Supporting Information

Multidimensional Screening Platform for Simultaneously Targeting Oncogenic KRAS and Hypoxia-Inducible Factors Pathways in Colorectal Cancer

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SUPPLEMENTAL RESULTS

Upstream analysis of genes with a minimum of 2 active siRNAs predict that RICTOR, a subunit of mTORC2, is a major upstream regulator of the HIF and KRAS pathways (**Supplementary Figure S3**). mTORC2 is involved in actin cytoskeletal rearrangement[1,2]. mTORC induces oncogenic AKT1 'Ser-473'phosphorylation, possibly facilitating the activating AKT1 activation loop phosphorylation on 'Thr-308'by PDK1[3]. It has been previously shown that inhibition of the PI3K/Akt pathway using BEZ-235, a small molecule inhibitor of Pdk1/mTORC1, that prototypic arenavirus lymphocytic choriomeningitis virus (LCMV) budding is also inhibited, demonstrating overlap between these prolific processes[4]. Phosphorylation of PRKCA on 'Ser-657'is also modulated by the mTORC2 complex[3]. PRKCA has been associated with a decrease in apoptosis by p53/TP53-mediated activation of IGFBP3 in glioma cells[5] as well as by phosphorylation of BCL2 in leukemia[6]. Additionally, PRKCA has been previously demonstrated roles in angiogenesis[7] (74), cell migration[8], adhesion[9], VEGFA mRNA stability and VEGFA-induced cell proliferation[10], and inflammatory responses via the LPS and NFKB pathway[11,12]. GO analysis also revealed that numerous of the top shared genes have functionality in DNA damage checkpoints, a function also largely regulated by PRKCA[13]. Ubiquitin protein ligase and transferase activity is also among the top biological processes as determined by GO, while IPA highlighted the protein ubiquitination pathway as a top canonical pathway among hits.

SUPPLEMENTAL MATERIALS AND METHODS

Gene Expression Profiling. HCT116, HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}}$, HCT116$^{HIF\text{-}2\alpha\text{-}/\text{-}}$, HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF\text{-}2\alpha\text{-}/\text{-}}$, and HCT116$^{WT\ KRAS}$ cells were seeded at low density 5000 cells per well on 6-well tissue culture plates and allowed to grow undisturbed at 37ºC, in 5% CO_2 for 10 days. Cells were then harvested and total RNA extracted. Gene expression analyses on the samples were performed at the University of Michigan Comprehensive Cancer Center Affymetrix Core Facility. Commercial high-density oligonucleotide arrays were used (GeneChip Human Genome U133A; Affymetrix, Inc., Santa Clara, CA), following protocols and methods developed by the supplier.

Credentialing Isogenic Cell Lines for HIF and KRAS Targets Each isogenic cell line was grown to full confluency at at 37ºC, in 5% CO_2. VEGFA levels were evaluated using VEGFA AlphaLISA kit (PerkinElmer) in 6-well dishes using standard protocol. Protein was then isolated from the same cells (concentration of which was used to normalize VEGFA). Immunoblot analysis was used to evaluate relative LDHA levels between isogenic lines.

Genomic siRNA Screen. The siRNA library targeting 7,784 genes of the druggable human genome with quadruplicate coverage (four individual siRNAs for each gene) arrayed in 96-well format (*Silencer*® Human Druggable Genome siRNA Library V3.1) was obtained from Ambion/Life Technologies (Grand Island, NY). The siRNAs were spotted into 384-well screening sets. HCT116 (1 x 10^3 cells/well), HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF\text{-}2\alpha\text{-}/\text{-}}$ (1.5 x 10^3 cells/well), and HCT116$^{WT\ KRAS}$ (3 x 10^3 cells/well) were retro-transfected with 20 nM of siRNAs using siLentFect (Bio-Rad, Hercules, CA). The plates were incubated at 37°C and 5% CO_2 for 96 h. Cell viability was detected using ATPlite 1step according to the manufacturer's instructions (PerkinElmer, Waltham, MA). Individual siRNAs were plotted by their relative percent cell viability in HCT116 versus HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF\text{-}2\alpha\text{-}/\text{-}}$ or HCT116$^{WT\ KRAS}$ cell lines. High-confidence hits from the siRNA library screen were identified as those where the viability ratio of the wildtype to knockout was <0.6 with $p < 0.05$ across the four replicates, as determined using a two-tail *t*-test. A minimum of two active siRNAs were required for a gene to be considered to have differential toxicity in IPA. Priority for lead pathways, nodes, and functions were given to those genes which had 3 or 4 active siRNAs.

Ingenuity Pathway Analysis (IPA). Networks and canonical pathways were generated through the use of QIAGEN's Ingenuity Pathway Analysis (IPA®, QIAGEN Redwood City, www.qiagen.com/ingenuity). *Canonical Pathways:* All genes which met the established cutoffs were evaluated for shared canonical pathways. An experimentally set confidence was incorporated with the inclusion of publications from human, mouse, and rat species. A comparison analysis was used to screen for shared canonical pathways amongst hits with differential cytotoxicities in isogenic knockout lines. *Network Analyses:* By comparing the imported differential cytotoxicities of each siRNA, a list of biologically relevant canonical pathways and algorithmically generated mechanistic networks were generated by screening the Ingenuity® Knowledge Base. Individual siRNAs were considered hits if the differential cytotoxicity was ≤0.6 (wt:ko) with a $p \leq 0.05$ across replicates. Genes were prioritized based on the number of siRNAs which were differentially active. A cut-off of 2 active siRNAs was established for a gene to be considered a hit, with highest priority given to those genes targeted by 3 or 4 active siRNAs. For the network evaluation, all genes which had made the established criteria were uploaded in a dataset with equivalent values to generate a global view of the effected biology void of bias from varying siRNA functionality. Both direct and indirect relationships were considered with an experimentally set confidence with the inclusion of

human, mouse, and rat data. The global network was generated by connecting top networks with a minimum of 5 shared molecules. *Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Analyses*. A 2-fold differential cytotoxicity was used to determine active siRNAs. High confidence hits were identified as genes for which 3 or 4 siRNAs were active towards both HIF and oncogenic KRAS knockout. A total of 176 genes were evaluated using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) to determine top biological processes and molecular functions shared between active siRNAs.

Small Molecule Library Screen. The small molecule libraries were obtained from Sigma-Aldrich (St. Louis, MO), Prestwick Chemical (Illkirch, France), and Microsource Discovery Systems (Gaylordsville, CT). HCT116 (1 x 10^4 cells/well), HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF\text{-}2\alpha\text{-}/\text{-}}$ (1 x 10^4 cells/well), and HCT116$^{WT\ KRAS}$ (2 x 10^4 cells/well) were seeded in 96-well plates. The next day, cells were treated with either compound at a concentration of 10 μM or solvent control. Cell viability was detected using ATPlite 1Step according to the manufacturer's instructions (PerkinElmer, Waltham, MA). Compounds (261) that showed toxicity or the ratio >1.6 (HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF\text{-}2\alpha\text{-}/\text{-}}$ vs HCT116, HCT116$^{WT\ KRAS}$ vs HCT116) were selected for the dose-response validation.

Dose-Response Cell Viability Assays. The primary 261 hits HCT116 (1 x 10^4 cells/well), HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF\text{-}2\alpha\text{-}/\text{-}}$ (1 x 10^4 cells/well), and HCT116$^{WT\ KRAS}$ (2 x 10^4 cells/well) were seeded in 96-well plates. LoVo and RKO were seeded at 1 x 10^4 cells/well. The next day, cells were treated with various concentrations of the compound or solvent control. After 48 h of incubation, cell viability was detected using ATPlite 1Step according to the manufacturer's instructions (PerkinElmer, Waltham, MA); 55 compounds showed differential activity wherein a differential toxicity of ≥1.99-fold (HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF\text{-}2\alpha\text{-}/\text{-}}$ vs HCT116, HCT116$^{WT\ KRAS}$ vs HCT116) was seen in at least one concentration for each cell type. HUVECs were seeded (quadruplicate) into a 96-well plate at 3600 cells/well. Following treatment with largazole for 18 h, MTT reagent was added and the absorbance read at 570 nm, according to the manufacturer's instructions (Promega, Madison, WI).

RT-qPCR Analysis. HCT116 (4 x 10^5 cells/well) were seeded in 60-mm dishes. HUVECs were seeded into 6-well plates at 96,000 cells per well. The next day, cells were treated with compound or solvent control for 16 h and then total RNA was extracted with the RNeasy Mini Kit (Qiagen, Valencia, CA). cDNA was synthesized from 2 μg of total RNA by using SuperScript II Reverse Transcriptase (Invitrogen/Life Technologies, Grand Island, NY) and Oligo(dT)12-18 Primer (Invitrogen/Life Technologies). Real-time PCR was performed by using the ABI 7300 sequence detection systems (Applied Biosystems/Life Technologies). Each assay was carried out in triplicate. β-Actin expression was used as internal control for normalization.

Colony Formation Assay. HCT116 cells were seeded in 6-well dishes at a density of 1 x 10^3 cells/well. The cells were treated with compound or solvent control and allowed to grow undisturbed for 10 d at 37 °C and 5% CO_2. Colony formation was determined by staining with crystal violet (Sigma-Aldrich, St. Louis, MO).

Immunoblot Analysis. HCT116 cells were plated in 60-mm dishes at a density of 4 x 10^5 cells/well. The next day, cells were given the treatment of compound or solvent control. 16 h later, whole cell lysates were collected using PhosphoSafe buffer (EMD Chemicals, Inc, Gibbstown,

NJ). Protein concentrations were measured with the BCA Protein Assay kit (Thermo Fisher Scientific, Rockford, IL). Lysates containing equal amounts of protein were separated by SDS polyacrylamide gel electrophoresis (4–12%), transferred to polyvinylidene difluoride membranes, probed with primary and secondary antibodies, and detected with the SuperSignal West Femto Maximum Sensitivity Substrate (Thermo Fisher Scientific). Anti-HIF-1α antibody was obtained from BD Biosciences (San Jose, CA). Anti-HIF-1β, β-actin, and secondary anti-mouse and rabbit antibodies were from Cell Signaling Technology, Inc (Danvers, MA).

Angiogenesis Assay. Huvec cells (Lonza) were seeded into a 24-well plate coated with 0.1 ml Basement membrane matrix (Invitrogen) at 125,000 cells per well. Largazole, solubilized in ethanol was added at the concentrations indicated. Following an 18 h incubation, three images were captured for each treatment using a Nikon inverted microscope equipped with NIS-Elements software. Branch points were counted for each image and averaged.

