

Table S1. Top 50 SD6 Resistance Candidates, Related to Figure 2

Gene	Cumulative shRNA log ₂ (fold change)	Gene p-value	# of significant hairpins
TAOK1	8.04414468	1.00E-20	6
UBA3	6.63984415	1.00E-20	5
BAZ1A	5.87510061	1.00E-20	5
KLHL13	7.92046118	1.79E-13	8
CUL5	4.39125921	1.00E-20	4
USP8	6.56952388	5.63E-13	6
RNF182	6.74517742	1.41E-11	3
RNF128	4.20659046	1.85E-16	5
SYTL4	3.27353806	7.56E-18	3
CDC7	4.34694221	1.40E-13	5
RNF125	5.88971906	9.73E-10	5
UBE2D1	2.82231272	5.63E-19	5
UBQLN2	3.80693777	4.86E-14	4
PCGF1	4.73299613	4.26E-11	4
RNF115	4.3967988	1.01E-11	4
KCTD6	4.52538423	2.20E-11	5
ZBTB44	4.42752323	1.30E-11	4
ASB17	4.38528384	1.54E-11	4
USP40	3.53388064	9.14E-14	4
PTPN23	4.28792269	3.80E-11	3
BTRC	4.12880696	2.24E-11	4
TRIM24	2.20193294	1.00E-20	2
CYLD	2.15236148	1.00E-20	2
GUCY2C	4.05644529	4.06E-11	5
USP1	4.0670757	4.74E-11	5
MUSK	2.73436368	5.30E-16	2
FBXO3	3.23397803	2.03E-13	5
RNF13	4.31949409	3.84E-10	4
SIK2	3.73590999	1.44E-11	3
PI4KB	2.84187714	4.16E-14	2
TWF1	4.45823251	3.92E-09	4
STAM	2.21065948	1.83E-17	2
RHOBTB3	3.15919122	2.30E-12	3
KLHL5	3.12660851	5.88E-12	5
KLHL31	3.60106907	2.09E-10	3
SOCS5	3.79372122	7.44E-10	4

PTPRG	2.09440823	3.44E-17	3
MAPK8	2.69131243	5.55E-13	5
TBK1	2.13179891	6.07E-16	3
DRG1	3.54555772	9.37E-10	4
GRK7	2.13946927	1.13E-15	2
TRIM42	3.13974462	1.35E-10	4
DUSP14	2.73787236	7.99E-12	2
TRIM33	3.05028527	1.06E-10	3
STK17A	3.22911736	4.64E-10	3
PEX2	3.74411682	1.30E-08	5
WNK1	2.6579083	1.45E-11	4
NEK11	1.41437839	1.00E-20	2
TKT	2.6168577	2.92E-11	3
USP34	3.14868563	1.77E-09	3

Table S2. Resistance Candidate MeSH Enrichment, Related to Figure 2

MeSH Term Description	GeneID	Category	Enrichment p-value	Enrichment p-value adjusted
Genome, Fungal	221687/7321/84759/27246/8805/11342		4.40E-07	9.76E-05
G2 Phase Cell Cycle Checkpoints	11177/8317/7321/8945/22836/5599/79858	Cell cycle	4.13E-06	0.000457929
M Phase Cell Cycle Checkpoints	11177/7321/8945/1540/51592/79858	Cell cycle	9.45E-06	0.000699618
Haploidy	9101/7321/25930/1540/5298	Cell cycle	0.00012554	0.006967595
Osmotic Pressure	29978/23235/5599/65125	Osmosis	0.00048917	0.021719076
Ankyrin Repeat	90293/8065/7321/127247		0.000606	0.022421821
Clonal Anergy	9101/79589/5599	Immune	0.00087295	0.024731605
Larva	8065/9101/5599		0.00089123	0.024731605
Cross-Priming	27246/8945/26273	Immune	0.00117303	0.028934794
Pressure	1540/2984/5599	Osmosis	0.00183315	0.038534312
Virus Inactivation	8065/7321	Immune	0.00190936	0.038534312
Virus Release	8945/8027/5599	Immune	0.00279914	0.049592737
DNA End-Joining Repair	11177/7321/79858		0.00323365	0.049592737
Genes, Modifier	2984/5793		0.00326374	0.049592737
Mitochondrial Degradation	9101/7321/29110		0.00348713	0.049592737
Replication Origin	11177/8317/8945	Cell cycle	0.00357425	0.049592737
RNA, Double-Stranded	54941/7321/29110/51592	Immune	0.00402372	0.052545024
RING Finger Domains	79589/7321/11342		0.00446882	0.052804531
Genetic Fitness	9101/25930/5298		0.00451931	0.052804531
Protein Modification, Translational	1540/51592		0.00801537	0.088970603
Osmosis	57551/5599	Osmosis	0.00880367	0.093067388
Immune Evasion	8065/8945/29110	Immune	0.00965177	0.094709044

