Supplementary Information

Genome-scale transcriptional activation by an engineered CRISPR-Cas9 complex

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Supplementary Sequences

SgRNA Scaffolds

Standard guide scaffold (sgRNA 1.0)

NNNNNNNNNNNNNNNNNNNNNGTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAA
AGTGGCACCGAGTCGGTGCTTTTT

Tetraloop MS2 stem loop insertion sgRNA scaffold (sgRNA 1.1)

NNNNNNNNNNNNNNNNNNNNNGTTTTAGAGCTAGGCCAACATGAGGATCACCCATGTCTGCAGGGCCTAGCAAGTTAA
AATAAGGCTAGTCCGTTATCACGCCGAAAGGCGGGCACCGAGTCGGTGCTTTTT

Loop 2 MS2 stem loop insertion sgRNA scaffold (sgRNA 1.2)

NNNNNNNNNNNNNNNNNNNNNGTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGGCCA
ACATGAGGATCACCCATGTCTGCAGGGCCAAGTGGCACCGAGTCGGTGCTTTTT

Tetraloop and Loop 2 MS2 stem loop insertion sgRNA scaffold (sgRNA 2.0)

NNNNNNNNNNNNNNNNNNNNNGTTTTAGAGCTAGGCCAACATGAGGATCACCCATGTCTGCAGGGCCTAGCAAGTTAA
AATAAGGCTAGTCCGTTATCAACTTGGCCAACATGAGGATCACCCATGTCTGCAGGGCCAAGTGGCACCGAGTCGGT
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SAM Components

MS2-NLS-VP64

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MS2-NLS-P65

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MS2-NLS-P65-HSF1

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MS2-NLS-P65-Myod1

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EF1α-MS2-NLS-p65-HSF1-P2A-Hygro

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U6-sgRNA-EF1α-Zeo

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U6-sgRNA-EF1α-Puro

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Supplementary Tables

Supplementary Table 1 | Top 100 genes from the output of the RIGER algorithm for the sgRNA-Zeo PLX screen comparing PLX (mean of the two replicates at Day 21) to DMSO control (mean of the two replicates at Day 21). The Kolmogorov-Smirnov method was used to score genes.

Gene	NES	Gene rank	p-value	p-value rank
EGFR	1.9319	1	0.00000001	1
LPAR5	1.9292	2	0.00000001	2
GPR35	1.9277	3	0.0000001	3
LPAR1	1.9262	4	0.00000045	4
P2RY8	1.9248	5	0.00000045	5
ARHGEF1	1.9184	6	0.0000009	6
ITGB3	1.9116	7	0.0000031	7
ITGA9	1.894	8	0.0000201	8
ITGB5	1.89	9	0.000026	9
CRB2	1.8895	10	0.00002695	10
TYW1	1.8833	11	0.00003825	11
VSX1	1.8752	12	0.00005925	12
LOC102724862	1.8698	13	0.0000772	13
BCAR3	1.8552	14	0.0001412	14
PCDH7	1.8521	15	0.0001584	15
KIAA0040	1.8506	16	0.0001687	16
TFAP2C	1.8468	17	0.0001934	17
PHB	1.6441	112	0.0002845	18
IGF1R	1.8125	18	0.0005271	19
CGB8	1.8105	19	0.0005533	20
RNF223	1.8075	20	0.0005983	21
TFEB	1.7961	21	0.0007757	22
TOR3A	1.7826	22	0.00103	23
MRFAP1	1.7815	23	0.001049	24
WNT7A	1.7763	24	0.001158	25
MEIS2	1.775	25	0.001189	26
KCTD20	1.7703	26	0.001303	27
SHB	1.7691	27	0.001331	28
PLEKHG5	1.7665	28	0.001393	29
DAG1	1.7612	29	0.00153	30
RAPGEF1	1.7575	30	0.001632	31
SSC5D	1.7571	31	0.001645	32
PSMF1	1.7564	32	0.001665	33
ZNF747	1.7539	33	0.001736	34
SIGIRR	1.7537	34	0.001741	35
ISLR2	1.7503	35	0.001843	36
AARSD1	1.7439	36	0.002044	37

