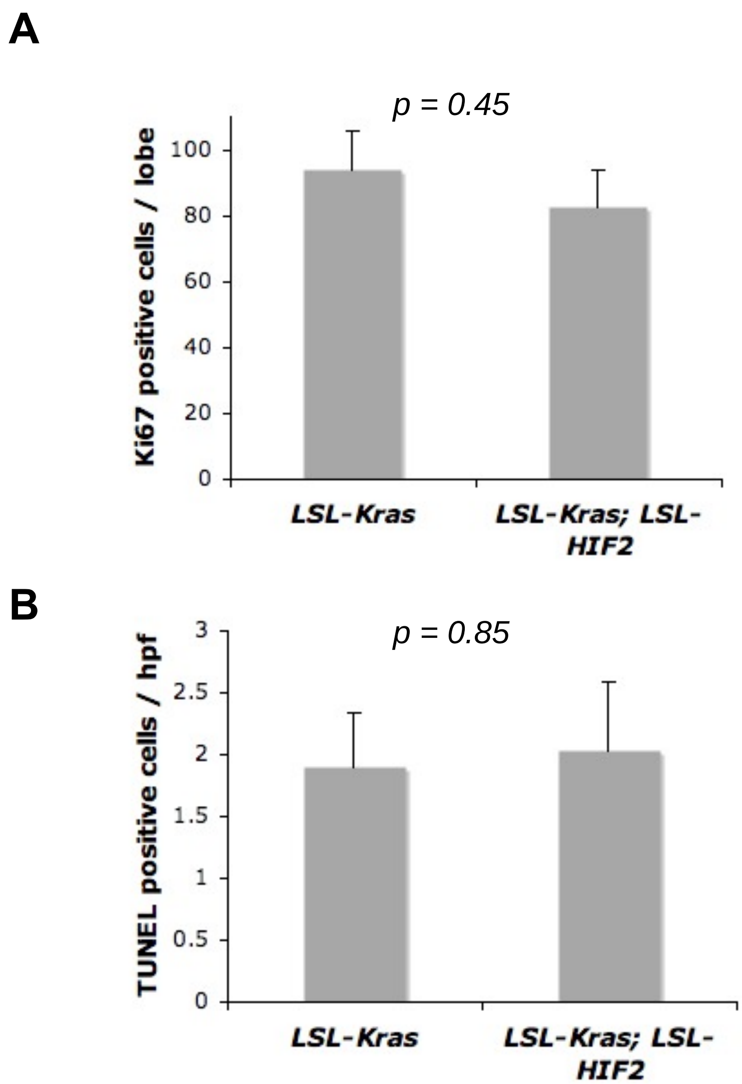
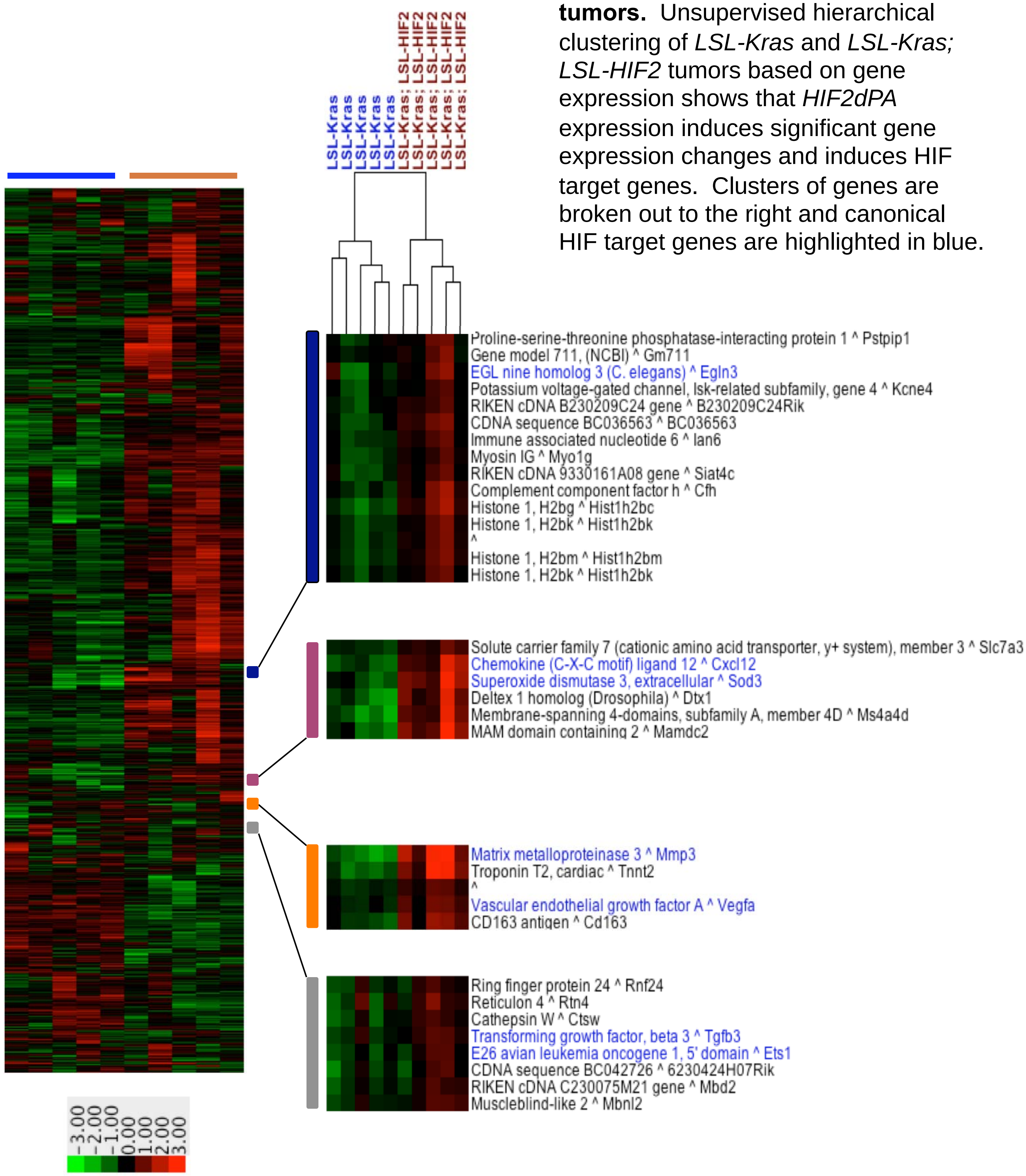
Supplemental Figure 1.



