Table S1: Percentage of experimental animals with abnormal growths in tissues other than the lungs

Screen	Genotype	N	Chest Cavity	Fat Pads	GI Tract	Head & Neck	Heart	Kidney	Liver	Lymph Nodes	Limbs	Pancreas	Peritoneal cavity	Seminal Vexicles	Skin	Spleen	Thymus
wild-type	*Rosa26-LsL-SB11 x T2/Onc x Spc-Cre*	53	2%	0%	2%	4%	8%	0%	13%	11%	17%	4%	0%	15%	4%	28%	4%
p19	*Rosa26-LsL-SB11 x T2/Onc x Spc-Cre x p19ARF-/-*	99	10%	1%	1%	6%	1%	0%	48%	28%	12%	3%	1%	2%	0%	82%	6%
p53	*Rosa26-LsL-SB11 x T2/Onc x Spc-Cre x p53+/flR270H*	116	9%	2%	7%	10%	1%	5%	25%	17%	27%	5%	9%	5%	0%	59%	7%
Pten	*Rosa26-LsL-SB11 x T2/Onc x Spc-Cre x Ptenfl/fl*	62	5%	2%	6%	48%	0%	0%	5%	37%	23%	2%	2%	6%	0%	35%	2%

Table S3: Candidate Lung Cancer Genes based on CIS

Candidate Mouse Gene	Mouse Gene ID	Candidate Human Gene	Human Gene ID	Total # of insertions in gene	Predicted Effect	Other genes in CIS	CIS locus (NCBI37/mm9)	% of mice	# of mice
Serinc3	26943	SERINC3	10955	43	Gain		chr2:163459000-163481000	50%	12
Nckap5	210356	NCKAP5	344148	39	Loss		chr1:128334400-128531400	33%	8
Magi1	14924	MAGI1	9223	35	Loss		chr6:93709200-93749200,	33%	8
Ppp3ca	19055	PPP3CA	5530	16	Loss		chr3:136358800-136481800	33%	8
Ank3	11735	ANK3	288	16	Loss		chr10:69052600-69175600	29%	7
Gab2	14389	GAB2	9846	12	Loss	Nars2	chr7:104192700-104315700	33%	8
Stag2	20843	STAG2	10735	12	Loss		chrX:39548500-39639500	25%	6
Arfgef1	211673	ARFGEF1	10565	12	Loss		chr1:10134100-10198100	21%	5
Mllt10	17354	MLLT10	8028	11	Loss		chr2:17981900-18104900	38%	9
Rock1	19877	ROCK1	6093	11	Loss		chr18:10051700-10142700	38%	9
Wac	225131	WAC	51322	11	Loss		chr18:7833700-7924700	38%	9
Map4k3	225028	MAP4K3	8491	11	Loss		chr17:80996700-81119700	33%	8
Cobll1	319876	COBLL1	22837	11	Loss		chr2:64978000-65069000	29%	7
Stim2	116873	STIM2	57620	11	Loss		chr5:54401100-54492100	29%	7
Cul3	26554	CUL3	8452	11	Loss		chr1:80282000-80322000	25%	6
Magi3	99470	MAGI3	260425	11	Gain		chr3:103913100-103953100	25%	6
Slmap	83997	SLMAP	7871	11	Gain		chr14:27302300-27366300	25%	6
Gsk3b	56637	GSK3B	2932	11	Loss		chr16:38197500-38219500	17%	4
Tle4	21888	TLE4	7091	10	Loss		chr19:14554000-14677000	33%	8
Sptbn1	20742	SPTBN1	6711	10	Loss		chr11:30001400-30124400	29%	7
Crebbp	12914	CREBBP	1387	10	Loss		chr16:4125900-4189900	21%	5
Btbd7	238386	BTBD7	55727	9	Loss		chr12:104037200-104077200	29%	7
Cdk13	69562	CDK13	8621	9	Loss	2810021B07Rik	chr13:17794700-17885700	29%	7
Stard13	243362	STARD13	90627	9	Gain		chr5:151913300-152004300	29%	7
Vps54	245944	VPS54	51542	9	Loss		chr11:21164900-21204900	29%	7
Arhgap5	11855	ARHGAP5	394	9	Loss		chr12:53620200-53660200	25%	6
Setd2	235626	SETD2	29072	9	Loss	Nradd	chr9:110486900-110526900	25%	6
Pbrm1	66923	PBRM1	55193	9	Loss		chr14:31869900-31891900	21%	5
Map3k8	26410	MAP3K8	1326	9	Loss		chr18:4316000-4338000	13%	3
Mpp5	56217	MPP5	64398	8	Loss		chr12:79852500-79943500	33%	8
Psd3	234353	PSD3	23362	8	Gain		chr8:70454700-70577700	33%	8
