific hit	TRCN0000488432	4.56	4.96	1	TRCN0000488432	0.41	0.59	0	TRCN0000488432	0.17	0.19	0
62	Hit	CXCR1	SK-N-BE(2)-C specific hit	TRCN0000488528	5.43	5.59	1	TRCN0000491640	0.81	0.52	0	TRCN0000488528	0.16	0.55	0
63	Hit	NFIB	SK-N-BE(2)-C specific hit	TRCN0000468617	5.67	4.75	1	TRCN0000468617	0.42	-0.10	0	TRCN0000468617	0.13	-0.15	0
64	Hit	PTGER3	SK-N-BE(2)-C specific hit	TRCN0000488834	2.91	3.77	1	TRCN0000470039	0.82	1.13	0	TRCN0000488834	0.12	0.13	0
65	Hit	P2RY13	SK-N-BE(2)-C specific hit	TRCN0000466042	4.3	5.14	1	TRCN0000488388	0.67	0.61	0	TRCN0000466042	0.08	1.68	0
66	Hit	GRM3	SK-N-BE(2)-C specific hit	TRCN0000487741	4.03	4.85	1	TRCN0000489865	0.28	-0.10	0	TRCN0000487741	-0.01	2.05	0
67	Hit	RXFP4	SK-N-BE(2)-C specific hit	TRCN0000491613	3.48	3.73	1	TRCN0000489021	0.50	0.20	0	TRCN0000491613	-0.03	0.38	0
68	Hit	PPF1A	SK-N-BE(2)-C specific hit	TRCN0000492109	3.36	4.27	1	TRCN0000492109	-0.43	-1.57	0	TRCN0000492109	-0.04	0.36	0
69	Hit	HTR1B	SK-N-BE(2)-C specific hit	TRCN0000488224	5.54	5.68	1	TRCN0000471924	0.13	-0.12	0	TRCN0000488224	-0.07	0.16	0
70	Hit	P2RY14	SK-N-BE(2)-C specific hit	TRCN0000488505	6.61	7.32	1	TRCN0000488505	0.19	0.29	0	TRCN0000488505	-0.14	0.28	0
71	Hit	GRM2	SK-N-BE(2)-C specific hit	TRCN0000488215	3.79	4.1	1	TRCN0000488215	-0.53	-0.73	0	TRCN0000488215	-0.22	2.34	0
72	Hit	HTR5A	SK-N-BE(2)-C specific hit	TRCN0000489686	4.55	3.63	1	TRCN0000475616	0.46	0.25	0	TRCN0000489686	-0.24	0.88	0
73	Hit	ADORA3	SK-N-BE(2)-C specific hit	TRCN0000488502	5.27	4.17	1	TRCN0000474239	1.18	0.93	0	TRCN0000488502	-0.28	-0.21	0
74	Hit	HTR1E	SK-N-BE(2)-C specific hit	TRCN0000489111	7.78	7.22	1	TRCN0000475926	0.53	0.72	0	TRCN0000489111	-0.30	0.04	0
75	Hit	MTNR1A	SK-N-BE(2)-C specific hit	TRCN0000492315	8.59	7.35	1	TRCN0000488582	-0.19	0.07	0	TRCN0000492315	-0.31	0.03	0
76	Hit	GPR34	Growth factors/RTKs	TRCN0000489826	6.75	6.88	1	TRCN0000492042	1.05	1.20	0	TRCN0000489826	-0.34	0.93	0
77	Hit	CNR2	SK-N-BE(2)-C specific hit	TRCN0000492091	7.25	7.83	1	TRCN0000488729	-0.01	-0.30	0	TRCN0000492091	-0.35	0.46	0
78	Hit	GPR20	Growth factors/RTKs	TRCN0000488074	5.93	5.55	1	TRCN0000478486	-0.09	-0.21	0	TRCN0000488074	-0.38	-0.08	0
79	Hit	DRD3	SK-N-BE(2)-C specific hit	TRCN0000488434	5.2	5.12	1	TRCN0000476045	0.41	0.60	0	TRCN0000488434	-0.40	0.29	0
80	Hit	CSNK1A1L	SK-N-BE(2)-C specific hit	TRCN0000489911	3.74	3.06	1	TRCN0000479515	-0.15	-0.17	0	TRCN0000489911	-0.43	-0.09	0
81	Hit	GPR22	Growth factors/RTKs	TRCN0000488708	5.81	6.95	1	TRCN0000469954	0.29	0.23	0	TRCN0000488708	-0.45	0.53	0
82	Hit	FFAR4	SK-N-BE(2)-C specific hit	TRCN0000488711	3.48	4.77	1	TRCN0000472203	-0.01	0.22	0	TRCN0000488711	-0.47	0.26	0
83	Hit	HCAR1	SK-N-BE(2)-C specific hit	TRCN0000489708	5.48	5.98	1	TRCN0000477429	0.28	0.28	0	TRCN0000489708	-0.48	1.05	0
84	Hit	S1PR1	SK-N-BE(2)-C specific hit	TRCN0000467249	8.09	7.44	1	TRCN0000487798	-0.34	-0.60	0	TRCN0000467249	-0.55	0.20	0
85	Hit	GPR82	Growth factors/RTKs	TRCN0000489463	6.74	7.67	1	TRCN0000489463	-0.17	-0.42	0	TRCN0000489463	-0.58	0.09	0
86	Hit	S1PR5	SK-N-BE(2)-C specific hit	TRCN0000487761	7.9	6.67	1	TRCN0000487973	-1.02	-0.63	0	TRCN0000487761	-0.76	0.33	0
87	Hit	GRM8	SK-N-BE(2)-C specific hit	TRCN0000492137	4.77	5.44	1	TRCN0000489225	0.06	-0.79	0	TRCN0000492137	-0.78	0.19	0
88	Hit	S1PR4	SK-N-BE(2)-C specific hit	TRCN0000489149	6.4	6.97	1	TRCN0000473906	-0.01	0.12	0	TRCN0000489149	-0.91	0.15	0
89	Hit	NFIC	SK-N-BE(2)-C specific hit	TRCN0000472445	4.72	5.23	1	TRCN0000472445	-0.78	-1.59	0	TRCN0000472445	-0.93	-1.47	0
90	Hit	P2RY12	SK-N-BE(2)-C specific hit	TRCN0000491982	3.35	4.36	1	TRCN0000470996	-0.17	-0.32	0	TRCN0000491982	-1.10	0.34	0
91	Neutral control	ADD1		TRCN0000471276	0.17	0.27	0	TRCN0000471276	0.25	0.40	0	TRCN0000471276	0.60	-0.70	0
92	Neutral control	ANKRD23		TRCN0000468423	0.03	0.18	0	TRCN0000468423	0.09	0.41	0	TRCN0000468423	0.59	0.15	0
93	Neutral control	ANKRD55		TRCN0000475370	0.13	0.39	0	TRCN0000475370	0.22	0.48	0	TRCN0000475370	0.63	0.19	0
94	Neutral control	C14orf159		TRCN0000466769	0.16	0.02	0	TRCN0000466769	0.27	0.08	0	TRCN0000466769	0.23	-0.65	0
95	Neutral control	C9orf72		TRCN0000471027	0.01	0.42	0	TRCN0000471027	0.30	0.24	0	TRCN0000471027	0.34	-0.04	0
96	Neutral control	CALR3		TRCN0000468886	0.36	0.12	0	TRCN0000468886	-0.15	-0.09	0	TRCN0000468886	0.05	0.08	0
97	Neutral control	CASP14		TRCN0000468053	0.14	0.39	0	TRCN0000468053	0.11	0.18	0	TRCN0000468053	0.52	0.28	0
98	Neutral control	CLEC3B		TRCN0000468526	0.32	0.26	0	TRCN0000468526	0.31	0.25	0	TRCN0000468526	0.28	-2.76	0
99	Neutral control	DDAH1		TRCN0000477029	0.02	0.21	0	TRCN0000477029	0.07	0.09	0	TRCN0000477029	0.18	-1.74	0
100	Neutral control	DKK3		TRCN0000472220	0.30	0.36	0	TRCN0000472220	0.43	0.23	0	TRCN0000472220	0.37	0.09	0
101	Neutral control	DPYS		TRCN0000472173	0.25	0.02	0	TRCN0000472173	0.38	0.27	0	TRCN0000472173	0.42	-0.06	0
102	Neutral control	ENPP5		TRCN0000480733	0.08	0.26	0	TRCN0000480733	0.11	0.20	0	TRCN0000480733	0.20	-0.78	0
103	Neutral control	EPT1		TRCN0000472043	0.42	0.06	0	TRCN0000472043	0.28	0.06	0	TRCN0000472043	0.40	0.28	0
104	Neutral control	FGL1		TRCN0000467977	0.32	0.20	0	TRCN0000467977	0.22	0.17	0	TRCN0000467977	0.40	0.32	0
105	Neutral control	GBP6		TRCN0000468591	0.08	0.35	0	TRCN0000468591	0.30	0.34	0	TRCN0000468591	0.47	0.19	0
106	Neutral control	GFAP		TRCN0000470974	0.30	0.19	0	TRCN0000470974	0.46	0.19	0	TRCN0000470974	0.45	1.50	0
107	Neutral control	GSTT2B		TRCN0000477749	0.25	0.04	0	TRCN0000477749	0.26	0.37	0	TRCN0000477749	0.41	-0.50	0
108	Neutral control	HLA-B		TRCN0000466537	0.31	0.13	0	TRCN0000466537	0.47	0.15	0	TRCN0000466537	0.31	-0.76	0
109	Neutral control	HSD3B1		TRCN0000467445	0.10	0.20	0	TRCN0000467445	0.12	0.30	0	TRCN0000467445	0.37	1.16	0
110	Neutral control	IL12B		TRCN0000470130	0.31	0.29	0	TRCN0000470130	0.25	0.34	0	TRCN0000470130	0.57	-0.06	0
111	Neutral control	KCNJ13		TRCN0000471741	0.05	0.27	0	TRCN0000471741	0.41	0.26	0	TRCN0000471741	0.25	0.39	0
112	Neutral control	LYRM1		TRCN0000472126	0.37	0.14	0	TRCN0000472126	0.29	0.11	0	TRCN0000472126	0.29	-0.14	0
113	Neutral control	MRPS5		TRCN0000468744	0.15	0.04	0	TRCN0000468744	0.11	0.38	0	TRCN0000468744	0.45	-2.00	0
114	Neutral control	MRTO4		TRCN0000466401	0.36	0.31	0	TRCN0000466401	0.23	0.28	0	TRCN0000466401	0.66	0.18	0
115	Neutral control	NPIP5A		TRCN0000473627	0.12	0.46	0	TRCN0000473627	0.16	0.35	0	TRCN0000473627	0.37	0.20	0
116	Neutral control	RNF2		TRCN0000472910	0.03	0.01	0	TRCN0000472910	0.29	0.31	0	TRCN0000472910	0.56	0.82	0
117	Neutral control	SCO1		TRCN0000480160	0.36	0.09	0	TRCN0000480160	0.19	0.43	0	TRCN0000480160	0.58	0.08	0