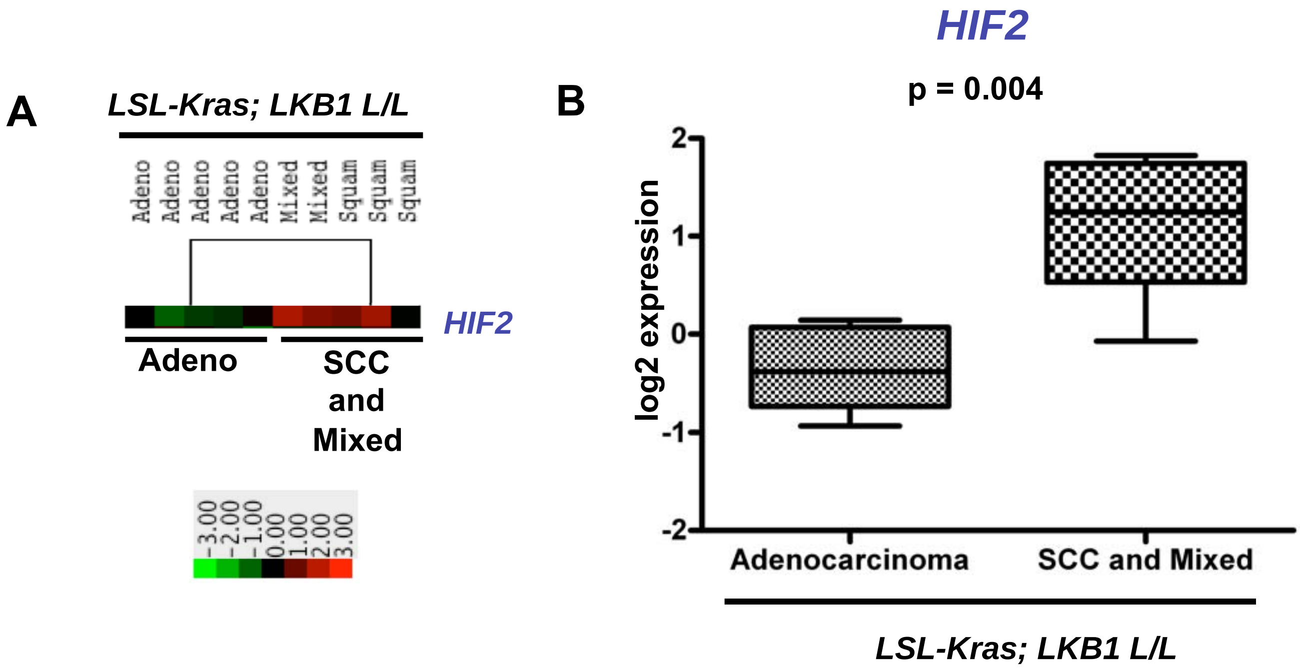
Supplemental Figure 1. HIF2α production in tumors does not increase proliferation or apoptosis. A) Quantification of Ki67+ tumor cells. Error bars = 1 SEM (p = 0.45). **B)** Quantification of TUNEL+ tumor cells. Error bars = 1 SEM (p = 0.85).