Atp13a3	224088	ATP13A3	79572	8	Loss		chr16:30327000-30418000	29%	7
Col4a3bp	68018	COL4A3BP	10087	8	Loss		chr13:97318100-97409100	29%	7
Hectd1	207304	HECTD1	25831	8	Loss		chr12:52861400-52925400	29%	7
Actr2	66713	ACTR2	10097	8	Loss		chr11:19985800-20007800	25%	6
Asxl2	75302	ASXL2	55252	8	Loss	1110002L01Rik, Kif3c	chr12:3397700-3488700	25%	6
Pan3	72587	PAN3	255967	8	Loss		chr5:148247700-148338700	25%	6
Wapal	218914	WAPAL	23063	8	Loss		chr14:35488800-35528800	25%	6
Cacul1	78832	CACUL1	143384	8	Loss		chr19:60635700-60657700	21%	5
Fbxw11	103583	FBXW11	23291	8	Gain		chr11:32582700-32604700	21%	5
Ints6	18130	INTS6	26512	8	Loss		chr14:63321500-63361500	21%	5
Smad4	17128	SMAD4	4089	8	Loss		chr18:73817500-73839500	21%	5
Tab2	68652	TAB2	23118	8	Loss		chr10:7631800-7671800	21%	5
Cblb	208650	CBLB	868	8	Loss		chr16:52142700-52164700	17%	4
Zfp148	22661	ZNF148	7707	8	Loss		chr16:33432400-33454400	17%	4
Scaf8	106583	SCAF8	22828	7	Loss		chr17:3146100-3237100	38%	9
Cnot1	234594	CNOT1	23019	7	Loss	Setd6	chr8:98241500-98332500	29%	7
Jmjd1c	108829	JMJD1C	221037	7	Loss	Nrbf2	chr10:66645000-66736000	29%	7
Eml4	78798	EML4	27436	7	Gain		chr17:83765000-83805000	25%	6
Atp11b	76295	ATP11B	23200	7	Gain		chr3:35657900-35679900	21%	5
Ctnna1	12385	CTNNA1	1495	7	Loss		chr18:35347700-35369700	21%	5
Rbpj	19664	RBPJ	3516	7	Loss		chr5:54001400-54041400	21%	5
Tnpo1	238799	TNPO1	3842	7	Loss		chr13:99633100-99655100	21%	5
Wdr7	104082	WDR7	23335	7	Loss		chr18:63974300-63996300	21%	5
Cnot4	53621	CNOT4	4850	7	Loss		chr6:34958800-34998800	17%	4
Pcm1	18536	PCM1	5108	6	Loss	Asah1, Frg1	chr8:42327700-42486700	33%	8
Kif2a	16563	KIF2A	3796	6	Loss	Dimt1	chr13:107747000-107811000	29%	7
Chd1	12648	CHD1	1105	6	Loss		chr17:15861600-15925600	25%	6
Ggnbp2	217039	GGNBP2	79893	6	Loss		chr11:84654000-84694000	25%	6
Gpbp1	73274	GPBP1	65056	6	Loss		chr13:112239700-112279700	25%	6
Adam19	11492	ADAM19	8728	6	Gain		chr11:45888700-45910700	21%	5
Jhdm1d	338523	JHDM1D	80853	6	Loss		chr6:39107500-39129500	21%	5
Ndfip1	65113	NDFIP1	80762	6	Loss		chr18:38598900-38620900	21%	5
Ranbp9	56705	RANBP9	10048	6	Loss		chr13:43498900-43538900	21%	5
Cnot2	72068	CNOT2	4848	6	Loss		chr10:115973200-115995200	17%	4
Rab1	19324	RAB1A	5861	6	Loss		chr11:20105600-20127600	17%	4
Trpc4ap	56407	TRPC4AP	26133	6	Loss		chr2:155474000-155514000	17%	4
Svil	225115	SVIL	6840	5	Loss		chr18:4933000-5130000	38%	9
Fam179b	328108	FAM179B	23116	5	Loss	Prpf39	chr12:66069200-66160200	33%	8
Ehd4	98878	EHD4	30844	5	Loss		chr2:119932600-119954600	17%	4
Tbc1d20	67231	TBC1D20	128637	4	Loss		chr2:152116400-152138400	21%	5
Zfp62	22720	ZFP62	643836	4	Loss		chr11:49019600-49041600	21%	5
Rab9	56382	RAB9A	9367	4	Loss		chrX:162894200-162916200	17%	4
1700020I14Rik	66602	No Ortholog	No Ortholog	2	Loss	1500003O03Rik	chr2:119393700-119433700	25%	6
Cct7	12516	CCT7	10574	2	Loss	Smyd5, 1700040I03Rik	chr6:85393500-85415500	21%	5
Cntnap5a	636808	CNTNAP5	129684	0	Unknown		chr1:118870000-118961000	29%	7