#	Category	Gene symbol	Pathway	Genome-wide ORF screen: SK-N-BE(2)-C				Genome-wide ORF screen: LAN-1				Validation ORF screen: LAN-1 CHP-212			Validation screen hit
				Construct ID	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Genome-wide screen hit	Construct ID	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Genome-wide screen hit	Construct ID	z-score JQ1 vs. ETP	z-score JQ1 vs. ETP	
118	Neutral control	SH3GLB1		TRCN0000465766	0.21	0.44	0	TRCN0000465766	0.26	0.14	0	TRCN0000465766	0.15	0.33	0
119	Neutral control	SHMT1		TRCN0000480756	0.22	0.36	0	TRCN0000480756	0.31	0.32	0	TRCN0000480756	0.41	0.14	0
120	Neutral control	SNRNP25		TRCN0000478472	0.26	0.18	0	TRCN0000478472	0.25	0.24	0	TRCN0000478472	0.50	0.60	0
121	Neutral control	SNUPN		TRCN0000474119	0.34	0.22	0	TRCN0000474119	0.20	0.07	0	TRCN0000474119	0.06	-0.25	0
122	Neutral control	ST6GALNAC6		TRCN0000473467	0.15	0.35	0	TRCN0000473467	0.36	0.25	0	TRCN0000473467	0.31	-4.28	0
123	Neutral control	STAC		TRCN0000492333	0.29	0.28	0	TRCN0000492333	0.29	0.24	0	TRCN0000492333	0.47	0.72	0
124	Neutral control	THBS3		TRCN0000472509	0.14	0.17	0	TRCN0000472509	0.34	0.12	0	TRCN0000472509	0.33	0.30	0
125	Neutral control	TMOD3		TRCN0000470700	0.18	0.30	0	TRCN0000470700	0.32	0.16	0	TRCN0000470700	0.30	-2.58	0
126	Neutral control	TRH		TRCN0000492070	0.04	0.11	0	TRCN0000492070	0.25	0.32	0	TRCN0000492070	0.45	0.06	0
127	Neutral control	UFC1		TRCN0000471317	0.11	0.10	0	TRCN0000471317	0.26	0.36	0	TRCN0000471317	0.36	0.06	0
128	Neutral control	ZDHHC2		TRCN0000491998	0.42	0.26	0	TRCN0000491998	0.28	0.41	0	TRCN0000491998	0.49	-0.87	0
129	Neutral control	ZSCAN21		TRCN0000478659	0.34	0.28	0	TRCN0000478659	0.33	0.12	0	TRCN0000478659	0.37	-1.09	0
130	Neutral control	ASP		TRCN0000469338	0.01	0.45	0	TRCN0000469338	0.26	0.38	0	TRCN0000469338	0.54	-0.29	0
131	Neutral control	CCDC47		TRCN0000466188	0.38	0.06	0	TRCN0000466188	0.38	0.07	0	TRCN0000466188	0.40	0.76	0
132	Neutral control	HIPK1		TRCN0000472928	0.42	0.06	0	TRCN0000472928	0.26	0.29	0	TRCN0000472928	0.40	0.26	0
133	Neutral control	PDCD10		TRCN0000474286	0.38	0.07	0	TRCN0000474286	0.44	0.15	0	TRCN0000474286	0.21	-2.92	0
134	Neg control	BAD		TRCN0000466830	-3.88	-3.65	0	TRCN0000466830	-5.72	-5.31	0	TRCN0000466830	-5.23	0.12	0
135	Neg control	CCER1		TRCN0000473392	-3.71	-4.07	0	TRCN0000473392	-5.72	-5.63	0	TRCN0000473392	-4.47	0.24	0
136	Neg control	ELF2		TRCN0000469930	-3.65	-3.74	0	TRCN0000469930	-3.97	-4.35	0	TRCN0000469930	-2.20	0.19	0
137	Neg control	IRX6		TRCN0000478056	-3.16	-3.07	0	TRCN0000478056	-4.82	-4.55	0	TRCN0000478056	-3.00	0.11	0
138	Neg control	MITD1		TRCN0000480522	-4.36	-4.15	0	TRCN0000480522	-3.35	-2.93	0	TRCN0000480522	-2.76	0.29	0
139	Neg control	PPARG		TRCN0000488879	-2.73	-2.53	0	TRCN0000488879	-3.22	-3.94	0	TRCN0000488879	-1.98	-0.11	0
140	Neg control	SPATA25		TRCN0000481565	-4.40	-4.69	0	TRCN0000481565	-5.37	-5.13	0	TRCN0000481565	-4.81	0.17	0
141	Neg control	TCEB3B		TRCN0000467856	-4.30	-4.09	0	TRCN0000467856	-5.64	-5.49	0	TRCN0000467856	-5.62	0.25	0
142	Neg control	TFAP2A		TRCN0000481607	-3.30	-3.65	0	TRCN0000481607	-3.87	-3.89	0	TRCN0000481607	-2.57	0.25	0
143	Neg control	THAP1		TRCN0000480905	-2.76	-3.69	0	TRCN0000480905	-3.70	-4.33	0	TRCN0000480905	-2.21	-3.31	0
144	External control	BFP		BRDN0000559460	na	na	0	BRDN0000559460	na	na	0	BRDN0000559460	0.18	-0.15	0
145	External control	LacZ		BRDN0000559461	na	na	0	BRDN0000559461	na	na	0	BRDN0000559461	-1.37	1.20	0
146	External control	HcRed		BRDN0000559463	na	na	0	BRDN0000559463	na	na	0	BRDN0000559463	0.20	0.03	0
147	External control	LUCIFERASE		BRDN0000559468	na	na	0	BRDN0000559468	na	na	0	BRDN0000559468	-1.47	-0.48	0
148	External control	eGFP		BRDN0000559466	na	na	0	BRDN0000559466	na	na	0	BRDN0000559466	0.49	0.28	0
149	External candidate	cMYC		BRDN0000553495	na	na	0	BRDN0000553495	na	na	0	BRDN0000553495	-0.79	0.13	0
150	External candidate	MYCN		BRDN0001487020	na	na	0	BRDN0001487020	na	na	0	BRDN0001487020	-1.28	0.19	0

Table S4, Related to Figure 1. Results of the CRISPR-Cas9 BET1 rescue screen in SK-N-BE(2)-C cells and LAN-1 cells.