Genes, cdc	8317/7321/5793		0.0098122	0.094709044
Chromatids	7321/8945/8805	Cell cycle	0.01055343	0.097619264

Table S4. ssGSEA TCGA IR vs. Immune Compartment Gene Signature, Related to Figure 7

Signature	Correlation Coefficient	p-value	-log10 (p-value)	BH_FDR	-log10 (FDR)	ssGSEA_high	ssGSEA_low	Delta_ssGSEA
T_MEMOR Y_CENTRAL	0.4187765	5.08E-43	42.2939063	1.17E-41	40.932178	0.4990108	-0.7466821	1.2456928
EOSINOPHILS	0.3032163	2.37E-22	21.6248589	2.73E-21	20.564161	0.588367	-0.405587	0.993954
T_HELPER_CELL	0.2882402	2.91E-20	19.5354871	2.23E-19	18.65088	0.4269991	-0.6167479	1.043747
T_MEMOR Y_EFFECTOR	0.2183096	4.53E-12	11.3438002	2.61E-11	10.584132	0.3487881	-0.2683266	0.6171147
T_FOLLICULAR_HELPER	0.2099808	2.94E-11	10.5311742	1.35E-10	9.8684164	0.2866724	-0.360368	0.6470404
CD8_T_CELLS	0.1116015	0.0004557	3.34131827	0.00174686	2.7577417	0.2671312	-0.0900127	0.3571439
NK_CELLS	0.0767315	0.0161178	1.79269484	0.04633861	1.334057	0.1783265	-0.0642305	0.242557
T_CELLS	0.0631186	0.0478835	1.31981393	0.09177675	1.0372673	0.0330376	-0.0222619	0.0552994
CYTOTOXIC_CELLS	0.0348354	0.2752163	0.56032584	0.42199833	0.3746893	-0.0055081	0.0374822	-0.0429903
T_GAMMA_DELTA	0.0237298	0.4573878	0.33971545	0.61881875	0.2084365	0.0194707	-0.0680551	0.0875257
iDC	0.0213835	0.5030776	0.29836503	0.64282136	0.1919097	0.134529	0.1539546	-0.0194255
MACROPHAGES	0.0047259	0.8823558	0.05435624	0.93304189	0.0300989	-0.0429834	-0.0487454	0.005762
NK_CD56_DIM_CELLS	-0.0026832	0.9330419	0.03009886	0.93304189	0.0300989	-0.055788	0.0495413	-0.1053293
NK_CD56_BRIGHT_CELLS	-0.0034123	0.9149087	0.03862224	0.93304189	0.0300989	0.1712629	0.1185251	0.0527378
TH1	-0.0144846	0.6501327	0.186998	0.7476526	0.1263002	-0.0768608	0.0046449	-0.0815057
MAST_CELLS	-0.0152438	0.6331081	0.19852211	0.7476526	0.1263002	0.0018863	0.1363572	-0.1344709