Table S4: CIS human ortholog overlap with human cancer genes

p-Value*	**0.0001**	**5.3 e-8**	**3.5 e-11**	**0.018**	**0.003**	**0.004**	**0.001**	
Overlap Total	**9**	**52**	**44**	**29**	**2**	**12**	**2**	
CIS Human Ortholog	**Cancer Gene Census**	**COSMIC >9 Lung Mutations**	**TCGA >9 Lung Mutations**	**Hammerman Sig amp/del**	**Hammerman Sig Mutations**	**Imielinski Sig Rearrangements**	**Imielinski Sig Mutations**	**CGC + COSMIC + TCGA + Hammerman + Imielinski**
CBLB	Yes	Yes	Yes	Yes				4
CREBBP	Yes	Yes	Yes		Yes			4
EML4	Yes	Yes						2
MLLT10	Yes	Yes	Yes					3
PBRM1	Yes	Yes	Yes			Yes		4
PCM1	Yes	Yes	Yes					3
SETD2	Yes	Yes	Yes				Yes	4
SMAD4	Yes	Yes	Yes		Yes		Yes	3
STAG2	Yes	Yes	Yes					2
ACTR2								0
ADAM19		Yes	Yes	Yes				3
ANK3		Yes	Yes			Yes		3
ARFGEF1		Yes	Yes					2
ARHGAP5		Yes	Yes	Yes				3
ASXL2		Yes	Yes					2
ATP11B		Yes	Yes	Yes		Yes		3
ATP13A3		Yes	Yes					2
BTBD7		Yes						1
CACUL1								0
CCT7								0
CDK13		Yes				Yes		2
CHD1		Yes	Yes	Yes				3
CNOT1		Yes	Yes					2
CNOT2		Yes	Yes	Yes				3
CNOT4		Yes	Yes	Yes				3
CNTNAP5		Yes	Yes					2
COBLL1		Yes				Yes		2
COL4A3BP				Yes				1
CTNNA1			Yes	Yes				2
CUL3		Yes	Yes	Yes				3
EHD4				Yes				1
FAM179B		Yes	Yes	Yes				3
FBXW11				Yes				1
GAB2								0
GGNBP2		Yes	Yes					2
GPBP1				Yes				1
GSK3B		Yes		Yes				2
HECTD1		Yes	Yes	Yes				3
INTS6		Yes						1
JHDM1D		Yes	Yes	Yes				3
JMJD1C		Yes	Yes			Yes		3
KIF2A				Yes				1
MAGI1		Yes	Yes			Yes		3
MAGI3		Yes	Yes	Yes		Yes		3
MAP3K8								0
MAP4K3		Yes	Yes					2
MPP5								0
NCKAP5		Yes	Yes					2
NDFIP1				Yes				1
PAN3		Yes		Yes				2
PPP3CA		Yes	Yes	Yes				3
PSD3		Yes	Yes					2
RAB1A								0
RAB9A								0
RANBP9								0
RBPJ				Yes				1
ROCK1		Yes	Yes			Yes		3
SCAF8		Yes	Yes					2
SERINC3		Yes				Yes		2
SLMAP		Yes						1
SPTBN1		Yes	Yes			Yes		3
STARD13		Yes	Yes					2
STIM2			Yes	Yes				2
SVIL		Yes	Yes					2
TAB2				Yes				1
TBC1D20								0
TLE4		Yes	Yes					2
TNPO1				Yes				1
TRPC4AP		Yes						1
VPS54		Yes						1
WAC			Yes					1
WAPAL		Yes	Yes	Yes				3
WDR7		Yes	Yes			Yes		3
ZFP62				Yes				1
ZNF148		Yes	Yes	Yes				3

***p-Value based on 2-Tailed Fisher's Exact Test**

Table S5: Ingenuity Pathway Analysis significant canonical pathways with 3 or more molecules

