Supplementary Information

Effect of Oncogene Activating Mutations and Kinase Inhibitors on Amino Acid Metabolism of Human Isogenic Breast Cancer Cells

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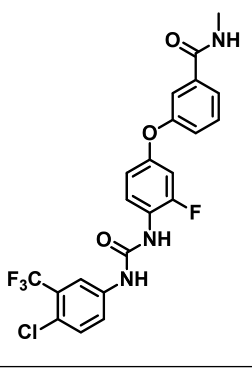
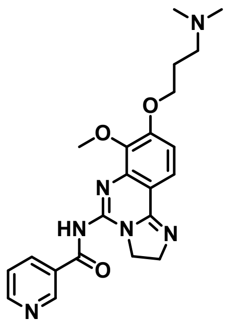
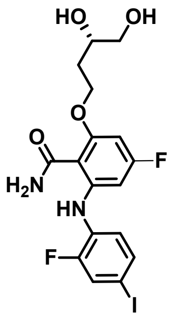
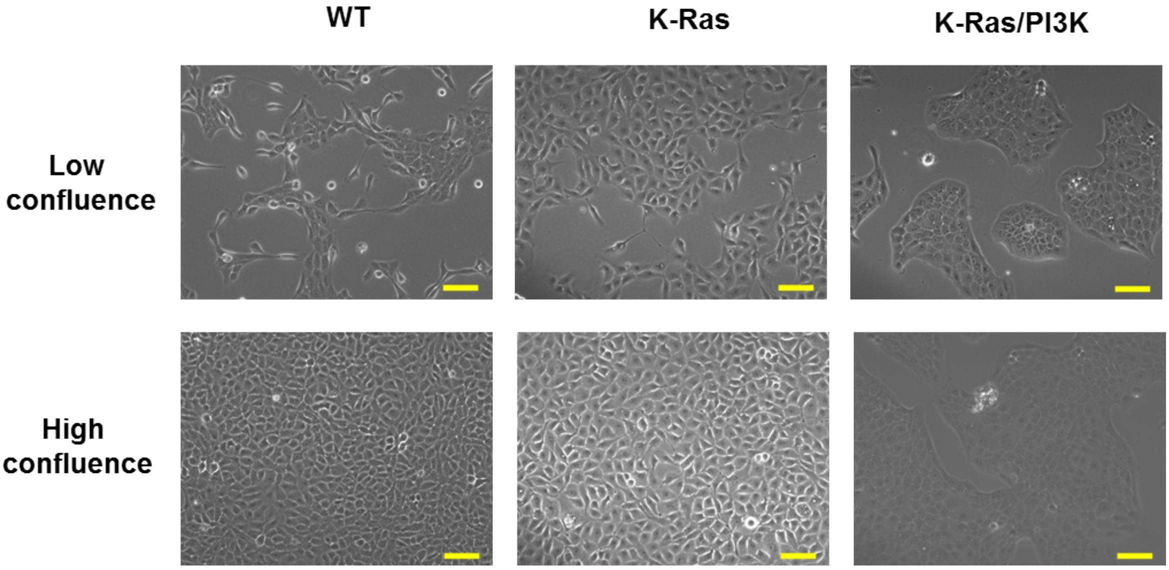
SI.1. Chemical structure of the kinase inhibitors.

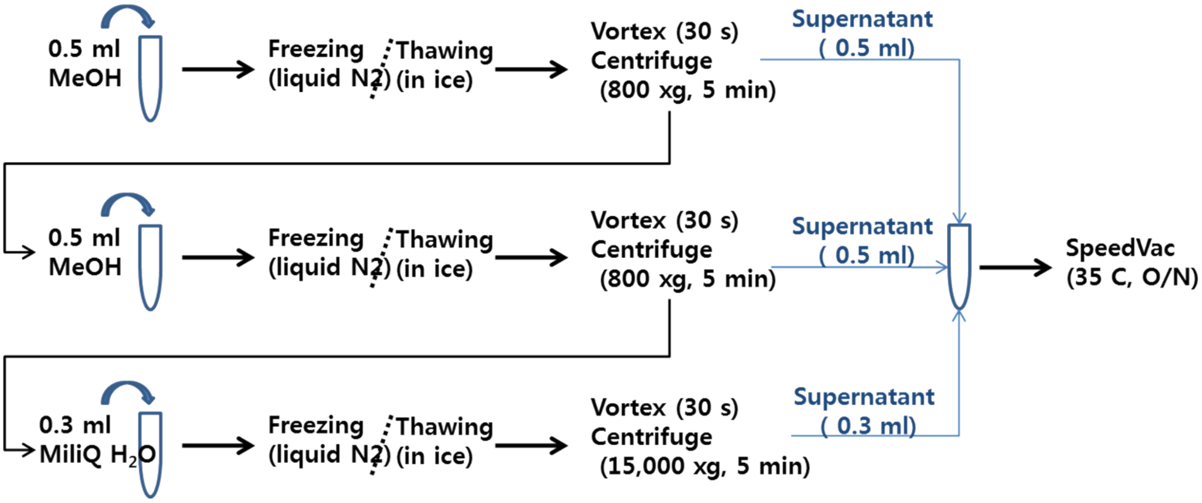
	REGO	**PI3K-i**	**MEK-i**
Chemical formula	C22H16ClF4N3O3	C22H26N6O3	C17H17F2IN2O4
Molecular weight [g/mole]	482.82	422.49	478.23
Structure			

SI.2. Comparison of cell morphology under a light microscope



Scale bar: 100 µm
10x objective lens at Ti microscope (Nikon)

SI.3. Scheme of the experimental method for metabolite extraction



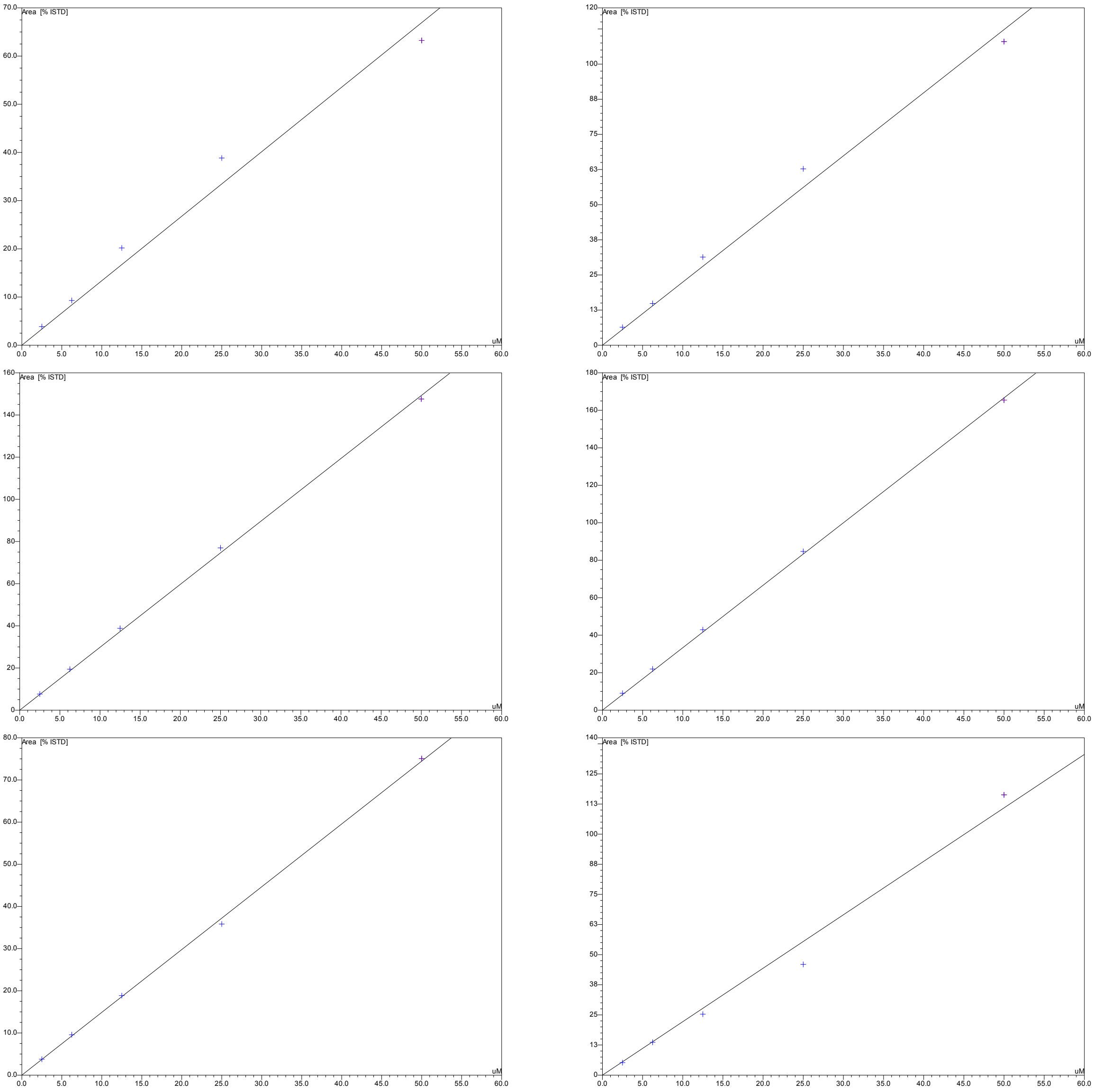
SI.4. Gradient profile of HPLC run.