DENDRITIC_CELLS	-0.0310288	0.3311311	0.47999998	0.47600101	0.3223921	-0.0282034	0.1154147	-0.1436181
aDC	-0.0364105	0.2540788	0.5950316	0.41741514	0.3794318	0.0043405	0.0533295	-0.0489889
TH2	-0.0572221	0.0729311	1.13708738	0.12903191	0.8893029	-0.2557284	-0.2000029	-0.0557255
TH17	-0.0682005	0.0325129	1.48794429	0.06798152	1.1676091	-0.0968732	-0.0019974	-0.0948758
GSE24102_Granulocytic_MDSC_VS_Neutrophil_UP	-0.0702938	0.0275362	1.56009565	0.06333331	1.1983678	-0.1366645	0.112066	-0.2487305
B_CELLS	-0.0702967	0.0275297	1.56019808	0.06333331	1.1983678	-0.1789825	0.0907453	-0.2697278
NEUTROPHILS	-0.0803011	0.0117846	1.92868615	0.03872074	1.4120564	-0.0409211	0.1077468	-0.1486679

Table S5. shRNA and siRNA Sequences, Related to STAR Methods

Figure Panel	shRNA	Sequence
2C, S2C-D	ZBTB1-1 (shControl 1)	AACATCAGAATTTTTTGTGTA
2C, S2C-D	TBC1D1-1 (shControl 2)	AGAGAAAAATTTTAAGGAGAT
2C (sh1)	UBE2D1-1	ATGACTGTATCAAAAGTTTTA
2C (sh2)	UBE2D1-2	ACAAACATAAACAGTAATGGA
2C (sh3), 2D (sh1), S2E (sh1)	UBE2D1-3	CGGAAGTATTTGTCTCGATAT
2C (sh4)	UBE2D1-4	CCCGACAGATTATCCTTTTAA
2C (sh5), 2D (sh2), S2E (sh2)	UBE2D1-5	CCAGATTATCCTTTTAAACCA
2C (sh1)	RNF128-1	AGCATCTTAACGTGCAACCAT
2C (sh2)	RNF128-2	ATTGGGTGAATCACTATTCAA
2C (sh3), 2D (sh1), S2F (sh1)	RNF128-3	ATGTGTGCATTGAATTGTATA
2C (sh4), 2D (sh2), S2F (sh2)	RNF128-4	ATGTTCGAGAAATTAATCTT
2C (sh5)	RNF128-5	CGCAGTAGACATTGTTGCAAT
S2C (sh1)	USP1-1	AAGCATAGAGATGGACAGTAT
S2C (sh2)	USP1-2	CAAGGACAATCTAAAGAAAAT
S2C (sh3)	USP1-3	CCAAACCAAGGAGTCAAAGGA
S2C (sh4)	USP1-4	CACCCTATGTATGAAGGATAT
S2C (sh5)	USP1-5	AAAAGAGGAAATGAATGGTAT
S2D (sh1)	FBXO3-1	CGAGACCAAATTTTCAGATAT
S2D (sh2)	FBXO3-2	CCACTATCGTTCTGAAGATTT
S2D (sh3)	FBXO3-3	AAGGGACTGAAATACTGTCTC
S2D (sh4)	FBXO3-4	CCAGGATACATGGAAGGATAT
S2D (sh5)	FBXO3-5	ACAGAACTTAGCTCTGTACAT
2C (sh1)	RNF125-1	CGGCCTGTGTTCTGTCCACTT
2C (sh2)	RNF125-2	CGCAAGGTGTGTATGTCCCTT
2C (sh3)	RNF125-3	AGCCTGTGTTCTGTCCACTTT
2C (sh4), 2D (sh1), S2G (sh1)	RNF125-4	CCCACTACAAGAACTTGAGGA
2C (sh5), 2D (sh2), S2G (sh2)	RNF125-5	CTCTGTCCACTTTGCCGTTTA

