

Supplementary Materials for

Airway PI3K Pathway Activation Is an Early and Reversible Event in Lung Cancer Development

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Published 7 April 2010, *Sci. Transl. Med.* **2**, 26ra25 (2010)
DOI: 10.1126/scitranslmed.3000251

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Supplemental Figure 1

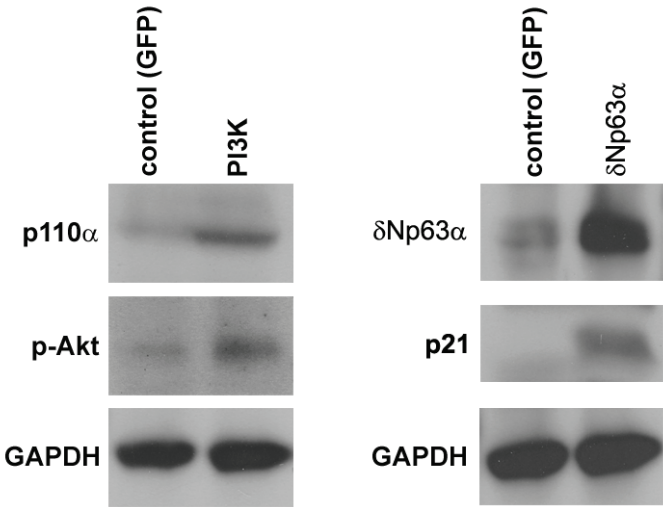
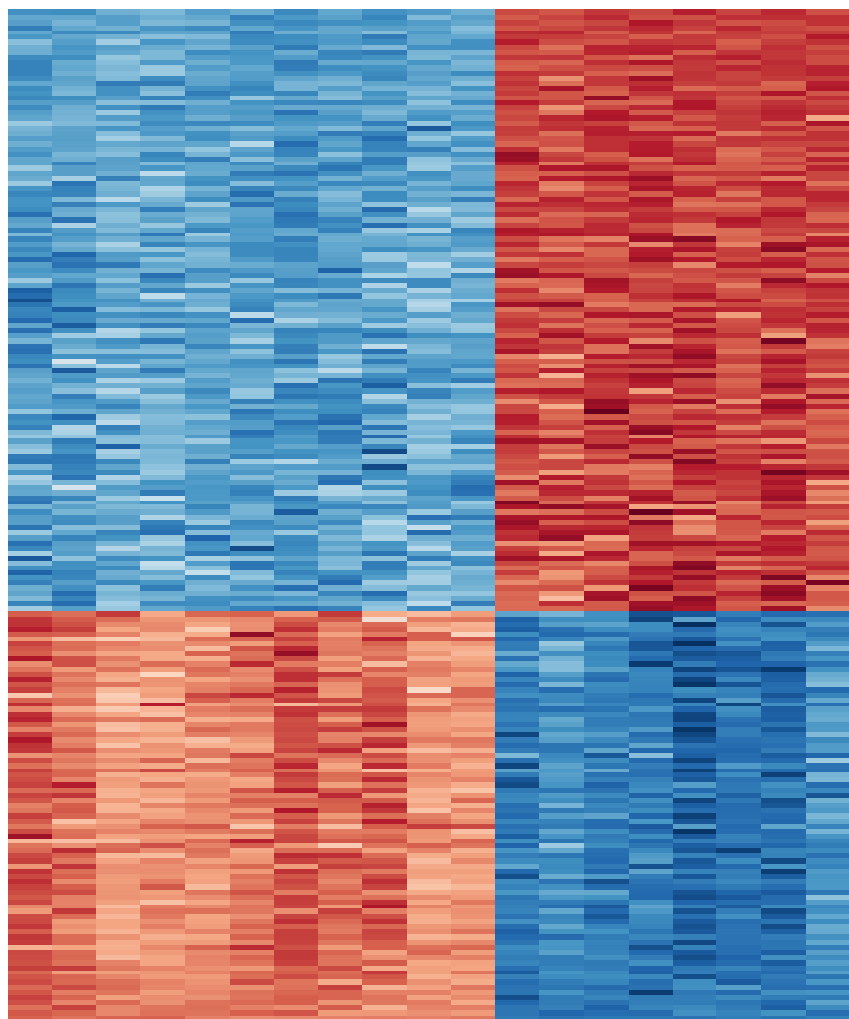


Figure S1. Generation of PI3K and deltaNp63 pathway signatures. We used human primary mammary epithelial cell cultures (HMECs) to develop the PI3K and deltaNp63 α signatures. Recombinant adenoviruses were used to express the p110 α isoform of PI3K and deltaNp63 in an otherwise quiescent cell, thereby specifically isolating the subsequent events as defined by the activation/deregulation of pathway. Eighteen hours after infection, cells were collected for RNA isolation, and expression of the PI3K p110 α subunit and deltaNp63 protein and activation of their downstream targets, phosphor-Akt and p21, respectively, was determined by a standard Western blotting. RNA from multiple independent infections was collected for DNA microarray analysis using Affymetrix Human Genome U133 Array. A set of genes for which the expression levels are most highly correlated with the classification of HMEC samples into oncogene-activated/deregulated versus control (green fluorescent protein, GFP) are selected for generation of the pathway signatures. The dominant principal components from such a set of genes then defines a relevant phenotype-related metagene, and regression models assign the relative probability of pathway deregulation in tumor or cell line samples.