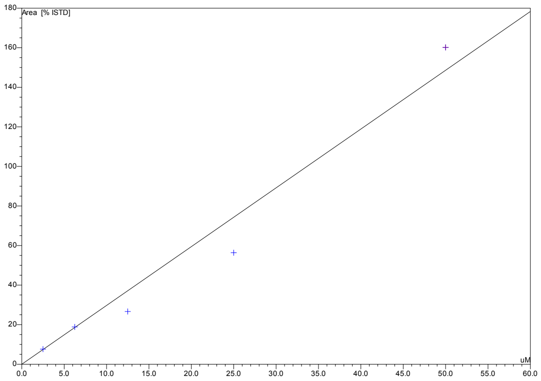
Time (min)	A : Buffer solution (40 mM $NaHPO_4$, pH7.8 at RT) (%)	B: Mobile phase (MeOH/ACN/H_2O, 45:45:10, v/v/v) (%)	H_2O (%)	Flow rate (ml/min)
0	100	0	0	1.0

3	90	10	0	1.0
15	87	13	0	1.0
25	70	30	0	1.0
37	65	35	0	1.0
43	58	42	0	1.0
52	43	57	0	1.0
55	0	100	0	1.0
60	0	0	100	1.0
65 to 80	100	0	0	1.0

SI.5. Standard curves for the linear calibration of 19 amino acids.

1. 19 standard curves (x-axis: concentration of an amino acid (μM), y-axis: Area under the peak (a.u.) from chromatograms of each standard AA solution of 10, 25, 50, 100, and 200 uM.

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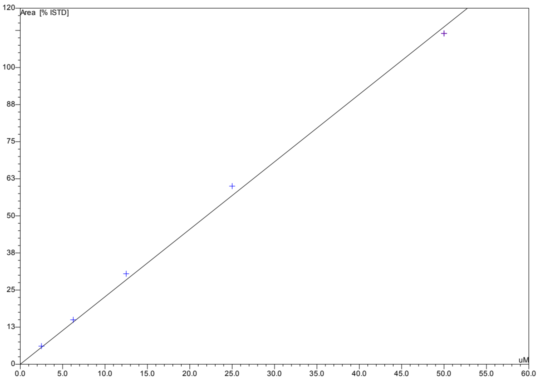
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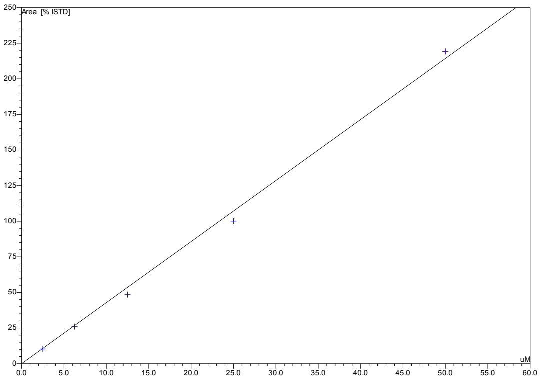
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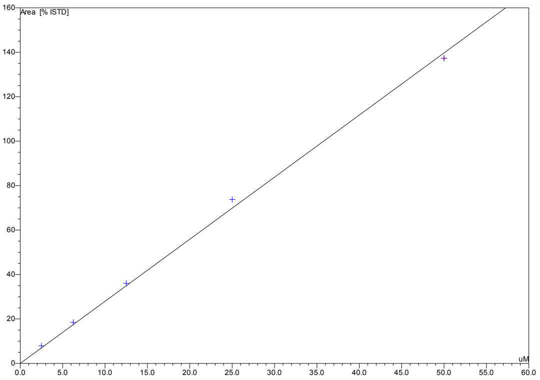
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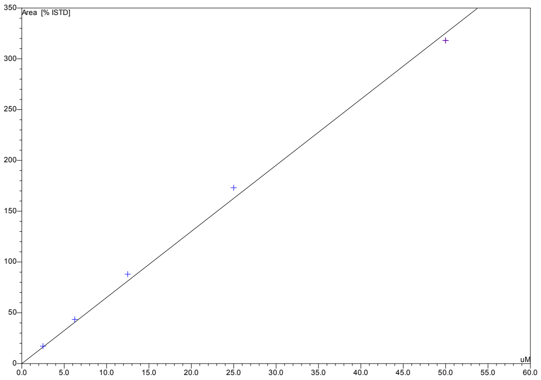
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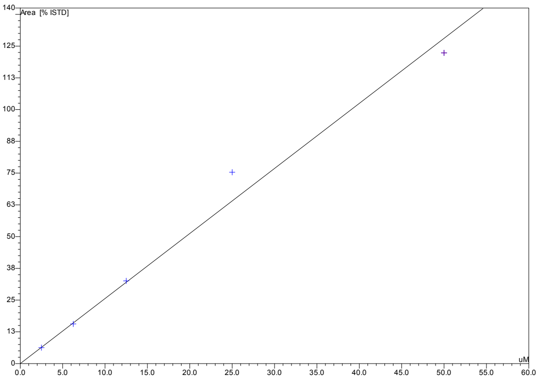
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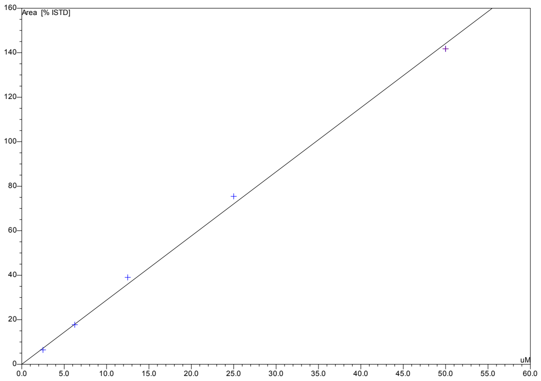
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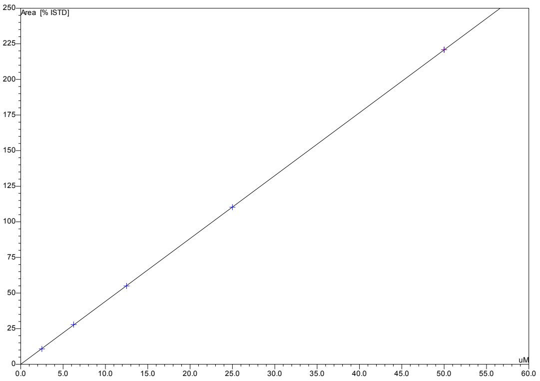
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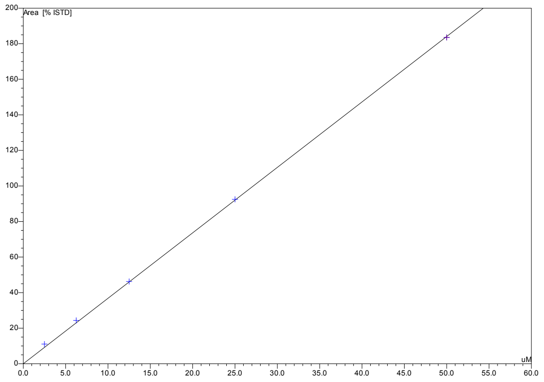
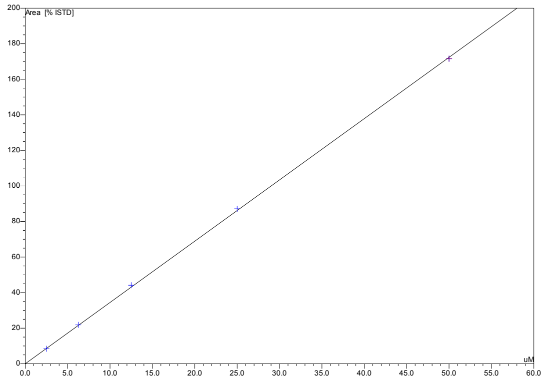
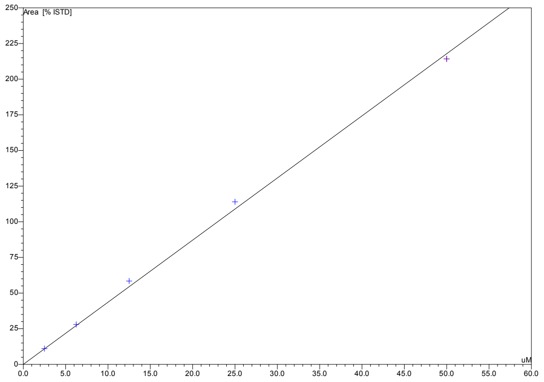
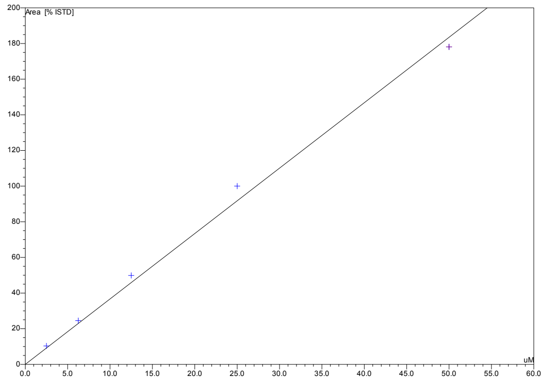
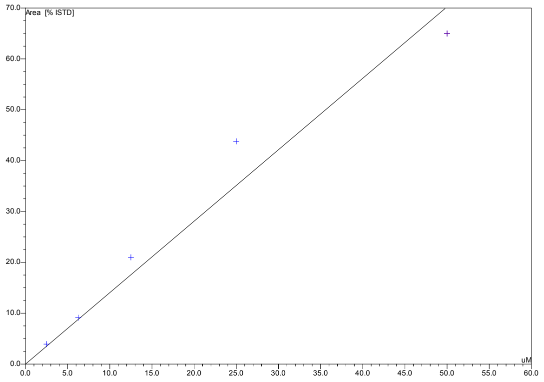