2D, S2E-G, 5J-K, S5U	FF2-1 (shControl)	CCCGCCTGAAGTCTCTGATTAA
5J-K, S5U	MAVS-1	AACTTGGCTCCTTCTCTCT
5J-K, S5U	MAVS-2	TATACTCATTCTCCTCTGG
Figure Panel	siRNA	Sense Sequence
5E-F, S5H-J, S5O-Q, S5T	NTC	Silencer Select Negative Control No. 1 siRNA
5E-F, S5T	PKR	GGAACUUUGCGAUACAUGATT
5E-F, S5T	DDX1-1	GAAUCUAUCCCAUUGAUCUTT
5E-F, S5T	DDX1-2	GGCACCGGAUGGUUACAUUTT
5E-F, S5T	DDX21-1	CUACCGCAUCAGUAACAGATT
5E-F, S5T	DDX21-2	GGAGGUCAAUUUGAACGCATT
5E-F, S5T	DHX36-1	CAGUGUUAGUCAUAUCGUATT
5E-F, S5T	DHX36-2	CCUGUAGACUGGAAUGACATT
5E-F, S5T	DHX9-1	GAGUGUAACAUCGUAGUAATT
5E-F, S5T	DHX9-2	GGUUGAAGCUUACUCCGGATT
5E-F, S5T	MDA5-1	GUAACAUUGUUUAUCCGUUATT
5E-F, S5T	MDA5-2	GGUGUAAGAGAGCUACUAATT
5E-F, S5T	RIG-I-1	GAAUUAUCCCAACCGAUUUTT
5E-F, S5T	RIG-I-2	CCAGAAUUAUCCCAACCGATT
5E-F, S5T	DHX33-1	CAAUGAAAGUCCCAAUGUTT
5E-F, S5T	DHX33-2	UGACUCCAAUGGGAAGAAATT
S5H-J	RIPK3-1	GGAGAACCAUAGAAAACCATT
S5H-J	RIPK3-2	GGCAAGUCUGGAUAACGAATT
S5H-J	RIPK3-3	GAACUGUUUGUUAACGUAATT
S5O-Q	TNFRSF1A-1	CGGUGACUGUCCCAACUUUTT
S5O-Q	TNFRSF1A-2	GAACCUACUUGUACAAUGATT
S5O-Q	TNFRSF1A-3	CCCUCAAAAUAUUUCGAUUTT