SK-N-BE(2)-C

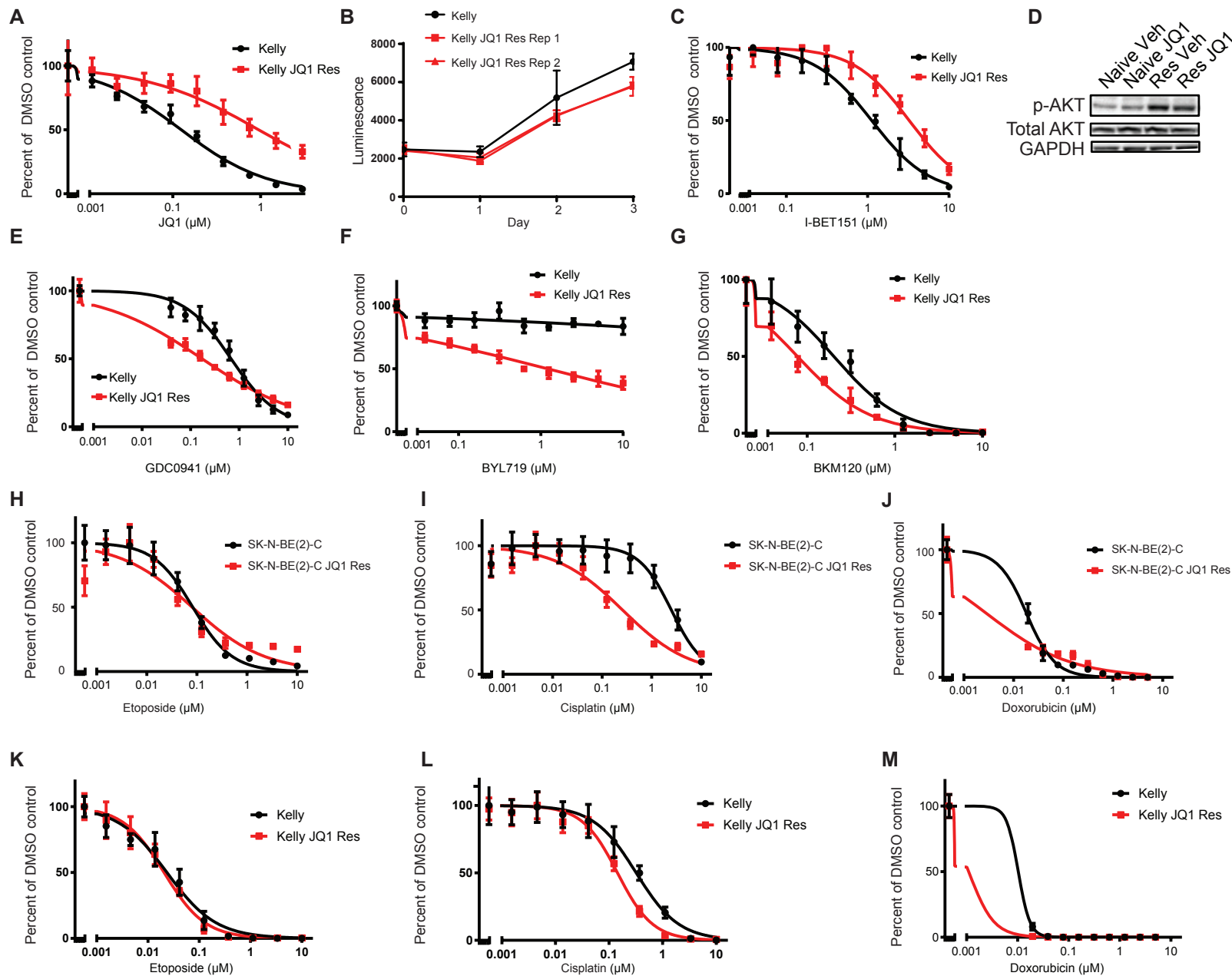
#	Construct ID	Gene [# sgRNA hits / total # sgRNAs]	Pathway	Hit specificity	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Av. z-scores I-BET151 and JQ1 vs. ETP
1	BRDN0000938810	RASA2 [4/4]		SK-N-BE(2)-C specific hit	12.70	5.60	9.15
2	BRDN0000938813	RASA2 [4/4]		SK-N-BE(2)-C specific hit	11.30	5.60	8.45
3	BRDN0000938811	RASA2 [4/4]		SK-N-BE(2)-C specific hit	11.00	4.90	7.95
4	BRDN0000882124	CSK [4/4]		SK-N-BE(2)-C specific hit	11.10	4.70	7.90
5	BRDN0000938812	RASA2 [4/4]	PI3K/AKT	SK-N-BE(2)-C specific hit	10.00	3.70	6.85
6	BRDN0000882126	CSK [4/4]		SK-N-BE(2)-C specific hit	9.10	3.60	6.35
7	BRDN0000914147	LZTR1 [4/4]		SK-N-BE(2)-C specific hit	8.50	3.70	6.10
8	BRDN0000957757	TMEM127 [3/4]	PI3K/AKT	SK-N-BE(2)-C specific hit	7.80	4.20	6.00
9	BRDN0000932280	PLCG1 [4/4]	PI3K/AKT	SK-N-BE(2)-C specific hit	7.50	4.20	5.85
10	BRDN0000957754	TMEM127 [3/4]	PI3K/AKT	SK-N-BE(2)-C specific hit	8.10	3.60	5.85
11	BRDN0000932278	PLCG1 [4/4]	PI3K/AKT	SK-N-BE(2)-C specific hit	7.10	4.30	5.70
12	BRDN0000914146	LZTR1 [4/4]		SK-N-BE(2)-C specific hit	7.70	3.30	5.50
13	BRDN0000957755	TMEM127 [3/4]	PI3K/AKT	SK-N-BE(2)-C specific hit	6.00	4.10	5.05
14	BRDN0000882125	CSK [4/4]		SK-N-BE(2)-C specific hit	6.00	3.90	4.95
15	BRDN0000914150	LZTR1 [4/4]		SK-N-BE(2)-C specific hit	6.60	3.30	4.95
16	BRDN0000936813	PTEN [4/4]	PI3K/AKT	Core hit	5.40	3.90	4.65
17	BRDN0000867256	ATP6V1B1 [1/4]		SK-N-BE(2)-C specific hit	5.30	4.00	4.65
18	BRDN0000937083	PTPN1 [3/4]		SK-N-BE(2)-C specific hit	6.00	3.20	4.60
19	BRDN0000936812	PTEN [4/4]	PI3K/AKT	Core hit	5.50	3.60	4.55
20	BRDN0000885353	DET1 [2/4]		SK-N-BE(2)-C specific hit	5.50	3.50	4.50
21	BRDN0000885352	DET1 [2/4]		SK-N-BE(2)-C specific hit	5.70	3.10	4.40
22	BRDN0000932279	PLCG1 [4/4]	PI3K/AKT	SK-N-BE(2)-C specific hit	5.80	2.90	4.35
23	BRDN0000952872	STK11 [2/4]		SK-N-BE(2)-C specific hit	6.00	2.70	4.35
24	BRDN0000936815	PTEN [4/4]	PI3K/AKT	Core hit	5.20	3.40	4.30
25	BRDN0000914151	LZTR1 [4/4]		SK-N-BE(2)-C specific hit	6.00	2.60	4.30
26	BRDN0000937084	PTPN1 [3/4]		SK-N-BE(2)-C specific hit	5.70	2.60	4.15
27	BRDN0000940114	RFWD2 [1/4]		SK-N-BE(2)-C specific hit	5.30	2.90	4.10
28	BRDN0000957058	TIPRL [1/4]		SK-N-BE(2)-C specific hit	3.90	4.20	4.05
29	BRDN0000882127	CSK [4/4]		SK-N-BE(2)-C specific hit	4.30	3.50	3.90
30	BRDN0000878824	CIC [1/4]		SK-N-BE(2)-C specific hit	4.80	2.80	3.80
31	BRDN0000932281	PLCG1 [4/4]	PI3K/AKT	SK-N-BE(2)-C specific hit	3.60	3.50	3.55
32	BRDN0000868117	BAX [2/4]	Apoptosis	Core hit	4.10	2.90	3.50
33	BRDN0000894396	FKBP1 [1/4]	Cell cycle	SK-N-BE(2)-C specific hit	4.10	2.60	3.35
34	BRDN0000963126	UBE2N [2/4]		SK-N-BE(2)-C specific hit	3.90	2.80	3.35
35	BRDN0000874213	CSLB [1/4]		SK-N-BE(2)-C specific hit	3.90	2.60	3.25
36	BRDN0000952871	STK11 [2/4]		SK-N-BE(2)-C specific hit	3.80	2.70	3.25
37	BRDN0000936814	PTEN [4/4]	PI3K/AKT	Core hit	3.80	2.60	3.20
38	BRDN0000868114	BAX [2/4]	Apoptosis	Core hit	3.00	2.90	2.95
39	BRDN0000937085	PTPN1 [3/4]		SK-N-BE(2)-C specific hit	2.90	2.80	2.85
40	BRDN0000949460	SMEK1 [1/4]		SK-N-BE(2)-C specific hit	2.90	2.50	2.70
41	BRDN0000963127	UBE2N [2/4]		SK-N-BE(2)-C specific hit	2.90	2.50	2.70
42	BRDN0000914774	MAP1LC3A [1/4]		SK-N-BE(2)-C specific hit	2.60	2.50	2.55