SLC32A1	1.7418	37	0.002115	38
PLXDC2	1.7393	38	0.002204	39
FGF17	1.7376	39	0.002262	40
SLC25A20	1.7366	40	0.002296	41
DCAF7	1.7365	41	0.002299	42
CA12	1.7364	42	0.002303	43
MSRB3	1.7356	43	0.002335	44
TRIM7	1.7353	44	0.002345	45
RRAS2	1.7338	45	0.002397	46
OSBPL1A	1.7278	46	0.002622	47
CEP63	1.7275	47	0.002638	48
PHC2	1.7252	48	0.002725	49
SPHK1	1.7246	49	0.00275	50
ACP6	1.7206	50	0.002914	51
NEIL3	1.7182	51	0.003017	52
TNNC1	1.7141	52	0.003201	53
KIAA1804	1.7133	53	0.003233	54
MAP3K11	1.7131	54	0.003242	55
ZNF582	1.7128	55	0.003256	56
SNX13	1.7111	56	0.003333	57
CPLX2	1.7104	57	0.003366	58
FGD1	1.7102	58	0.003377	59
DTX3	1.7093	59	0.003416	60
IFNGR1	1.7078	60	0.003484	61
LRRC10B	1.7075	61	0.003499	62
UBE2E3	1.7048	62	0.003629	63
VKORC1	1.7028	63	0.003727	64
PPDPF	1.6994	64	0.003893	65
CCND2	1.697	65	0.004017	66
TEAD4	1.6967	66	0.004032	67
TMEM26	1.6961	67	0.004065	68
HMGXB3	1.6959	68	0.004074	69
PDCD4	1.6936	69	0.004192	70
COA3	1.6924	70	0.004258	71
LAMP5	1.6918	71	0.004287	72
NEK5	1.6912	72	0.004322	73
MRPS35	1.6901	73	0.004382	74
TAPBP	1.6892	74	0.004431	75
FGF8	1.689	75	0.00444	76
GBE1	1.6887	76	0.004455	77
KCND1	1.6887	77	0.004458	78
TRIB1	1.6883	78	0.004475	79
SEBOX	1.688	79	0.004493	80

ATP10A	1.6859	80	0.004614	81
RNF41	1.6849	81	0.004673	82
PROM1	1.6848	82	0.004676	83
BCAP29	1.6819	83	0.004845	84
EFNA1	1.6783	84	0.005063	85
ZNF83	1.6778	85	0.005091	86
MAGEB6	1.6774	86	0.005119	87
TAS2R19	1.6766	87	0.005166	88
BCAR1	1.6744	88	0.005307	89
STAT4	1.6739	89	0.005336	90
RPS16	1.6721	90	0.005454	91
FICD	1.6718	91	0.005475	92
CPEB1	1.6713	92	0.005503	93
TMEM133	1.6694	93	0.005625	94
SNED1	1.6693	94	0.005635	95
TCEA2	1.6684	95	0.005691	96
GSR	1.6667	96	0.005808	97
IQGAP3	1.6618	97	0.006145	98
RAB42	1.6617	98	0.006149	99
ADORA1	1.6603	99	0.006254	100

Supplementary Table 2 | Top 100 genes from the output of the RIGER algorithm for the sgRNA-Puro PLX screen comparing PLX (mean of the two replicates at Day 21) to DMSO control (mean of the two replicates at Day 21). The Kolmogorov-Smirnov method was used to score genes.

Gene	NES	Gene rank	p-value	p-value rank
EGFR	1.8164	3	0.00000001	1
LPAR5	1.8175	1	0.00000001	2
P2RY8	1.8165	2	0.00000001	3
MECOM	1.8111	4	0.0000003	4
CRB2	1.8109	5	0.00000035	5
GLIS3	1.7914	6	0.000014	6
PCDH7	1.7879	7	0.00002015	7
TFAP2C	1.7749	8	0.00005425	8
C9orf50	1.7679	9	0.00008335	9
LPAR1	1.7678	10	0.000084	10
CNR1	1.758	11	0.0001413	11
BCAR3	1.7565	12	0.0001516	12
ITGB3	1.7542	13	0.000169	13
CGNL1	1.7529	14	0.0001793	14
ZASP	1.747	15	0.0002318	15
P2RY1	1.7435	16	0.0002672	16
TNRC18	1.7352	17	0.000363	17
GPR35	1.7297	18	0.0004385	18
ARHGEF2	1.7293	19	0.0004437	19
KRAS	1.7254	20	0.000504	20
PBX2	1.7227	21	0.0005528	21
PYGO1	1.719	22	0.0006131	22
RASSF5	1.7167	23	0.0006551	23
AKR1B1	1.7122	24	0.000745	24
ZFHX4	1.7106	25	0.0007778	25
ACVR2A	1.7104	26	0.0007828	26
ITGB5	1.7078	27	0.0008385	27
LOC730183	1.7072	28	0.0008523	28
COL25A1	1.7057	29	0.0008865	29
EPAS1	1.7044	30	0.0009167	30
RPS16	1.7022	31	0.0009716	31
CST5	1.7015	32	0.000991	32
CHN2	1.6984	33	0.001067	33
RAPGEF1	1.6968	34	0.001111	34
ABLIM2	1.6921	35	0.001241	35
GAB2	1.69	36	0.001305	36
INHBA	1.6861	37	0.001424	37
C11orf21	1.6851	38	0.001456	38