Supplemental Figure 2.



Supplemental Figure 2. *HIF2dPA* expression induces gene expression changes in *Kras*-induced lung tumors. Unsupervised hierarchical clustering of *LSL-Kras* and *LSL-Kras; LSL-HIF2* tumors based on gene expression shows that *HIF2dPA* expression induces significant gene expression changes and induces HIF target genes. Clusters of genes are broken out to the right and canonical HIF target genes are highlighted in blue.

Supplemental Figure 3.



Supplemental Figure 3. HIF2α is associated with squamous differentiation. (A,B) The relative gene expression of HIF2α in *Kras*-induced, *LKB1*-deficient adenocarcinomas versus squamous cell or mixed (adeno-squamous) carcinomas is shown visually **(A)** and graphically [**(B)**, p = 0.004].

Supplemental Figure 4.

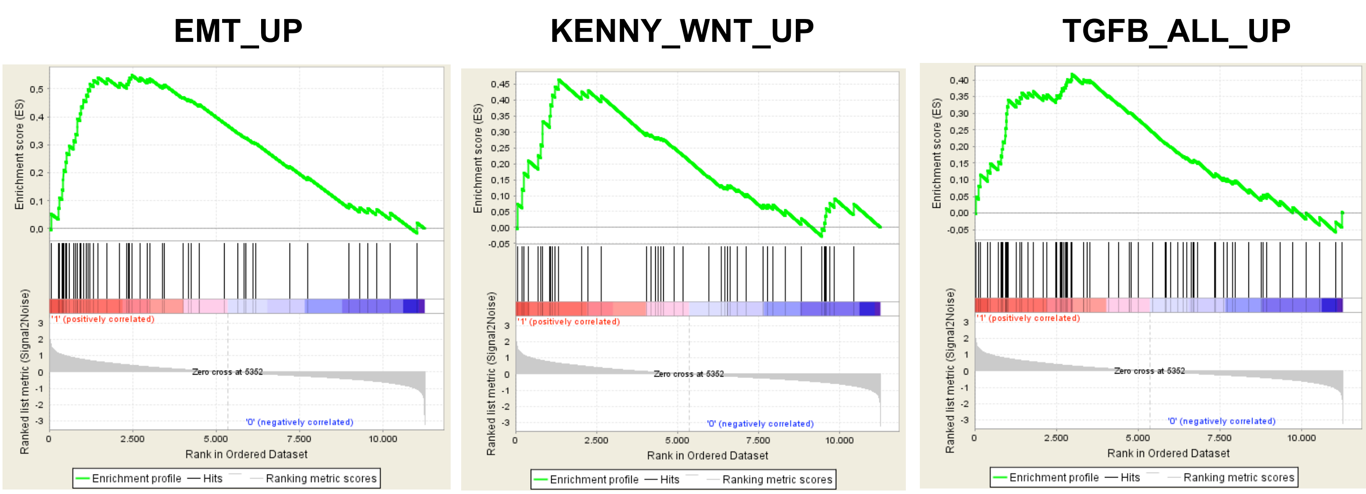
A

Gene sets enriched in HIF2α producing tumors

Signature	NOM p-val	FDR q-val
EMT_UP	0.000	0.000
YU_C-MYC_DOWN	0.000	0.000
JECHLINGER_EMT_UP	0.000	0.001
CORDERO_KRAS_KD_VS_CONTROL_UP	0.002	0.002
Coller_Myc_DOWN	0.000	0.004
LEE_E2F1_UP	0.003	0.009
WNT/TGFB_UP	0.000	0.012
STEMCELL_COMMON_DOWN	0.005	0.013
KENNY_WNT_UP	0.007	0.016
Lamb_cyclinD1_DOWN	0.000	0.022
TGFB_ALL_UP	0.005	0.023
COLLER_MYC_DOWN	0.006	0.025
H3K27_targets	0.000	0.032
PRC2_targets	0.001	0.044

Gene sets enriched in LSL-Kras; LSL-HIF2 tumors

B