2. Analysis of standard curves above.

Peak Name	#Points	Rel.Std.Dev. (%)	Coeff.Det. (%)	Offset	Slope
Asp	5	13.7669	97.6328	0	1.3386
Glu	5	9.6163	98.9254	0	2.2454
Asn	5	2.8863	99.912	0	2.9848
Ser	5	2.0015	99.9578	0	3.3325
Gln	5	2.7303	99.9256	0	1.4891
His	5	13.5727	98.426	0	2.2183
Gly	5	22.0666	96.3243	0	2.9723
Thr	5	5.0035	99.726	0	2.2741
Arg	5	6.2423	99.6433	0	4.286
Ala	5	4.4964	99.7807	0	2.7941
Tyr	5	5.7284	99.6368	0	6.5062

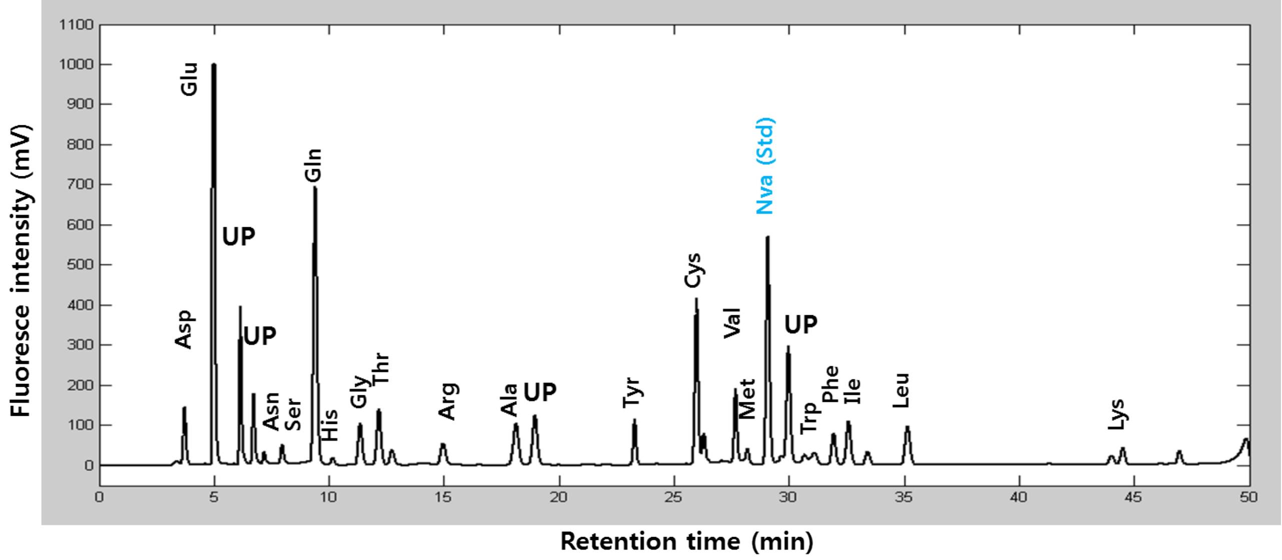
Cys	5	12.585	98.2625	0	2.5612
Val	5	4.6174	99.7753	0	2.8824
Met	5	0.2751	99.9992	0	4.4149
Trp	5	1.6937	99.9699	0	3.6815
Phe	5	1.2633	99.9836	0	3.4471
Ile	5	4.3576	99.7958	0	4.357
Leu	5	7.4569	99.37	0	3.6698
Lys	5	18.7769	95.5785	0	1.4048

SI.6. Determination of IC50 concentrations for the three drugs by MTS assay

Drug [MW(g/mole)]	IC_{50} values in WT cells (uM)	IC_{50} values in K-Ras cells (uM)	IC_{50} values in K-Ras/PI3K cells (uM)
REGO	20	5	30
PI3K-i	10	5	3
MEK-i	5	3	100

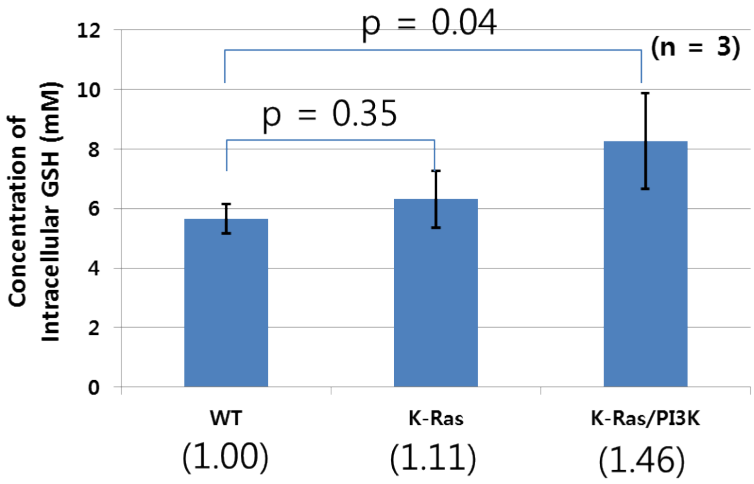
Estimated by MTS assay (n=3)

SI.7. Typical HPLC profile showing distinctive peaks of amino acids



Note: UP means an unidentified peak. Nva stands for norvalin used as the internal standard amino acid for a chromatogram.

SI.8. Comparison of glutathione (GSH) levels in cells.



The intracellular GSH concentration is expressed as mean as mean±S.D. (n =3). The p value (<0.05) indicates the statistical significance. The figure in the parenthesis presents the GSH level normalized against that of WT cells.