LAN-1

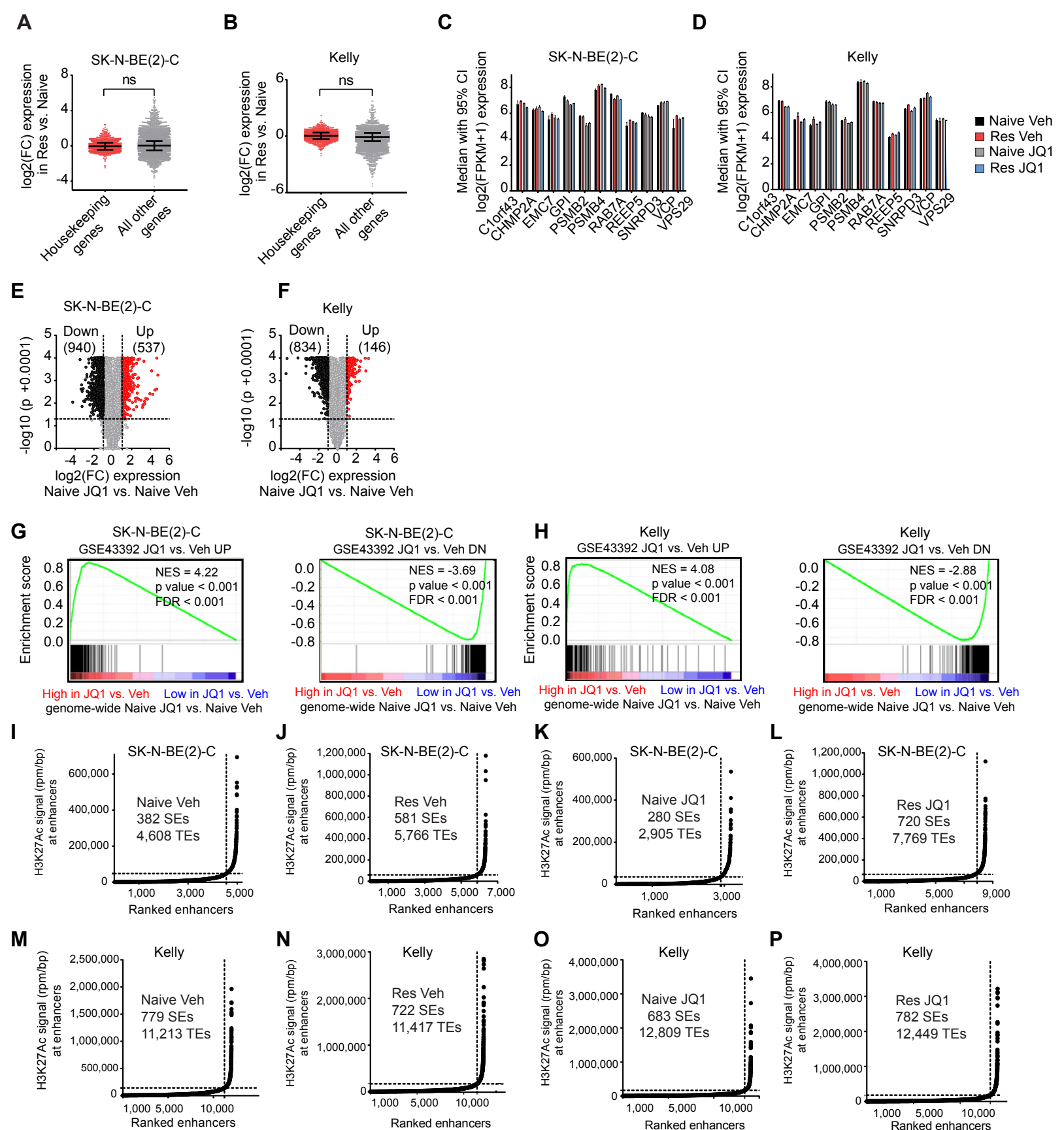
#	Construct ID	Gene [# sgRNA hits / total # sgRNAs]	Pathway	Hit specificity	z-score I-BET151 vs. ETP	z-score JQ1 vs. ETP	Av. z-scores I-BET151 and JQ1 vs. ETP
1	BRDN0000876725	CDH2 [4/4]		LAN-1 specific hit	8.65	7.81	8.23
2	BRDN0000876727	CDH2 [4/4]		LAN-1 specific hit	8.18	7.18	7.68
3	BRDN0000876726	CDH2 [4/4]		LAN-1 specific hit	8.19	6.99	7.59
4	BRDN0000876724	CDH2 [4/4]		LAN-1 specific hit	7.89	6.80	7.34
5	BRDN0000932840	PMAIP1 [3/4]	Apoptosis	LAN-1 specific hit	5.46	6.91	6.18
6	BRDN0000932841	PMAIP1 [3/4]	Apoptosis	LAN-1 specific hit	5.12	6.50	5.81
7	BRDN0000971194	ZNF787 [4/4]		LAN-1 specific hit	4.99	5.42	5.20
8	BRDN0000884867	DEAF1 [3/4]		LAN-1 specific hit	4.52	5.74	5.13
9	BRDN0000932842	PMAIP1 [3/4]	Apoptosis	LAN-1 specific hit	4.37	5.86	5.11
10	BRDN0000868117	BAX [4/4]	Apoptosis	Core hit	4.72	5.50	5.11
11	BRDN0000929711	PCSK7 [3/4]		LAN-1 specific hit	4.11	5.49	4.80
12	BRDN0000884866	DEAF1 [3/4]		LAN-1 specific hit	4.28	5.31	4.80
13	BRDN0000929714	PCSK7 [3/4]		LAN-1 specific hit	4.52	5.03	4.77
14	BRDN0000971197	ZNF787 [4/4]		LAN-1 specific hit	4.47	4.85	4.66
15	BRDN0000937766	R3HDM1 [3/4]		LAN-1 specific hit	4.03	5.22	4.62
16	BRDN0000954325	TADA2B [1/4]		LAN-1 specific hit	3.51	5.59	4.55
17	BRDN0000968520	ZMYM4 [1/4]		LAN-1 specific hit	4.31	4.71	4.51
18	BRDN0000929715	PCSK7 [3/4]		LAN-1 specific hit	4.00	4.97	4.48
19	BRDN0000868114	BAX [4/4]	Apoptosis	Core hit	3.85	5.00	4.43
20	BRDN0000868116	BAX [4/4]	Apoptosis	Core hit	3.90	4.92	4.41
21	BRDN0000868115	BAX [4/4]	Apoptosis	Core hit	3.82	4.92	4.37
22	BRDN0000884868	DEAF1 [3/4]		LAN-1 specific hit	3.50	4.60	4.05
23	BRDN0000936813	PTEN [2/4]	PI3K/AKT	Core hit	4.68	3.30	3.99
24	BRDN0000936815	PTEN [2/4]	PI3K/AKT	Core hit	4.77	2.94	3.85
25	BRDN0000919129	MTCH2 [1/4]		LAN-1 specific hit	3.46	4.20	3.83
26	BRDN0000882743	CTNND1 [3/4]		LAN-1 specific hit	3.59	4.06	3.82



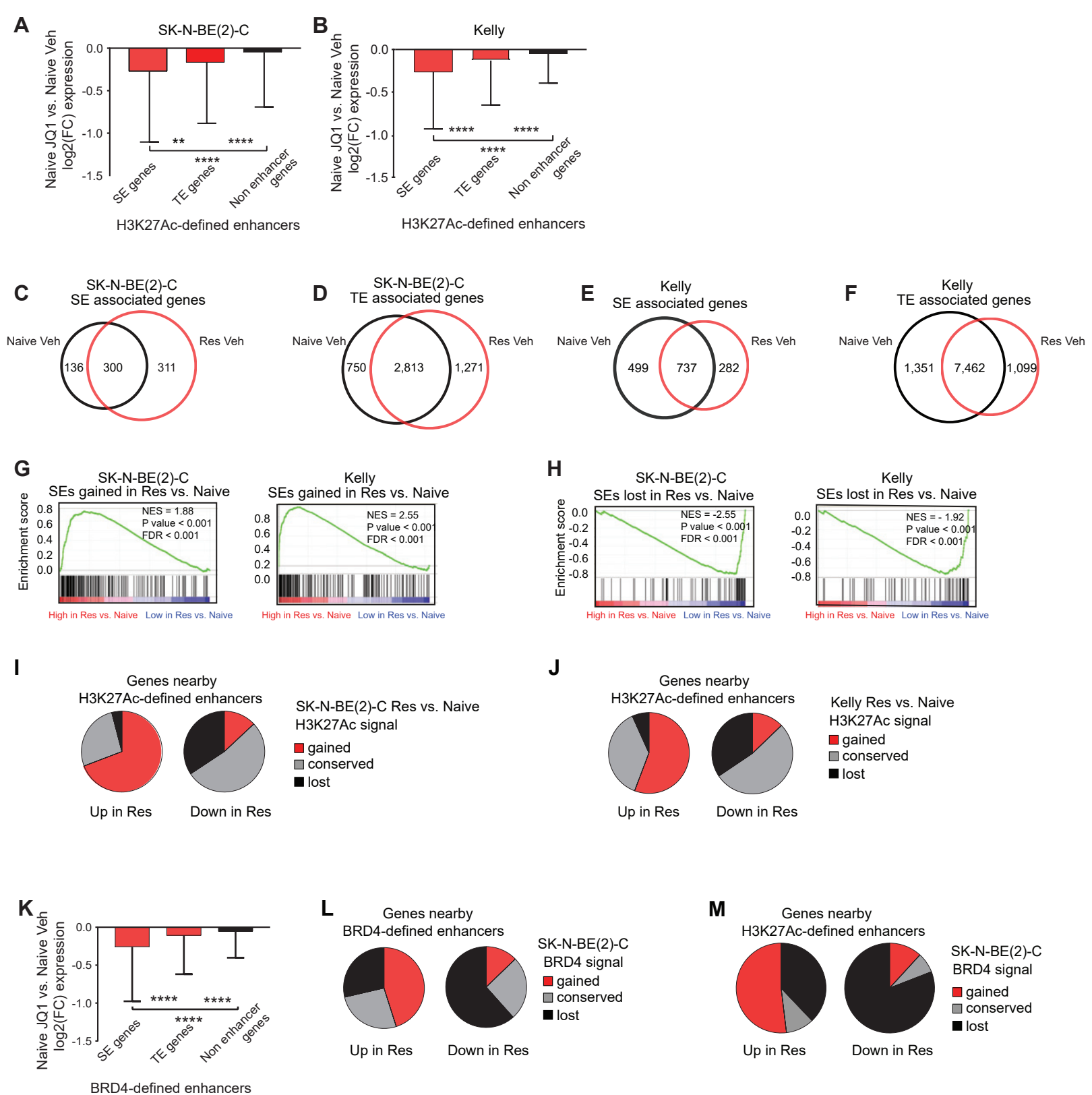
27	BRDN0000971195	ZNF787 [4/4]		LAN-1 specific hit	3.58	3.74	3.66
28	BRDN0000937768	R3HDM1 [3/4]		LAN-1 specific hit	2.75	4.14	3.45
29	BRDN0000882745	CTNND1 [3/4]		LAN-1 specific hit	3.73	3.13	3.43
30	BRDN0000868021	BAK1 [1/4]	Apoptosis	LAN-1 specific hit	3.40	3.32	3.36
31	BRDN0000971196	ZNF787 [4/4]		LAN-1 specific hit	3.16	3.54	3.35
32	BRDN0000877991	CFL1 [3/4]		LAN-1 specific hit	3.33	3.35	3.34
33	BRDN0000938534	RALGAPB [1/4]	PI3K/AKT	LAN-1 specific hit	4.02	2.61	3.31
34	BRDN0000934695	PPTC7 [1/4]		LAN-1 specific hit	3.31	3.31	3.31
35	BRDN0000877992	CFL1 [3/4]		LAN-1 specific hit	3.35	3.20	3.28
36	BRDN0000953128	STRAP [2/4]		LAN-1 specific hit	2.97	3.55	3.26
37	BRDN0000937726	QSER1 [2/4]		LAN-1 specific hit	3.01	3.49	3.25
38	BRDN0000877993	CFL1 [3/4]		LAN-1 specific hit	3.08	3.41	3.24
39	BRDN0000917316	MLLT10 [2/4]		LAN-1 specific hit	3.26	3.22	3.24
40	BRDN0000882742	CTNND1 [3/4]		LAN-1 specific hit	2.99	3.47	3.23
41	BRDN0000937767	R3HDM1 [3/4]		LAN-1 specific hit	2.56	3.86	3.21
42	BRDN0000882043	CSDE1 [1/4]		LAN-1 specific hit	2.64	3.55	3.10
43	BRDN0000953129	STRAP [2/4]		LAN-1 specific hit	2.50	3.61	3.05
44	BRDN0000963317	UBP1 [1/4]		LAN-1 specific hit	2.95	3.04	3.00
45	BRDN0000868367	BCL2L11 [1/4]	Apoptosis	LAN-1 specific hit	3.05	2.92	2.98
46	BRDN0000882702	CTNNA1 [1/4]		LAN-1 specific hit	2.94	2.98	2.96
47	BRDN0000882988	CUL5 [1/4]		LAN-1 specific hit	3.05	2.80	2.92
48	BRDN0000877234	CDYL [1/4]		LAN-1 specific hit	3.14	2.67	2.91
49	BRDN0000952139	SRSF6 [1/4]		LAN-1 specific hit	2.60	3.18	2.89
50	BRDN0000878236	CHD7 [1/4]		LAN-1 specific hit	2.92	2.80	2.86
51	BRDN0000865621	ARIH2 [1/4]		LAN-1 specific hit	3.18	2.53	2.86
52	BRDN0000937727	QSER1 [2/4]		LAN-1 specific hit	2.67	3.00	2.83
53	BRDN0000963241	UBE4A [2/4]		LAN-1 specific hit	2.87	2.61	2.74
54	BRDN0000917314	MLLT10 [2/4]		LAN-1 specific hit	2.65	2.72	2.69
55	BRDN0000963238	UBE4A [2/4]		LAN-1 specific hit	2.51	2.79	2.65
56	BRDN0000922481	NKIRAS2 [1/4]		LAN-1 specific hit	2.56	2.50	2.53
57	BRDN0000866033	ARRDC3 [1/4]		LAN-1 specific hit	2.52	2.53	2.53