NEFM	1.6843	39	0.001484	39
C19orf18	1.6841	40	0.00149	40
SLC19A2	1.681	41	0.001591	41
DYRK3	1.6775	42	0.001718	42
ARHGAP6	1.6742	43	0.001842	43
FOXO4	1.6723	44	0.001913	44
EIF4EBP2	1.6711	45	0.001955	45
TMEM199	1.6694	46	0.002024	46
ZCCHC11	1.6692	47	0.00203	47
CHID1	1.668	48	0.002082	48
MGAT3	1.6669	49	0.002129	49
CHST15	1.6667	50	0.002138	50
C14orf39	1.6649	51	0.002214	51
FSD1	1.6636	52	0.002271	52
STAU2	1.6629	53	0.002296	53
TRIM65	1.6579	54	0.002526	54
JUN	1.6571	55	0.002561	55
MMRN2	1.6555	56	0.002639	56
TMEM129	1.6532	57	0.002748	57
BRINP1	1.6507	58	0.002872	58
BCL7C	1.6494	59	0.002938	59
NFS1	1.6492	60	0.002947	60
AP4B1	1.6487	61	0.002971	61
41885	1.6474	62	0.003039	62
B4GALNT2	1.6472	63	0.003052	63
MDK	1.6447	64	0.003186	64
PABPC5	1.6424	65	0.003309	65
TNFRSF1B	1.6404	66	0.003425	66
MLLT6	1.6398	67	0.003458	67
IER3IP1	1.6344	68	0.003784	68
PBX1	1.6325	69	0.003907	69
BCAS3	1.631	70	0.003993	70
HDX	1.6291	71	0.00412	71
RNF6	1.6271	72	0.00425	72
MAP3K11	1.6268	73	0.00427	73
CA3	1.62	74	0.004741	74
APBB1	1.6196	75	0.004776	75
FOXJ1	1.6179	76	0.004905	76
LYPD2	1.6162	77	0.005023	77
DNASE1L2	1.6151	78	0.005103	78
BRI3	1.6132	79	0.005249	79
GCK	1.6112	80	0.0054	80
PRKCE	1.6081	81	0.005637	81

GCNT1	1.6074	82	0.005693	82
CDR2	1.6071	83	0.005713	83
DDX11	1.6059	84	0.005807	84
SLC2A3	1.6015	85	0.00618	85
PAK7	1.5993	86	0.006366	86
TCF7L1	1.599	87	0.006387	87
SOCS6	1.5969	88	0.006578	88
C19orf68	1.594	89	0.006839	89
C3orf27	1.5938	90	0.006853	90
NBL1	1.592	91	0.007023	91
ARHGEF5	1.5909	92	0.007126	92
GABRQ	1.5879	93	0.007405	93
ANKRD29	1.5877	94	0.007428	94
ZNF704	1.586	95	0.007587	95
RHOG	1.5853	96	0.007657	96
HOXB4	1.5849	97	0.007701	97
CCER1	1.5836	98	0.007833	98
ATL1	1.5832	99	0.007874	99
RASGRF1	1.5831	100	0.00788	100

Supplementary Table 3 | Top 300 depleted genes for A375. Mean depletion for each gene is given as the log2 ratio of Day 21 vs. Day 3 averaged over all sgRNAs for the gene.

Gene	Mean Depletion	Rank
CDKN1A	-2.992660039	1
MXI1	-2.897744853	2
STRBP	-2.829748727	3
ZNF619	-2.804758127	4
SPANXF1	-2.726815579	5
FAM129B	-2.719695757	6
CDKN1A	-2.656298721	7
ARPP21	-2.653166497	8
NFATC1	-2.629949555	9
ADAMTS12	-2.590207051	10
SYNCRIP	-2.543127112	11
DUSP9	-2.525451884	12
JUNB	-2.490663237	13
YAF2	-2.448742407	14
SLC19A1	-2.448391667	15
MYBL1	-2.447625101	16
MEX3A	-2.409240548	17
TRIB1	-2.398434141	18
CHST8	-2.335622871	19
ENOX2	-2.304989857	20
RNPEP	-2.279404126	21
GRB10	-2.278152274	22
NKX2-1	-2.277268968	23
RTFDC1	-2.276773205	24
PRKAG2	-2.257706064	25
DUSP5	-2.257470856	26
CPEB4	-2.257275333	27
PRAME	-2.253782388	28
ZNF583	-2.236146291	29
NTRK2	-2.187236566	30
MEIS3	-2.18329438	31
CRY1	-2.181419445	32
GPR137B	-2.153058431	33
TTLL12	-2.14262453	34
EEF1A1	-2.136133061	35
SPNS2	-2.130267043	36
BAG1	-2.12875898	37
PRDM1	-2.126237386	38
NAT8L	-2.11667318	39