Ingenuity Canonical Pathways	-log(p-value)	Ratio	Molecules	# Molecules
Molecular Mechanisms of Cancer	3.32E+00	1.84E-02	GAB2,TAB2,CREBBP,CTNNA1,RBPJ,SMAD4,GSK3B	7
B Cell Receptor Signaling	3.32E+00	2.92E-02	GAB2,CREBBP,MAP3K8,GSK3B,PPP3CA	5
Cardiac Hypertrophy Signaling	2.66E+00	2.02E-02	ROCK1,CREBBP,MAP3K8,GSK3B,PPP3CA	5
NF-κB Signaling	2.33E+00	2.30E-02	TAB2,CREBBP,MAP3K8,GSK3B	4
RANK Signaling in Osteoclasts	2.27E+00	3.16E-02	TAB2,MAP3K8,PPP3CA	3
RhoGDI Signaling	2.26E+00	2.01E-02	ROCK1,ARHGAP5,ACTR2,CREBBP	4
Sertoli Cell-Sertoli Cell Junction Signaling	2.23E+00	2.04E-02	SPTBN1,CTNNA1,MAP3K8,GSK3B	4
Mouse Embryonic Stem Cell Pluripotency	2.16E+00	3.03E-02	CREBBP,SMAD4,GSK3B	3
Integrin Signaling	2.07E+00	1.92E-02	ROCK1,ARHGAP5,ACTR2,GSK3B	4
NGF Signaling	2.02E+00	2.52E-02	ROCK1,CREBBP,MAP3K8	3
Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis	1.91E+00	1.67E-02	TAB2,SMAD4,GSK3B,PPP3CA	4
PTEN Signaling	1.91E+00	2.26E-02	MAGI1,GSK3B,MAGI3	3
RhoA Signaling	1.91E+00	2.50E-02	ROCK1,ARHGAP5,ACTR2	3
PI3K/AKT Signaling	1.86E+00	2.08E-02	GAB2,MAP3K8,GSK3B	3
Protein Kinase A Signaling	1.71E+00	1.25E-02	ROCK1,CREBBP,SMAD4,GSK3B,PPP3CA	5
Epithelial Adherens Junction Signaling	1.66E+00	2.03E-02	ACTR2,MAGI1,CTNNA1	3
Gαq Signaling	1.64E+00	1.78E-02	ROCK1,GSK3B,PPP3CA	3
Axonal Guidance Signaling	1.51E+00	1.06E-02	ROCK1,ACTR2,ADAM19,GSK3B,PPP3CA	5
Wnt/β-catenin Signaling	1.48E+00	1.71E-02	CREBBP,TLE4,GSK3B	3
Ephrin Receptor Signaling	1.46E+00	1.48E-02	ROCK1,ACTR2,CREBBP	3
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	1.44E+00	1.19E-02	ROCK1,CREBBP,GSK3B,PPP3CA	4
NRF2-mediated Oxidative Stress Response	1.43E+00	1.56E-02	CUL3,CREBBP,GSK3B	3
Regulation of the Epithelial-Mesenchymal Transition Pathway	1.42E+00	1.56E-02	RBPJ,SMAD4,GSK3B	3
Leukocyte Extravasation Signaling	1.33E+00	1.45E-02	ROCK1,ARHGAP5,CTNNA1	3
Glucocorticoid Receptor Signaling	1.04E+00	1.02E-02	CREBBP,SMAD4,PPP3CA	3
Xenobiotic Metabolism Signaling	9.49E-01	1.00E-02	CUL3,CREBBP,MAP3K8	3

Table S6: Sets of genes with transposon insertions in multiple mice based on frequent itemset mining

Itemset #	Gene set	Mouse IDs	FDR q-value	-Log (p-value)
1	Cobl, Cpxcr1, Gm20268, Cadm2	1152-Lng-A-T, 1223-Lng-B-T, 901-Lng-D-T	0.260829	13.37
2	Cdh8, Cntnap5a, Socs6, Mbd5	1223-Lng-B-T, 846-Lng-A-T, 901-Lng-B-T	0.359576	10.84
3	Cntnap5a, Cadm2, Socs6, Grb14	1223-Lng-B-T, 846-Lng-A-T, 901-Lng-D-T	0.256512	10.45
4	Serinc3, Luzp2, Svil, Tcf4	1065-Lng-B-T, 1090-Lng-B-T, 1223-Lng-A-T	0.223951	10.08
5	Serinc3, Cdh8, Lrp1b, Mir1186b	1065-Lng-A-T, 1152-Lng-A-T, 1223-Lng-B-T	0.459091	8.43
6	Cdh8, Cntnap5a, Psme4	1188-Lng-A-T, 846-Lng-A-T, 901-Lng-B-T	0.843428	6.39
7	Serinc3, Flrt2, Magi3	1151-Lng-A-T, 1152-Lng-A-T, 846-Lng-A-T	0.765641	5.84
8	Serinc3, Foxa2, Gpbp1	1100-Lng-A-T, 1188-Lng-A-T, 1223-Lng-C-T	0.765641	5.84
9	Cdh8, Cntnap5a, Rock1	1188-Lng-A-T, 1223-Lng-B-T, 901-Lng-B-T	0.709821	5.58
10	Serinc3, Gm10440, Wnk1	1152-Lng-A-T, 1188-Lng-A-T, 901-Lng-C-T	0.808772	5.04

Table S7: Differentially expressed genes in A549 cells with CUL3, PTEN, or CUL3 and PTEN knocked down