Supplemental Figure 2

Control

PI3K Activated



Low Expression



High Expression

Figure S2: Heat map of in vitro defined PI3K pathway signature. Expression patterns of the 200 genes that make up the PI3K genomic signature are presented here, shown for the in vitro samples where the signature originated (control and PI3K activated HMEC culture). The genes in this heatmap are listed (in same order) in Table S1.

Supplemental Figure 3

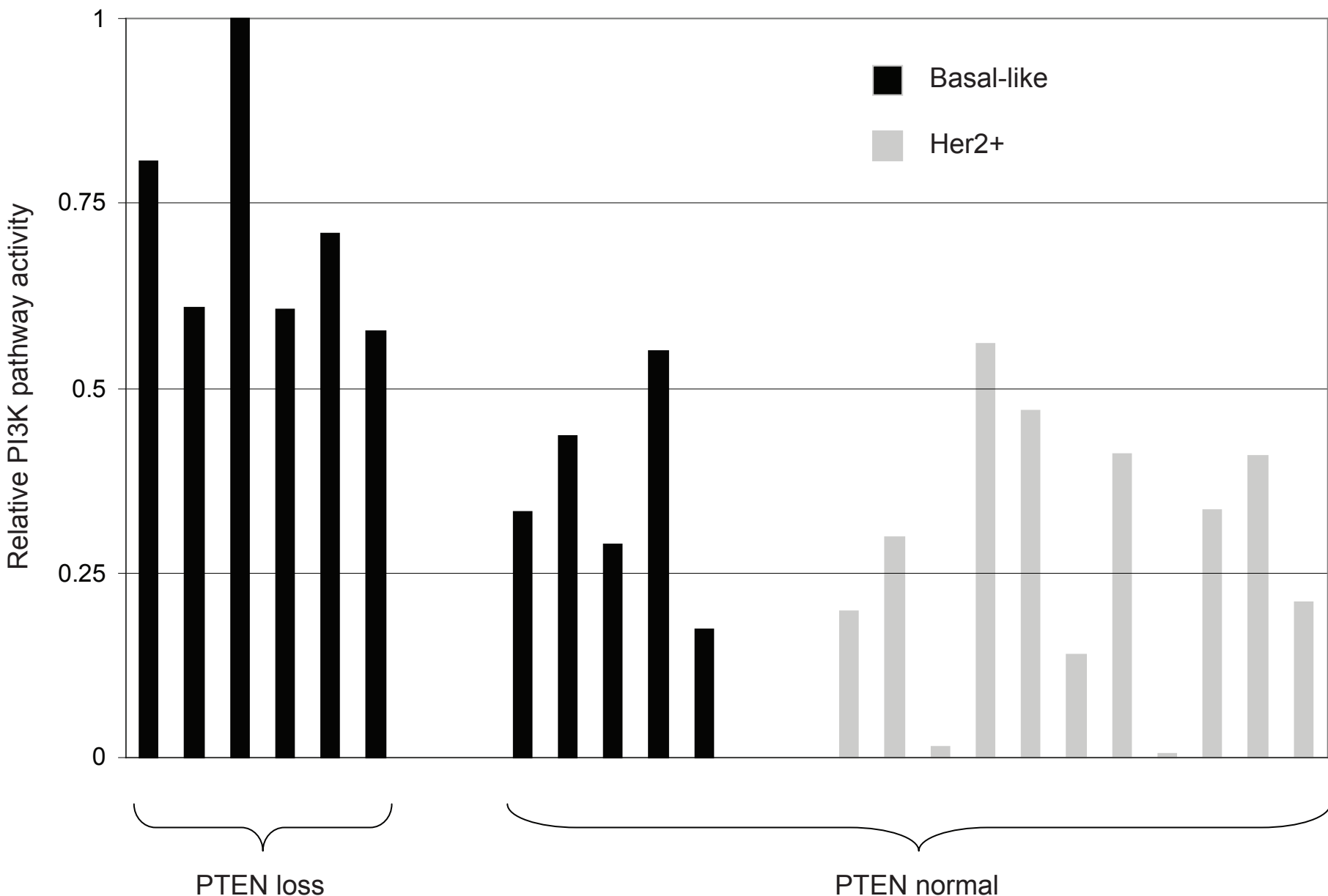


Figure S3: Computationally predicted PI3K activity in breast cancer samples with known PTEN copy number status. In samples exhibiting a loss of PTEN, which was primarily observed to occur in the Basal-like breast cancer subtype, a statistically significant increase in PI3K activity was predicted when compared to Basal-like samples without PTEN loss ($p=2.7 \times 10^{-5}$), and when compared to all samples without PTEN loss ($p=4.3 \times 10^{-3}$). As PTEN is known to be a negative regulator of PI3K pathway activity, this result successfully validates the accuracy of the PI3K pathway signature and computational prediction methodology. The y-axis represents computationally predicted PI3K activity, while the individual tumor samples are depicted on the x-axis. Basal-like samples are in black, while HER2+ samples are in gray.