HSD17B8	-2.106531573	40
GALNT7	-2.095244894	41
WNT3A	-2.090472623	42
TGFBR2	-2.074145064	43
RBM47	-2.071991956	44
LOXL4	-2.061797982	45
JADE3	-2.038321308	46
TMSB4Y	-2.026889341	47
CHPF	-2.025890484	48
MSRB3	-2.02586623	49
ZNF641	-2.023295975	50
DUX4L2	-2.015241148	51
BLOC1S2	-2.002638012	52
FAM49A	-2.001061567	53
AUP1	-1.997624613	54
CDKN1C	-1.995664305	55
SLC1A1	-1.990961882	56
ASB10	-1.989066237	57
WNK2	-1.977746737	58
ITGA5	-1.954342921	59
NFIC	-1.953212838	60
KLK11	-1.948539824	61
WDR91	-1.938490545	62
S100A13	-1.935432269	63
PXDC1	-1.927854467	64
NDNF	-1.921200613	65
BRI3	-1.911739793	66
TMEM220	-1.903966859	67
DUSP14	-1.898023448	68
NAA35	-1.885506504	69
ZNF395	-1.878461929	70
MIA3	-1.870671759	71
KCNK10	-1.867897168	72
IGF2BP3	-1.859186347	73
ATP6V0A1	-1.848977641	74
POU3F3	-1.848092491	75
LMNA	-1.847152595	76
LHFPL3	-1.8465067	77
ZNF665	-1.84640875	78
DYM	-1.837513747	79
KLHL8	-1.836730363	80
WNT7A	-1.836730124	81
SEC61A1	-1.832537638	82

TCF7L2	-1.827830567	83
GPRASP2	-1.823465993	84
CACNA1C	-1.821967953	85
INO80	-1.819581697	86
MEX3C	-1.818591589	87
ERG	-1.808903306	88
ESPL1	-1.801783358	89
KLF2	-1.798003457	90
COL1A1	-1.795687915	91
RCC2	-1.789402047	92
PAK1	-1.781478474	93
GALNT13	-1.779304272	94
TMCC3	-1.779143425	95
WDR45B	-1.769033944	96
RNF111	-1.768775527	97
BCL3	-1.76223965	98
FAM110B	-1.760460731	99
LATS2	-1.753053715	100
GRTP1	-1.749316218	101
41891	-1.740174795	102
SPIRE2	-1.737385676	103
BIVM-ERCC5	-1.73527893	104
HOXC13	-1.727592439	105
SKI	-1.727146495	106
HEXDC	-1.726799679	107
BTG2	-1.723525381	108
EID2B	-1.719706185	109
NELL2	-1.718412006	110
CELF1	-1.710704793	111
FXYD1	-1.709774577	112
GATA1	-1.703530563	113
AGPAT6	-1.703304319	114
PDGFRB	-1.702489783	115
EFHB	-1.699297265	116
OTX1	-1.69840649	117
CLIC1	-1.698145729	118
GNAO1	-1.69117871	119
TSPAN5	-1.690531306	120
GLB1	-1.688687106	121
PHF2	-1.688502906	122
MIIP	-1.687831215	123
BFSP1	-1.685843655	124

PKDCC	-1.681959775	125
UCN3	-1.681603774	126
AKAP11	-1.681106799	127
STK3	-1.680125551	128
DOT1L	-1.679505143	129
CRHR1	-1.678232195	130
PLEKHO1	-1.674893272	131
ANKEF1	-1.674522971	132
EBF2	-1.671684092	133
COPE	-1.667505883	134
USP28	-1.666943424	135
KMT2B	-1.664730943	136
RIMS4	-1.664556738	137
ADAMTS7	-1.664444631	138
FAM9A	-1.661881924	139
EPHA2	-1.65846104	140
REEP6	-1.657571504	141
SIAH1	-1.656570969	142
FPR2	-1.651081286	143
AVL9	-1.650350499	144
SP3	-1.649187872	145
PCNXL3	-1.646537811	146
SHROOM4	-1.645105253	147
HNRNPAB	-1.642348412	148
CACNA2D1	-1.639847135	149
FGFRL1	-1.63856667	150
SHB	-1.632097534	151
CA2	-1.631971681	152
CAMK2N1	-1.629137656	153
ARHGAP4	-1.62825701	154
CPLX2	-1.626599879	155
HOXC11	-1.626203388	156
ITM2C	-1.625957387	157
TRNT1	-1.624893641	158
DNAAF2	-1.624882836	159
GCC2	-1.624354479	160
TTC9	-1.624140349	161
IFT81	-1.622920533	162
PLEKHF1	-1.62180107	163
C10orf82	-1.620405891	164
KIAA0753	-1.619239696	165
WDR89	-1.617607367	166
CRCP	-1.611109935	167