Up	28	6	44	8	44
Down	59	5	76	4	68
Total	87	11	120	12	112

NCBI Gene Symbol	**Entrez Gene ID**	**CUL3 vs Control: Fold-Change**	**PTEN vs Control: Fold-Change**	**CUL3/PTEN vs Control: Fold-Change**	**CUL3/PTEN vs CUL3: Fold-Change**	**CUL3/PTEN vs PTEN: Fold-Change**	**# of conditions**
AARD	441376	2.7		2.2		2.2	3
ACY1	95			-2.0			1
AHNAK2	113146	-2.3		-2.3		-2.2	3
ALDH1A1	216			-2.8		-2.4	2
ALDOC	230					-2.1	1
ANKRD34B	340120	-8.9	-2.7	-10.0		-3.7	4
ANXA2R	389289	-2.0		-2.5		-2.1	3
ARHGAP21	57584	-2.7		-2.1		-2.1	3
ASNS	440					2.3	1
B4GALT7	11285			2.1			1
BAMBI	25805	2.9		2.9		3.3	3
BCHE	590			2.9		2.7	2
BHLHE40	8553	-3.1		-2.6		-2.4	3
BMP7	655	-2.1					1
C11orf88	399949		2.6			-2.4	2
CABLES1	91768			-2.4			1
CCNA1	8900	3.2		2.7		2.6	3
CD74	972	-2.4		-2.3			2
CHGB	1114		2.3				1
CKB	1152	-2.1		-2.7		-2.7	3
CNTNAP1	8506	2.0					1
COL5A2	1290					2.5	1
COLGALT2	23127	3.7		3.0		3.3	3
COX20	116228	-2.5	-2.3	-2.4			3
CRIP2	1397			-3.7	-2.0	-3.0	3
CTGF	1490	2.1		2.8		3.2	3
CXXC5	51523	-2.4		-3.0		-2.5	3
CYB5B	80777	-2.1		-2.4		-2.3	3
CYBRD1	79901	2.6		2.3		2.3	3
CYR61	3491	2.1				2.2	2
DBNDD2	55861	-2.3		-2.7			2
DDIT4	54541				2.2		1
DHCR24	1718					-2.1	1
DHFRP2	729816	-2.2		-2.1			2
DKK1	22943	-3.1	3.8	-3.9		-14.7	4
DNAJB1	3337					-2.0	1
DUSP6	1848	-3.2		-3.0		-2.5	3
EFCAB4A	283229	-2.4		-2.3		-2.3	3
EGR1	1958	-4.2		-5.9		-6.5	3
FABP5	2171			-2.0		-2.2	2
FABP5P2	729163	-2.0		-2.9		-2.8	3
FAH	2184			2.0		2.0	2
FAM129A	116496	2.7		3.8		3.1	3
FAM133A	286499					2.8	1
FAM84B	157638			2.2		2.3	2
FGF2	2247	-4.0		-4.3		-4.5	3
FGF9	2254	3.5		3.2		2.6	3
FGFR3	2261	-3.6		-4.2		-3.5	3
FNDC3B	64778	2.6		2.2		2.1	3
FOS	2353			-2.8		-3.9	2
FOSB	2354					-2.2	1
FOXA1	3169	-3.1		-3.0		-2.8	3
FTH1P20	729009					2.0	1
GAMT	2593			-2.2			1
GCLM	2730			2.5		2.2	2
GLA	2717			2.5		2.1	2
GLRB	2743	-5.8		-5.0		-5.2	3
GRIA2	2891	-2.5		-2.6		-4.4	3
H19	283120					-2.1	1
HES6	55502	-2.3					1
HEY1	23462	-3.8		-6.7		-7.4	3
HLA-B	3106			2.0			1
HMMR	3161			-2.2			1
HMOX1	3162			4.7	2.4	4.5	3
HOXA-AS2	285943	-2.1		-2.2			2
HOXA2	3199	-3.1		-3.2		-2.8	3
HOXA4	3201	-2.2		-2.4		-2.3	3
HOXA5	3202	-5.2		-7.3		-6.9	3
HSD17B1	3292					-2.4	1
IFITM2	10581	-3.0		-2.3		-2.3	3
IFITM3	10410	-2.6		-2.1		-2.5	3
INPP1	3628					-2.2	1
ISL1	3670	2.9		2.5		3.4	3
JAG2	3714			-2.2		-2.1	2
KIF1A	547	2.2		3.0		2.6	3
KITLG	4254	-3.3		-3.5		-3.7	3

Table S7: Differentially expressed genes in A549 cells with CUL3, PTEN, or CUL3 and PTEN knocked down