SI.9. Fold change of amino acid levels in drug-treated cells

	Drug	Cell type	Amino acids																		
			Asp	Glu	Asn	Ser	Gln	His	Gly	Thr	Arg	Ala	Tyr	Cys	Val	Met	Trp	Phe	Ile	Leu	Lys
24h	REGO	WT	0.4	0.86	1.58	1.72	1.02	1	1.91	1.01	0.83	1.29	1	1.79	1.17	1.6	0.87	1.02	1.02	1.08	0.93
		K-Ras	0.16	0.51	2.14	2.46	1.5	1.34	2.16	1.41	1.14	1.41	1.22	2.06	1.18	1.73	1.04	1.27	1.28	1.38	1.79
		K-Ras/PI3K	0.42	0.92	1.22	1.13	1.11	1.16	1.11	1.16	1.22	1.14	1.16	1.29	1.13	1.36	1.05	1.18	1.12	1.15	1.32
	PI3K-i	WT	1.86	0.74	1.08	1.25	1.11	0.76	1.3	0.97	1.13	0.82	0.91	1.05	0.91	1.22	0.75	0.91	0.89	0.93	1.2
		K-Ras	1.38	0.89	0.82	0.86	1.05	0.99	0.86	0.93	1.36	0.67	0.98	0.67	0.98	1.1	0.84	1.01	1.01	1.02	2.01
		K-Ras/PI3K	1.13	0.59	1.77	1.54	1.14	0.81	1.36	1.04	1.29	0.84	0.93	1.68	0.95	1.34	1.05	0.93	0.95	1.04	1.55
	MEK-i	WT	0.53	0.66	1.46	1.87	1.27	0.81	1.58	0.99	1.12	1.21	0.89	2.25	0.99	1.53	0.83	0.91	0.92	1.01	1.15
		K-Ras	0.54	0.52	1.69	1.68	1.52	1.21	1.38	1.21	1.47	1.25	1.08	1.96	1.21	1.51	0.87	1.14	1.16	1.24	1.64
		K-Ras/PI3K	0.67	0.69	1.35	1.46	1.08	0.86	1.59	0.92	0.93	0.94	0.87	1.96	0.97	1.12	0.83	0.88	0.91	0.95	1.04
48h	REGO	WT	0.19	0.89	1.63	1.45	0.9	1.23	1.96	1.06	0.64	1.17	1.16	1.79	1.26	1.63	1.78	1.23	1.4	1.42	0.82
		K-Ras	0.19	0.56	1.9	3.4	1.38	1.04	1.51	0.97	1.19	0.98	0.97	2.18	1.1	1.54	0.88	1.08	1.24	1.36	1.62
		K-Ras/PI3K	0.27	1	0.99	1.26	0.8	1.15	1.01	0.95	1.29	0.86	1.04	1.58	1.01	1.15	0.87	1.09	1.09	1.24	1.28
	PI3K-i	WT	1.46	0.72	1.01	1.1	1.27	0.97	1.14	1.08	1.07	0.78	1.02	1.09	1.08	1.34	1.47	1.06	1.08	1.16	1.06
		K-Ras	1.35	0.88	0.91	0.97	1.16	1	0.99	0.92	0.97	0.58	0.89	0.92	0.94	1.11	0.89	0.96	0.97	0.99	1.33
		K-Ras/PI3K	1.28	0.7	1.96	1.52	0.97	0.86	1.19	0.91	1.27	0.68	0.85	1.3	0.92	1.05	0.89	0.91	1.01	1.18	1.52
	MEK-i	WT	0.49	0.67	1.28	1.54	1.49	0.97	1.74	1.08	1	0.89	0.96	2.13	0.7	0.81	0.71	1	1.03	1.13	0.92
		K-Ras	0.55	0.46	1.47	2.01	1.62	0.9	1.67	1.01	1.18	0.88	0.86	2.37	1.08	1.27	0.95	0.97	1.08	1.14	1.17
		K-Ras/PI3K	0.49	0.68	0.87	1.48	0.81	0.84	1.62	0.65	0.93	0.67	0.72	2.09	0.77	0.86	0.5	0.77	0.79	0.91	0.93

Note: fold change = AAi, drug /AAi, NT

SI.10. Differentially Expressed Genes (DEGs) in qPCR plate I.

Plate I			Fold Change (comparing to control group)					
			REGO		PI3K-i		MEK-i	
Gene ID Gene Description	**Cells**	**Ct, ctrl**	**FC**	**95% CI**	**FC**	**95% CI**	**FC**	**95% CI**
ACADM Acyl-CoA dehydrogenase, C-4 to C-12 straight chain	WT	21.25	0.76	(0.69, 0.82)	1.04	(0.96, 1.12)	1.37	(1.25, 1.50)
	K-Ras	20.87	0.28	(0.26, 0.30)	0.81	(0.72, 0.89)	0.75	(0.69, 0.81)
	K-Ras/PI3K	22.65	0.95	(0.89, 1.02)	0.98	(0.86, 1.09)	0.96	(0.90, 1.02)
ACY1 Aminoacylase 1	WT	23.07	0.84	(0.74, 0.94)	1.05	(0.95, 1.15)	0.80	(0.67, 0.93)
	K-Ras	22.57	0.39	(0.36, 0.43)	0.80	(0.68, 0.92)	0.37	(0.33, 0.41)
	K-Ras/PI3K	23.38	0.81	(0.75, 0.87)	0.52	(0.44, 0.60)	0.33	(0.30, 0.36)
AHCY Adenosylhomocysteinase	WT	20.52	0.87	(0.76, 0.98)	1.29	(1.14, 1.43)	0.82	(0.64, 1.01)
	K-Ras	19.85	0.60	(0.53, 0.66)	0.94	(0.81, 1.06)	0.47	(0.42, 0.52)
	K-Ras/PI3K	20.54	0.75	(0.68, 0.81)	0.71	(0.61, 0.81)	0.40	(0.38, 0.42)
ALDH18A1 Aldehyde dehydrogenase 18 family, member A1	WT	22.74	0.78	(0.71, 0.85)	1.03	(0.94, 1.12)	0.73	(0.67, 0.80)
	K-Ras	21.94	0.82	(0.73, 0.92)	0.75	(0.67, 0.83)	0.41	(0.37, 0.45)
	K-Ras/PI3K	23.21	0.78	(0.64, 0.92)	0.66	(0.49, 0.82)	0.54	(0.46, 0.61)
AMD1 Adenosylmethionine decarboxylase 1	WT	21.24	0.55	(0.50, 0.60)	0.78	(0.74, 0.82)	0.87	(0.75, 0.98)
	K-Ras	19.98	0.18	(0.17, 0.18)	0.73	(0.69, 0.76)	0.50	(0.37, 0.64)
	K-Ras/PI3K	20.97	0.78	(0.73, 0.84)	0.77	(0.65, 0.90)	0.68	(0.65, 0.70)
APIP APAF1 interacting protein	WT	22.74	0.82	(0.74, 0.91)	0.71	(0.64, 0.78)	0.60	(0.54, 0.66)
	K-Ras	22.46	0.71	(0.67, 0.75)	0.59	(0.56, 0.63)	0.48	(0.44, 0.52)
	K-Ras/PI3K	23.57	0.80	(0.76, 0.84)	0.55	(0.53, 0.57)	0.51	(0.49, 0.53)
ARG2 Arginase, type II	WT	23.37	1.24	(1.12, 1.35)	0.79	(0.74, 0.84)	0.59	(0.51, 0.67)
	K-Ras	22.45	3.35	(3.00, 3.69)	1.39	(1.09, 1.69)	0.44	(0.41, 0.47)
	K-Ras/PI3K	23.20	0.54	(0.48, 0.60)	0.63	(0.53, 0.74)	0.46	(0.43, 0.49)
ASS1 Argininosuccinate synthase 1	WT	20.34	1.19	(1.02, 1.37)	1.41	(1.28, 1.54)	2.13	(1.89, 2.37)
	K-Ras	20.32	1.27	(1.22, 1.31)	1.73	(1.60, 1.85)	2.38	(2.13, 2.63)
	K-Ras/PI3K	19.22	0.76	(0.70, 0.82)	0.84	(0.78, 0.89)	0.85	(0.78, 0.92)
BCKDHA Branched chain keto acid dehydrogenase E1, alpha polypeptide	WT	24.38	1.94	(001, 4.15)	2.45	(0.001, 5.20)	2.71	(0.01, 5.79)
	K-Ras	22.40	0.88	(0.78, 0.98)	1.05	(0.95, 1.15)	1.16	(1.02, 1.29)
	K-Ras/PI3K	23.59	0.83	(0.78, 0.88)	0.79	(0.67, 0.90)	0.67	(0.62, 0.71)
CBS Cystathionine-beta-synthase	WT	25.77	0.95	(0.66, 1.25)	0.56	(0.41, 0.71)	0.68	(0.50, 0.87)
	K-Ras	25.81	3.38	(2.88, 3.88)	0.91	(0.78, 1.04)	0.88	(0.75, 1.02)
	K-Ras/PI3K	23.38	0.32	(0.25, 0.39)	0.08	(0.07, 0.10)	0.27	(0.23, 0.31)
CYP1B1 Cytochrome P450, family 1, subfamily B, polypeptide 1	WT	24.82	0.20	(0.16, 0.23)	0.32	(0.27, 0.37)	2.55	(1.91, 3.18)
	K-Ras	25.27	0.10	(0.09, 0.11)	0.34	(0.23, 0.44)	0.52	(0.38, 0.66)
	K-Ras/PI3K	26.69	0.43	(0.37, 0.49)	0.96	(0.75, 1.18)	2.08	(1.96, 2.20)
DNMT1 DNA (cytosine-5-)-methyltransferase 1	WT	24.08	0.60	(0.51, 0.69)	0.89	(0.76, 1.01)	0.30	(0.25, 0.35)
	K-Ras	22.82	0.24	(0.21, 0.27)	0.67	(0.61, 0.74)	0.12	(0.10, 0.13)
	K-Ras/PI3K	23.74	0.59	(0.52, 0.65)	0.49	(0.43, 0.56)	0.20	(0.16, 0.25)
ENOPH1 Enolase-phosphatase 1	WT	23.27	0.96	(0.90, 1.01)	0.96	(0.90, 1.03)	0.67	(0.61, 0.72)
	K-Ras	22.44	0.85	(0.79, 0.91)	0.76	(0.64, 0.87)	0.48	(0.42, 0.54)
	K-Ras/PI3K	23.44	0.89	(0.84, 0.94)	0.72	(0.62, 0.82)	0.59	(0.51, 0.67)
GFPT1 Glutamine--fructose-6-phosphate transaminase 1	WT	22.86	1.62	(1.53, 1.70)	0.92	(0.88, 0.95)	1.09	(0.99, 1.18)
	K-Ras	22.34	5.62	(4.81, 6.44)	0.81	(0.69, 0.92)	0.85	(0.72, 0.97)
	K-Ras/PI3K	21.80	0.67	(0.59, 0.75)	0.54	(0.47, 0.61)	0.55	(0.50, 0.60)
GLS Glutaminase	WT	21.63	0.77	(0.71, 0.82)	1.14	(1.06, 1.23)	0.84	(0.71, 0.97)
	K-Ras	21.33	0.49	(0.43, 0.56)	0.82	(0.61, 1.03)	0.50	(0.41, 0.58)
	K-Ras/PI3K	21.77	1.06	(0.89, 1.23)	0.90	(0.72, 1.08)	0.67	(0.55, 0.78)
GLUD1 Glutamate dehydrogenase 1	WT	20.52	1.14	(1.02, 1.26)	2.91	(2.56, 3.25)	2.06	(1.79, 2.34)
	K-Ras	19.57	0.75	(0.69, 0.80)	1.66	(1.44, 1.88)	1.82	(1.63, 2.01)
	K-Ras/PI3K	20.68	0.82	(0.67, 0.96)	1.18	(1.04, 1.32)	0.80	(0.72, 0.89)
HMGCL	WT	24.09	1.96	(1.58, 2.34)	1.01	(0.82, 1.20)	1.42	(1.11, 1.73)