Zebrafish Experiments. Zebrafish used for analysis were obtained from natural crosses of the AB wild-type strain or *vhl*$^{+/hu2117}$ carriers on the *fli1a:egfp*^{y1} transgenic background (which fluorescently marks the vasculature[14]. Fish were housed in the IMCB Zebrafish facility and embryos staged according to Kimmel et al[15]. Largazole was dissolved in DMSO and applied to embryos at either 500 nM or 2 μM, with 0.5% DMSO carrier used for control experiments. Following mounting in low-melting point agarose, the tail vascular plexus was imaged on a Zeiss LSM700 confocal microscope, whilst brightfield images were captured with a Leica MZ16FA.

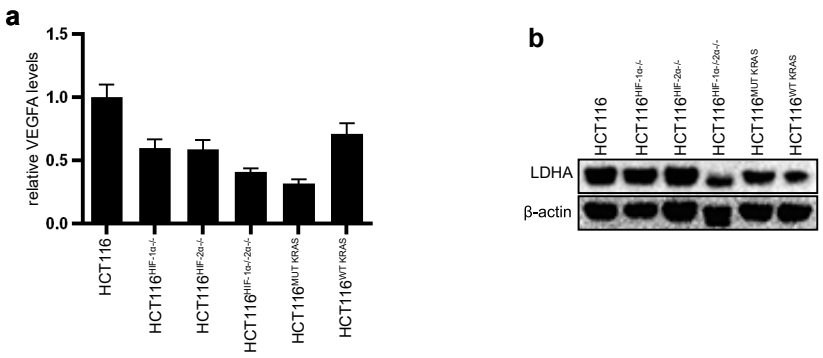

Figure S1. Isogenic cell lines of HCT116 contain decreased levels of HIF-regulated proteins. All isogenic lines contain a decrease in VEGFA relative to the parental line (a) and HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF\text{-}2\alpha\text{-}/\text{-}}$ and HCT116$^{WT\ KRAS}$ cells contain similarly decreased levels of LDHA protein (b).

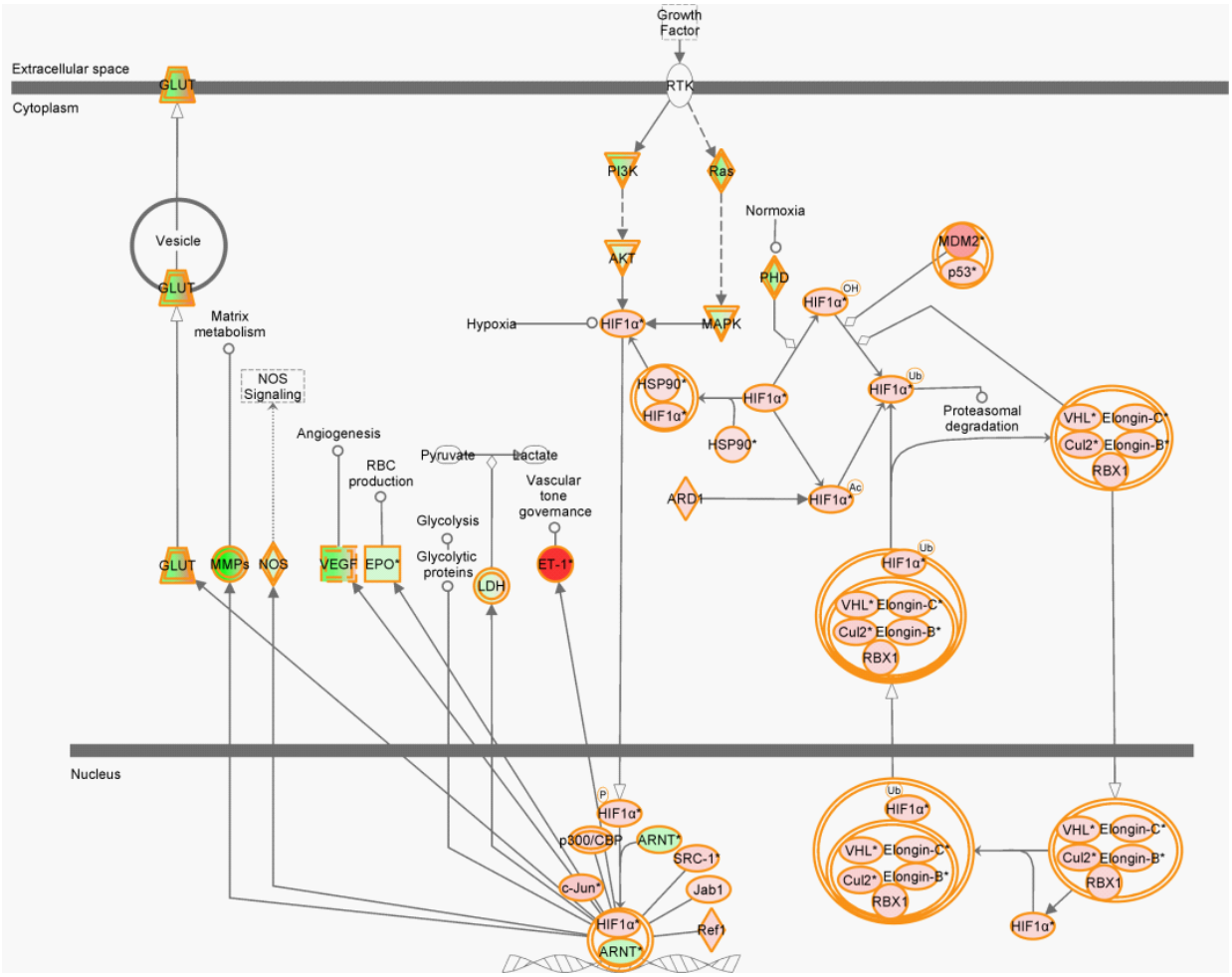

Figure S2a. HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF2\text{-}\alpha\text{-}/\text{-}}$ and HCT116$^{WT\ KRAS}$ demonstrate similar affects on genes within the HIF-1α signaling pathway. Comparison of the HCT116 and HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF2\text{-}\alpha\text{-}/\text{-}}$ expression profiles reveals genes which are upregulated (red) and downregulated (green) within the pathway. Color intensity correlates with the logarithmic fold induction of a gene. Symbols colored both red and green represent complexes wherein members demonstrate different relative gene expression changes.

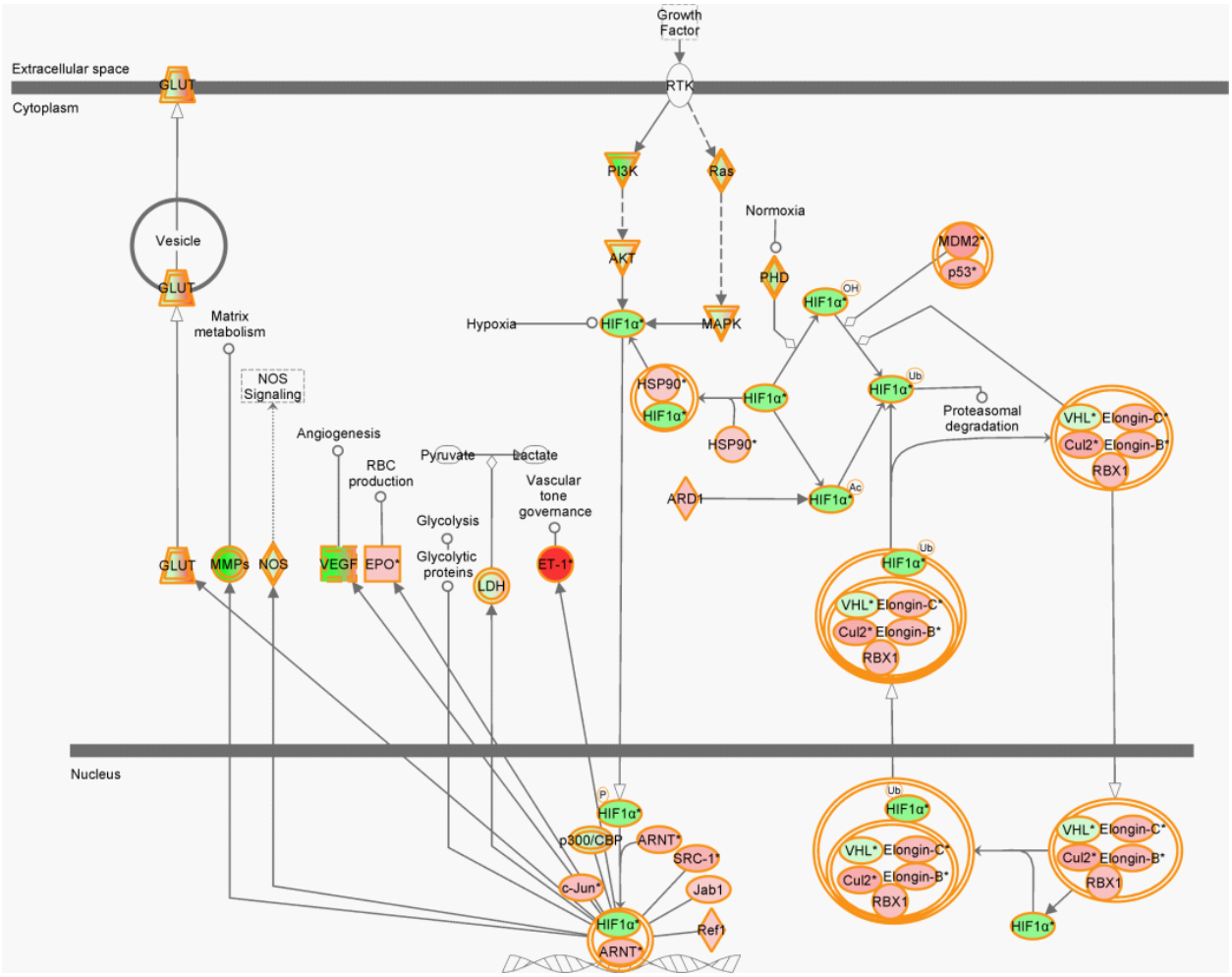

Figure S2b. HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}HIF2\text{-}\alpha\text{-}/\text{-}}$ and HCT116$^{WT\ KRAS}$ demonstrate similar affects on genes within the HIF-1α signaling pathway. Comparison of the HCT116 and HCT116^{KRAS}expression profiles reveals genes which are upregulated (red) and downregulated (green) within the pathway. Color intensity correlates with the logarithmic fold induction of a gene. Symbols colored both red and green represent complexes wherein members demonstrate different relative gene expression changes.