Supplemental Figure 4

Genes Regulating Actin Organization and Cell Migration:

FAK	0.8
ITGB1	0.89
RHOA	1.17
ILK	1.21
CDC42	1.63

Genes involved in DNA Repair:

CDKN1A	1.3
POLD3	1.75
BARD1	2.54
MSH2	3.21
MSH6	3.21
GADD45B	4.17

AKT and PI3K Family Members and Their Regulators:

PRKCB1	0.43
PIK3CG	0.6
FASLG	0.67
TCL1A	0.77
AKT3	0.82
PIK3R1 (p85a)	0.84
AKT2	0.85
PDK1	1.15
PRKCA	1.15
HSPB1	1.16
PIK3CA (p110a)	1.16
PDPK1	1.22

Inactivation of Gsk3 and the Accumulation of β -Catenin:

GJA1	0.71
TLR4	0.82
APC	1.24
TOLLIP	1.32
TIRAP	1.39
CD14	1.51

Genes Involved in the mTOR Signaling Pathway:

TSC1	0.57
TSC2	0.64
FRAP1(mTOR)	0.9
PDK1	1.15
RHEB	2.29

Regulation of eIF4e and p70 S6 Kinase:

EIF4G1	1.08
RPS6KB1	1.25
EIF4B	1.44
EIF4E	1.55
EIF4EBP1 (4E-BP1)	1.64

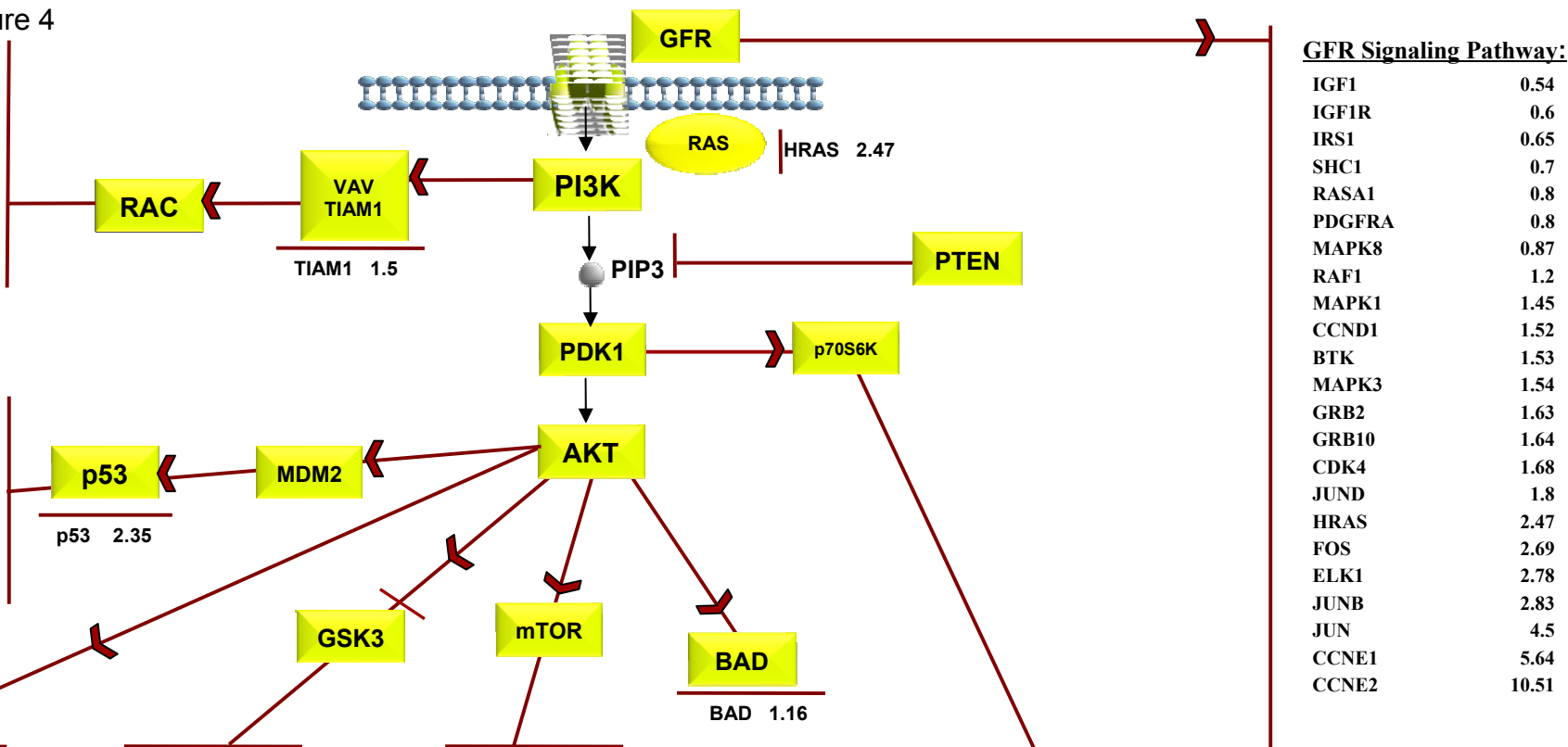
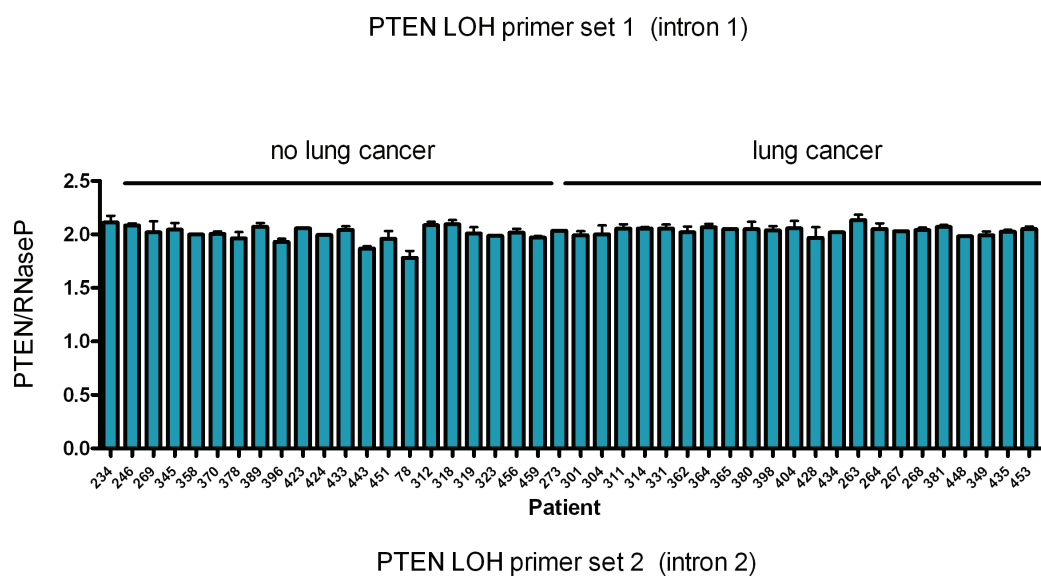