KLF2	10365					-2.2	1
KLF9	687			2.2			1
LAMB1	3912	-4.3		-4.3		-2.3	3
LDOC1	23641	2.1		2.6		2.5	3
LGALS1	3956			-3.6	-2.5	-4.2	3
LINC00052	145978				2.3	2.6	2
LMO4	8543			2.4	2.2	2.4	3
LOC100129129	100129129			2.1			1
LOC642590	642590	2.2				2.2	2
LOC646347	646347	2.0				2.4	2
LYN	4067			-2.3		-2.1	2
MEGF9	1955			-2.1			1
METRN	79006			-2.2			1
MFSD6	54842					-2.6	1
MRPS28	28957			-2.0			1
MYOF	26509	-13.4		-12.6		-11.3	3
NAB1	4664	-2.0		-2.2		-2.5	3
NBPF22P	285622	-3.1	-3.1	-3.0			3
NELL2	4753				2.8		1
NQO1	1728			2.0			1
NR2F1	7025	-2.5					1
NR2F6	2063			-2.0		-2.1	2
NUDT6	11162	-2.6		-2.5			2
OCEL1	79629	-2.2		-2.9		-2.5	3
OMG	4974			-2.1			1
OSGIN1	29948	4.9		7.5		7.7	3
OVOL2	58495		-2.2				1
PAM	5066	2.6		2.4		2.6	3
PANX2	56666			2.0		2.4	2
PCDH18	54510			2.4		2.3	2
PCED1B	91523	-2.5		-2.4		-2.3	3
PDGFC	56034	-7.9				-5.5	2
PIR	8544					2.0	1
PLD1	5337	2.1				2.0	2
PLEKHG4B	153478	2.1			-2.1		2
PLEKHO1	51177					-2.2	1
PPM1H	57460				2.9		1
PRKCB	5579	-2.1		-2.1		-2.2	3
PROK2	60675	2.6					1
PSAT1	29968			2.2		2.3	2
PTEN	5728		-2.1				1
RAB32	10981	-3.4		-5.6		-4.9	3
RDX	5962	-2.2		-2.2		-2.1	3
RGCC	28984	6.1		4.1		2.4	3
RGL1	23179	2.4		2.2			2
RHOBTB3	22836	2.0		2.2			2
RHOJ	57381			-2.1		-2.2	2
RNY1	6084			2.1			1
RNY4	6086			3.1		2.4	2
RPRML	388394	-2.3					1
RRAGD	58528	-3.7		-3.0		-2.8	3
RSBN1	54665			-2.0			1
S100A10	6281	-3.4	2.3			-3.8	3
SCD	6319	-10.0		-6.9		-5.5	3
SCG2	7857		2.8	-2.9		-8.3	3
SEL1L3	23231	-11.7		-6.1		-6.5	3
SERPINE2	5270		2.2			-2.4	2
SH3RF1	57630			-2.1			1
SKAP2	8935	-2.0		-2.0			2
SLC2A3	6515			4.2	2.4	2.6	3
SLC30A3	7781	-2.1					1
SLIT2	9353	-2.0					1
SMS	6611					2.2	1
SNHG6	641638			-2.0			1
SOCS2	8835			-2.3		-2.1	2
SOSTDC1	25928			3.1		2.6	2
SOX18	54345			-2.1			1
SPP1	6696			2.3	2.3	2.3	3
SQSTM1	8878			2.1			1
SRGAP1	57522	-2.6		-2.5		-2.5	3
SRXN1	140809	2.0		3.3		3.6	3
STEAP1B	256227			2.0			1
STMN2	11075			-2.8		-3.2	2
STOM	2040	-2.3		-2.2			2
TBC1D4	9882	-2.9		-2.7		-2.6	3
TBX2	6909	-2.5		-5.5	-2.2	-5.7	4
TLE2	7089	-2.2					1
TNNC1	7134			-2.1		-2.3	2
TP53I3	9540			-2.2			1
TRO	7216	4.1		4.3		4.5	3
TXNRD1	7296	2.4		3.3		3.4	3
VGF	7425			2.3			1
ZMIZ1	57178	-2.7		-3.0		-2.8	3
ZNF143	7702	-4.6		-4.2		-4.2	3
ZNF239	8187	2.7		3.0		3.0	3

Table S8: NRF2 pathway genes differentially expressed in A549 CUL3/PTEN knockdown cells

NCBI Gene Symbol	Entrez Gene ID	Fold change CUL3/PTEN vs Ctrl[1]	NRF2 Target gene[2]	Sulforaphane induced gene[3]
GCLM	2730	2.5	Yes	
HMOX1	3162	4.7	Yes	Yes
NQO1	1728	2.0	Yes	Yes
OSGIN1	29948	7.5		Yes
PANX2	56666	2		Yes
PRKCB	5579	-2.1	Yes	
SQSTM1	8878	2.1	Yes	Yes
SRXN1	140809	3.3	Yes	Yes
TXNRD1	7296	3.3	Yes	Yes

[1] From Table S7, this publication

[2] Genes were identified as NRF2 target genes by Chorley, et al., 2012 and were significantly changed in our study

[3] Genes were identified as sulforaphane-induced by Chorley, et al.,2012 and were significant chagned in our study

Table S9: Top 50 canonical pathways enriched for significantly altered genes in CUL3/PTEN knockdown cells compared to controls