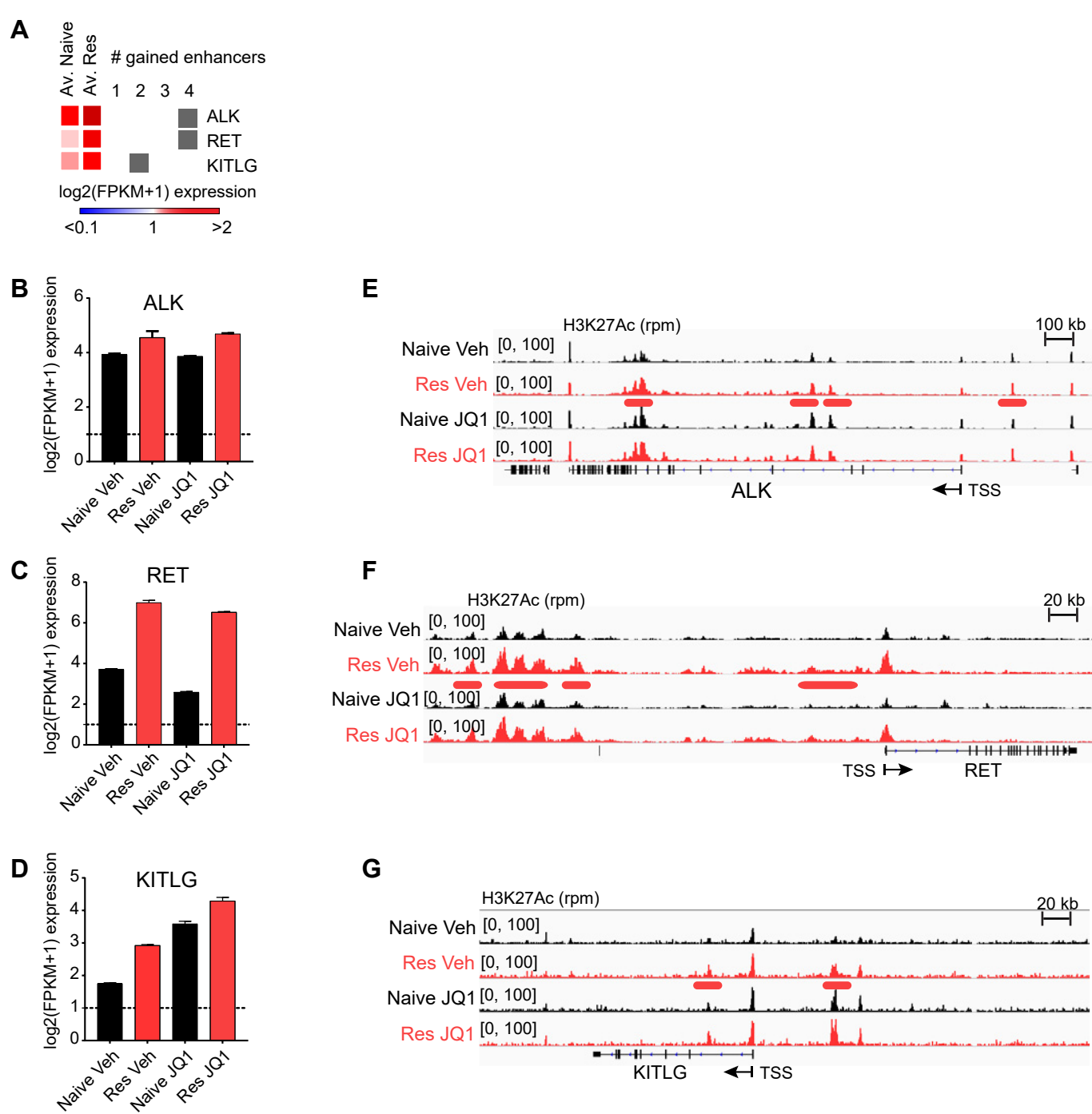
**Figure S2, Related to Figure 2: Characterization of cells with acquired resistance to JQ1.** **A.** Viability analysis with JQ1 treatment. **B.** Absolute growth rates of Kelly naive cells treated with vehicle control and two replicates of JQ1 resistant cells treated with 1  $\mu\text{M}$  JQ1. **C.** Viability analysis of IBET-151 treatment. **D.** Western blot showing downstream effectors of PI3K signaling in Kelly naive and JQ1 resistant cells. Viability analysis of **E.** GDC0941 **F.** BYL719 **G.** BKM120 and indicated chemotherapeutic drugs in **H-J.** SK-N-BE(2)-C and K-M. Kelly naive and JQ1 resistant cells.