3-hydroxymethyl-3-methylglutaryl-CoA lyase	K-Ras	24.48	2.15	(1.78, 2.51)	1.31	(1.13, 1.48)	2.13	(1.83, 2.42)
	K-Ras/PI3K	24.57	1.12	(1.00, 1.25)	1.10	(1.00, 1.21)	0.93	(0.84, 1.01)
HMGCS1 3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	WT	21.79	0.78	(0.59, 0.98)	1.07	(0.85, 1.30)	0.64	(0.46, 0.82)
	K-Ras	20.5	1.45	(1.18, 1.72)	0.48	(0.47, 0.50)	0.18	(0.15, 0.21)
	K-Ras/PI3K	21.82	1.89	(1.49, 2.30)	1.06	(0.83, 1.28)	1.50	(1.20, 1.80)
KYNU Kynureninase	WT	23.45	0.68	(0.62, 0.75)	0.84	(0.79, 0.90)	0.42	(0.37, 0.46)
	K-Ras	21.82	0.19	(0.17, 0.21)	1.06	(0.90, 1.22)	0.76	(0.69, 0.82)
	K-Ras/PI3K	26.3	1.24	(1.08, 1.39)	1.52	(1.25, 1.79)	1.21	(1.04, 1.38)
LAP3 Leucine aminopeptidase 3	WT	20.94	0.41	(0.01, 1.10)	1.43	(0.001, 4.74)	0.30	(0.001, 0.80)
	K-Ras	15.41	1.02	(0.86, 1.18)	0.85	(0.77, 0.92)	1.07	(0.43, 1.70)
	K-Ras/PI3K	22.75	0.81	(0.66, 0.96)	0.64	(0.55, 0.73)	1.37	(0.01, 3.49)
LARS Leucyl-tRNA synthetase	WT	21.83	0.86	(0.80, 0.92)	0.95	(0.90, 0.99)	0.68	(0.61, 0.74)
	K-Ras	21.25	0.79	(0.65, 0.92)	0.77	(0.61, 0.94)	0.45	(0.35, 0.54)
	K-Ras/PI3K	21.51	0.69	(0.62, 0.75)	0.47	(0.40, 0.53)	0.48	(0.43, 0.54)
LDHA Lactate dehydrogenase A	WT	17.57	0.64	(0.56, 0.73)	0.85	(0.76, 0.95)	0.60	(0.50, 0.70)
	K-Ras	16.84	0.24	(0.22, 0.27)	0.62	(0.53, 0.70)	0.30	(0.24, 0.36)
	K-Ras/PI3K	16.72	0.68	(0.64, 0.73)	0.78	(0.68, 0.88)	0.56	(0.51, 0.61)
NIT2 Nitrilase family, member 2	WT	23.78	0.90	(0.77, 1.03)	0.90	(0.77, 1.02)	0.64	(0.44, 0.85)
	K-Ras	23.81	0.48	(0.27, 0.68)	0.77	(0.68, 0.86)	0.59	(0.49, 0.70)
	K-Ras/PI3K	24.99	0.86	(0.78, 0.95)	0.73	(0.64, 0.82)	0.60	(0.53, 0.67)
ODC1 Ornithine decarboxylase 1	WT	21.21	0.51	(0.48, 0.53)	0.82	(0.78, 0.85)	0.39	(0.37, 0.41)
	K-Ras	20.85	0.32	(0.28, 0.35)	0.81	(0.72, 0.89)	0.21	(0.18, 0.24)
	K-Ras/PI3K	21.93	0.52	(0.52, 0.53)	0.36	(0.35, 0.38)	0.30	(0.29, 0.31)
PDHB Pyruvate dehydrogenase (lipoamide) beta	WT	21.11	0.80	(0.67, 0.93)	0.79	(0.67, 0.91)	0.75	(0.62, 0.89)
	K-Ras	20.98	0.34	(0.30, 0.38)	0.81	(0.74, 0.89)	0.54	(0.49, 0.59)
	K-Ras/PI3K	21.80	0.87	(0.85, 0.89)	0.75	(0.70, 0.81)	0.69	(0.66, 0.71)
PPAT Phosphoribosyl pyrophosphate amidotransferase	WT	23.45	0.93	(0.76, 1.10)	0.90	(0.77, 1.02)	0.63	(0.48, 0.79)
	K-Ras	23.21	0.52	(0.47, 0.56)	0.82	(0.75, 0.90)	0.49	(0.45, 0.54)
	K-Ras/PI3K	24.70	0.86	(0.74, 0.98)	0.65	(0.60, 0.70)	0.37	(0.32, 0.42)
PRODH Proline dehydrogenase (oxidase) 1	WT	26.86	2.93	(2.62, 3.24)	3.10	(2.78, 3.43)	8.79	(7.51, 10.07)
	K-Ras	25.40	2.75	(2.23, 3.28)	2.11	(1.62, 2.60)	11.02	(9.10, 12.94)
	K-Ras/PI3K	23.56	1.03	(0.88, 1.19)	1.66	(1.29, 2.03)	2.17	(1.74, 2.60)
PYCR1 Pyrroline-5-carboxylate reductase 1	WT	23.86	1.05	(0.87, 1.23)	0.78	(0.66, 0.91)	0.69	(0.54, 0.84)
	K-Ras	23.48	2.24	(1.86, 2.62)	0.97	(0.84, 1.09)	0.53	(0.48, 0.59)
	K-Ras/PI3K	22.76	0.48	(0.40, 0.55)	0.26	(0.20, 0.32)	0.30	(0.25, 0.34)
SAT1 Spermidine/spermine N1-acetyltransferase 1	WT	21.43	2.03	(1.64, 2.41)	1.88	(1.59, 2.18)	0.92	(0.78, 1.07)
	K-Ras	20.49	1.33	(1.26, 1.41)	1.82	(1.57, 2.06)	0.71	(0.67, 0.75)
	K-Ras/PI3K	19.91	0.99	(0.86, 1.12)	2.67	(2.17, 3.16)	0.80	(0.69, 0.91)
SRM Spermidine synthase	WT	20.73	0.56	(0.49, 0.63)	1.18	(1.03, 1.33)	0.63	(0.54, 0.71)
	K-Ras	19.52	0.45	(0.43, 0.47)	0.78	(0.69, 0.86)	0.28	(0.22, 0.33)
	K-Ras/PI3K	20.37	0.64	(0.62, 0.67)	0.54	(0.49, 0.60)	0.43	(0.39, 0.46)
WARS Tryptophanyl-tRNA synthetase	WT	22.51	0.52	(0.46, 0.58)	0.70	(0.61, 0.78)	0.43	(0.33, 0.53)
	K-Ras	22.13	2.09	(1.86, 2.33)	0.57	(0.48, 0.65)	0.27	(0.23, 0.31)
	K-Ras/PI3K	20.41	0.38	(0.31, 0.45)	0.19	(0.15, 0.23)	0.27	(0.24, 0.31)

SI.11. Differentially Expressed Genes (DEGs) in qPCR plate II.