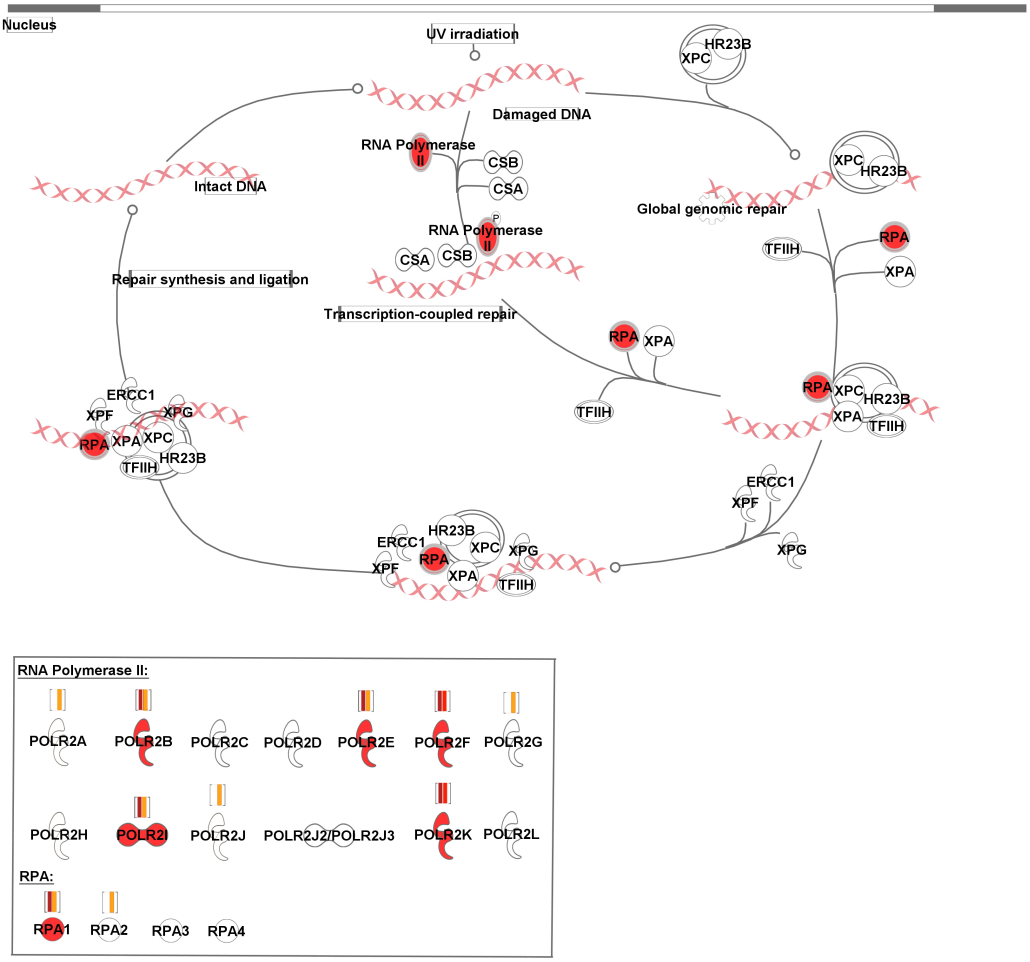

Figure S3. IPA analysis of canonical pathways reveals that siRNAs associated with HIF (red) or KRAS (orange) activity are involved in the nucleotide excision repair pathway.

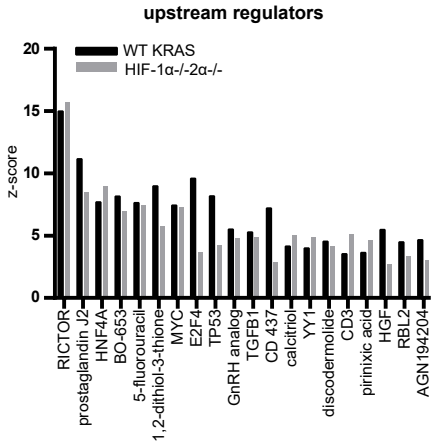

Figure S4. IPA analysis of active siRNAs reveal several common upstream regulators, ranked by activation z-score using Ingenuity comparison analysis.

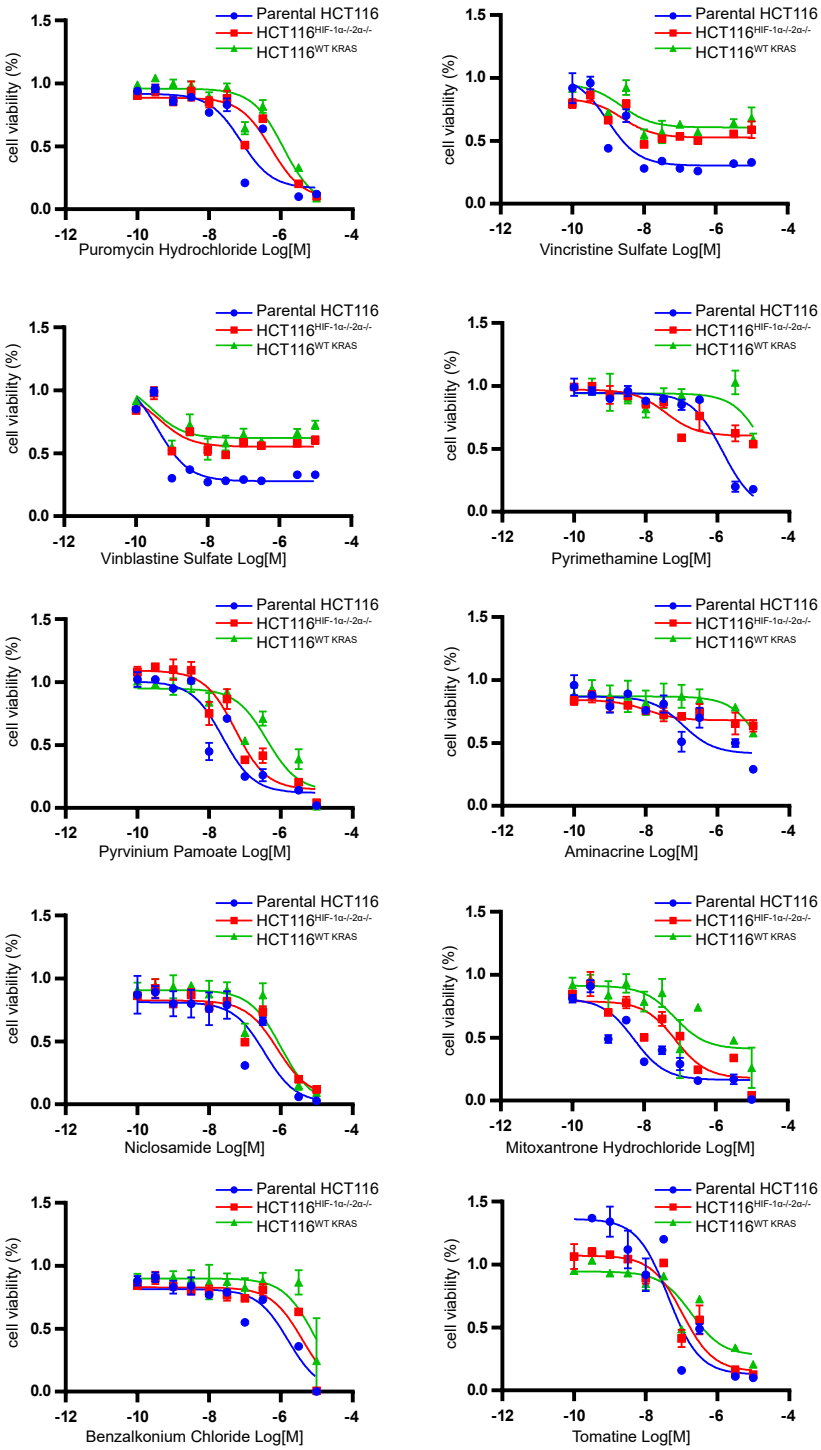

Figure S5a. Dose-response analysis of remaining top 55 drugs (drugs 6-15) showing differential toxicity and efficacy trends (see corresponding SupplementaryTable S7).

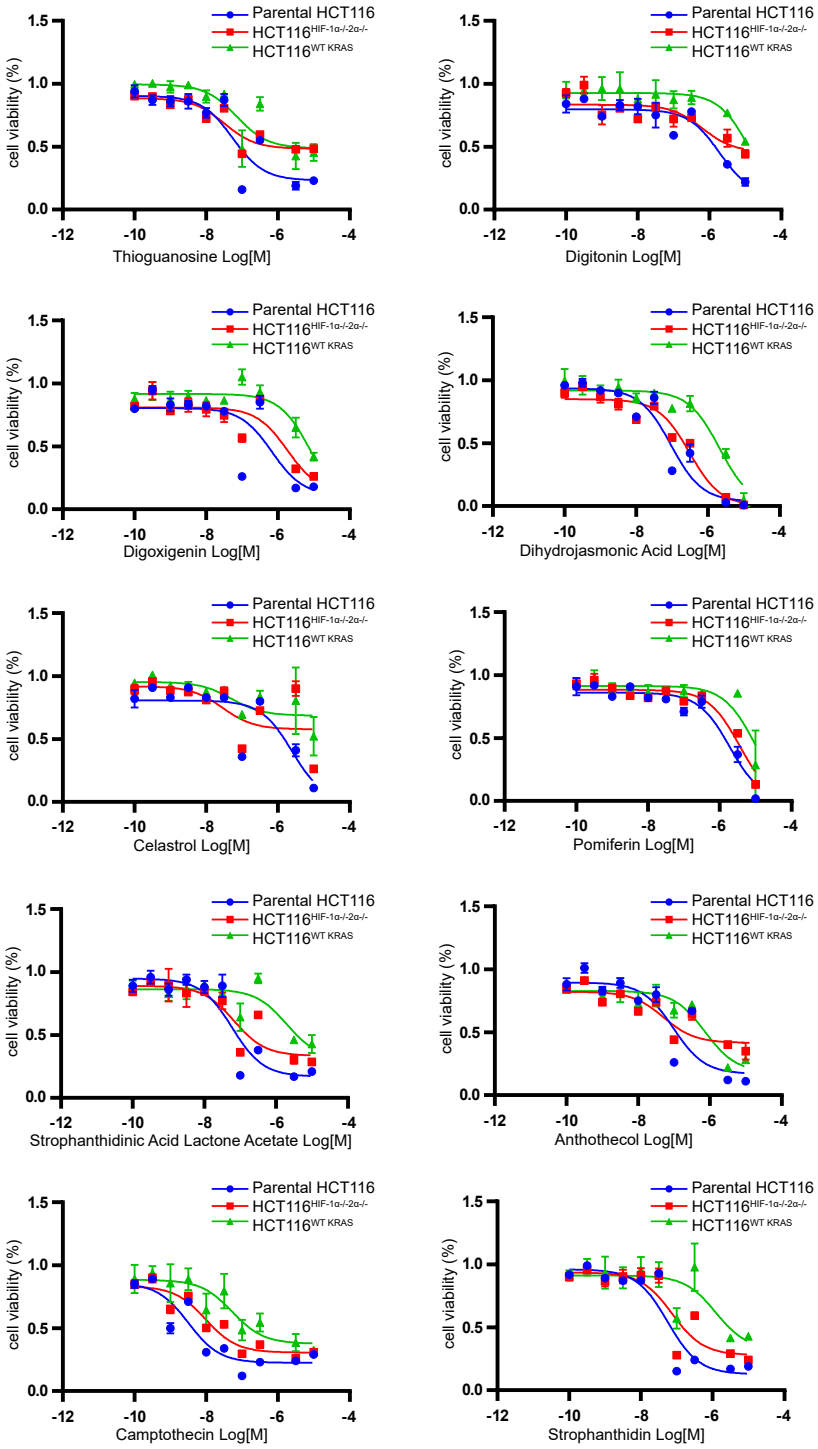

Figure S5b. Dose-response analysis of remaining top 55 drugs (drugs 16-25) showing differential toxicity and efficacy trends (see corresponding SupplementaryTable S7).