ADRA1A	-1.602361316	168
TXLNG	-1.601904094	169
ANKZF1	-1.601604975	170
EFHD2	-1.599046924	171
SERPINI1	-1.598621083	172
MIB1	-1.597274936	173
MEAF6	-1.593894564	174
HLCS	-1.59025755	175
ING2	-1.589728576	176
PYROXD2	-1.589535269	177
PPARGC1A	-1.587408566	178
ANKRD30A	-1.586667965	179
BTBD2	-1.586118313	180
IGSF8	-1.580902664	181
FAM69C	-1.577696726	182
PAXIP1	-1.576009399	183
PAOX	-1.575951644	184
ZNF667	-1.572756871	185
TCF3	-1.56874959	186
IMPA2	-1.567559877	187
UBE3D	-1.566869169	188
SPATA31A1	-1.566628243	189
SLCO4A1	-1.562067095	190
PAPOLB	-1.561157727	191
RHOBTB2	-1.557854541	192
WWC1	-1.557454101	193
MLXIP	-1.556308378	194
MSH6	-1.555493523	195
TEX28	-1.555077182	196
TLR7	-1.554718342	197
TBC1D22A	-1.553299902	198
COBL	-1.552319793	199
ZBTB40	-1.551377333	200
EBAG9	-1.551195482	201
BHLHE23	-1.549931838	202
CCNE1	-1.549380807	203
FOSL2	-1.548586206	204
KANK1	-1.545495013	205
UBE2G1	-1.545073693	206
CTSZ	-1.544508991	207
PIK3R1	-1.541543206	208
PLCD1	-1.540526535	209
CFHR1	-1.540322263	210

EAPP	-1.539559841	211
FOXN2	-1.536894335	212
NRXN3	-1.536756987	213
PRRG4	-1.536411123	214
AURKA	-1.535632929	215
POLR2I	-1.535013569	216
TEX38	-1.534957213	217
SNRPF	-1.534928953	218
FZD6	-1.534873785	219
CHRDL2	-1.53363039	220
CAMK1D	-1.532738633	221
TSPAN4	-1.532033491	222
ZNF514	-1.53035277	223
CTAG1A	-1.528262121	224
TSPY1	-1.518969471	225
FAM45A	-1.515966792	226
PHF23	-1.514788961	227
NRD1	-1.514485943	228
UBR5	-1.514476856	229
GTPBP10	-1.51320279	230
PLEKHM3	-1.512593991	231
TMEM181	-1.512024763	232
ANKRD44	-1.510607784	233
SULT4A1	-1.510256216	234
PDGFC	-1.509051383	235
CDYL	-1.508799208	236
CDC42EP2	-1.508624776	237
KCNMB3	-1.507843102	238
FOXI1	-1.507819638	239
FHL1	-1.507785919	240
JRK	-1.507056803	241
FAM110C	-1.506457203	242
NPEPPS	-1.506442168	243
CNKSR3	-1.505895119	244
SYNGR1	-1.50378579	245
LIG1	-1.50220227	246
UCK1	-1.498574732	247
PLEKHG3	-1.498493459	248
SHANK2	-1.496266754	249
SYNGR2	-1.495929066	250
FRMPD2	-1.495810709	251
SCAP	-1.494636312	252
RGS22	-1.493115397	253

GALNT18	-1.49152462	254
GPAT2	-1.491059745	255
TRIM6-TRIM34	-1.490703347	256
AJUBA	-1.488388821	257
GAS8	-1.486564139	258
PLXNA2	-1.486492818	259
RPN2	-1.485389319	260
RBMX	-1.485222602	261
FOXF2	-1.484610716	262
ARHGAP31	-1.483785576	263
PNMA5	-1.4816382	264
SLAMF6	-1.481389938	265
HIST1H3J	-1.479761902	266
HHAT	-1.479346095	267
KCNC3	-1.478985068	268
PFKM	-1.477414591	269
CDHR5	-1.476532282	270
GABRB3	-1.476436096	271
POLR1D	-1.476282564	272
TTYH2	-1.475655292	273
TMEM198	-1.475348451	274
NRP2	-1.474615777	275
UBE3B	-1.474189706	276
ZNF618	-1.471872622	277
PYGO1	-1.471843021	278
SLFN11	-1.470539972	279
LONRF3	-1.470166863	280
TSPAN17	-1.468806125	281
STARD8	-1.468402107	282
HFE2	-1.467933276	283
LTBP1	-1.466001082	284
ENKD1	-1.464456854	285
PIGP	-1.462758078	286
CHTF8	-1.462614997	287
EHD2	-1.462454773	288
ST6GAL1	-1.460732993	289
ZNF527	-1.45924688	290
SLC22A17	-1.459181743	291
C17orf62	-1.458600852	292
POLR2G	-1.457145699	293
WDR88	-1.455886365	294
USP32	-1.455612942	295

CTNNA2	-1.452748274	296
LCOR	-1.452523453	297
HDAC9	-1.450768923	298
WNT7B	-1.449752179	299
LRRC4B	-1.449610591	300

Supplementary Table 4 | Target guide sequences use for characterization and optimization of the SAM system.