Figure S4. Gene expression changes after PI3K activation in vitro that are known PI3K pathway family members. Shown here is the fold-change of genes previously published to be involved in the PI3K pathway.

A



B

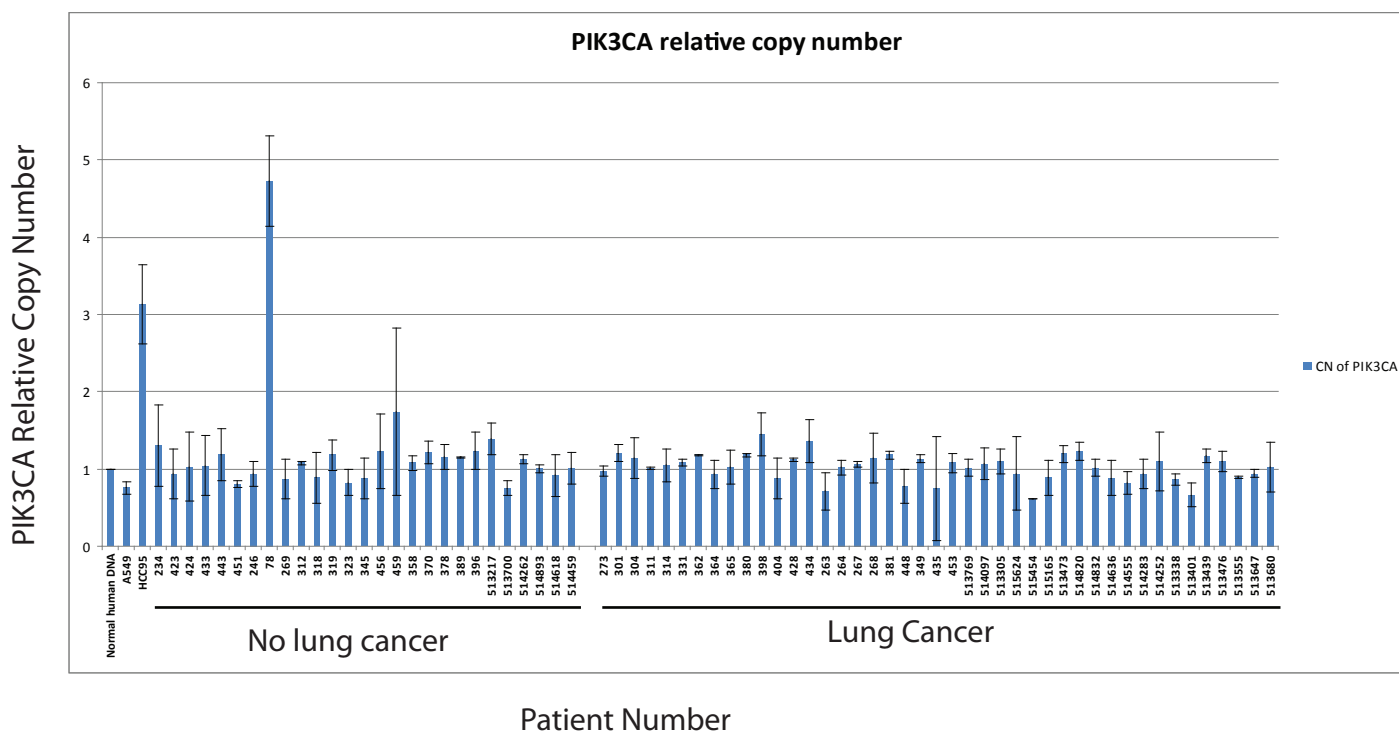


Figure S5: PTEN loss and PIK3CA amplification in the airway of smokers with and without lung cancer. A. PTEN LOH in normal airway epithelial cells from patients with lung cancer or other pathology as measured using qPCR with primers directed at intron 1 (upper panel) or intron 2 (lower panel). B. PI3K amplification in normal airway epithelial cells from patients with lung cancer or other pathologies as measured using qPCR.

Table S1

Pathway gene lists for the in vitro derived PI3K pathway.

Affxid	Gene Symbol	Expression Change
209305_s_at	GADD45B	Up
212192_at	KCTD12	Up
218585_s_at	DTL	Up
204768_s_at	FEN1	Up
207275_s_at	ACSL1	Up
207574_s_at	GADD45B	Up
201466_s_at	JUN	Up
206052_s_at	SLBP	Up
202911_at	MSH6	Up
203817_at	GUCY1B3	Up
202107_s_at	MCM2	Up
209806_at	HIST1H2BK	Up
209304_x_at	GADD45B	Up
213523_at	CCNE1	Up
214911_s_at	BRD2	Up
213076_at	ITPKC	Up
213711_at	KRTHB6	Up
201555_at	MCM3	Up
211555_s_at	GUCY1B3	Up
208685_x_at	BRD2	Up
201202_at	PCNA	Up
211814_s_at	CCNE2	Up
201464_x_at	JUN	Up
37892_at	COL11A1	Up
205053_at	PRIM1	Up
201930_at	MCM6	Up
204127_at	RFC3	Up
1053_at	RFC2	Up
206595_at	CST6	Up
201465_s_at	JUN	Up