			Fold Change (comparing to control group)					
Plate II			**REGO**		**PI3K-i**		**MEK-i**	
Gene ID Gene Description	**Cells**	**Ct, ctrl**	**FC**	**95% CI**	**FC**	**95% CI**	**FC**	**95% CI**
AASDHPPT Aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase	WT	21.81	0.59	(0.51, 0.66)	0.76	(0.69, 0.82)	0.56	(0.50, 0.63)
	K-Ras	23.31	0.37	(0.24, 0.51)	0.86	(0.61, 1.11)	0.50	(0.38, 0.63)
	K-Ras/PI3K	22.17	0.56	(0.48, 0.64)	0.54	(0.49, 0.59)	0.40	(0.35, 0.45)

AASS Aminoadipate-semialdehyde synthase	WT	24.46	0.91	(0.73, 1.10)	0.51	(0.43, 0.58)	0.32	(0.19, 0.44)
	K-Ras	24.31	0.58	(0.50, 0.65)	0.69	(0.55, 0.83)	0.65	(0.50, 0.80)
	K-Ras/PI3K	26.07	0.84	(0.77, 0.92)	0.46	(0.39, 0.52)	0.46	(0.38, 0.54)
ACADM Acyl-CoA dehydrogenase, C-4 to C-12 straight chain	WT	20.66	0.56	(0.52, 0.60)	0.92	(0.90, 0.95)	1.02	(0.95, 1.09)
	K-Ras	24.63	0.38	(0.01, 0.77)	0.84	(0.01, 1.71)	0.74	(0.14, 1.34)
	K-Ras/PI3K	21.78	0.79	(0.72, 0.86)	0.89	(0.82, 0.96)	0.77	(0.68, 0.87)
ACADSB Acyl-CoA dehydrogenase, short/branched chain	WT	24.36	0.65	(0.47, 0.83)	0.98	(0.89, 1.08)	0.99	(0.77, 1.20)
	K-Ras	24.55	0.44	(0.40, 0.49)	1.12	(0.90, 1.33)	1.26	(1.01, 1.51)
	K-Ras/PI3K	25.6	1.25	(1.03, 1.46)	0.96	(0.77, 1.15)	1.04	(0.77, 1.31)
ACAT2 Acetyl-CoA acetyltransferase 2	WT	20.62	0.84	(0.73, 0.95)	0.97	(0.94, 1.01)	0.56	(0.52, 0.61)
	K-Ras	21.16	0.64	(0.53, 0.74)	0.75	(0.63, 0.87)	0.25	(0.22, 0.28)
	K-Ras/PI3K	20.87	1.30	(1.20, 1.41)	0.50	(0.45, 0.56)	0.69	(0.62, 0.77)
ADSL Adenylosuccinate lyase	WT	21.8	0.43	(0.32, 0.53)	0.76	(0.73, 0.79)	0.37	(0.31, 0.43)
	K-Ras	22.22	0.33	(0.29, 0.37)	0.92	(0.75, 1.08)	0.35	(0.29, 0.42)
	K-Ras/PI3K	22.53	0.60	(0.54, 0.67)	0.47	(0.40, 0.53)	0.29	(0.23, 0.35)
ADSS Adenylosuccinate synthase	WT	21.06	0.51	(0.37, 0.65)	0.87	(0.75, 0.99)	0.48	(0.40, 0.55)
	K-Ras	21.61	0.30	(0.26, 0.33)	1.00	(0.82, 1.17)	0.46	(0.38, 0.54)
	K-Ras/PI3K	21.65	0.60	(0.54, 0.67)	0.64	(0.55, 0.73)	0.35	(0.29, 0.42)
ALDH5A1 Aldehyde dehydrogenase 5 family, member A1	WT	24.23	0.58	(0.43, 0.73)	0.61	(0.53, 0.70)	0.61	(0.47, 0.76)
	K-Ras	24.14	0.38	(0.34, 0.43)	0.76	(0.65, 0.87)	0.55	(0.49, 0.61)
	K-Ras/PI3K	25.26	1.10	(0.99, 1.22)	0.58	(0.53, 0.64)	0.70	(0.59, 0.80)
ALDH6A1 Aldehyde dehydrogenase 6 family, member A1	WT	24.49	1.30	(1.01, 1.59)	1.43	(1.17, 1.68)	1.11	(0.85, 1.38)
	K-Ras	24.59	2.21	(1.74, 2.69)	1.96	(1.56, 2.35)	1.98	(1.57, 2.40)
	K-Ras/PI3K	25.25	1.08	(0.92, 1.25)	1.17	(1.00, 1.34)	0.79	(0.64, 0.95)
ASNS Asparagine synthetase (glutamine-hydrolyzing)	WT	20.4	0.83	(0.70, 0.97)	0.25	(0.22, 0.28)	0.24	(0.21, 0.27)
	K-Ras	22.49	5.02	(3.81, 6.22)	0.46	(0.35, 0.58)	0.29	(0.22, 0.36)
	K-Ras/PI3K	18.84	0.22	(0.17, 0.26)	0.05	(0.05, 0.06)	0.17	(0.13, 0.21)
DLST Dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex)	WT	21.23	0.54	(0.37, 0.72)	0.78	(0.69, 0.88)	0.52	(0.41, 0.62)
	K-Ras	21.5	0.53	(0.44, 0.63)	0.92	(0.75, 1.09)	0.62	(0.51, 0.73)
	K-Ras/PI3K	21.68	0.63	(0.56, 0.70)	0.68	(0.60, 0.76)	0.41	(0.29, 0.52)
ECHS1 Enoyl CoA hydratase, short chain, 1, mitochondrial	WT	20.74	0.62	(0.45, 0.79)	0.72	(0.66, 0.77)	0.54	(0.28, 0.80)
	K-Ras	21.05	0.55	(0.49, 0.61)	0.82	(0.66, 0.98)	0.58	(0.49, 0.67)
	K-Ras/PI3K	21.16	0.81	(0.75, 0.86)	0.52	(0.48, 0.56)	0.57	(0.42, 0.71)
GCAT Glycine C-acetyltransferase	WT	24.9	0.79	(0.51, 1.07)	0.74	(0.67, 0.82)	0.50	(0.39, 0.61)
	K-Ras	25	0.98	(0.81, 1.15)	0.96	(0.69, 1.23)	0.56	(0.43, 0.69)
	K-Ras/PI3K	26.28	0.76	(0.66, 0.87)	0.47	(0.40, 0.54)	0.35	(0.29, 0.41)
GCDH Glutaryl-CoA dehydrogenase	WT	24.42	0.58	(0.44, 0.73)	0.83	(0.80, 0.86)	0.38	(0.30, 0.46)
	K-Ras	24.82	0.46	(0.42, 0.50)	0.95	(0.76, 1.13)	0.37	(0.31, 0.44)
	K-Ras/PI3K	24.88	0.63	(0.58, 0.68)	0.53	(0.45, 0.60)	0.42	(0.32, 0.53)
GOT1 Glutamic-oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1)	WT	21.04	0.73	(0.51, 0.94)	0.50	(0.41, 0.58)	0.37	(0.30, 0.45)
	K-Ras	22.11	0.99	(0.87, 1.11)	0.67	(0.61, 0.74)	0.56	(0.49, 0.62)
	K-Ras/PI3K	21.45	0.51	(0.48, 0.54)	0.32	(0.30, 0.34)	0.35	(0.25, 0.45)
HADHB Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/ enoyl-CoA hydratase (trifunctional protein), beta subunit	WT	20.57	0.76	(0.64, 0.88)	1.37	(1.27, 1.48)	1.75	(1.58, 1.92)
	K-Ras	20.85	0.63	(0.59, 0.67)	1.18	(1.04, 1.32)	2.20	(1.83, 2.58)
	K-Ras/PI3K	21	0.86	(0.83, 0.89)	0.94	(0.88, 0.99)	1.12	(0.89, 1.35)
HIBADH 3-hydroxyisobutyrate dehydrogenase	WT	21.62	0.87	(0.77, 0.97)	0.88	(0.84, 0.92)	0.81	(0.76, 0.85)
	K-Ras	22.93	0.97	(0.84, 1.11)	0.87	(0.79, 0.94)	1.00	(0.87, 1.13)
	K-Ras/PI3K	22.3	0.71	(0.63, 0.79)	0.59	(0.54, 0.63)	0.47	(0.44, 0.51)
HIBCH 3-hydroxyisobutyryl-CoA hydrolase	WT	22.16	0.88	(0.81, 0.96)	0.87	(0.80, 0.93)	0.94	(0.85, 1.03)
	K-Ras	23.48	0.46	(0.36, 0.57)	0.78	(0.65, 0.91)	0.67	(0.58, 0.76)
	K-Ras/PI3K	22.81	1.09	(0.99, 1.20)	0.72	(0.66, 0.79)	0.83	(0.72, 0.94)
HSD17B10 Hydroxysteroid (17-beta) dehydrogenase 10	WT	20.76	0.60	(0.50, 0.70)	0.82	(0.77, 0.87)	0.71	(0.67, 0.75)
	K-Ras	21.92	0.47	(0.37, 0.58)	0.85	(0.72, 0.97)	0.59	(0.47, 0.71)
	K-Ras/PI3K	21.54	0.70	(0.67, 0.73)	0.58	(0.53, 0.62)	0.69	(0.65, 0.73)