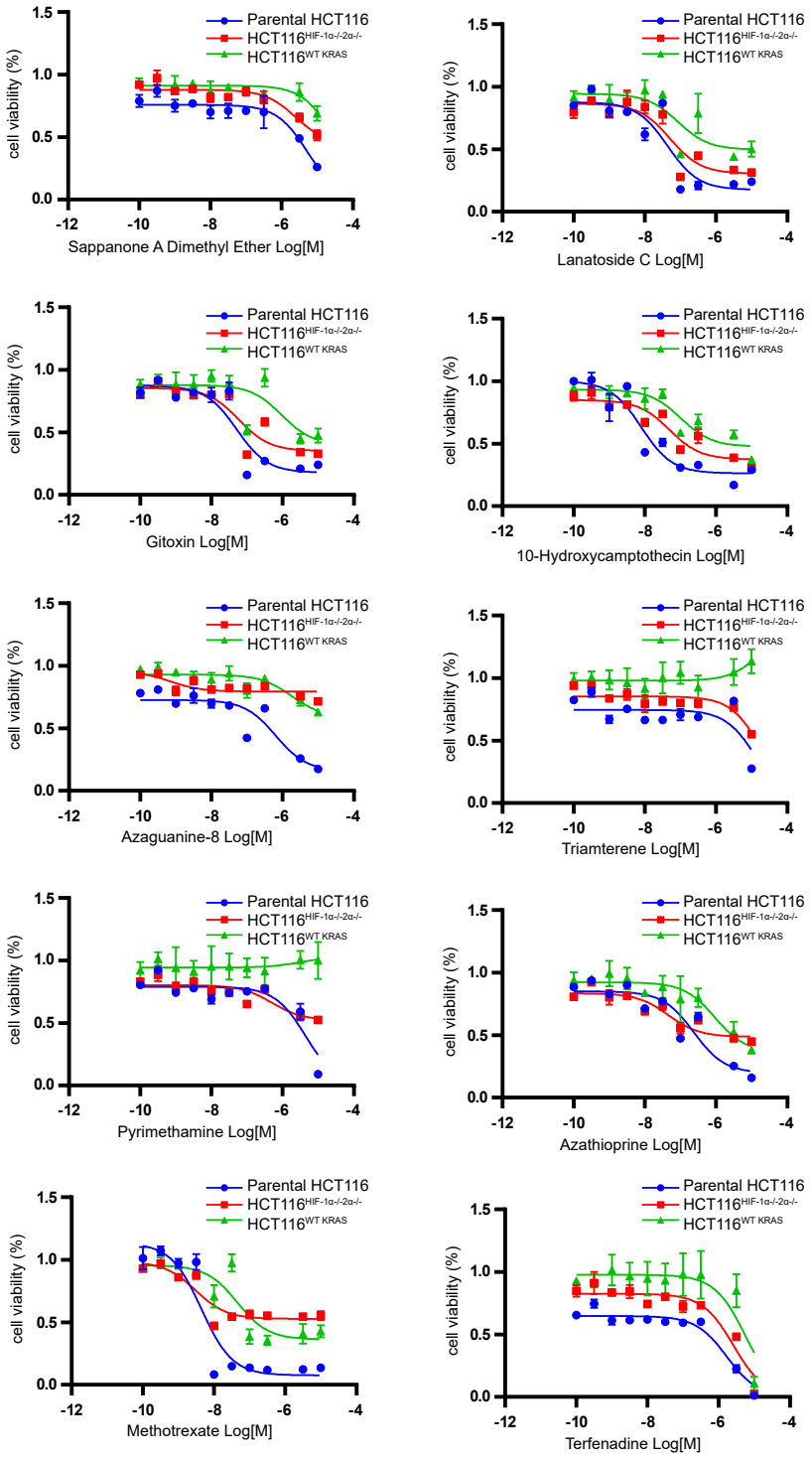

Figure S5c. Dose-response analysis of remaining top 55 drugs (drugs 26-35) showing differential toxicity and efficacy trends (see corresponding SupplementaryTable S7).

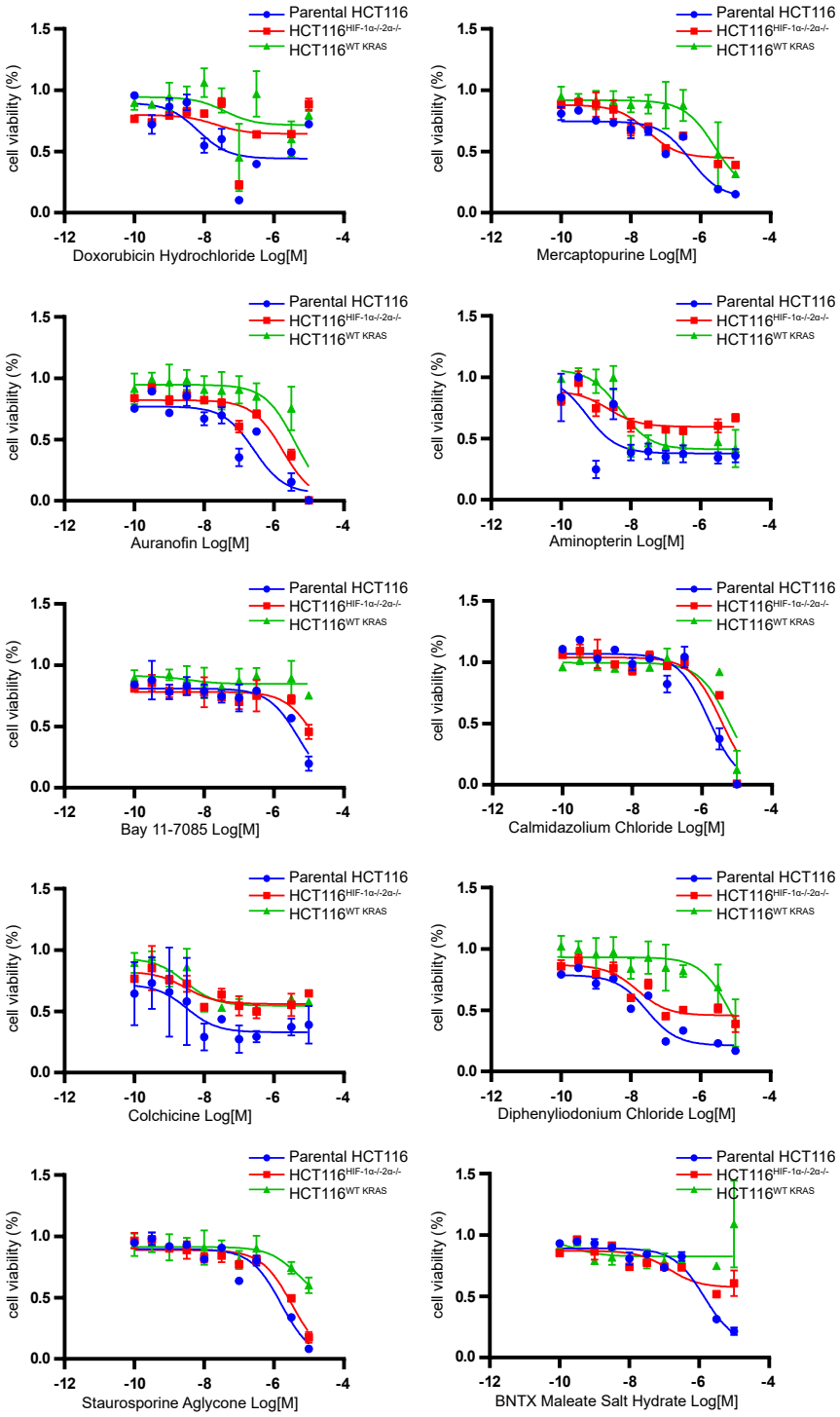

Figure S5d. Dose-response analysis of remaining top 55 drugs (drugs 36-45) showing differential toxicity and efficacy trends (see corresponding SupplementaryTable S7).