205436_s_at	H2AFX	Up
212281_s_at	TMEM97	Up
218350_s_at	GMNN	Up
201428_at	CLDN4	Up
203304_at	BAMBI	Up
207843_x_at	CYB5A	Up
209161_at	PRPF4	Up
203395_s_at	HES1	Up
212836_at	POLD3	Up
211450_s_at	MSH6	Up
209581_at	HRASLS3	Up
208949_s_at	LGALS3	Up
212188_at	KCTD12	Up
205778_at	KLK7	Up
220177_s_at	TMPRSS3	Up
201463_s_at	TALDO1	Up
209421_at	MSH2	Up

218866_s_at	POLR3K	Up
221942_s_at	GUCY1A3	Up
210046_s_at	IDH2	Up
202501_at	MAPRE2	Up
208579_x_at	H2BFS	Up
210166_at	TLR5	Up
209433_s_at	PPAT	Up
219405_at	TRIM68	Up
212141_at	MCM4	Up
216903_s_at	CBARA1	Up
206200_s_at	ANXA11	Up
201473_at	JUNB	Up
221588_x_at	ALDH6A1	Up
209832_s_at	CDT1	Up
211597_s_at	HOP	Up
210983_s_at	MCM7	Up
210519_s_at	NQO1	Up
208647_at	FDFT1	Up
217967_s_at	C1ORF24	Up
201650_at	KRT19	Up
209772_s_at	CD24	Up
204695_at	CDC25A	Up
202672_s_at	ATF3	Up
205687_at	UBPH	Up
203221_at	TLE1	Up
219143_s_at	RPP25	Up
201695_s_at	NP	Up
203696_s_at	RFC2	Up
211354_s_at	LEPR	Up
202581_at	HSPA1B	Up
219673_at	C6ORF61	Up
221521_s_at	PFS2	Up
218170_at	ISOC1	Up
219529_at	CLIC3	Up
212279_at	TMEM97	Up
216457_s_at	n/a	Up
215165_x_at	UMPS	Up
44669_at	n/a	Up
210139_s_at	PMP22	Up
203752_s_at	JUND	Up
218997_at	POLR1E	Up
209366_x_at	CYB5A	Up
222037_at	MCM4	Up
202246_s_at	CDK4	Up
212142_at	MCM4	Up
211675_s_at	MDFIC	Up
219060_at	C8ORF32	Up
201041_s_at	DUSP1	Up
202081_at	IER2	Up
205345_at	BARD1	Up
212092_at	PEG10	Up
205768_s_at	SLC27A2	Up