IARS Isoleucyl-tRNA synthetase	WT	19.39	0.50	(0.43, 0.57)	0.61	(0.54, 0.67)	0.37	(0.33, 0.40)
	K-Ras	20.44	0.86	(0.80, 0.92)	0.63	(0.60, 0.65)	0.34	(0.32, 0.36)
	K-Ras/PI3K	19.27	0.41	(0.38, 0.45)	0.20	(0.19, 0.22)	0.24	(0.22, 0.25)
PHGDH Phosphoglycerate dehydrogenase	WT	22.23	0.82	(0.62, 1.01)	0.25	(0.22, 0.28)	0.21	(0.17, 0.25)
	K-Ras	23.47	2.71	(2.54, 2.87)	0.54	(0.43, 0.64)	0.32	(0.28, 0.35)
	K-Ras/PI3K	21.2	0.21	(0.17, 0.26)	0.04	(0.02, 0.07)	0.05	(0.04, 0.06)
PSAT1 Phosphoserine aminotransferase 1	WT	21.03	0.51	(0.34, 0.68)	0.18	(0.14, 0.23)	0.19	(0.14, 0.24)
	K-Ras	21.86	2.34	(2.01, 2.67)	0.39	(0.28, 0.50)	0.34	(0.28, 0.41)
	K-Ras/PI3K	19.44	0.23	(0.17, 0.29)	0.03	(0.03, 0.03)	0.12	(0.11, 0.13)
PSPH Phosphoserine phosphatase	WT	23.95	0.50	(0.36, 0.65)	0.72	(0.62, 0.81)	0.45	(0.31, 0.60)
	K-Ras	24.31	0.36	(0.33, 0.40)	0.91	(0.76, 1.06)	0.44	(0.34, 0.54)
	K-Ras/PI3K	24.79	0.72	(0.61, 0.83)	0.58	(0.48, 0.67)	0.33	(0.26, 0.40)
SHMT2 Serine hydroxymethyltransferase 2 (mitochondrial)	WT	19.88	0.63	(0.50, 0.76)	0.70	(0.66, 0.75)	0.44	(0.38, 0.49)
	K-Ras	20.67	0.98	(0.92, 1.05)	0.85	(0.72, 0.98)	0.54	(0.49, 0.58)
	K-Ras/PI3K	19.6	0.40	(0.35, 0.46)	0.27	(0.25, 0.29)	0.22	(0.20, 0.25)
VARS2 Valyl-tRNA synthetase 2, mitochondrial (putative)	WT	24.73	0.70	(0.52, 0.88)	1.08	(0.92, 1.23)	1.64	(1.16, 2.13)
	K-Ras	25.51	0.81	(0.63, 0.98)	1.11	(0.96, 1.26)	0.99	(0.63, 1.36)
	K-Ras/PI3K	24.66	0.75	(0.64, 0.85)	0.35	(0.29, 0.40)	0.37	(0.24, 0.51)
WBSCR22 Williams Beuren syndrome chromosome region 22	WT	22.36	0.46	(0.31, 0.62)	0.62	(0.54, 0.69)	0.46	(0.36, 0.55)
	K-Ras	22.65	0.46	(0.40, 0.52)	0.62	(0.48, 0.75)	0.42	(0.33, 0.51)
	K-Ras/PI3K	22.71	0.62	(0.57, 0.68)	0.47	(0.40, 0.55)	0.49	(0.35, 0.62)

SI.12. Number of unique genes compared to number of common genes in WT vs mutant cells under drug treatment

	WT vs. K-Ras cells	WT vs. K-Ras/PI3K cells
REGO	32/3	10/3
PI3K-i	5/4	20/4
MEK-i	25/14	17/14

Table S1. Effect of knock-in of oncogenes on amino acid levels in WT cells

	Culture time	Upregulated amino acids	Downregulated amino acids
K-Ras vs. WT	24 h	-	-
	48 h	Tyr (1.50) Trp (1.61) Ile (1.50)	-
K-Ras/PI3K vs. WT	24 h	Cys (1.58)	His (0.53) Tyr (0.65) Trp (0.68) Phe (0.67) Ile (0.59) Leu (0.62) Lys (0.65)
	48 h	Gln (1.58) Gly (1.79) Cys (1.98)	His (0.56) Arg (0.53) Tyr (0.67) Val (0.60) Phe (0.67) Ile (0.51) Leu (0.53) Lys (0.45)

Table S2. Effect of kinase inhibitors on amino acid levels in WT cells

	Culture time	Upregulated amino acids	Downregulated amino acids
B73	24 h	Asn (1.58) Ser (1.72) Gly (1.79) Cys (1.79) Met (1.60)	Asp (0.40)
	48 h	Asn (1.63) Gly (1.96) Cys (1.79) Met (1.63) Trp (1.78)	Asp (0.19)
B81	24 h	Asp (1.86)	-
	48 h	-	-
B83	24 h	Ser (1.87) Gly (1.58) Cys (2.25) Met (1.53)	Asp (0.53) Glu (0.66)
	48 h	Ser (1.54) Gly (1.74) Cys (2.13)	Asp (0.49) Glu (0.67)

Table S3. Amino acids with significant fold changes upon treatment of the three drugs to mutant cells.

	Mutant Cells	Culture time	Upregulated amino acids	Downregulated amino acids
B73	K-Ras	24 h	Asn (1.58) Ser (2.46) Gln (1.50) Gly (2.16) Cys (2.06) Met (1.73) Lys (1.79)	Asp (0.16)
		48h	Asn (1.90) Ser (3.40) Gly (1.51) Cys (2.18) Met (1.54) Lys (1.62)	Asp (0.16)
	K-Ras/PI3K	24 h	-	Asp (0.16)
		48h	Cys (1.58)	Asp (0.27)
B81	K-Ras	24 h	Lys (2.01)	Ala (0.67)
		48h	-	Ala (0.58)
	K-Ras/PI3K	24 h	Asn (1.77) Ser (1.54) Cys (1.68) Lys (1.55)	Glu (0.59)
		48h	Lys (1.52)	Ala (0.68)
B83	K-Ras	24 h	Asn (1.69) Ser (1.68) Gln (1.52) Cys (1.96) Met (1.51) Lys (1.64)	Asp (0.54) Glu (0.52)
		48h	Ser (2.01) Gln (1.62) Gly (1.67) Cys (2.32)	Asp (0.55) Glu (0.46)
	K-Ras/PI3K	24 h	Gly (1.59) Cys (1.96)	Asp (0.67) Glu (0.67)
		48h	Gly (1.62) Cys (2.09)	Asp (0.49) Glu (0.68) Ala (0.67) Trp (0.50)

Table S4. Selection of Differentially Expressed Genes (DEGs) in nontreated mutant cells compared WT cells

Pathway ID	**Gene ID** Gene Description	**K-Ras**	**K-Ras/PI3K**
1	**ODC1** Ornithine decarboxylase 1	0.71	2.68
1, 2	**ASNS** Asparagine synthetase (glutamine-hydrolyzing)	0.40	3.33
3	**BHMT** Betaine-homocysteine S-methyltransferase	0.40	3.87
4	**GCAT** Glycine C-acetyltransferase	1.60	0.43
4	**PDHB** Pyruvate dehydrogenase (lipoamide) beta	0.95	3.94
4	**PHGDH** Phosphoglycerate dehydrogenase	0.73	2.30
4	**PSAT1** Phosphoserine aminotransferase 1	0.96	3.39
5	**AASS** Aminoadipate-semialdehyde synthase	1.92	0.37