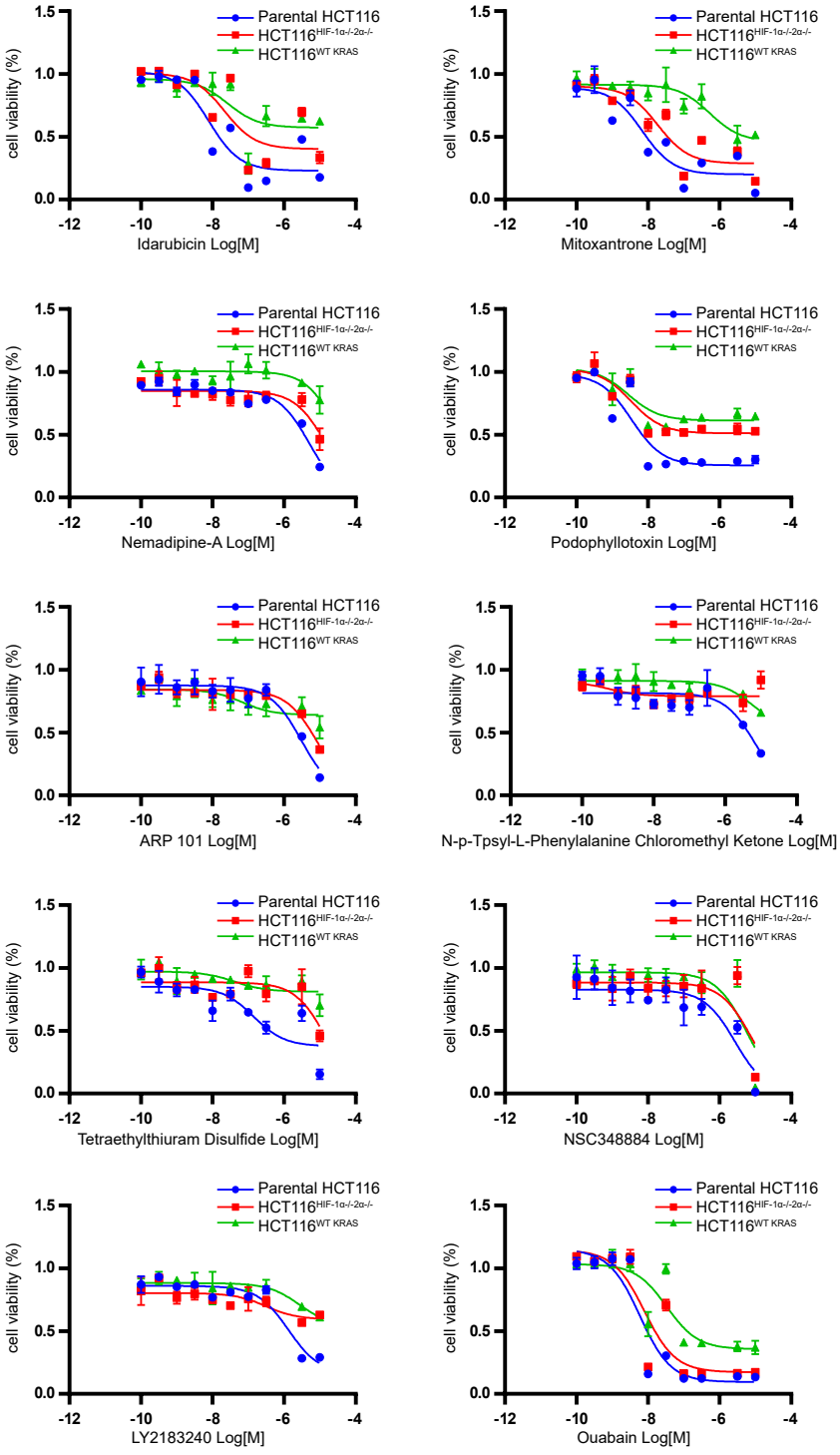

Figure S5e. Dose-response analysis of remaining top 55 drugs (drugs 46-55) showing differential toxicity and efficacy trends (see corresponding SupplementaryTable S7).

Table S1a. Gene perturbations affecting the canonical HIF pathway. Values indicate fold changes in HIF pathway genes on the logarithmic scale. Positive values indicate a gene expression higher than parental HCT116, whereas a negative value indicates a reduced expression level.

Symbol	Entrez Gene Name	HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}}$	HCT116$^{HIF\text{-}2\alpha\text{-}/\text{-}}$	HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}2\alpha\text{-}/\text{-}}$	HCT116$^{MUT\ KRAS}$	HCT116$^{WT\ KRAS}$
AKT1	v-akt murine thymoma viral oncogene homolog 1	-1.071	-1.439	1.283	-1.12	-1.026
AKT2	v-akt murine thymoma viral oncogene homolog 2	1.24	1.73	-1.253	1.224	1.343
AKT3	v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma)	-1.194	-1.178	-1.222	-1.341	1.215
APEX1	APEX nuclease (multifunctional DNA repair enzyme) 1	-1.428	-1.126	1.113	1.024	1.368
ARNT	aryl hydrocarbon receptor nuclear translocator	1.922	-1.646	1.446	1.712	-1.489
ATM	ataxia telangiectasia mutated	-1.303	-2.576	-1.427	1.648	-1.393
COPS5	COP9 constitutive photomorphogenic homolog subunit 5 (Arabidopsis)	-1.015	-1.017	1.082	1.092	1.041
CREBBP	CREB binding protein	-1.238	1.981	-1.24	1.195	1.365
CUL2	cullin 2	1.225	-1.275	1.789	1.089	1.541
EDN1	endothelin 1	1.174	1.289	13.843	-1.049	45.303
EGLN1	egl nine homolog 1 (C. elegans)	-1.513	-1.872	-1.621	1.724	1.479
EGLN2	egl nine homolog 2 (C. elegans)	1.137	1.991	1.723	1.131	1.257
EGLN3	egl nine homolog 3 (C. elegans)	-1.741	-2.829	-2.175	-1.161	-2.661
EP300	E1A binding protein p300	-1.195	-3.206	-1.074	1.134	1.155
EPO	erythropoietin	-1.2	1.749	1.229	1.343	-1.11
FIGF	c-fos induced growth factor (vascular endothelial growth factor D)	1.022	1.047	1.31	1.048	1.238
HIF1A	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	-7.972	-1.318	-2.77	-1.195	1.322
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	1.22	-1.179	1.979	1.009	1.432
HSP90AA1	heat shock protein 90kDa alpha (cytosolic), class A member 1	-1.398	1.024	1.119	-1.068	1.017
JUN	jun proto-oncogene	1.151	-1.951	1.382	-1.419	1.75
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	1.842	-1.714	-1.324	-1.537	-2.203
LDHA	lactate dehydrogenase A	-1.219	-1.085	-1.239	1.014	-1.166
LDHB	lactate dehydrogenase B	-1.173	1.082	1.255	-1.086	1.201
LDHC	lactate dehydrogenase C	-1.074	1.184	-1.033	1.328	1.094
MAPK1	mitogen-activated protein kinase 1	1.454	-3.092	1.569	1.63	1.543
MAPK3	mitogen-activated protein kinase 3	1.037	1.333	-1.056	-1.041	-1.086
MAPK4	mitogen-activated protein kinase 4	1.202	2.568	-1.099	-1.36	1.077
MAPK6	mitogen-activated protein kinase 6	1.118	1.022	-1.029	1.302	-1.251
MAPK7	mitogen-activated protein kinase 7	-1.072	1.151	1.133	-1.038	1.12
MAPK8	mitogen-activated protein kinase 8	-1.127	-1.164	-1.27	1.377	-1.348
MAPK9	mitogen-activated protein kinase 9	1.303	-1.281	-1.358	1.062	-1.641
MAPK10	mitogen-activated protein kinase 10	-1.161	1.382	-1.116	-1.134	-1.298
MAPK11	mitogen-activated protein kinase 11	1.609	1.3	-1.079	-1.22	-1.24
MAPK12	mitogen-activated protein kinase 12	1.159	2.312	2.163	-1.253	1.462
MAPK13	mitogen-activated protein kinase 13	-1.359	-2.189	1.057	-1.143	1.343
MAPK14	mitogen-activated protein kinase 14	1.155	-1.804	1.192	1.107	1.198
MAPK15	mitogen-activated protein kinase 15	1.137	1.805	-1.242	1.174	-1.2
MDM2	Mdm2, p53 E3 ubiquitin protein ligase homolog (mouse)	2.008	-1.37	2.115	1.665	3.378
MMP2	matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	-1.084	2.182	1.094	-1.17	-1.1
MMP3	matrix metallopeptidase 3 (stromelysin 1, progelatinase)	-1.023	-1.01	1.1	1.007	1.029
MMP7	matrix metallopeptidase 7 (matrilysin, uterine)	-1.236	-1.304	-1.405	-1.243	2.022
MMP8	matrix metallopeptidase 8 (neutrophil collagenase)	-1.003	1.29	1.003	-1.042	-1.01
MMP9	matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)	1.296	1.698	1.482	1.229	1.347
MMP10	matrix metallopeptidase 10 (stromelysin 2)	-1.282	-1.227	-1.768	-1.336	-1.691
MMP11	matrix metallopeptidase 11 (stromelysin 3)	1.259	2.044	1.384	1.27	1.065
MMP12	matrix metallopeptidase 12 (macrophage elastase)	-1.056	-1.178	-1.059	-1.152	1.059

Table S1b. Gene perturbations affecting the canonical HIF pathway (cont). Values indicate fold changes in HIF pathway genes on the logarithmic scale. Positive values indicate a gene expression higher than parental HCT116, whereas a negative value indicates a reduced expression level.