216237_s_at	MCM5	Up
218953_s_at	MGC3265	Up
205470_s_at	KLK11	Up
209792_s_at	KLK10	Up
202286_s_at	TACSTD2	Up
200687_s_at	SF3B3	Up
207707_s_at	SEC13L1	Up
218963_s_at	KRT23	Up
218929_at	CARF	Up
204733_at	KLK6	Up
215726_s_at	CYB5A	Up
203557_s_at	PCBD1	Up
219270_at	CHAC1	Up
222216_s_at	MRPL17	Up
208795_s_at	MCM7	Up
215729_s_at	VGLL1	Up
209567_at	RRS1	Up
219258_at	FLJ20516	Up
200696_s_at	GSN	Up
203335_at	PHYH	Up
204359_at	FLRT2	Down
217997_at	PHLDA1	Down
221899_at	PFAAP5	Down
215203_at	GOLGA4	Down
220866_at	ADAMTS6	Down
222015_at	CSNK1E	Down
221768_at	SFPQ	Down
215504_x_at	n/a	Down
218801_at	UGCGL2	Down
222034_at	GNB2L1	Down
206237_s_at	NRG1	Down
214164_x_at	CA12	Down
218380_at	NALP1	Down
206792_x_at	PDE4C	Down
212266_s_at	SFRS5	Down
206027_at	S100A3	Down
216052_x_at	ARTN	Down
214870_x_at	n/a	Down
212848_s_at	C9ORF3	Down
203385_at	DGKA	Down
214035_x_at	n/a	Down
214016_s_at	SFPQ	Down
213939_s_at	RUFY3	Down
221501_x_at	LOC339047	Down
212307_s_at	OGT	Down
214760_at	ZNF337	Down
213605_s_at	n/a	Down
202644_s_at	TNFAIP3	Down
216524_x_at	n/a	Down
212036_s_at	PNN	Down
212337_at	TUG1	Down
214085_x_at	HRB2	Down

202380_s_at	NKTR	Down
204143_s_at	ENOSF1	Down
202462_s_at	DDX46	Down
214731_at	CTTNBP2NL	Down
219471_at	C13ORF18	Down
211454_x_at	n/a	Down
212001_at	SFRS14	Down
221850_x_at	n/a	Down
221989_at	RPL10	Down
204193_at	CPT1B	Down
209286_at	CDC42EP3	Down
214291_at	RPL17	Down
214722_at	n/a	Down
210237_at	ARTN	Down
204457_s_at	GAS1	Down
203633_at	CPT1A	Down
212473_s_at	MICAL2	Down
216187_x_at	n/a	Down
208191_x_at	PSG4	Down
215978_x_at	n/a	Down
214753_at	PFAAP5	Down
210365_at	RUNX1	Down
207382_at	TP73L	Down
209921_at	SLC7A11	Down
207563_s_at	OGT	Down
220940_at	n/a	Down
214924_s_at	TRAK1	Down
216918_s_at	n/a	Down
215123_at	n/a	Down
215588_x_at	RIOK3	Down
210686_x_at	SLC25A16	Down
204537_s_at	GABRE	Down
205525_at	CALD1	Down
213593_s_at	TRA2A	Down
207675_x_at	ARTN	Down
207345_at	FST	Down
213998_s_at	DDX17	Down
222380_s_at	n/a	Down
210118_s_at	IL1A	Down
222303_at	ETS2	Down
213645_at	n/a	Down
214696_at	MGC14376	Down
39402_at	IL1B	Down
219934_s_at	SULT1E1	Down
208241_at	NRG1	Down
203074_at	ANXA8	Down
205067_at	IL1B	Down
205130_at	RAGE	Down
222227_at	ZNF236	Down

Table S2

Cohort	Patient ID/Track Numer	Lung Cancer	Age	Smoking Status	Time Since Quit (months)	Pack-Years	Histology
Utah	1	No	82	Never Smoker		0	pulmonary fibrosis
Utah	2	No	55	Never Smoker		0	rheumatoid lung
Utah	3	No	64	Current Smoker		40	septic emboli
Utah	4	No	47	Never Smoker		0	metastatic renal cell carcinoma
Utah	5	No	38	Never Smoker		0	atypical mycobacterial infection
Utah	6	No	60	Former smoker	60	111	hypersensitivity pneumonitis
Utah	7	No	70	Never Smoker		0	well differentiated carcinoid
Utah	8	Yes	59	Current Smoker		90	squamous cell lung carcinoma
Utah	9	Yes	57	Current Smoker		60	NSCLC, nondifferentiated,
Utah	10	Yes	65	Former smoker	228	15	lung adenocarcinoma
Utah	11	Yes	57	Current Smoker		90	NSCLC, poorly differentiated
Utah	12	Yes	61	Current Smoker		80	squamous cell lung carcinoma
Utah	13	Yes	63	Current Smoker		15	squamous cell lung carcinoma
Boston	14	No	54	Former smoker	1	21	chronic inflammation/ foreign body material
Boston	15	No	40	Former smoker	36	48	non-caseating granulomas -sarcoid
Boston	16	No	49	Former smoker	240	15	No cancer
Boston	17	No	71	Never smoker, 2nd hand exposure		NA	non-necrotizing granulomatous inflammation-sarcoid
Boston	18	No	NA	Not Available		NA	No cancer
Boston	19	Yes	70	Former smoker	360	24	large cell lung cancer
Boston	20	Yes	73	Former smoker	1	58	squamous cell lung carcinoma
Boston	21	Yes	63	Current Smoker		20	NSCLC poorly differentiated
Vanderbilt	22	No	70	Ex-smoker	36	50	No cancer
Vanderbilt	23	No	42	Ex-smoker	0	36	No cancer

Table S2: Patient demographics for prospective series of smokers undergoing bronchoscopy for suspicion of lung cancer (at the University of Utah and Boston University) as well as cohort of endo-bronchial biopsy specimens collected from the proximal airway of smokers with and without lung cancer at Vanderbilt University. These samples were used to biochemically validate increased activity of PI3K. The column labeled Patient ID represents the track number listed in Fig. 4.