Supplemental Figure 4. Gene sets enriched in HIF2α producing tumors. A) The fourteen gene signatures that were found to be enriched in HIF2α producing tumors relative to their mutant *Kras* controls using a false discovery rate (FDR) calculation ($p < 0.05$) to account for multiple hypothesis testing. **B)** Representative GSEA enrichment plots of EMT, b-catenin, and TGFb gene signatures.

Supplemental Table 1

HIF2_UP_200genes	EMT_UP	KENNY_WNT_UP	TGFBETA_ALL_UP
AAK1	ADA	ACTN4	ADAM9
ABI3	ADSSL1	AES	ARHGAP1
ACAS2L	ASNS	AGRN	ARHGDIA
ACIN1	B2M	ALG3	BSG
ADAMTS8	BCL3	ARHGDIA	CD44
ADAMTSL2	CD68	ATP6V0A1	CD59
ADH1	CDH15	BCAP31	CDH6
AGA	CDH2	CAPN1	COL16A1
AIF1	CFH	CCND1	COL1A2
AMY2	COL6A1	CD99	COL3A1
ANXA6	COL6A2	CENTB1	COL6A1
APLP1	CSN3	CPSF4	COL6A3
APOBEC1	CTSZ	CTDSPL	COL8A1
ARID5B	CXCL5	EIF5A	CSPG2
ART3	CXCL6	ETS1	CTNNA1
ASPN	CXCR7	EVA1	CTNNB1
ATP6V0E	CYP1B1	FLOT2	DSP
AW112010	DAB2	GJB1	DVL1
BC026657	DCN	GLTSCR2	DVL3
BHC80	DDR2	GNA12	EFNA5
C1QA	FMO1	HDGF	EPHA2
C1QB	GALK1	HMG20B	EPHB2
C1QTNF5	GAS1	HNRPA0	EPHB3
C1QTNF7	HIF1A	HNRPUL1	EPHB4
CARD4	HTRA1	HSPE1	FGD1
CAV3	IFIT1L	IFITM1	FN1
CCL19	IFIT3	IMPDH2	HSPG2
CD52	IFITM3	INE1	ICAM1
CD83	IL11	KIAA0683	IGF2R
CD86	INHBA	KRT5	IGFBP2
CDC27	IRF7	KRT7	IGFBP3
CDH11	ISG15	LMNA	IGFBP4
CFH	LAMB1	LOC492304	IGFBP5
CFH	MMP12	LY6E	ITGA3
CFH	MMP13	MAP3K11	ITGA4
CILP	MMP2	MMP14	ITGA5
CKLFSF3	MTHFD2	MTA1	ITGB2
CLCA3	PCOLCE	PCDH9	ITGB3
COL14A1	PDGFRA	PCNA	ITGB5
COL2A1	PDGFRB	PDAP1	ITGB8
COLEC12	PHGDH	PFN1	JUP
COMP	PLA2G7	PKP3	LAMA4
CPXM1	PMP22	POLR2A	LAMB1
CPXM2	PPIC	POLR2E	LRP1
CREB3L3	PROCR	PRKCSH	LRRC17
CRHR2	PTGS1	RAB1B	MARCKSL1
CSRP3	PTPN22	RPL39L	MMP1
CX3CR1	RNASET2	SCAP	MMP11
CXCL10	RRAS	SEC61A1	MMP14
CXCL13	S100A8	SF3A1	MMP17
CXCL3	SDC2	SLC1A5	MMP19
CYGB	SLC3A2	SYK	MMP2