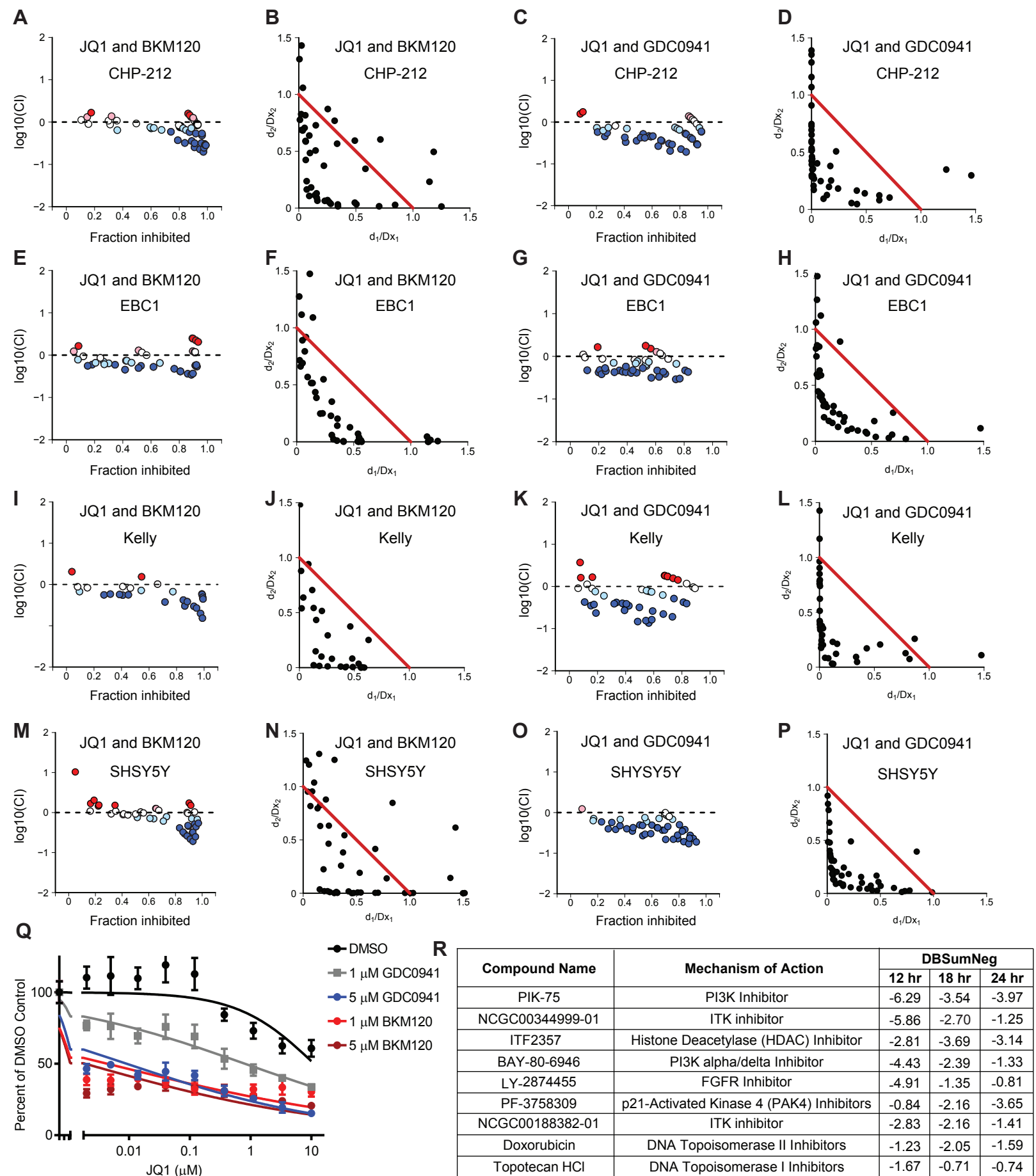
**Figure S3, Related to Figure 3: Differential gene expression profiling of JQ1 naïve and JQ1 resistant cells.**  $\log_2(\text{FC})$  gene expression for the collection of 3,804 human housekeeping genes vs. all other hg19 RefSeq genes across RNA-seq samples shown in Figure 3A and B in **A**. SK-N-BE(2)-C and **B**. Kelly cells. Difference in expression is estimated based on unpaired non-parametric t-test with Welch correction. ns= not significant.  $\log_2(\text{FPKM}+1)$  expression in JQ1 resistant vs. naïve SK-N-BE(2)-C cells for a core subset of housekeeping genes in **C**. SK-N-BE(2)-C and **D**. Kelly cells. Volcano plots highlighting the genes differentially expressed in JQ1 treated vs. untreated **E**. SK-N-BE(2)-C and **F**. Kelly naïve cells. The number of differentially upregulated and downregulated genes in resistant vs. naïve cells are shown in parentheses. GSEA demonstrating enrichment of genes upregulated by JQ1 vs. DMSO in the published microarray data GSE43392 among the genes upregulated by JQ1 treatment in naïve **G**, left: SK-N-BE(2)-C and **H**, left: Kelly cells. GSEA demonstrating enrichment of genes downregulated by JQ1 vs. DMSO in the published microarray data GSE43392 among the genes downregulated by JQ1 treatment in naïve **G**, right: SK-N-BE(2)-C and **H**, right: Kelly cells. Ranked plots of H3K27Ac enhancers in SK-N-BE(2)-C naïve cells treated with vehicle (**I**), JQ1 resistant cells treated with vehicle (**J**), naïve cells treated with JQ1 (**K**), and JQ1 resistant cells treated with JQ1 (**L**). Ranked plots of H3K27Ac enhancers in Kelly naïve cells treated with vehicle (**M**), JQ1 resistant cells treated with vehicle (**N**), naïve cells treated with JQ1 (**O**), and JQ1 resistant cells treated with JQ1 (**P**). Enhancers are defined as 12.5 kb stitched regions of H3K27Ac binding not contained in promoters (TSS +/- 2 kb). Cutoffs for discriminating typical from super-enhancers are shown as dashed gray lines. Enhancers are ranked by increasing reads per million mapped reads per base pair (rmp/bp) H3K27Ac binding signal.



**Figure S4, Related to Figure 3: Differential enhancer remodeling in JQ1 resistant cells is associated with transcriptional changes observed in the resistant state.** Bar plots presenting the  $\log_2(\text{FC})$  in gene expression for JQ1 vs. vehicle treatment among the genes associated with SEs (red), TEs (red), and the genes not associated to enhancers (black) defined by H3K27Ac signal in **A**. SK-N-BE(2)-C and **B**. Kelly cells. SE and TE associated genes are more significantly downregulated by JQ1 treatment (\*\* p value < 0.01, \*\*\*\* p value < 0.0001, un-paired two sample Student t-test with Welch correction). Venn diagrams showing the overlap between the genes associated with **C**. SEs and **D**. TEs in the resistant and naive state for SK-N-BE(2)-C cells. Venn diagrams showing the overlap between the genes associated with **E**. SEs and **F**. TEs in the resistant and naive state for Kelly cells. **G**. Gene set enrichment plot for genes which gain a SE in resistance enriched for genes which are upregulated in resistance in left: SK-N-BE(2)-C and right: Kelly cells. **H**. Gene set enrichment plot for genes which have lost a SE in resistance enriched for genes which are downregulated in resistance in left: SK-N-BE(2)-C and right: Kelly cells. Pie charts showing the percentages of genes associated with gained, conserved and lost H3K27Ac signal in enhancers among the genes nearby H3K27Ac-defined enhancers which are transcriptionally upregulated and downregulated in **I**. SK-N-BE(2)-C and **J**. Kelly resistant vs. naive cells. **K**. Bar plots presenting the  $\log_2(\text{FC})$  in gene expression for JQ1 vs. vehicle treatment in naive SK-N-BE(2)-C cells among the genes associated with BRD4 SEs (red), BRD4 TEs (red), and the genes not associated to BRD4-defined enhancers (black). BRD4 SE and BRD4 TE associated genes are more significantly downregulated by JQ1 treatment (\*\* p value < 0.01, \*\*\*\* p value < 0.0001, un-paired two sample Student t-test with Welch correction). **L**. Pie charts showing the percentages of genes with gained, conserved and lost BRD4 signal in enhancers among upregulated and downregulated genes which can be assigned to nearby BRD4-defined enhancers in resistant vs. naive SK-N-BE(2)-C cells. **M**. Pie charts showing the percentages of genes with gained, conserved and lost BRD4 signal in enhancers among upregulated and downregulated genes which can be assigned to nearby H3K27Ac-defined enhancers in resistant vs. naive SK-N-BE(2)-C cells.



**Figure S5, Related to Figure 4. Enhancer remodeling of Kelly BET inhibitor resistant cells is associated with increased expression of growth factors and RTKs. A.** Leading edge gene analysis of growth factor and RTK gene sets enriched in Kelly BET inhibitor resistant cells. Three RTK-related genes are identified as associated with gained enhancers and have log<sub>2</sub>(FC) expression >1 in resistant vs. naive cells. Average log<sub>2</sub> FPKM expression for ALK (**B**) RET (**C**) and KITLG (**D**), error bars represent SD. H3K27Ac ChIP seq tracks for ALK (**E**) RET (**F**) and KITLG (**G**). Enhancers gained in resistance are underlined.



**Figure S6, Related to Figure 6: PI3K inhibitors are synergistic with BET inhibitors in a panel of neuroblastoma cell lines and resensitize innately resistant NGP cells to BET inhibition A-P.** Combination index scores and Chou-Talalay normalized isobolograms across the indicated cell lines with the indicated compounds. **Q.** Analysis of the viability effects of JQ1 treatment in NGP cells treated with the indicated concentrations of GDC0941 or BKM120. **R.** I-BET151 in combination with a library of 58 compounds in SK-N-BE(2)-C cells, at 12, 18, and 24 hrs post-treatment, measured by Caspase-Glo 3/7. Synergy was determined based on apoptotic readings using the Delta Bliss model where negative DBSumNeg scores signify synergy.

**Table S5, Related to Figure 6. JQ1 screened against the Mechanism Interrogation PlatE (MIPE) library in SK-N-BE(2)-C and LAN-1 MYCN-amplified neuroblastoma cell lines.**