Symbol	Entrez Gene Name	HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}}$	HCT116$^{HIF\text{-}2\alpha\text{-}/\text{-}}$	HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}2\alpha\text{-}/\text{-}}$	HCT116$^{MUT\ KRAS}$	HCT116$^{WT\ KRAS}$
MMP15	matrix metallopeptidase 15 (membrane-inserted)	1.034	1.679	-1.509	-1.502	-1.392
MMP16	matrix metallopeptidase 16 (membrane-inserted)	1.083	1.094	-1.159	-1.164	-1.232
MMP20	matrix metallopeptidase 20	-1.046	1.031	-1.115	-1.139	1.931
MMP24	matrix metallopeptidase 24 (membrane-inserted)	1.135	1.585	1.181	-1.182	1.843
MMP25	matrix metallopeptidase 25	-1.188	1.844	-1.342	-1.319	-1.342
MMP26	matrix metallopeptidase 26	-1.109	-1.075	-1.091	-1.278	-1.153
MMP27	matrix metallopeptidase 27	-1.032	1.37	1.047	1.043	1.113
MMP28	matrix metallopeptidase 28	2.605	-1.687	-1.685	1.335	-3.485
MMP1	matrix metallopeptidase 1 (interstitial collagenase)	-2.566	-17.932	-22.772	-16.734	-21.566
MRAS	muscle RAS oncogene homolog	1.329	1.821	1.299	-1.239	1.429
NAA10	N(alpha)-acetyltransferase 10, NatA catalytic subunit	1.187	1.113	1.362	1.332	1.294
NCOA1	nuclear receptor coactivator 1	1.728	-1.975	1.636	-1.331	1.428
NOS1	nitric oxide synthase 1 (neuronal)	-1.168	-1.328	-1.262	-1.462	-1.294
NOS2	nitric oxide synthase 2, inducible	1.411	1.573	1.493	1.114	1.549
NOS3	nitric oxide synthase 3 (endothelial cell)	2.018	-1.717	1.567	-1.194	1.284
NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog	1.386	-1.039	1.658	1.437	1.442
PDGFC	platelet derived growth factor C	-2.195	-2.427	2.647	-1.152	1.825
PGF	placental growth factor	2.169	1.5	2.404	1.368	1.5
PIK3C3	phosphoinositide-3-kinase, class 3	-1.243	-3.05	1.389	-1.438	-1.459
PIK3C2A	phosphoinositide-3-kinase, class 2, alpha polypeptide	2.156	-2.455	-4.284	1.955	-2.578
PIK3C2B	phosphoinositide-3-kinase, class 2, beta polypeptide	-1.053	-1.181	1.084	-1.213	1.263
PIK3C2G	phosphoinositide-3-kinase, class 2, gamma polypeptide	1.012	1.201	1.055	1.043	-1.035
PIK3CA	phosphoinositide-3-kinase, catalytic, alpha polypeptide	-1.357	-2.636	-2.041	-1.327	-2.56
PIK3CB	phosphoinositide-3-kinase, catalytic, beta polypeptide	1.734	-1.528	-1.374	1.449	-1.571
PIK3CD	phosphoinositide-3-kinase, catalytic, delta polypeptide	-1.176	-1.395	1.357	-1.251	-1.142
PIK3CG	phosphoinositide-3-kinase, catalytic, gamma polypeptide	1.183	1.286	-1.111	-1.131	1.111
PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	-1.871	-3.598	-1.713	-1.674	-1.144
PIK3R2	phosphoinositide-3-kinase, regulatory subunit 2 (beta)	-1.103	-1.236	1.22	-1.23	1.301
PIK3R3	phosphoinositide-3-kinase, regulatory subunit 3 (gamma)	-1.398	-2.242	-1.566	-1.578	2.227
PIK3R4	phosphoinositide-3-kinase, regulatory subunit 4	1.056	-1.227	1.255	1.269	1.135
PIK3R5	phosphoinositide-3-kinase, regulatory subunit 5	1.119	1.458	1.696	-1.091	-1.085
PIK3R6	phosphoinositide-3-kinase, regulatory subunit 6	1.147	1.811	-1.123	-1.015	-1.059
PROK1	prokineticin 1	-1.08	1.472	-1.144	-1.053	-1.005
RBX1	ring-box 1, E3 ubiquitin protein ligase	-1.102	1.175	1.373	1.336	1.347
RRAS2	related RAS viral (r-ras) oncogene homolog 2	1.131	-1.14	-1.273	1.153	1.157
RRAS	related RAS viral (r-ras) oncogene homolog	1.461	-1.107	-1.713	1.198	-3.105
SLC2A1	solute carrier family 2 (facilitated glucose transporter), member 1	1.256	2.113	2.46	-1.862	-3.282
SLC2A2	solute carrier family 2 (facilitated glucose transporter), member 2	-1.031	-1.11	-1.147	-1.115	-1.085
SLC2A3	solute carrier family 2 (facilitated glucose transporter), member 3	8.374	-1.881	6.937	-2.102	5.154
SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	1.132	1.154	-1.028	-1.205	-1.235
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	-1.337	1.293	-1.322	-1.193	-1.239
TCEB1	transcription elongation factor B (SIII), polypeptide 1 (15kDa, elongin C)	-1.07	1.075	1.434	1.151	1.078
TCEB2	transcription elongation factor B (SIII), polypeptide 2 (18kDa, elongin B)	1.271	1.338	1.443	1.281	1.184
TP53	tumor protein p53	-1.238	-1.647	1.61	-1.723	1.32
VEGFA	vascular endothelial growth factor A	-1.88	-2.423	-4.836	-2.135	-3.747
VEGFB	vascular endothelial growth factor B	-1.186	1.004	-1.035	-1.061	1.029
VEGFC	vascular endothelial growth factor C	-1.021	1.476	1.088	-1.013	1.142
VHL	von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase	-1.333	-1.71	-1.133	1.422	1.262

Table S2. Gene list for siRNAs which demonstrate differential cytotoxicity towards HCT116$^{HIF\text{-}1\alpha\text{-}/\text{-}2\alpha\text{-}/\text{-}}$, HCT116$^{WT\ KRAS}$, or both.

HIF Specific	ADAMTS2 ADAMTS20 AKT2 ALDOB ALG1 APC APOA2 AQP6 ARFRP1 ATP5J AURKB BACH BAX BMP7 BRS3 BZRP CD163 CFL1 CNGB1 COG4 COX7A2L CRB2 CSNK1A1 CSNK1D CSTF2 CTSK DDX5 DHX38 DKC1 DNCI2 DYRK3 E2F3 EDAR EIF2B1 EN1 FDXR FLT3 FOXN1 FOXN4 FUK FZD8 GABRR1 GTF2F1 HAND2 HAPIP HCK HIC1 INCENP ITGB7 ITGB8 KCNA10 KCNJ5 KCNK5 KIAA1613 KLRD1 KLRF1 KRTAP5-3 KRTHB1 LDHAL6B LGR8 LOC340351 LRP8 MAST4 METAP2 MRCL3 NKX6-2 NPAS1 NUP153 OAS1 OTX1 PLA2G1B PPM1D PPP2R1A PRKCDBP PRSSL1 PTHR2 RAC2 RAD23A RAD51 RALGPS2 RBM22 RGS7 RNASE1 RNF152 RNF7 SLC25A5 SPG4 SPRR2A TCFL4 TFPI TIMP2 TPH1 TPX2 TRAF1 TRIM36 TRPC4 TXNDC8 UBE2I UGT1A4 ZAN ZNRD1
KRAS Specific	A4GALT ABCD1 ABCE1 ACAS2L ADAM12 ADAM22 ADCY6 ADORA3 ADSL AGPAT1 AKIP AKR1B10 ALDH8A1 ALDOC ALK ALOXE3 ALX4 ANAPC2 ANGPT1 ANGPT2 ANGPT4 ANGPTL4 APC2 APG4A APM-1 APOL3 ARHGDIB ARID3B ASL ATE1 ATP6V1B2 ATP6V1G1 B3GNT7 BCL11A BIRC4 BTN2A1 BTN3A2 C5R1 CA6 CAD CARM1 CBLC CCNB2 CCR2 CD1D CD28 CDADC1 CHC1 CHD1 CHRNA5 CHST9 CLN2 CLTA CNGA3 CNOT4 CNOT6L COQ3 COX6B2 CPA1 CPA5 CPD CPNE3 CPSF2 CRSP2 CTSG CYP21A2 DBX1 DDX54 Dlc2 DLGAP1 DNAH8 DNAH9 DNCL2A DPEP2 DPP3 DUXA DZIP1 ECE2 EFO1 EGLN2 EIF5B EPOR ERAL1 ESAM ESR2 EVI5L EXOSC5 EXOSC7 EXOSC8 EZH1 FBL FDFT1 FLJ10326 FLJ12760 FLJ20257 FLJ20277 FLJ22955 FLJ23598 FLJ31121 FLJ31579 FLJ37300 FN3K FN3KRP FOLR3 FOXC1 FSD1 FTSJ3 FUT2 FXYD5 GALNT12 GAPD GDF8 GEM GLA GLO1 GLP1R GLS GMPPB GNAI3 GNAQ GNG13 GNG2 GNG4 GPAM GPR111 GPR147 GPR172A GPR19 GPR40 GPR52 GPR61 GPR75 GPRC5B GPT GRCA GRIA2 GRM1 GRM2 GSTA2 GSTM4 GSTP1 HAL HEMK1 HESX1 HNRPC HSD11B2 HSD3B7 HSF1 HYPB IL10RA IL2RA IL8RA IMP-3 INHA INHBA ITGA3 ITGAV JUP K5B KA35 KCNK17 KCTD5 KIAA0073 KIF23 KIF25 KIFC2 KIRREL3 KLK1 KLK10 KLRC1 KLRC2 KLRG1 KRTAP5-6 KRTHA7 LARS LOC113655 LOC375328 LOC387700 LOC90701 LSM4 LSM8 M160 MAGI-3 MAP3K1 MAP3K4 MAPKAP1 MARS MAST2 MAWBP MAX MCL1 MGAT1 MGC15668 MGC24132 MIR MMP12 MPP6 MYH1 NDOR1 NDUFA3 NDUFB10 NGFB NKIRAS2 NOL1 NOVA2 NR3C1 NRBP NS3TP1 NT5C1B NTS NUP155 NXF1 ORC4L P11 PABPN1 PADI2 PAK2 PAQR3 PAQR6 PARVB PCSK7 PCTK1 PDCD11 PDLIM3 PEX6 PFAS PGLYRP2 PHOSPHO1 PKD1L2 PKD1L3 PLAA PLCZ1 PMPCB POLK POLR2A POLR2C POLR2H POLR2L POLR3F PPP1R10 PPP1R14C PPP2CB PPP4R2 PRCP PRES PRKACG PRKCN PRKD2 PRLR PROZ PRSS35 PSAP PSFL PSMB1 PSMC2 PSMC4 PSMD14 PSMD7 PSPC1 PTBP1 PTDSR PTGIR PURA PYC1 RAB25 RAB3IP RAB5C RAD54L RAP1A RARB RASSF2 RENT1 RHOBTB2 RNF26 RORC RPA2 RPN2 RRH RRP22 RTN4RL1 RUVBL1 SCO2 SDHA SEMA3B SEMA3D SEMA4C SET8 SETDB1 SF1 SFPQ SIAT4B SIAT8B SIVA SLC10A2 SLC12A5 SLC15A2 SLC16A13 SLC26A9 SLC2A12 SLC7A4 SLIT1 SLU7 SMAD4 SMARCA4 SMARCD3 SMPD1 SMPDL3B SNRP70 SNRPA1 SNRPD2 SPG7 SR140 SRRM1 STARD5 STK10 SUCLA2 SYMPK SYNPO2L SYPL TAF1L TALDO1 TAZ TBDN100 TBX22 TBX5 TCF15 TDE2 TEKT3 Tenr TFIP11 TGM3 TGM6 THOC4 TIF1 TIMM13 TIMP3 TLR2 TMX2 TNP2 TOMM22 TOPORS TRRAP TYMS UBE2D2 UBE2G1 UBL5 USP16 USP40 USP5 USP9Y VHL VIPR1 VNN2 VTN WFIKKN2 WFS1 XAB1 XYLT1 XYLT2 ZMAT1 ZNF219
Both	ACTL6A ADAM33 ADAMTS5 ALDOA APOF ARPM2 ASAH2 ASB2 ASCC3L1 ATP8A1 BIRC3 BST1 BUB1B C6orf11 CALCB CCNA2 CD244 CDC2 CDC2L2 CDC45L CENPE CHERP ch-TOG COPB CRLF1 DARS DDX23 DDX48 DHX8 DNCH1 ESPL1 EXOSC3 FGD5 FOXP3 GART GNG5 GPR100 GPR158 GTF3C2 GTPBP1 GTPBP4 HAS3 HIF3A HUMAUANTIG ITGAL K-ALPHA-1 KCNH7 KCNK3 KIAA0052 KIF11 KIFC3 KPNB1 LSM6 LSM7 MAP2 MMP25 MTHFD1 MYBBP1A NCL NUP107 NUP214 NUP62 NUP98 PLK1 PNR POLA POLD1 POLN POLR1A POLR1B POLR1D POLR2B POLR2E POLR2F POLR2G POLR2I POLR2J POLR2K PPIE PPP1R15B PRIM1 PRP19 PRPF8 PSMA1 PSMA2 PSMA3 PSMA4 PSMA5 PSMA6 PSMA7 PSMB2 PSMB3 PSMB4 PSMB5 PSMB6 PSMB7 PSMC3 PSMC5 PSMC6 PSMD2 QPCT RAB33A RAB7B RAN RBM19 RBM8A RNPC2 RNPEPL1 RNPS1 RPA1 RPN1 RRM1 RUVBL2 SARS SERPINB6 SF3A1 SF3B3 SF3B4 SFRS3 SFRS7 SLC22A14 SMC2L1 SMC4L1 SNAI2 SNRPB SNRPD1 SNRPE SNRPF SNRPG SP2 SPRR2B SUPT5H SUPT6H TERF1 THAP7 THRAP6 TIMM23 TIMM44 TRIM46 TSG101 TXNL4A U2AF2 UBE1 UMPS UROD USP18 USP36 USP39 VCP VSX1 WRN XAB2 XPO1