DAAM1
DEPDC6
DSCAM
DXBAY18
EBF2
ETOHI1
ETV1
EXT1
FCGR2B
FCRL3
FGD5
FGL2
GAL
GPR124
GPR65
GRIT
HDH
HEYL
HIST1H2BC
HPS4
ICA1
IFI205
IGF1
IL10RA
IL18BP
IL1B
IL2RG
ITCH
ITGA1
ITGB5
ITM2C
JAM3
KCNMB2
KCTD12
KHDRBS3
KLK11
LEO1
LRRC25
LY86
LY96
MAMDC2
MAN2A1
MAN2A1
MATN2
MB
MCTS1
MDK
MFAP5
MMP3
MRPL55
MS4A4B
MS4A4D
MS4A6B

SLPI
SNAI1
SPARC
SRM
STAT1
TNC
TNXB
UPP1
VIM
VLDLR

TCF20
TGM2
UBE1
ZBTB7A

MMP3
MTA1
NEO1
NID1
NOTCH2
PAK1
PAK2
PLAT
PXN
RAC1
RHOA
RHOB
RHOG
RHOQ
RND3
SEMA3F
SERPINE1
SMO
SPARC
TCF7L2
THBS1
THBS2
TIMP1
TNC
TNFRSF1A
WNT2B
WNT8B
ZYX

MS4A6C
MS4A7
MTMR7
MXRA7
NAT5
NCOA5
NEB
NEBL
NFKBIE
NMI
NNMT
NOX4
NR4A2
NRG1
OCIL
OXR1
PACSIN3
PAICS
PDGFRL
PDZK3
PENK1
PHLDB1
PINX1
PKIA
PLAC8
PLAC9
PLCD1
PLSCR4
PLXDC2
PPP1R14A
PPP1R2
PRG1
PRICKLE2
PRSS35
PTGIR
PTHR1
PTPN8
QPCTL
RAB11FIP5
RAD51L1
RBP1
RHOJ
RNASE6
RPGRIP1
RTN1
SERPINA3F
SERPINA3G
SLAMF6
SLC12A6
SLC16A9
SLC35A5
SLC7A2
SLC7A3

SLC7A7
SLIT3
SLN
SMARCE1
SMFN
SPEER4A
SPEER4F
SPON1
STAG1
STFA1
STRA6
SULF1
TCF4
TES3
TFPI
THY1
TLR1
TM4SF6
TMIE
TNFAIP6
TNFAIP8
TNFRSF5
TNFSF13B
TNNI2
TPI1
TREM2
TRIM12
TRIM16
TRIM30
TRIM56
TRPM2
TRSPAP1
TSLPR
TSPAN18
UNC5A
UNC93B1
VPS37A
VIM
VTN
WDFY4
ZBP1
ZFP262
ZMYND15