Gene	Target Sequence
Neurog2	TGGTTCAGTGGCTGCGTGTC
ASCL1	GCAGCCGCTCGCTGCAGCAG
MYOD1	GGGCCCCTGCGGCCACCCCG
SOX2	GCCGGCCGCGCGGGGGAGGC
SOX2	CCATGTGACGGGGGCTGTCA
SOX2	GGCAGGCGAGGAGGGGGAGG
SOX2	GCTGCCGGGTTTTGCATGAA
SOX2	GTATCCCCTCTCGCAGCAAC
SOX2	AGGAGCCGCCGCGCGCTGAT
SOX2	TTTACCCACTTCCTTCGAAA
SOX2	GCAGGGTACTTAAATGAGGA
NANOG	CGCCAGGAGGGGTGGGTCTA
NANOG	GATTAACTGAGAATTCACAA
NANOG	TCTAGTTCCCCACCTAGTCT
NANOG	GCCTTGGTGAGACTGGTAGA
NANOG	TGTCTTCAGGTTCTGTTGCT
NANOG	TGATTTAAAAGTTGGAAACG
NANOG	CATATTCCTGATTTAAAAGT
NANOG	TCCCAATTTACTGGGATTAC
KLF4	GCGCGCTCCACACAACTCAC
KLF4	AAGGAACGCGCGCCGGCGGC
KLF4	ATGGGAGAAGGCGGAGGAAA
KLF4	GCAACGATGGAAGGGAGCCT
KLF4	GCGCACGTGGGGGCGGGGGA
KLF4	GCCTGGCTGGCGTCACGGCC
KLF4	GCCGCCGACACCACTGCCGC
KLF4	CGGTTCCTCGCGCCCCGCGC
POU5F1 (OCT4)	GACACAACTGGCGCCCCTCC
POU5F1 (OCT4)	GGGGGGAGAAACTGAGGCGA
POU5F1 (OCT4)	TCTGTGGGGGACCTGCACTG
POU5F1 (OCT4)	GGCACAGTGCCAGAGGTCTG
POU5F1 (OCT4)	GGTGAAATGAGGGCTTGCGA
POU5F1 (OCT4)	TCAAGGCTAGTGGGTGGGAC
POU5F1 (OCT4)	GGTGGTGGCAATGGTGTCTG

POU5F1 (OCT4)	ACAGGAATTCAAGACCAGCC
VEGFA	GCAAAGAGGGAACGGCTCTC
VEGFA	ACAGAGTTTCCGGGGGCGGA
VEGFA	CCCTTCATTGCGGCGGGCTG
VEGFA	GGCCCGAGCCGCGTGTGGAA
VEGFA	GCGGGCCGGGGGCGGGGTCC
VEGFA	TTTAAAAGTCGGCTGGTAGC
HBG1	TCCCTGAACTTTTCAAAAAT
HBG1	CACTGGAGCTAGAGACAAGA
HBG1	GTATCCTCTATGATGGGAGA
HBG1	AAAAACTGGAATGACTGAAT
HBG1	AAAATTAGCAGTATCCTCTT
HBG1	ATGCAAATATCTGTCTGAAA
HBG1	CTTGACCAATAGCCTTGACA
HBG1	GGCTAGGGATGAAGAATAAA
TERT	GCCGCACGCACCTGTTCCCA
TERT	CTGCACCCTGGGAGCGCGAG
TERT	GCCCGGAGCAGCTGCGCTGT
TERT	CCAGGACCGCGCTTCCCACG
TERT	GAGCTGGAAGGTGAAGGGGC
TERT	CCCGACCCCTCCCGGGTCCC
TERT	GGAAAGGAAGGGGAGGGGCT
TERT	GCGGCCCCGCCCTCTCCTCG
IL1B	TTAGTATATGTGGGACAAAG
IL1B	GAAAATCCAGTATTTTAATG
IL1B	GAAAACAATGCATATTTGCA
IL1B	CTCTGGTTCATGGAAGGGCA
IL1B	AGTATTGGTGGAAGCTTCTT
IL1B	TTTAACTTGATTGTGAAATC
IL1B	TGGCTTTCAAAAGCAGAAGT
IL1B	AAAAACAGCGAGGGAGAAAC
IL1R2	AAACTCCACAATCTAGAATA
IL1R2	TTAACAGTTAAAAATCATAC
IL1R2	TGGAAAACCAACTCTTCCAC
IL1R2	AGCATCTTTTTCTCTTTAAT
IL1R2	ATCACTTTAAAACCACCTCT
IL1R2	AAACTTATGCGGCGTTTCCT
IL1R2	GAGTACATGATCACCCAGAT
IL1R2	GACCCAGCACTGCAGCCTGG
ZFP42 (REX1)	TAGCAATACAGTCACATTAA
ZFP42 (REX1)	GCCGGGCGTCTGGGCTCTGG