Table S6. Primer Sequences used for RT-qPCR, Related to STAR Methods

Gene	Forward Primer	Reverse Primer
IFNB	CACGACAGCTCTTTCCATGA	AGCCAGTGCTCGATGAATCT
CXCL10	TGCCATTCTGATTTGCTGCC	TGATGGCCTTCGATTCTGGA
CD80	CGAGGGCACATACGAGTG	ACTAGGTGTAGGGAAGTCAGC
CCL3	ACTACTTTGAGACGAGCAGC	GACATATTTCTGGACCCACTCC
TNFA	ACTTTGGAGTGATCGGCC	GGGTTTCGAGAAGATGATCTGAC
MX1	CTCCGACACGAGTTCCACAA	GGCTCTTCCAGTGCCTTGAT
CCL5	TACACCAGTGGCAAGTGCTC	TGTACTIONCCGAACCCATTTC
GAPDH	GGGGTCATTGATGGCAACAATA	AAGGTGAAGGTCGGAGTCAAC
CXCL11	GCCTTGGCTGTGATATTGTG	CACTTTCACTGCTTTTACCCC
OAS1	GATCTCAGAAATACCCCAGCCA	AGCTACCTCGGAAGCACCTT
IL1B	CCACAGACCTTCCAGGAGAATG	GTGCAGTTCAGTGATCGTACAGG
UBE2D1	CGCTGAAGAGGATTCAGAAAGA	TCATCTCCCACAGGTCCA
RNF128	CTGGAGCCGTCATCTTTAACT	TCATGATTGCAACAATGTCTACTG
USP1	GCTTTGGATTTACAGATTCTCAA	TCTCCTCTCACAGTTTATAGGTGAAG
RNF125	CGTCACGTCCTTCGACGT	ATACAGGAACGGCAGAATACG
MAVS	CTGCTACCAAGGTGTCT	CTGAGCTGCCTCCAGTG
NADK 1	GGTCTTGCAGCATCACAGTC	GGTGCAGGGAACCTGACAAAC
REXO1 1	GAGAACGTAGCACCCGTAGG	AGCACATCTCTGAGCCCTTC
MRPL40 1	AGCCATCTGGTCGTGACTCT	ATGACAGCAAGGTCAACGTG
ACTB	TCCCTGGAGAAGAGCTACCAG	TCGATGCCAGAGGACTCCAT
PYCARD	CTCAGTCGGCAGCCAAG	TCCCGTACAGAGCATCCAG
MX2	CAGCCATCGCCGTCATC	CGGACACCTGGTTACGATTC
Eif1 intron	AGGGATCGCTGATGATTACG	ATCAACACGGACTCCCTTGA
Eif1 exon	AGGGATCGCTGATGATTACG	ATATGTTCTTGCCTGGTCAC
Srebf1 intron	AAGGATTGCAGGTCAGACACA	GCTGAGCTCTATGCCCTTACC
Srebf1 exon	GACACAGAAAGGCCAGTACACA	AGTGACTCTGAGCCCGACAG
Pop5 intron	GCTGCTGATCTTGTTGCAGAA	TGTCCTAGGGCATCGTCCTC
Pop5 exon	GCTGCTGATCTTGTTGCAGA	CCTCCTCACCAGCACTGTCT
Bcr intron	GGTTAAAGGTGGAGAGCAATGA	CCCTTATTTGCTCTCTGTGGAG
Bcr exon	TGGATGAATTGGAGGCACTAC	GCCCTTATTTGCTCTCTTCTCT
Scaf1 intron	ACGCTACGTCTTGACCTGCT	CCCTGACTCCTGTGAACGAG
Scaf1 exon	TGTGGGAAGCTCCCTTCAG	CCCTGACTCCTGTGAACGAG
U2AF2 intron	TGTTGGTCAGACTGAGGTTG	GTGGCACGTCCCAGTATTTA
U2AF2 exon	GAGCACGGTGGACTGATTC	GGTGATGTGCTCAAAGCCT
Cxcl10	AGTGCTGCCGTCATTTTCTGC	CAAGCTTCCCTATGGCCCTCA
Cxcl11	AGGAAGGTCACAGCCATAGCC	CCATTTTGACGGCTTTCATCC
Tlr9	TCTGAGAGACCCTGGTGTGGA	ACAAGGGGTGCAGAGTCCTTC
18s	GTAACCCGTTGAACCCATT	CCATCCAATCGGTAGTAGCG
RIPK3	AGAGAGAAGGAGATGGAGAAAGA	CTGGATGATGAAGTTGGAGAGAA
MDA5	GGGGCATGGAGAATAACTCA	AGCTGACACTTCCTTCTGCC
RIG-I	ATATCCGGAAGACCCTGGAC	GAGAAAAAGTGTGGCAGCCT

DDX1	GATATCCACGGTG TTCCTTATGT	CATCCTTTCAGCTCTTCCTACTC
DDX21	CGAGGAGTGACCTTCCTATTTTC	AAGGAGAATGTCTTCCCAGTTC
DHX36	GGGAACTGCGAAGAAGGTATT	TATCGGATGAGGGCAACAATC
DHX9	GAGGAGCCAACCTTGAAGGATTA	TCCATGAAGCCCAGCATTTA
DHX33	ACTTCATGTCGAAGCCATCTC	GGGTAAGCTGGTCATCCTTATG