Ingenuity Canonical Pathways	-log(p-value)	Ratio	Molecules
NRF2-mediated Oxidative Stress Response	3.85E+00	3.59E-02	HMOX1,FOS,NQO1,SQSTM1,GCLM,TXNRD1,PRKCB
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	2.56E+00	5.77E-02	SPP1,FOXA1,NR2F6
CXCR4 Signaling	2.55E+00	2.87E-02	FOS,EGR1,LYN,RHOJ,PRKCB
Vitamin-C Transport	2.52E+00	9.09E-02	SLC2A3,TXNRD1
Regulation of the Epithelial-Mesenchymal Transition Pathway	2.24E+00	2.55E-02	FGFR3,JAG2,FGF2,EGR1,FGF9
Growth Hormone Signaling	2.03E+00	3.85E-02	FOS,SOCS2,PRKCB
Aryl Hydrocarbon Receptor Signaling	1.98E+00	2.34E-02	FOS,ALDH1A1,CCNA1,NQO1
Prolactin Signaling	1.94E+00	3.57E-02	FOS,SOCS2,PRKCB
Glycine Degradation (Creatine Biosynthesis)	1.89E+00	1.11E-01	GAMT
Tec Kinase Signaling	1.81E+00	2.17E-02	FOS,LYN,RHOJ,PRKCB
FGF Signaling	1.77E+00	3.19E-02	FGFR3,FGF2,FGF9
Bladder Cancer Signaling	1.75E+00	3.09E-02	FGFR3,FGF2,FGF9
CDK5 Signaling	1.74E+00	3.09E-02	CABLES1,EGR1,LAMB1
Glutathione Biosynthesis	1.72E+00	9.09E-02	GCLM
FcÎ³ Receptor-mediated Phagocytosis in Macrophages and Monocytes	1.68E+00	2.83E-02	HMOX1,LYN,PRKCB
Antioxidant Action of Vitamin C	1.68E+00	2.70E-02	HMOX1,SLC2A3,TXNRD1
Antigen Presentation Pathway	1.66E+00	4.76E-02	HLA-B,CD74
Notch Signaling	1.63E+00	4.65E-02	JAG2,HEY1
IGF-1 Signaling	1.63E+00	2.80E-02	FOS,CTGF,SOCS2
RAR Activation	1.61E+00	2.05E-02	FOS,ALDH1A1,NR2F6,PRKCB
Creatine-phosphate Biosynthesis	1.60E+00	1.11E-01	CKB
Heme Degradation	1.60E+00	9.09E-02	HMOX1
Serine Biosynthesis	1.60E+00	7.69E-02	PSAT1
Neuropathic Pain Signaling In Dorsal Horn Neurons	1.59E+00	2.75E-02	FOS,GRIA2,PRKCB
Cholecystokinin/Gastrin-mediated Signaling	1.58E+00	2.83E-02	FOS,RHOJ,PRKCB
MIF Regulation of Innate Immunity	1.57E+00	3.85E-02	FOS,CD74
UVC-Induced MAPK Signaling	1.53E+00	4.55E-02	FOS,PRKCB
IL-8 Signaling	1.52E+00	1.78E-02	HMOX1,FOS,RHOJ,PRKCB
Role of Tissue Factor in Cancer	1.51E+00	2.31E-02	CTGF,EGR1,LYN
Thioredoxin Pathway	1.50E+00	1.25E-01	TXNRD1
Tyrosine Degradation I	1.50E+00	6.67E-02	FAH
Superoxide Radicals Degradation	1.42E+00	1.25E-01	NQO1
Superpathway of Serine and Glycine Biosynthesis I	1.42E+00	5.56E-02	PSAT1
Glycoaminoglycan-protein Linkage Region Biosynthesis	1.36E+00	6.25E-02	B4GALT7
UVB-Induced MAPK Signaling	1.36E+00	3.45E-02	FOS,PRKCB
PI3K Signaling in B Lymphocytes	1.35E+00	2.10E-02	FOS,LYN,PRKCB
Thrombopoietin Signaling	1.32E+00	3.12E-02	FOS,PRKCB
GNRH Signaling	1.32E+00	1.96E-02	FOS,EGR1,PRKCB
Glioma Invasiveness Signaling	1.29E+00	3.03E-02	HMMR,RHOJ
Phospholipase C Signaling	1.28E+00	1.51E-02	HMOX1,LYN,RHOJ,PRKCB
Synaptic Long Term Depression	1.26E+00	1.85E-02	GRIA2,LYN,PRKCB
Hepatic Fibrosis / Hepatic Stellate Cell Activation	1.24E+00	1.94E-02	CTGF,FGF2,BAMBI
GM-CSF Signaling	1.22E+00	2.94E-02	LYN,PRKCB
CCR5 Signaling in Macrophages	1.22E+00	2.06E-02	FOS,PRKCB
Embryonic Stem Cell Differentiation into Cardiac Lineages	1.21E+00	1.00E-01	ISL1
Oleate Biosynthesis II (Animals)	1.21E+00	5.26E-02	SCD
PXR/RXR Activation	1.21E+00	2.17E-02	SCD,ALDH1A1
GÎ±q Signaling	1.18E+00	1.75E-02	HMOX1,RHOJ,PRKCB
JAK/Stat Signaling	1.16E+00	2.82E-02	FOS,SOCS2
Erythropoietin Signaling	1.16E+00	2.53E-02	FOS,PRKCB

Table S10: Top 50 canonical pathways enriched for significantly altered genes in CUL3 knockdown cells compared to controls