ZFP42 (REX1)	TGCCCGGCGGCCGGGCTGAG
ZFP42 (REX1)	GCCTGGGGGCCCCGGGCTGA
ZFP42 (REX1)	CCGGGCAGAGAGTGAACGCG
ZFP42 (REX1)	GCGGCGCCCCAGGGCGGGGC
ZFP42 (REX1)	ACCCTGGCGGAGCTGATGGG
ZFP42 (REX1)	GGGTCTTGGGAGGGGGCGCA
MYC	GGCCCCACGGAAGCCTGAGC
MYC	CAGTGCGTTCTCGGTGTGGA
MYC	TTTGTCAAACAGTACTGCTA
MYC	GCGCGCGTAGTTAATTCATG
MYC	AGCTAGAGTGCTCGGCTGCC
MYC	GGTTCCCAAAGCAGAGGGCG
MYC	TCTCGCTAATCTCCGCCCAC
MYC	CCCTTTATAATGCGAGGGTC
LIN28A	AGAAGCAGGCCGCGCATTCC
LIN28A	GCGGGTCAGCTCCAAGCAGC
LIN28A	TCTGATTGGCCAGCGCCGCC
LIN28A	CCCATCTCCAGTTGTGCGTG
LIN28A	TCTGAGAAGGGACACCCCAG
LIN28A	CGGAGGGAAAGGGAGGGGAA
LIN28A	GGGGCTGCCCGCGGGGGGTT
LIN28A	GGGAGCCTTTGAAAAGCCGT
TINCR	TGGGCAGGCCCGGCCCGGCG
TINCR	GCGCACTCTGGGGCCAGCAG
TINCR	GGCTGGGATGACCTCGCTGA
TINCR	TGATCTTTTTAAGGACAGGC
TINCR	TCTCAAGTAGCTGGGACTAC
TINCR	CAGGTGCGGTGGCTCATGCC
TINCR	CTCACTGCAACCTCTGTCTG
HOTTIP	GGTGGGGCAGGGAAGGAAGG
HOTTIP	GCACCATTCACCCGGGGGAG
HOTTIP	TGCACCCGTCGTCCCCGCCG
HOTTIP	GTGGGCGGAGCGGGGGGGCC
HOTTIP	GCGCGCTCTTCACTTCTTGG
HOTTIP	TCGTAGAGAAACATGACGGT
HOTTIP	CGCGGCTGCGGCGGCGGCCG
HOTTIP	TTGGCGGCCTCTGCGCCCGC
PCAT-1	TCGGAGCCACTCCCTCCTCT
PCAT-1	AATTTGTCATAGTCTTGAGT

PCAT-1	TCTTTTTACATTGACTGATA
PCAT-1	TGCTTTTGAATGAACACCCA
PCAT-1	TTGGGGTCTACTCACAATTT
PCAT-1	GTTCTGTGAAGTCCAGTCCC
PCAT-1	AGCAAGTACTCAATATATTT
PCAT-1	AGTAGAGAGGCCAGGCACAG
LINC00925	TAAAATAGAGCGGAGATATC
LINC00925	CCTTCTTGAAGGTGCACTCA
LINC00925	CAGGCTGTGGTTGTGACCTG
LINC00925	TTTCTCTCCTGCGTCCTGGG
LINC00925	CACGCTTCCAGCCACCCGCT
LINC00925	CGATGCGCTTGCTGGGTCGC
LINC00925	GGCTCCCAGCCCCAGCCCCC
LINC00925	ACCAGCTGCCTTCTTCCCCC
LINC00514	CAGCCCCTCCTTCTACCCTT
LINC00514	GGGCAGGAGGTGGAGTGTCA
LINC00514	GGGGGCCGGAGGGGGAGAGG
LINC00514	GCAGGCTGAGAAGGGTGGGC
LINC00514	TCTCATCAAGTGTCCACTCA
LINC00514	GTCTCCCATCTCTCCTGCCC
LINC00514	GGGTGTGGAAAGCCTGGTCT
LINC00514	TGACTCTAGGCAGAGTGGGA
LINC00028	TCGCGGCTGGAGGACGCTGC
LINC00028	CGCCCCAGCCCCGGGGGACG
LINC00028	CAGGGACACGATGGTCCAAA
LINC00028	GTCAGGAGTTTCCAGCCCGA
LINC00028	CCCAGGAGGAGGCTGGGCCC
LINC00028	GAGTGAGTTGGATTAAACTG
LINC00028	CTGCTATACGCGAAGTTGCC
LINC00028	ACGTTCTAGATTCACATGTC
Scrambled guide 1	CTGAAAAAGGAAGGAGTTGA
Scrambled guide 2	AAGATGAAAGGAAAGGCGTT
EGFR	CCACCGCTGTCCACCGCCTC
EGFR	GACCCAAGGCCAGCGGCCGC
EGFR	GGAGGGAGGAGAACCAGCAG
LPAR5	AGGCTGGTGGGTTAGTCATC
LPAR5	CATCAGACGGTGGGTGTGCC
LPAR5	GAAGAGTTCCCAGACACAGC
GPR35	GCGTGCTGCACCCTGTCTTG
GPR35	GGCGAGCTGACCGCAGACCC
GPR35	TGGGCATGAGGCGCTGGGGA