#	Drug name	Drug target	SK-N-BE(2)-C DBSumNeg score	LAN-1 DBSumNeg score	Average DBSumNeg score	Selected hits
1	PF-3758309	p21-Activated Kinase 4 (PAK4) Inhibitors	-4.048	-8.237	-6.142	1
2	BAY-80-6946	PI3K alpha/delta Inhibitor	-3.527	-6.731	-5.129	1
3	BMS-754807	IGF-1R Inhibitor	-1.750	-4.792	-3.271	1
4	MK-5108	Aurora A Inhibitor	-2.421	-2.835	-2.628	1
5	PIK-90	PI3K Inhibitor	-1.967	-3.213	-2.590	1
6	Nanchangmycin	Polyether Antibiotic	-2.015	-2.977	-2.496	1
7	Aurora A Inhibitor I	Aurora A Inhibitor	-2.101	-2.528	-2.314	1
8	NCGC00344999-01	ITK inhibitor	-2.084	-2.472	-2.278	1
9	Oxamflatin	Histone Deacetylase (HDAC) Inhibitor	-1.954	-2.571	-2.262	1
10	GDC-0941	PI3K Inhibitor	-1.922	-2.535	-2.228	1
11	CH-5132799	PI3Kalpha, beta, gamma Inhibitor	-2.518	-1.916	-2.217	1
12	BAY61-3606	Syk Kinase inhibitor	-1.785	-2.610	-2.197	1
13	GNE-493	PI3K Inhibitor	-1.819	-2.435	-2.127	1
14	NSC319726	Mutant p53 Activator	-1.954	-2.293	-2.124	1
15	ZSTK-474	PI3K Inhibitor	-2.178	-1.910	-2.044	1
16	BYL-719	PI3K alpha Inhibitor	-2.104	-1.921	-2.012	1
17	Rapamycin	mTOR inhibitor	-2.046	-1.832	-1.939	1
18	GNE-490	PI3K Inhibitor	-1.923	-1.901	-1.912	1
19	Triciribine phosphate	PKB/Akt Inhibitor	-1.757	-1.880	-1.818	1
20	BKM-120	PI3Kalpha inhibitor	-1.786	-1.837	-1.812	1
21	Ispinesib	Kinesin-Like Spindle Protein Inhibitor	-1.605	-6.658	-4.132	0
22	SB-743921	Kinesin-Like Spindle Protein Inhibitor	-0.530	-7.614	-4.072	0
23	ARRY-520	Kinesin-Like Spindle Protein Inhibitor	-0.951	-6.734	-3.842	0
24	Cabazitaxel	Tubulin depolymerization inhibitor	-0.300	-6.805	-3.552	0
25	Epothilone B	Tubulin depolymerization inhibitor	-0.884	-6.051	-3.468	0
26	Danusertib	Aurora-A/B/C Kinase Inhibitor	-0.650	-6.160	-3.405	0
27	PHA-793887	CDK1,2,3,4,5 Inhibitor	-1.686	-4.891	-3.288	0
28	Vincristine sulfate	Tubulin polymerization inhibitor	-0.937	-4.860	-2.899	0
29	MK-3207	Calcitonin Gene-Related Peptides (CGRP) Antagonists	-5.242	-0.275	-2.758	0
30	Elactocin	Antineoplastic Antibiotics	-0.432	-5.085	-2.758	0
31	TAE-684	Anaplastic Lymphoma Kinase (ALK) Inhibitor	-1.511	-3.904	-2.707	0
32	Colchicine	Tubulin polymerization inhibitor	-0.717	-4.675	-2.696	0
33	Docetaxel	Tubulin depolymerization inhibitor	-0.241	-4.940	-2.591	0
34	GSK-1070916A	Aurora-B/C Inhibitor	-0.501	-4.581	-2.541	0
35	Epothilone A	Tubulin depolymerization inhibitor	-0.264	-4.795	-2.529	0
36	SNS-032	CDK2,7,9 Inhibitor	-3.368	-1.668	-2.518	0
37	NVP-AUY922	Heat Shock Protein 90 (hsp90) Inhibitor	-1.726	-3.285	-2.505	0
38	Plinabulin	Tubulin polymerization inhibitor	-0.425	-4.521	-2.473	0
39	Alisertib	Aurora-A inhibitor	-0.420	-4.518	-2.469	0
40	Linsitinib	IGF-1R Inhibitors	-1.469	-3.342	-2.406	0
41	GSK-2126458	PI3Kalpha/beta/delta/gamma Inhibitor	-1.739	-3.018	-2.379	0
42	NCGC00161703	NF-kB/AP-1 activation inhibitor	-1.405	-3.349	-2.377	0
43	PACLITAXEL	Tubulin depolymerization inhibitor	-0.421	-4.333	-2.377	0
44	Lestaurtinib???	Jak/Tyk/Flt inhibitor	-0.332	-4.383	-2.357	0
45	Demecolcine	Tubulin polymerization inhibitor	-0.894	-3.758	-2.326	0
46	GSK3 Inhibitor	GSK-3 inhibitor	-0.461	-4.035	-2.248	0
47	LY-2874455	FGFR Inhibitor	-0.991	-3.419	-2.205	0
48	Tozasertib	Aurora-A/B/C Kinase Inhibitor	-0.733	-3.622	-2.177	0
49	Cephalomannine	Tubulin depolymerization inhibitor	-0.158	-4.157	-2.158	0
50	GSK1838705A	IGF-1R Inhibitor	-0.701	-3.507	-2.104	0
51	Doxorubicin	DNA Topoisomerase II Inhibitors	-0.998	-3.179	-2.089	0
52	Emetine	antiprotozoal agent	-1.405	-2.759	-2.082	0
53	Vinflunine	Tubulin polymerization inhibitor	-0.950	-3.202	-2.076	0
54	KX-01	Src Kinase Inhibitors	-1.129	-3.018	-2.073	0
55	Panobinostat	Histone Deacetylase (HDAC) Inhibitor	-0.615	-3.493	-2.054	0
56	PD 0325901	MEK inhibitor	-2.467	-1.631	-2.049	0
57	Withaferin A	NF-kappaB Activation Inhibitor	-1.510	-2.574	-2.042	0
58	ADW-742	IGF-1R Inhibitor	-1.498	-2.585	-2.042	0
59	AZD-1152-HQPA	Aurora-A/B Inhibitor	-0.943	-3.129	-2.036	0
60	Mitomycin	DNA Alkylating Agent	-0.560	-3.487	-2.023	0
61	Ombrabulin	Tubulin polymerization inhibitor	-0.307	-3.706	-2.006	0
62	Apilimod	IL-12 Production Inhibitor	-0.971	-3.037	-2.004	0
63	Bleomycin sulfate	glycopeptide antibiotic	-0.906	-3.078	-1.992	0
64	Oprozomib	Proteasome Inhibitor	-1.710	-2.268	-1.989	0
65	WYE-125132	mTORC1/2 inhibitor	-1.540	-2.330	-1.935	0
66	GSK-461364A	Polo-like Kinase-1 (Plk-1) Inhibitor	-0.519	-3.342	-1.931	0
67	ITF2357 (Givinostat)	Histone Deacetylase (HDAC) Inhibitor	-1.532	-2.327	-1.929	0
68	AZ-960	Jak2/3 Inhibitor	-0.927	-2.927	-1.927	0
69	Lexibulin hydrochloride	Tubulin depolymerization inhibitor	-0.277	-3.468	-1.872	0
70	Oxibendazole	DNA Polymerase Inhibitors	-0.460	-3.256	-1.858	0
71	HMSL10016	EGFR (HER1; erbB1) Inhibitor	-0.697	-3.004	-1.851	0
72	ABT-737	Bcl-xL inhibitor	-0.980	-2.718	-1.849	0
73	AVN-944	psine 5'-Monophosphate Dehydrogenase (IMPDH) Inhibitor	-0.861	-2.831	-1.846	0
74	Belinostat	Histone Deacetylase (HDAC) 1/2 Inhibitor	-1.581	-2.094	-1.837	0
75	Tosedostat	Aminopeptidase N Inhibitor	-2.451	-1.219	-1.835	0
76	Birinapant	IAP Inhibitor	-3.182	-0.488	-1.835	0
77	Trametinib	Mek 1/2 inhibitor	-2.173	-1.490	-1.831	0
78	SNX-2112	Heat Shock Protein 90 (hsp90) Inhibitor	-1.521	-2.112	-1.817	0