Ingenuity Canonical Pathways	-log(p-value)	Ratio	Molecules
Bladder Cancer Signaling	3.22E+00	4.12E-02	FGFR3,FGF2,FGF9,PDGFC
Human Embryonic Stem Cell Pluripotency	2.54E+00	2.47E-02	FGFR3,FGF2,BMP7,PDGFC
Hepatic Fibrosis / Hepatic Stellate Cell Activation	2.48E+00	2.58E-02	CTGF,FGF2,BAMBI,PDGFC
FGF Signaling	2.18E+00	3.19E-02	FGFR3,FGF2,FGF9
Factors Promoting Cardiogenesis in Vertebrates	2.16E+00	3.03E-02	BMP7,DKK1,PRKCB
Regulation of the Epithelial-Mesenchymal Transition Pathway	2.08E+00	2.04E-02	FGFR3,FGF2,EGR1,FGF9
Role of Tissue Factor in Cancer	1.91E+00	2.31E-02	CTGF,EGR1,CYR61
Actin Cytoskeleton Signaling	1.84E+00	1.65E-02	FGF2,FGF9,RDX,PDGFC
Role of Oct4 in Mammalian Embryonic Stem Cell Pluripotency	1.78E+00	3.85E-02	NR2F1,FOXA1
Creatine-phosphate Biosynthesis	1.75E+00	1.11E-01	CKB
Thioredoxin Pathway	1.65E+00	1.25E-01	TXNRD1
Macropinocytosis Signaling	1.43E+00	2.60E-02	PDGFC,PRKCB
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	1.41E+00	1.17E-02	FGF2,DKK1,PDGFC,PRKCB
Axonal Guidance Signaling	1.38E+00	1.03E-02	SRGAP1,BMP7,SLIT2,PDGFC,PRKCB
Embryonic Stem Cell Differentiation into Cardiac Lineages	1.36E+00	1.00E-01	ISL1
Oleate Biosynthesis II (Animals)	1.36E+00	5.26E-02	SCD
Acute Myeloid Leukemia Signaling	1.34E+00	2.38E-02	KITLG,CCNA1
PDGF Signaling	1.33E+00	2.33E-02	PDGFC,PRKCB
mTOR Signaling	1.32E+00	1.41E-02	PDGFC,PLD1,PRKCB
Clathrin-mediated Endocytosis Signaling	1.31E+00	1.52E-02	FGF2,FGF9,PDGFC
IL-8 Signaling	1.31E+00	1.33E-02	PDGFC,PLD1,PRKCB
Hematopoiesis from Multipotent Stem Cells	1.28E+00	8.33E-02	KITLG
Choline Biosynthesis III	1.25E+00	4.55E-02	PLD1
Vitamin-C Transport	1.25E+00	4.55E-02	TXNRD1
CDK5 Signaling	1.24E+00	2.06E-02	EGR1,LAMB1
VEGF Signaling	1.22E+00	1.83E-02	PDGFC,PRKCB
PPAR Signaling	1.21E+00	1.87E-02	NR2F1,PDGFC
FcÎ³ Receptor-mediated Phagocytosis in Macrophages and Monocytes	1.19E+00	1.89E-02	PLD1,PRKCB
Antioxidant Action of Vitamin C	1.19E+00	1.80E-02	PLD1,TXNRD1
Glioma Signaling	1.18E+00	1.77E-02	PDGFC,PRKCB
Nitric Oxide Signaling in the Cardiovascular System	1.17E+00	1.60E-02	PDGFC,PRKCB
IGF-1 Signaling	1.16E+00	1.87E-02	CTGF,CYR61
Amyotrophic Lateral Sclerosis Signaling	1.15E+00	1.59E-02	GRIA2,PDGFC
Neuropathic Pain Signaling In Dorsal Horn Neurons	1.14E+00	1.83E-02	GRIA2,PRKCB
Pancreatic Adenocarcinoma Signaling	1.09E+00	1.56E-02	PDGFC,PLD1
Cardiomyocyte Differentiation via BMP Receptors	1.09E+00	4.35E-02	BMP7
Synaptic Long Term Potentiation	1.02E+00	1.54E-02	GRIA2,PRKCB
p70S6K Signaling	1.01E+00	1.52E-02	PLD1,PRKCB
RhoA Signaling	9.96E-01	1.56E-02	RDX,PLD1
Estrogen-mediated S-phase Entry	9.91E-01	3.57E-02	CCNA1
eNOS Signaling	9.72E-01	1.29E-02	CCNA1,PDGFC
Antiproliferative Role of TOB in T Cell Signaling	9.58E-01	3.85E-02	CCNA1
GNRH Signaling	9.55E-01	1.31E-02	EGR1,PRKCB
Ovarian Cancer Signaling	9.38E-01	1.32E-02	FGF9,PDGFC
Aryl Hydrocarbon Receptor Signaling	9.22E-01	1.17E-02	NR2F1,CCNA1
Synaptic Long Term Depression	9.17E-01	1.23E-02	GRIA2,PRKCB
Hematopoiesis from Pluripotent Stem Cells	8.99E-01	1.59E-02	KITLG
MIF-mediated Glucocorticoid Regulation	8.73E-01	2.38E-02	CD74
GÎ±q Signaling	8.61E-01	1.17E-02	PLD1,PRKCB
Circadian Rhythm Signaling	8.61E-01	2.63E-02	BHLHE40