Table S3a. Top 10 canonical pathways associated with HIF

Ingenuity Canonical Pathways	Molecules
Protein Ubiquitination Pathway	UBA1,PSMA4,PSMC3,PSMA6,PSMA3,USP18,PSMB5,USP36,USP39,PSMA7,PSMB4,PSMB7,UBE2I,PSMC5,PSMA2,PSMB2,PSMB3,PSMC6,PSMA1,PSMA5
Nucleotide Excision Repair Pathway	POLR2B,POLR2E,POLR2J,POLR2F,RPA1,POLR2I,POLR2G
Systemic Lupus Erythematosus Signaling	SNRPG,LSM6,RNU2-1,SNRPE,SNRPD1,PRPF19,SNRNP200,SNRPF,TXNL4A,MAPK1,IGHM,SNRPB,IFNA4
Assembly of RNA Polymerase II Complex	POLR2B,GTF2F1,POLR2E,POLR2J,POLR2F,POLR2I,POLR2G
Estrogen Receptor Signaling	POLR2B,MED30,GTF2F1,POLR2E,POLR2J,POLR2F,MAPK1,DDX5,POLR2I,POLR2G
Hereditary Breast Cancer Signaling	POLR2B,POLR2E,POLR2J,POLR2F,RPA1,POLR2I,RAD51,POLR2G,CDK1
Androgen Signaling	POLR2B,GTF2F1,POLR2E,POLR2J,POLR2F,MAPK1,POLR2I,POLR2G
Glucocorticoid Receptor Signaling	POLR2B,TSG101,GTF2F1,UBE2I,POLR2E,POLR2J,POLR2F,MAPK1,CD163,POLR2I,POLR2G
Regulation of eIF4 and p70S6K Signaling	GTP,EIF2S1,RPS26,RPS7,PPP2R1A,MAPK1,EIF4A2,EIF4A3
Huntington's Disease Signaling	POLR2B,DYNC1I2,PENK,POLR2E,POLR2J,POLR2F,MAPK1,ATP5J,POLR2I,POLR2G

Table S3b. Top 10 canonical pathways associated with KRAS

Ingenuity Canonical Pathways	Molecules
Protein Ubiquitination Pathway	UBA1,PSMD7,PSMA3,USP18,PSMB5,USP5,PSMC4,USP36,PSMA7,PSMB7,PSMA2,PSMD14,PSMB2,PSMB3,PSMA1,PSMA5,USP16,PSMA4,PSMC3,PSMA6,UBE2G1,USP40,PSMC2,VHL,USP39,USP9Y,PSMB4,PSMC5,PSMC6
CREB Signaling in Neurons	GTF2B,CREB1,ADCY6,PRKD3,POLR2E,POLR2F,POLR2C,GNAI3,POLR2B,POLR2H,GNAQ,POLR2L,GNG4,GRIA2,POLR2J,GRM1,GNG2,GNG13,PLCZ1,PRKCH,POLR2I,POLR2G
Nucleotide Excision Repair Pathway	POLR2B,POLR2H,POLR2L,RPA2,POLR2E,POLR2J,POLR2F,RPA1,POLR2C,POLR2I,POLR2G
Androgen Signaling	GTF2B,PRKD3,POLR2E,POLR2F,POLR2C,GNAI3,POLR2B,POLR2H,GNAQ,POLR2L,GNG4,POLR2J,GNG2,GNG13,PRKCH,POLR2I,POLR2G
Huntington's Disease Signaling	CREB1,PENK,PRKD3,POLR2E,SDHA,POLR2F,POLR2C,POLR2B,POLR2H,GNAQ,POLR2L,CLTA,GNG4,POLR2J,GRM1,GNG2,GNG13,PRKCH,POLR2I,NGF,POLR2G,GLS
Assembly of RNA Polymerase II Complex	GTF2B,POLR2B,POLR2H,POLR2L,POLR2E,POLR2J,TAF1L,POLR2F,POLR2C,POLR2I,POLR2G
Estrogen Receptor Signaling	GTF2B,POLR2E,POLR2F,POLR2C,POLR2B,POLR2H,POLR2L,MED30,NR3C1,MED14,POLR2J,TAF1L,POLR2I,POLR2G,CARM1,TRRAP
Systemic Lupus Erythematosus Signaling	SNRPG,LSM6,SNRPE,LSM8,SNRPD1,HNRNPC,LSM4,PRPF19,SNRNP70,SNRPD2,SNRNP200,KLK1,SNRPF,SNRPA1,TXNL4A,IGHM,SNRPB
Glucocorticoid Receptor Signaling	GTF2B,TSG101,CREB1,POLR2E,POLR2F,VIPR1,POLR2C,SMAD4,POLR2B,POLR2H,POLR2L,NR3C1,MED14,MAP3K1,POLR2J,TAF1L,POLR2I,POLR2G
GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells	GNAQ,ADCY6,PRKD3,GNG4,PLCZ1,GNG2,GNG13,PRKCH,FFAR1,GNAI3

Table S4. IPA network analysis of siRNAs on differential toxicity

ID	Analysis	Molecules in Network	Score	Focus Molecules	Top Diseases and Functions
1	HIF-associated toxicity	3-hydroxyanthranilic acid,CSTF2,DBT,DHX38, DUB,EDAR, EIF4A2,EIF4A3, GNL2, GTPBP4, IFNA4,Igh (family),LSM6,NFkB (complex), PPIE,PRPF19, RBM39, RBM8A,RNPS1,RNU2-1,RPLP1,SF3A1 SF3B3,snRNP, SNRNP200,S NRPB,SNRPD1, SNRPE,SNRPF, SNRPG, TXNL4A, USP18,USP36,USP39,XAB2	63	31	RNA Post-Transcriptional Modification, Cellular Assembly and Organization, Infectious Disease
1	KRAS-associated toxicity	Akt,ALYREF,CHERP,DHX8,EIF4A3,FABP3,FOXC1,GEM,Impo rtin beta, KCTD5,KPNB1,MAPKAP1, Nucleoporin,NUP62, NUP155,NUP214, NXF1,PAQR3,PSAP, RBM39,RBM8A,RNPS1, SEMA3B,SF1,SF3A1,SF3B3,SMARCD3,SRSF3,Tap, TCF15, TFIP11,U2AF2,U2SURP,UPF1,XPO1	53	31	Molecular Transport, RNA Trafficking, RNA Post-Transcriptional Modification
2	KRAS-associated toxicity	3-hydroxyanthranilic acid,DUB,FBL, FTSJ3,GLA,GNL2,G TPBP4,IFITM3, Ifnar,LSM4, LSM6,LSM8,MAST2,NFkB(complex), NKIRAS2, PDCD11, SLC15A2,snRNP, SNRNP200, SNRPA1, SNRPD1 SNRPD2, SNRPE, SNRPF, SNRPG,STK10, TALDO1, TXNL4A, USP5, USP16,USP18, USP36, USP39,USP40, USP9Y	53	31	RNA Post-Transcriptional Modification, Cellular Assembly and Organization, Cell Cycle
2	HIF-associated toxicity	19S proteasome,20s proteasome,26s Proteasome,alcohol group acceptor phosphotransferase,ATPase,Calcineurin protein(s), CK1,COG4,CSNK1A1, CSNK1D,CTSK, CYB561, EIF2S1, Hsp70,KALRN,MAPK1,METAP2,PDE6G, PLK1,POLR2G,PP1 protein complex group, PPP1R15B,PSMA1, PSMA2,PSMA6, PSMA7, PSMB5,PSMC3,PSMC5, PSMC6,SOD1, SPAST, taurodeoxycholic acid,Ubiquitin,VCP	46	24	Cell Death and Survival, Developmental Disorder, Hereditary Disorder
3	KRAS-associated toxicity	CDC45,CRLF1,DNA-directed DNA polymerase, EGLN2, EXOSC3, EXOSC7, EXOSC8, GTF3C2, HBE1,KIF11,Ku, MTHFD1, MYBBP1A, NOP2, ORC4, PABPN1,POLA1,POLD1, POLN, PRIM1, PRPF19, PSMA3,PTBP1,RCC1,RPA, RPA1,RPA2, RPS7,SKIV2L2, SMC2, SMC4,SNRPB, SYMPK, Vegf,WRN	50	31	RNA Post-Transcriptional Modification, Cell Cycle, Cellular Assembly and Organization
3	HIF-associated toxicity	Akt,CDC45,CHERP,Ctbp,DNA-directed DNA polymerase,DNA-directed RNA polymerase, DPEP1, E2f,E2F3,FLT3,FOXN1, HIC1, HIF3A, LRP8, MTHFD1,P-TEFb,POLA1,POLD1, POLN, POLR1A,POLR1B,POLR2E,POLR2F,POLR2I,POLR2J,PRIM1, Ptk,QPCT,RAD51,RNA polymerase I,Rnr,RPA,RPA1,TCF,WRN	44	24	Gene Expression, DNA Replication, Recombination, and Repair, Cancer
4	HIF-associated toxicity	Alpha tubulin,DDX5,DYNC1H1,DYNC1I2,ERK, EXOSC3, GABRR1, Immunoproteasome Pa28/20s,MED30,mediator,MYBBP1A ,NDUFA10, POLR2B, Proteasome PA700/20s,PSMA,PSMA3, PSMA4,PSMA5,PSMB,PSMB2,PSMB3, PSMB4, PSMB7, PSMC,Ribosomal 40s subunit, RPS7, RPS26, SKIV2L2,SMC2, SMC4, SRSF3, TRAP/Media,TUBA1B,tubulin (family),UBQLN1	43	24	Cell Cycle, Cellular Assembly and Organization, Cellular Function and Maintenance
4	KRAS-associated toxicity	APOL3,CCNB2,Cdc2,Cytoplasmic Dynein,DDX54, DLGAP1,DYNC1H1,DYNLL2, DYNLRB1,GLO1, GLUD1, IARS2,MED14,MED30, mediator, Mitochondrial complex 1,NADH dehydrogenase, NDUFA5,NDUFA10,NDUFB10, NDUFS4,NR3C1, Pka,Pka catalytic subunit,PSMD7, RASSF2, REN, RUVBL2, SERPINB6, SLC10A2 ,taurodeoxycholic acid,TRAP/Media,TRRAP,trypsin,YWHAQ	41	26	Hereditary Disorder, Metabolic Disease, Neurological Disease
5	KRAS-associated toxicity	Actin,ATP6V1G1,CD3,Ck2,CLTA,CTSG,Erm,estrogen receptor, ETS1 GAPDH,GRIA2,Histone h3, HNRNPC,HSF1,MAX, MMP25,NCL,p70 S6k ,PAM,PKD1L3,PPIE,PSMC5,RNA polymerase II,RPL11,Secretase gamma,SETD2, SNRNP70, TNPO3,TRIM24,TUBA1B,UBQLN1,VCP,VHL,XAB2,ZMAT2	41	26	Cellular Compromise, Cell Death and Survival, Gene Expression

Table S5. IPA generated top diseases and biofunctions of siRNAs with differential cytotoxicity (score: -log(p-value)).