#	Drug name	Drug target	SK-N-BE(2)-C DBSumNeg score	LAN-1 DBSumNeg score	Average DBSumNeg score	Selected hits
79	SCH-79797	PAR1 Antagonist	-0.683	-2.950	-1.817	0
80	AMG-900	Aurora-A/B/C Kinase Inhibitor	-0.379	-3.244	-1.811	0
81	Indibulin	Tubulin polymerization inhibitor	-0.535	-3.082	-1.808	0
82	Axitinib	VEGFR-1/2/3 Inhibitor	-0.583	-3.028	-1.806	0
83	GDC-0980	mTOR inhibitor	-1.278	-2.323	-1.801	0
84	PIK-75	PI3K Inhibitor	-1.031	-2.569	-1.800	0
85	GSK-923295	Centromere Associated Protein (CENP) Inhibitors	-0.683	-2.913	-1.798	0
86	Podofilox	Antimitotic Agent; IGF-1R Inhibitors	-0.257	-3.331	-1.794	0
87	Purflacamine	Calcium Dependent Protein Kinase (CDPK) 1 Inhibitor	-1.353	-2.229	-1.791	0
88	Parbendazole	Tubulin depolymerization inhibitor	-0.894	-2.681	-1.788	0
89	Quisnostat hydrochlorid	HDAC1 Inhibitor	-0.879	-2.694	-1.787	0
90	Rotenone	NADH-Ubiquinone Oxidoreductase (Complex I) Inhibitor	-1.492	-2.039	-1.766	0
91	BI-2536	Polo-like Kinase-1 (Plk-1) Inhibitor	-0.760	-2.748	-1.754	0
92	Remethylepipodophyllotoxin	Antimitotic Agent	-0.546	-2.956	-1.751	0
93	Antimycin A	Antifungal Agent	-1.375	-2.127	-1.751	0
94	Combretastatin A-4	Tubulin polymerization inhibitor	-0.733	-2.764	-1.748	0
95	Flubendazole	antiparasitic agent	-0.900	-2.596	-1.748	0
96	Daunorubicin	Antineoplastic Antibiotics	-0.894	-2.594	-1.744	0
97	Torin-2	mTORC1 Inhibitor	-1.105	-2.378	-1.741	0
98	2-Methoxyestradiol	Hypoxia Inducible Factor 1-alpha Inhibitor	-0.796	-2.683	-1.740	0
99	PD-318088	Mek 1/2 inhibitor	-1.762	-1.713	-1.738	0
100	AT-13387AU	Heat Shock Protein 90 (hsp90) Inhibitor	-0.590	-2.884	-1.737	0
101	NCGC00344990-01	ITK inhibitor	-0.474	-2.953	-1.714	0
102	Salinomycin	Anticoccidial/Antibacterial	-0.703	-2.709	-1.706	0
103	MK-1775	Wee1 Kinase Inhibitor	-0.914	-2.442	-1.678	0
104	NVP-TAE226	Focal Adhesion Kinase (FAK) Inhibitor	-0.948	-2.400	-1.674	0
105	Tivantinib	HGFR (MET; c-Met) Inhibitor	-1.563	-1.785	-1.674	0
106	Pirarubicin	DNA Topoisomerase II Inhibitors	-0.880	-2.444	-1.662	0
107	Triptolide	Inhibition of RNA polymerase II?mediated transcription	-0.496	-2.821	-1.659	0
108	PF-05212384	mTOR inhibitor	-0.659	-2.654	-1.657	0
109	PI-103	PI3Kalpha, beta, gamma Inhibitor	-1.991	-1.307	-1.649	0
110	Dorsomorphin	TGF-beta1 (ALK5) inhibitor	-1.785	-1.507	-1.646	0
111	NCGC00188382-01	ITK inhibitor	-1.487	-1.803	-1.645	0
112	Ansamitocin P3	Tubulin polymerization inhibitor	-0.152	-3.125	-1.639	0
113	SNS-314	Aurora-A/B/C Kinase Inhibitor	-0.319	-2.956	-1.637	0
114	A-66	PI3Kalpha inhibitor	-1.536	-1.734	-1.635	0
115	HMSL10019	Lck Kinase Inhibitors	-1.941	-1.315	-1.628	0
116	BMS-265246	CDK1/2 Inhibitor	-1.561	-1.680	-1.620	0
117	Actinomycin D	DNA-Directed RNA Polymerase Inhibitor	-1.245	-1.986	-1.616	0
118	ASP-3026	Anaplastic Lymphoma Kinase (ALK) Inhibitor	-1.238	-1.952	-1.595	0
119	TAK-733	MEK inhibitor	-2.140	-1.042	-1.591	0
120	XRP-44X	Tubulin polymerization inhibitor	-0.519	-2.653	-1.586	0
121	HMSL10015	Bcr-Abl inhibitor	-0.873	-2.297	-1.585	0
122	BMS-536924	IGF-1R Inhibitor	-0.957	-2.194	-1.576	0
123	MLN-4924	NEDD8-Activating Enzyme (NAE) Inhibitors	-0.652	-2.495	-1.574	0
124	Flavopiridol	CDK1/2/4/6/7/9 Inhibitor	-1.480	-1.666	-1.573	0
125	CHS-828	IKK Inhibitor	-0.366	-2.778	-1.572	0
126	CUDC-101	EGFR (HER1; erbB1) inhibitor	-0.904	-2.234	-1.569	0
127	PP-121	PDGFR Inhibitor	-1.579	-1.556	-1.568	0
128	PD-0332991	CDK4, 6 Inhibitor	-1.971	-1.164	-1.568	0
129	Ponatinib	FGFR Inhibitor	-1.031	-2.085	-1.558	0
130	SNX-5422	Heat Shock Protein 90 (hsp90) Inhibitor	-1.560	-1.549	-1.554	0
131	Serdemetan	MDM2 (hdm2) Inhibitor	-0.734	-2.373	-1.554	0
132	SB1518	Jak2 inhibitor	-2.324	-0.767	-1.545	0
133	Mitoxantrone	DNA Topoisomerase II Inhibitors	-0.558	-2.516	-1.537	0
134	AZD-8055	mTORC1/2 Inhibitor	-1.419	-1.643	-1.531	0
135	Camptothecin	DNA Topoisomerase I Inhibitors	-0.618	-2.441	-1.530	0
136	Diclazuril	antiprotozoal agent	-2.607	-0.449	-1.528	0
137	Carfilzomib	Proteasome Inhibitor	-0.554	-2.490	-1.522	0
138	Dacinostat	HDAC Inhibitor	-1.322	-1.718	-1.520	0
139	Nocodazole	Tubulin depolymerization inhibitor	-0.920	-2.119	-1.519	0
140	10-hydroxycamptothecin	DNA Topoisomerase I Inhibitors	-0.469	-2.562	-1.515	0
141	Rebeccamycin	DNA Topoisomerase I Inhibitors	-0.324	-2.658	-1.491	0
142	JZL-184	Monoacylglycerol lipase (MAGL) inhibitor	-1.727	-1.251	-1.489	0
143	Crenolanib	PDGFR beta inhibitor	-1.608	-1.342	-1.475	0
144	CAY10581	Indoleamine 2,3-dioxygenase (IDO) inhibitor	-0.986	-1.940	-1.463	0
145	CAY10626	PI3Kalpha inhibitor	-0.210	-2.706	-1.458	0
146	Emcitabine hydrochloride	ribonucleotide reductase inhibitor	-0.415	-2.474	-1.445	0
147	TAK-901	Aurora-A/B Inhibitor	-0.490	-2.395	-1.443	0
148	PHA-690509	CDK2/Cyclin A Inhibitor	-1.294	-1.589	-1.442	0
149	SB612111	Opioid receptor antagonist	-1.216	-1.666	-1.441	0
150	Oridonin	Nuclear Factor, Erythroid Derived 2, Like 2 (Nrf2) Activator	-1.439	-1.442	-1.441	0
151	CX-6258	Pim 1/2/3 Kinase Inhibitor	-1.208	-1.667	-1.437	0
152	Monensin sodium salt	Polyether Antibiotic	-0.880	-1.991	-1.435	0
153	Cucurbitacin I	Jak2 inhibitor	-0.872	-1.994	-1.433	0
154	Nitazoxanide	antiprotozoal agent	-2.479	-0.385	-1.432	0
155	TG-46	Jak2 inhibitor	-0.730	-2.129	-1.430	0
156	Tricirbine	PKB/Akt Inhibitor	-1.606	-1.247	-1.426	0
157	NVP-AEW541	IGF-1R Inhibitor	-0.962	-1.887	-1.424	0
158	Dacomitinib	EGFR (HER1; erbB1) inhibitor	-0.601	-2.236	-1.418	0
159	NVP-BGT226	PI3K Inhibitor	-1.285	-1.537	-1.411	0
160	TAK-875	Insulin Secretagogues	-0.792	-2.023	-1.407	0



#	Drug name	Drug target	SK-N-BE(2)-C DBSumNeg score	LAN-1 DBSumNeg score	Average DBSumNeg score	Selected hits
161	PD-173955	cSRC inhibitor	-0.137	-2.671	-1.404	0
162	AZD-2014	mTORC1/2 inhibitor	-0.690	-2.109	-1.399	0
163	Vinorelbine tartrate	Tubulin polymerization inhibitor	0.000	-2.790	-1.395	0
164	JK 184	Alcohol dehydrogenase 7 inhibitor	-0.815	-1.971	-1.393	0
165	D-159687	Phosphodiesterase III D (PDE4D) inhibitor	-1.081	-1.705	-1.393	0
166	RGB-286147	CDK1/2/3/7/9 inhibitor	-1.771	-0.997	-1.384	0
167	SB-415286	GSK-3 inhibitor	-2.097	-0.666	-1.382	0
168	GBR-12935	Dopamine Reuptake Inhibitor	-0.970	-1.789	-1.379	0
169	Mebendazole	Tubulin depolymerization inhibitor	-1.092	-1.657	-1.375	0
170	Risedronate sodium	Farnesyl Pyrophosphate Synthase Inhibitors	-1.509	-1.230	-1.369	0
171	CCT-137690	Aurora-A/B/C Kinase Inhibitor	-0.080	-2.656	-1.368	0
172	Aclarubicin	DNA Topoisomerase II Inhibitors	-0.776	-1.957	-1.366	0
173	Foretinib	VEGFR-2 Inhibitor	-0.952	-1.777	-1.365	0
174	CCT-241533	Checkpoint Kinase 2 (Chk2) Inhibitors	-0.530	-2.187	-1.359	0
175	MLN-8054	Aurora-A Inhibitor	-0.400	-2.303	-1.351	0
176	KU 0060648	DNA-Dependent Protein Kinase (DNA-PK) Inhibitor	-0.742	-1.959	-1.350	0
177	vespimycin hydrochloride	Heat Shock Protein 90 (hsp90) Inhibitor	-1.005	-1.669	-1.337	0
178	LLL-12	STAT-3 Inhibitor	-1.070	-1.602	-1.336	0
179	Omecamtiv mecarbil	Cardiac Myosin Activators	-1.089	-1.565	-1.327	0
180	SCH-900776	Chk1 Inhibitor	-0.965	-1.689	-1.327	0
181	Voriconazole	Lanosterol 14alpha-demethylase Inhibitors	-1.277	-1.342	-1.309	0
182	CNF-2024	Heat Shock Protein 90 (hsp90) Inhibitor	-0.911	-1.696	-1.303	0
183	PF-04691502	PI3K Inhibitor	-0.861	-1.737	-1.299	0
184	Mubritinib	HER2 (erbB2) Inhibitor	-2.000	-0.567	-1.284	0
185	G?-6976	PKC inhibitor	-0.141	-2.426	-1.283	0
186	GSK-615	PI3Kalpha inhibitor	-0.798	-1.768	-1.283	0
187	GW 843682X	Polo-like Kinase-1 (Plk-1) Inhibitor	-0.472	-2.092	-1.282	0
188	Lonafarnib	Farnesyltransferase Inhibitor	-0.353	-2.199	-1.276	0
189	Temsirolimus	mTOR inhibitor	-1.328	-1.221	-1.275	0
190	PH-797804	p38 MAPK Inhibitor	-1.448	-1.099	-1.273	0
191	CUDC-907	PI3K Inhibitor	-1.030	-1.516	-1.273	0
192	Picropodophyllin	Antimitotic Agent; IGF-1R Inhibitors	-0.405	-2.133	-1.269	0
193	Adapalene	topical retinoid	-0.288	-2.248	-1.268	0
194	Suramin sodium	Fibroblast Growth Factor (FGF) Inhibitors	-1.424	-1.099	-1.262	0
195	Ganetespib	Heat Shock Protein 90 (hsp90) Inhibitor	-0.532	-1.990	-1.261	0
196	AMG-47a	Lck Kinase Inhibitors	-0.663	-1.858	-1.261	0
197	AZD-7762	Chk1/2 Inhibitor	-0.769	-1.751	-1.260	0
198	ENMD-981693	Aurora-A Inhibitor	-0.672	-1.847	-1.260	0
199	NVP231	Ceramide kinase inhibitor	-1.021	-1.474	-1.247	0
200	PHA-680632	Aurora-A/B/c Inhibitor	-0.594	-1.895	-1.244	0

Twenty synergistic drug hits were identified (DBSumNeg values  $\leq -1.75$  for both cell lines), based on the significance cutoffs  $\geq 2.5$  for the absolute z-scores computed separately for the DBSumNeg values on each cell line. 10 out of 54 PI3K inhibitors scored as hits, odds ratios = 53.5, p value =  $2.21 \times 10^{-12}$ , based on the two tailed Fisher exact test. Only the top 200 compounds are shown.