P2RY8	CACAGCGACGTTACTCCAGT
P2RY8	CGACTCAGGCTTAGGTGGAA
P2RY8	GAGTGTTCAGACAGTTACAG
CRB2	GATGTCTAGGGACGTCCACG
CRB2	GTCAGGAGGGAGAAACCAGT
CRB2	CTAGGGGGCTTGAGGACTTG
LPAR1	GCCTGAAGCCAGCCCGGGGG
LPAR1	GCGAGCGCAGGTAAGGGGGC
LPAR1	GGCAGGAGAGGGACGCGCGG
ARHGEF1	CGGCGAGAAGGGGAAGGAAG
ARHGEF1	GCAGCGGGGAAAGGAGGGGC
ARHGEF1	GCCGGTGCCCGCAGGGACCC
ITGB3	ACGCGGTGGGTGGGACGCAA
ITGB3	AGGGGATCTAGAGAAGCCGG
ITGB3	CTCTAGACCCTGCGCCTGAG
ITGA9	GCCCGAGAAGTCTGCGCGAG
ITGA9	GGGCGCTGAAGGCGAGCACA
ITGA9	ACTGAGGACGCCGCCGCTCG
ITGB5	GAAAGTGGAGCCTGGCGGGC
ITGB5	TCCCCTGCCAGGCCCTCGCC
ITGB5	AAGCTGACCGTGTGGCGGCC
PCDH7	AGGGAGGAGAGAGAGGAGGG
PCDH7	AGGGGGAAAGGGGAAAGGAG
PCDH7	GAGCGTGCAAGAGAGCGAGT
TFAP2C	GCGCCGAGCCCCACGCTGTG
TFAP2C	GGGACGAAGCGCGGAGTCAG
TFAP2C	AGCTAGGCTGGGACTGGCTG
BCAR3	ATGTCTCGGGGGGTTCCGCA
BCAR3	ACTTGAGGACTGGCTCCTTG
BCAR3	AGAGCCAAACTCTAAAATCC

Supplementary Table 5 | TaqMan qPCR probe ID's used to quantify relative RNA expression levels for each gene (Life Technologies)

Gene	Probe ID
ASCL1	Hs00269932_m1
HBG1/HBG2	Hs00361131_g1
HOTTIP	Hs00955374_s1
IL1B	Hs01555410_m1
IL1R2	Hs01030384_m1
KLF4	Hs00358836_m1
LIN28A	Hs00702808_s1
LINC00028	Hs04233790_s1
LINC00514	Hs04273769_m1
LINC00925	Hs00288663_m1
MYC	Hs00153408_m1
MYOD1	Hs02330075_g1
NANOG	Hs04260366_g1
NEUROG2	Mm00437603_g1
PCAT-1	Hs04275836_s1
POU5F1	Hs00999632_g1
SOX2	Hs01053049_s1
TERT	Hs00972656_m1
TINCR	Hs00542141_m1
VEGFA	Hs00900055_m1
ZFP42	Hs00399279_m1
EGFR	Hs01076078_m1
LPAR5	Hs00252675_s1
GPR35	Hs00271114_s1
P2RY8	Hs01938524_s1
CRB2	Hs00543624_m1
LPAR1	Hs00173500_m1
ARHGEF1	Hs00180327_m1
ITGB3	Hs01001469_m1
ITGA9	Hs00979865_m1
ITGB5	Hs00174435_m1
PCDH7	Hs00941345_m1
TFAP2C	Hs00231476_m1
BCAR3	Hs00981962_m1

Supplementary Table 6 | List of sgRNA target sequences for the human genome. 70,290 guides were designed to target all RefSeq coding sequences.

Supplementary Table 7 | Normalized raw counts of sgRNAs from all of the screens conducted in this study.