6	**ACADM** Acyl-CoA dehydrogenase, C-4 to C-12 straight chain	0.11	0.52

Table S5. DEGs in Pathway 1 for Arg/Asp/polyamine/AMP Metabolism

Gene ID Gene Description	**Cells**	**B73**	**B81**	**B83**
ACY1 Aminoacylase 1	WT	0.84	1.05	0.80
	K-Ras	0.39	0.80	0.37
	K-Ras/PI3K	0.81	0.52	0.33
ADSL Adenylosuccinate lyase	WT	0.43	0.76	0.37
	K-Ras	0.33	0.92	0.35
	K-Ras/PI3K	0.60	0.47	0.29
ADSS Adenylosuccinate synthase	WT	0.51	0.87	0.48
	K-Ras	0.30	1.00	0.46
	K-Ras/PI3K	0.60	0.64	0.35
AMD1 Adenosylmethionine decarboxylase 1	WT	0.55	0.78	0.87
	K-Ras	0.18	0.73	0.50
	K-Ras/PI3K	0.78	0.77	0.68
ARG2 Arginase, type II	WT	1.24	0.79	0.59
	K-Ras	3.35	1.39	0.44
	K-Ras/PI3K	0.54	0.63	0.46
ASNS Asparagine synthetase (glutamine-hydrolyzing)	WT	0.83	0.25	0.24
	K-Ras	5.02	0.46	0.29
	K-Ras/PI3K	0.22	0.05	0.17
ASS1 Argininosuccinate synthase 1	WT	1.19	1.41	2.13
	K-Ras	1.27	1.73	2.38
	K-Ras/PI3K	0.76	0.84	0.85
GOT1 Glutamic-oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1)	WT	0.73	0.50	0.37
	K-Ras	0.99	0.67	0.56
	K-Ras/PI3K	0.51	0.32	0.35
ODC1 Ornithine decarboxylase 1	WT	0.51	0.82	0.39
	K-Ras	0.32	0.81	0.21
	K-Ras/PI3K	0.52	0.36	0.30
SAT1 Spermidine/spermine N1-acetyltransferase 1	WT	2.03	1.88	0.92
	K-Ras	1.33	1.82	0.71
	K-Ras/PI3K	0.99	2.67	0.80
SRM Spermidine synthase	WT	0.56	1.18	0.63
	K-Ras	0.45	0.78	0.28
	K-Ras/PI3K	0.64	0.54	0.43

Table S6. DEGs in Pathway 2 for Glu/Gln Metabolism

Gene ID Gene Description	**Cells**	**B73**	**B81**	**B83**
ALDH18A1 Aldehyde dehydrogenase 18 family, member A1	WT	0.78	1.03	0.73
	K-Ras	0.82	0.75	0.41
	K-Ras/PI3K	0.78	0.66	0.54
ASNS Asparagine synthetase (glutamine-hydrolyzing)	WT	0.83	0.25	0.24
	K-Ras	5.02	0.46	0.29
	K-Ras/PI3K	0.22	0.05	0.17
GFPT1 Glutamine--fructose-6-phosphate transaminase 1	WT	1.62	0.92	1.09
	K-Ras	5.62	0.81	0.85
	K-Ras/PI3K	0.67	0.54	0.55
GLS Glutaminase	WT	0.77	1.14	0.84
	K-Ras	0.49	0.82	0.50
	K-Ras/PI3K	1.06	0.90	0.67
GLUD1 Glutamate dehydrogenase 1	WT	1.14	2.91	2.06
	K-Ras	0.75	1.66	1.82
	K-Ras/PI3K	0.82	1.18	0.80
PPAT Phosphoribosyl pyrophosphate amidotransferase	WT	0.93	0.90	0.63
	K-Ras	0.52	0.82	0.49
	K-Ras/PI3K	0.86	0.65	0.37

Table S7. DEGs in Pathway 3 for Cys/Met Metabolism

Gene ID Gene Description	**Cells**	**B73**	**B81**	**B83**
AHCY Adenosylhomocysteinase	WT	0.87	1.29	0.82
	K-Ras	0.60	0.94	0.47
	K-Ras/PI3K	0.75	0.71	0.40
APIP APAF1 interacting protein	WT	0.82	0.71	0.60
	K-Ras	0.71	0.59	0.48
	K-Ras/PI3K	0.80	0.55	0.51
CBS Cystathionine-beta-synthase	WT	0.95	0.56	0.68
	K-Ras	3.38	0.91	0.88
	K-Ras/PI3K	0.32	0.08	0.27
DNMT1 DNA (cytosine-5-)-methyltransferase 1	WT	0.60	0.89	0.30
	K-Ras	0.24	0.67	0.12
	K-Ras/PI3K	0.59	0.49	0.20
ENOPH1 Enolase-phosphatase 1	WT	0.96	0.96	0.67
	K-Ras	0.85	0.76	0.48
	K-Ras/PI3K	0.89	0.72	0.59

Table S8. DEGs in Pathway 4 for Ser/Gly/Thr Metabolism

Gene ID Gene Description	**Cells**	**B73**	**B81**	**B83**
ACAT2 Acetyl-CoA acetyltransferase 2	WT	0.84	0.97	0.56
	K-Ras	0.64	0.75	0.25
	K-Ras/PI3K	1.30	0.50	0.69
GCAT Glycine C-acetyltransferase	WT	0.79	0.74	0.50
	K-Ras	0.98	0.96	0.56
	K-Ras/PI3K	0.76	0.47	0.35
HMGCS1 3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	WT	0.78	1.07	0.64
	K-Ras	1.45	0.48	0.18
	K-Ras/PI3K	1.89	1.06	1.50
LDHA Lactate dehydrogenase A	WT	0.64	0.85	0.60
	K-Ras	0.24	0.62	0.30
	K-Ras/PI3K	0.68	0.78	0.56
PDHB Pyruvate dehydrogenase (lipoamide) beta	WT	0.80	0.79	0.75
	K-Ras	0.34	0.81	0.54
	K-Ras/PI3K	0.87	0.75	0.69
PHGDH Phosphoglycerate dehydrogenase	WT	0.82	0.25	0.21
	K-Ras	2.71	0.54	0.32
	K-Ras/PI3K	0.21	0.04	0.05
PSAT1 Phosphoserine aminotransferase 1	WT	0.51	0.18	0.19
	K-Ras	2.34	0.39	0.34
	K-Ras/PI3K	0.23	0.03	0.12
PSPH Phosphoserine phosphatase	WT	0.50	0.72	0.45
	K-Ras	0.36	0.91	0.44
	K-Ras/PI3K	0.72	0.58	0.33
SHMT2 Serine hydroxymethyltransferase 2 (mitochondrial)	WT	0.63	0.70	0.44
	K-Ras	0.98	0.85	0.54
	K-Ras/PI3K	0.40	0.27	0.22

Table S9. DEGs in Pathway 5 for Lys degradation

Gene ID Gene Description	**Cells**	**B73**	**B81**	**B83**
AASDHPPT Aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase	WT	0.59	0.76	0.56
	K-Ras	0.37	0.86	0.50
	K-Ras/PI3K	0.56	0.54	0.40
AASS Aminoadipate-semialdehyde synthase	WT	0.91	0.51	0.32
	K-Ras	0.58	0.69	0.65
	K-Ras/PI3K	0.84	0.46	0.46
ACAT2 Acetyl-CoA acetyltransferase 2	WT	0.84	0.97	0.56
	K-Ras	0.64	0.75	0.25
	K-Ras/PI3K	1.30	0.50	0.69
DLST Dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex)	WT	0.54	0.78	0.52
	K-Ras	0.53	0.92	0.62
	K-Ras/PI3K	0.63	0.68	0.41
ECHS1 Enoyl CoA hydratase, short chain, 1, mitochondrial	WT	0.62	0.72	0.54
	K-Ras	0.55	0.82	0.58
	K-Ras/PI3K	0.81	0.50	0.57
GCDH Glutaryl-CoA dehydrogenase	WT	0.58	0.83	0.38
	K-Ras	0.46	0.95	0.37
	K-Ras/PI3K	0.63	0.53	0.42

Table S10. DEGs in Pathway 6 for β-oxidation of fatty acids

Gene ID Gene Description	**Cells**	**B73**	**B81**	**B83**
ACADM Acyl-CoA dehydrogenase, C-4 to C-12 straight chain	WT	0.76	1.04	1.37
	K-Ras	0.28	0.81	0.75
	K-Ras/PI3K	0.95	0.98	0.96
ACAT2 Acetyl-CoA acetyltransferase 2	WT	0.84	0.97	0.56
	K-Ras	0.64	0.75	0.25
	K-Ras/PI3K	1.30	0.50	0.69
HADHB Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/ enoyl-CoA hydratase, beta subunit	WT	0.76	1.37	1.75
	K-Ras	0.63	1.18	2.20
	K-Ras/PI3K	0.86	0.94	1.12