Supplemental Table 2

Gene set	Source
EMT_DN	MSigDB (broad.mit.edu/gsea/msigdb)
EMT_UP	MSigDB (broad.mit.edu/gsea/msigdb)
JECHLINGER_EMT_DN	MSigDB (broad.mit.edu/gsea/msigdb)
JECHLINGER_EMT_UP	MSigDB (broad.mit.edu/gsea/msigdb)
KENNY_WNT_DN	MSigDB (broad.mit.edu/gsea/msigdb)
KENNY_WNT_UP	MSigDB (broad.mit.edu/gsea/msigdb)
LIN_WNT_UP	MSigDB (broad.mit.edu/gsea/msigdb)
WILLERT_WNT_NCCIT_ALL_UP	MSigDB (broad.mit.edu/gsea/msigdb)
STEMCELL_COMMON_DN	MSigDB (broad.mit.edu/gsea/msigdb)
STEMCELL_COMMON_UP	MSigDB (broad.mit.edu/gsea/msigdb)
STEMCELL_EMBRYONIC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
STEMCELL_HEMATOPOIETIC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
STEMCELL_NEURAL_UP	MSigDB (broad.mit.edu/gsea/msigdb)
KANNAN_P53_DN	MSigDB (broad.mit.edu/gsea/msigdb)
KANNAN_P53_UP	MSigDB (broad.mit.edu/gsea/msigdb)
P21_ANY_DN	MSigDB (broad.mit.edu/gsea/msigdb)
P21_ANY_UP	MSigDB (broad.mit.edu/gsea/msigdb)
P21_EARLY_DN	MSigDB (broad.mit.edu/gsea/msigdb)
P21_MIDDLE_DN	MSigDB (broad.mit.edu/gsea/msigdb)
P21_P53_ANY_DN	MSigDB (broad.mit.edu/gsea/msigdb)
P21_P53_EARLY_DN	MSigDB (broad.mit.edu/gsea/msigdb)
P21_P53_LATE_DN	MSigDB (broad.mit.edu/gsea/msigdb)
P21_P53_MIDDLE_DN	MSigDB (broad.mit.edu/gsea/msigdb)
P53_BRCA1_UP	MSigDB (broad.mit.edu/gsea/msigdb)
P53GENES_ALL	MSigDB (broad.mit.edu/gsea/msigdb)
YEN_MYC_MUT	MSigDB (broad.mit.edu/gsea/msigdb)
YEN_MYC_WT	MSigDB (broad.mit.edu/gsea/msigdb)
YU_CMYC_DN	MSigDB (broad.mit.edu/gsea/msigdb)
YU_CMYC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
ZELLER_MYC_DN	MSigDB (broad.mit.edu/gsea/msigdb)
ZELLER_MYC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
COLLER_MYC_DN	MSigDB (broad.mit.edu/gsea/msigdb)
COLLER_MYC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
FERNANDEZ_MYC_TARGETS	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_E2F1_DN	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_E2F1_UP	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_MYC_DN	MSigDB (broad.mit.edu/gsea/msigdb)