Vanderbilt	24	No	43	Current smoker		66	No cancer
Vanderbilt	25	No	74	Current smoker		64	No cancer
Vanderbilt	26	No	72	Ex-smoker	396	30	No cancer
Vanderbilt	27	No	59	Ex-smoker	36	38	No cancer
Vanderbilt	28	No	60	Never smoked		0	No cancer
Vanderbilt	29	Yes	72	Ex-smoker	84	10	Adenocarcinoma
Vanderbilt	30	Yes	38	Current smoker		30	Large Cell Carcinoma
Vanderbilt	31	Yes	68	Ex-smoker	0	40	Adenocarcinoma
Vanderbilt	32	Yes	78	Never smoked		0	Adenocarcinoma
Vanderbilt	33	Yes	51	Ex-smoker	0	33	Adenocarcinoma
Vanderbilt	34	Yes	70	Ex-smoker	0	75	Adenocarcinoma
Vanderbilt	35	Yes	55	Ex-smoker	12	80	Squamous Cell Carcinoma
Vanderbilt	36	No	47	Ex-smoker	120	50	No cancer
Vanderbilt	37	No	67	Ex-smoker	312	80	No cancer
Vanderbilt	38	No	56	Ex-smoker	0	60	No cancer
Vanderbilt	39	No	37	Never smoked		0	No cancer
Vanderbilt	40	No	61	Ex-smoker	24	46	No cancer
Vanderbilt	41	No	76	Ex-smoker	12	56	No cancer
Vanderbilt	42	No	55	Never smoked		0	No cancer
Vanderbilt	43	Yes	68	Ex-smoker	12	100	Adenocarcinoma
Vanderbilt	44	Yes	73	Ex-smoker	420	15	Adenocarcinoma
Vanderbilt	45	Yes	65	Ex-smoker	0	150	Adenocarcinoma
Vanderbilt	46	Yes	69	Ex-smoker	300	40	Adenocarcinoma
Vanderbilt	47	Yes	56	Ex-smoker	0	90	Squamous Cell Carcinoma
Vanderbilt	48	Yes	63	Current smoker		72	Squamous Cell Carcinoma

Table S3

Patient Number	Lung Cancer Status	PIP3	p-PKC (raw)	p-AKT (raw)	GAPDH (raw)
1	No	0	n/a	n/a	0
2	No	0	n/a	n/a	646278
3	No	25365	n/a	n/a	571642
4	No	0	n/a	n/a	175719
5	No	227482	n/a	n/a	664160
6	No	0	n/a	n/a	704082
7	No	0	n/a	n/a	726911
8	Yes	48180	n/a	n/a	956113
9	Yes	149069	n/a	n/a	763205
10	Yes	0	n/a	n/a	698688
11	Yes	465527	n/a	n/a	835254
12	Yes	0	n/a	n/a	572470
13	Yes	845195	n/a	n/a	710090
14	No	502281	n/a	n/a	812116
15	No	383162.83	n/a	n/a	666036
16	No	9614715.6	n/a	n/a	692132
17	No	1454959.89	n/a	n/a	448157
18	No	5500428.8	n/a	n/a	739793
19	Yes	13093634.16	n/a	n/a	782399
20	Yes	1169843.28	n/a	n/a	701783
21	Yes	11591772.31	n/a	n/a	799560
22	No	n/a	98.27	139.92	219.51
23	No	n/a	93.56	113.13	211.44
24	No	n/a	103.45	129.98	221.95
25	No	n/a	96.11	118.03	223.24
26	No	n/a	111.64	138.38	215.69
27	No	n/a	97.73	148.57	215.59
28	No	n/a	98.62	182.06	220.18
29	Yes	n/a	118.25	178.63	216.35
30	Yes	n/a	113.19	150.18	221.55
31	Yes	n/a	121.22	150.44	226.06
32	Yes	n/a	134.58	154.56	217.14
33	Yes	n/a	131.8	115.34	212.56
34	Yes	n/a	116.65	141.4	226.94
35	Yes	n/a	113.22	123.8	225.44
36	No	n/a	104.68	122.89	202.39
37	No	n/a	101.14	174.05	210
38	No	n/a	112.11	124.38	208.7
39	No	n/a	107.62	131.86	208.42
40	No	n/a	128.83	174.74	207.46
41	No	n/a	170.98	177.66	207.12
42	No	n/a	105.41	150.13	211.89
43	Yes	n/a	143.14	143.72	204.1
44	Yes	n/a	123.2	180.52	209.79
45	Yes	n/a	156.36	162.89	211.56
46	Yes	n/a	159.5	175.62	209.77
47	Yes	n/a	141.66	172.41	210.55
48	Yes	n/a	173.43	114.99	210.17

Table S3: Quantified values for western blots presented in Figure 4.