Diseases and Bio Functions	HIF-associated toxicity	KRAS-associated toxicity
cell viability of myeloma cell lines	13.971	11.904
processing of RNA	13.446	11.112
Viral Infection	9.172	10.955
splicing of RNA	11.619	7.906
infection by HIV-1	8.419	9.232
infection of epithelial cell lines	8.136	9.268
infection of embryonic cell lines	8.136	9.268
infection of cells	8.368	8.839
infection by RNA virus	7.527	9.401
infection of kidney cell lines	7.870	8.891
cell viability of tumor cell lines	9.028	7.503
cell survival	10.370	6.012
proliferation of cells	8.291	7.936
replication of RNA virus	8.292	7.107
metabolism of protein	4.757	10.488
replication of virus	7.847	6.744
replication of Influenza A virus	6.901	7.332
catabolism of ATP	8.195	6.022
cell viability	8.698	5.519
transcription	6.234	7.748
catabolism of protein	2.890	11.078
transcription of RNA	6.093	7.801
processing of mRNA	7.811	5.627
expression of RNA	5.629	7.802
splicing of mRNA	7.734	5.635
metabolism of nucleotide	7.333	5.299
metabolism of nucleoside triphosphate	7.991	4.334
metabolism of nucleic acid component or derivative	7.254	4.766
transcription of DNA	5.403	5.452
expression of DNA	5.0058	5.5130

Table S6. Hits from the siRNA library screen for HIF and KRAS overlap with synthetic lethals used for targeting KRAS

	synthetic lethals	siRNA Screen
Protein Ubiquitination Pathway	PSMA1, PSMA2, PSMB6, PSMD14	ANAPC2, BIRC3, PSMA1, PSMA2, PSMA3, PSMA4, PSMA5, PSMA6, PSMA7, PSMB1, PSMB2, PSMB3, PSMB4, PSMB5, PSMB6, PSMB7, PSMC2, PSMC4, PSMC4, PSMC5, PCM6, PSMD2, PSMD7, PSMD14, UBA1, UBE2D2, UBE2G1, UBE2I, USP5, USP16, USP18, USP36, USP39, SUP40, USP9Y, VHL, XIAP
Nucleotide Excision Repair	POLR2B, POLR2G	POLR2A, POLR2B, POLR2C, POLR2E, POLR2F, POLR2G, POLR2H, POLR2I, POLR2J, POLR2K, POLR2L, RPA1, RPA2
Estrogen Receptor Signaling	ESR1, POLR2B, POLR2G, RUNX2	CARM1, DDX5, ESR2, GTF2F1, MED14, MED30, NR3C1, POLR2A, POLR2B, POLR2C, POLR2E, POLR2F, POLR2G, POLR2H, POLR2I, POLR2J, POLR2K, POLR2L, SMARCA4, TAF1L, TRRAP
Glucocorticoid Receptor Signaling	CREBZF, ESR1, FOS, POLR2B, POLR2G	CD163, GTF2F1, MED14, MAP3K1, NRC1, POLR2A, POLR2B, POLR2C, POLR2E, POLR2F, POLR2G, POLR2H, POLR2I, POLR2J, POLR2K, POLR2L, PRKACG, SMAD4, SMARKA4, SMARCD3, TAF1L, TSG101, UBE21, AKT2, VIPR1
Hereditary Breast Cancer Signaling	E2F1, POLR2B, POLR2G	AKT2, CDK1, POLR2A, POLR2B, POLR2C, POLR2E, POLR2F, POLR2G, POLR2H, POLR2I, POLR2J, POLR2K, POLR2L, RAD51, RPA1, SMARCA4, SMARCD3
Assembly of RNA Polymerase II Complex	POLR2B, POLR2G	GTF2F1, POLR2A, POLR2B, POLR2C, POLR2E, POLR2F, POLR2G, POLR2H, POLR2I, POLR2J, POLR2K, POLR2L,TAF1L

Table S7. Dose-response analysis of top 55 compounds

#	Compound	IC50 (μM)			Efficacy (relative to parental)	
		Parental	HIF-1a-/-HIF-2a-/-	WT KRAS	HIF-1a-/-HIF-2a-/-	WT KRAS
1	**Deoxysappanone B 7,3'-dimethyl ether acetate**	1.4E-01	1.1E-02	2.8E-01	44%	49%
2	**Parbendazole**	2.2E-02	3.4E-02	3.1E-02	87%	61%
3	**Peruvoside**	5.3E-03	6.8E-03	6.1E-03	75%	60%
4	**Proscillaridin A**	2.6E-03	6.4E-03	5.2E-03	98%	78%
5	**Verteporfin**	1.4E+00	3.0E-04	9.9E+00	-4%	42%
6	Puromycin hydrochloride	1.5E-01	6.5E-01	9.9E-01	100%	114%
7	Vincristine sulfate	5.2E-04	5.1E-04	5.9E-04	44%	47%
8	Vinblastine sulfate	8.1E-04	5.3E-03	4.7E-03	57%	39%
9	Pyrimethamine	9.4E-01	4.9E-02	1.0E+01	59%	54%
10	Pyrvinium pamoate	2.4E-02	6.3E-02	6.0E-01	108%	97%
11	Aminacrine	1.6E+00	1.4E-04	1.7E+01	39%	60%
12	Niclosamide	2.9E-01	8.3E-01	1.1E+00	93%	99%
13	Mitoxantrone hydeochloride	4.4E-04	7.4E-02	1.1E+00	98%	78%
14	Benzalkonium chloride	1.2E+00	4.0E+00	8.0E+00	98%	74%
15	Tomatine	3.6E-02	1.3E-01	6.7E-01	77%	65%
16	Thioguanosine	6.2E-02	3.7E-02	1.8E-01	65%	86%
17	Digitonin	2.6E+00	1.1E+01	1.5E+01	83%	62%
18	Digoxigenin	6.2E-01	2.8E+00	3.1E+00	88%	68%
19	Dihydrojasmonic acid	9.9E-02	2.7E-01	2.2E+00	97%	94%
20	Celastrol	1.3E+00	3.7E-02	6.9E+01	87%	61%
21	Pomiferin	2.9E+00	4.1E+00	7.9E+00	92%	77%
22	Strophanthidinic acid lactone acetate	3.7E-02	1.1E-01	2.7E+00	85%	66%
23	Anthothecol	1.9E-01	5.9E-01	6.5E-01	62%	71%
24	Camtothecin	2.6E-03	7.4E-03	6.6E-02	78%	59%
25	Strophanthidin	4.3E-02	5.5E-02	2.0E+00	89%	69%
26	Sappanone A dimethyl ether	5.2E+00	2.3E+01	8.2E+02	75%	49%
27	Lanatoside C	5.7E-02	3.6E-02	6.4E-02	77%	64%
28	Gitoxin	5.0E-02	3.7E-02	1.5E+00	84%	85%
29	10-hydroxycamptothecin	7.9E-03	1.1E-01	3.0E+00	84%	81%
30	Azaguanine-8	1.0E+00	7.9E-06	7.9E+01	35%	57%
31	Triamterene	9.6E+00	1.5E+02	3.3E+00	64%	-21%
32	Rotterlin	8.2E-01	2.3E+00	3.2E+00	76%	74%
33	Azathioprine	4.7E-01	6.7E-02	4.7E+00	61%	73%
34	Methotrexate	3.9E-03	3.4E-03	9.0E-02	44%	58%
35	Terfenadine	2.3E+00	3.6E+00	4.8E+00	121%	112%
36	Doxorubicin hydrochloride	8.9E-03	4.8E-02	7.2E-02	83%	70%
37	Mercaptopurine	6.6E-01	6.2E-02	2.0E+00	75%	90%
38	Auranofin	2.9E-01	1.4E+00	4.1E+00	102%	111%
39	Aminopterin	3.6E-04	2.6E-03	4.8E-03	44%	95%
40	Bay 11-7085	5.3E+00	1.2E+01	3.7E+02	59%	23%
41	Calmidazolium chloride	2.8E+00	3.8E+00	6.1E+00	92%	76%
42	Colchicine	3.4E-03	3.4E-03	3.7E-03	60%	107%
43	Diphenyleneiodonium chloride	2.6E-02	1.5E-02	8.2E+00	77%	88%
44	Staurosporine aglycone	1.3E+00	3.0E+00	3.7E+01	89%	39%
45	BNTX maleate salt hydrate	1.9E+00	1.5E-01	0.0E+00	49%	-19%
46	Idarubicin	6.7E-03	5.6E-02	3.7E-02	86%	43%
47	Mitoxantrone	6.5E-03	1.7E-02	8.9E-01	90%	50%
48	Nemadipine-A	5.2E+00	1.1E+01	3.4E+00	72%	35%
49	Podophyllotoxin	4.6E-03	4.1E-03	3.8E-03	77%	55%
50	ARP 101	3.5E+00	8.3E+00	2.4E+02	74%	49%
51	N-p-Tosyl-L-phenylalanine chloromethyl ketone	7.0E+00	9.1E-04	4.2E+02	-2%	48%
52	Tetraethylthiuram disulfide	1.1E+00	1.0E+01	1.3E+04	73%	47%
53	NSC348884 hydrate	3.7E+00	8.5E+00	8.0E+00	85%	107%
54	LY2183240	7.1E-01	1.6E+02	4.4E+01	46%	49%
55	Ouabain	6.7E-03	7.2E-03	2.8E-02	97%	73%

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