LEE_MYC_E2F1_DN	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_MYC_E2F1_UP	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_MYC_TGFA_DN	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_MYC_TGFA_UP	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_MYC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
YEN_MYC_MUT	MSigDB (broad.mit.edu/gsea/msigdb)
YEN_MYC_WT	MSigDB (broad.mit.edu/gsea/msigdb)
YU_CMYC_DN	MSigDB (broad.mit.edu/gsea/msigdb)
YU_CMYC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
ZELLER_MYC_DN	MSigDB (broad.mit.edu/gsea/msigdb)
ZELLER_MYC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
MYC_ONCOGENIC_SIGNATURE	MSigDB (broad.mit.edu/gsea/msigdb)
MYC_TARGETS	MSigDB (broad.mit.edu/gsea/msigdb)
PENG_RAPAMYCIN_DN	MSigDB (broad.mit.edu/gsea/msigdb)
PENG_RAPAMYCIN_UP	MSigDB (broad.mit.edu/gsea/msigdb)
CORDERO_KRAS_KD_VS_CONTROL_DN	MSigDB (broad.mit.edu/gsea/msigdb)
CORDERO_KRAS_KD_VS_CONTROL_UP	MSigDB (broad.mit.edu/gsea/msigdb)
METASTASIS_ADENOCARC_DN	MSigDB (broad.mit.edu/gsea/msigdb)
METASTASIS_ADENOCARC_UP	MSigDB (broad.mit.edu/gsea/msigdb)
TGFBETA_ALL_UP	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_MYC_TGFA_DN	MSigDB (broad.mit.edu/gsea/msigdb)
LEE_MYC_TGFA_UP	MSigDB (broad.mit.edu/gsea/msigdb)
HYPOXIA_REVIEW	MSigDB (broad.mit.edu/gsea/msigdb)
MANALO_HYPOXIA_DN	MSigDB (broad.mit.edu/gsea/msigdb)
MANALO_HYPOXIA_UP	MSigDB (broad.mit.edu/gsea/msigdb)
WNT/TGF UP	MSigDB (broad.mit.edu/gsea/msigdb)
WNT/TGF DOWN	MSigDB (broad.mit.edu/gsea/msigdb)
HIF1_TARGETS	MSigDB (broad.mit.edu/gsea/msigdb)
HIFPATHWAY	MSigDB (broad.mit.edu/gsea/msigdb)
HYPOXIA_REG_UP	MSigDB (broad.mit.edu/gsea/msigdb)
CHI_HYPOXIA_UP	MSigDB (broad.mit.edu/gsea/msigdb)
CHI_HYPOXIA_DN	MSigDB (broad.mit.edu/gsea/msigdb)
KO_CDH1	Onder et al., 2008
KO_CDH1_BCATENIN	Onder et al., 2009
ES1	Ben-Porath et al., 2008
ES2	Ben-Porath et al., 2008
Myc1_targets	Ben-Porath et al., 2008
Myc2_targets	Ben-Porath et al., 2008

Nanog_targets	Ben-Porath et al., 2008
OCT4_targets	Ben-Porath et al., 2008
Sox2_targets	Ben-Porath et al., 2008
NOS_targets	Ben-Porath et al., 2008
NOSTFs	Ben-Porath et al., 2008
Suz12_targets	Ben-Porath et al., 2008
Eed_targets	Ben-Porath et al., 2008
H3K27_targets	Ben-Porath et al., 2008
PRC2_targets	Ben-Porath et al., 2008
TCF3_Cole	Cole et al., 2008
OCT4_Cole	Cole et al., 2008
NANOG_Cole	Cole et al., 2008
TCF3/OCT4/NANOG_Cole	Cole et al., 2008
CORE9_TFs	Ben-Porath et al., 2008
MYC_NEVINS	Bild et al., 2006
E2F3_NEVINS	Bild et al., 2006
RAS_NEVINS	Bild et al., 2006
SRC_NEVINS	Bild et al., 2006
BCAT_NEVINS	Bild et al., 2006
Cell_cycle_Whitfield	Creighton et al., 2008
Myc_up_Coller	Creighton et al., 2008
Myc_up_Bild	Creighton et al., 2008
Ras_up_Bild	Creighton et al., 2008
E2F3_up_Bild	Creighton et al., 2008
Bcat_up_Bild	Creighton et al., 2008
Src_up_Bild	Creighton et al., 2008
ERBB2_up_Creighton	Creighton et al., 2008
MEK_up_Creighton	Creighton et al., 2008
EGFR_up_Creighton	Creighton et al., 2008
Raf1_up_Creighton	Creighton et al., 2008
MAPK_up_Creighton	Creighton et al., 2008
cyclinD1_up_Lamb	Creighton et al., 2008
Akt_up_Majumder	Creighton et al., 2008
Myc_down_Coller	Creighton et al., 2008
Myc_down_Bild	Creighton et al., 2008
Ras_down_Bild	Creighton et al., 2008
E2F3_down_Bild	Creighton et al., 2008
Bild_down_Bild	Creighton et al., 2008

Src_down_Bild	Creighton et al., 2008
ERBB2_down_Creighton	Creighton et al., 2008
MEK_down_Creighton	Creighton et al., 2008
EGFR_down_Creighton	Creighton et al., 2008
Raf1_down_Creighton	Creighton et al., 2008
MAPK_down_Creighton	Creighton et al., 2008
cyclinD1_down_Lamb	Creighton et al., 2008
Akt_down_Majumder	Creighton et al., 2008

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