Table S4

	PIK3CA amplification (DNA) <i>Vanderbilt</i>			LOH and PIK3CA amplification (DNA) <i>Boston</i>	
	No Cancer	Cancer		No cancer	Cancer
Num. Samples	6	20		21	23
Age	61.5 (12.6)	67.25 (7.9)		64.5 (14.8)	64.2 (10.6)
Pyers	30.33 (23.03)*	74.3 (36.91)*		44.0 (28.9)	56.8 (29.2)
% Former smokers (current)	66.6 (16.7)	75		42.9	52.2
Months since formers quit	105 (33.1)	115.7 (125.5)		205.3 (176.0)	172.1 (153.4)

Table S4: Demographics for DNA airway cohorts used for PTEN LOH and PI3K amplification studies

Table S5

List of PI3K signature genes that had counterparts on the Affymetrix exon array.

Gene	Expression change upon PI3K activation
KRTHB6	Up
MCM3	Up
ALDH6A1	Up
IDH1	Up
SEC13L1	Up
TLE1	Up
PCBD1	Up
MCM4	Up
MGC3265	Up
RFC2	Up
CBARA1	Up
COL11A1	Up
GSN	Up
FLJ20516	Up
PRIM1	Up
BARD1	Up
PPAT	Up
CARF	Up
PHYH	Up
TMPRSS3	Up
HOP	Up
HRASLS3	Up
ISOC1	Up
TRIM68	Up
CLDN4	Up
IDH2	Up
CST6	Up
CDK4	Up
UMPS	Up
NQO1	Up
KLK6	Up
KLK7	Up
KLK10	Up
KLK11	Up
MRPL17	Up
CCNE1	Up
CDC25A	Up
H2AFX	Up
HSPA1B	Up
PMP22	Up
CLIC3	Up
MCM2	Up
VGLL1	Up
ACSL1	Up

DTL	Up
BRD2	Up
ATF3	Up
RFC3	Up
CDT1	Up
DUSP1	Up
MCM5	Up
KCTD12	Up
RPP25	Up
ANXA11	Up
HES1	Up
JUNB	Up
GUCY1A3	Up
GUCY1B3	Up
BAMBI	Up
JUND	Up
KRT23	Up
IER2	Up
SLBP	Up
POLR3K	Up
NP	Up
PCNA	Up
RRS1	Up
KRT19	Up
MDFIC	Up
CD24	Up
SF3B3	Up
SLC27A2	Up
MCM6	Up
LEPR	Up
LGALS3	Up
FDFT1	Up
POLD3	Up
JUN	Up
TALDO1	Up
TLR5	Up
PEG10	Up
GMNN	Up
MSH2	Up
PRPF4	Up
MSH6	Up
GADD45B	Up
FEN1	Up
PKMYT1	Up
UBPH	Up
CCNE2	Up
MAPRE2	Up
ITPKC	Up
MCM7	Up
OGT	Down
SLC25A16	Down
SLC25A16	Down

SPTBN5	Down
IL1B	Down
IL1A	Down
NALP1	Down
UGCGL2	Down
ARTN	Down
RPL17	Down
RUNX1	Down
RPL17	Down
NKTR	Down
SFPQ	Down
PHLDA1	Down
HRB2	Down
ETS2	Down
SFRS14	Down
RIOK3	Down
MGC14376	Down
2-Sep	Down
CPT1A	Down
PDE4C	Down
NRG1	Down
DDX17	Down
GOLGA4	Down
CSNK1E	Down
GABRE	Down
SULT1E1	Down
TP73L	Down
SFRS5	Down
DDX46	Down
ENOSF1	Down
TNFAIP3	Down
MICAL2	Down
CALD1	Down
ZNF337	Down
PNN	Down
PFAAP5	Down
TUG1	Down
TRA2A	Down
GAS1	Down
ZNF236	Down
SLC7A11	Down
DGKA	Down
CDC42EP3	Down
ADAMTS6	Down
ADAMTS6	Down
RAGE	Down
FLRT2	Down
FST	Down
CA12	Down
GNB2L1	Down

Table S6

Order of genes in Fig 5 heatmap.

KRTHB6
MCM3
ALDH6A1
IDH1
SEC13L1
TLE1
PCBD1
MCM4
MGC3265
RFC2
CBARA1
COL11A1
GSN
FLJ20516
PRIM1
BARD1
PPAT
CARF
PHYH
TMPRSS3
HOP
HRASLS3
ISOC1
TRIM68
CLDN4
IDH2
CST6
CDK4
UMPS
NQO1
KLK6
KLK7
KLK10
KLK11
MRPL17
CCNE1
CDC25A
H2AFX
HSPA1B
PMP22
CLIC3
MCM2
VGLL1
ACSL1
DTL
BRD2
ATF3
RFC3

CDT1
DUSP1
MCM5
KCTD12
RPP25
ANXA11
HES1
JUNB
GUCY1A3
GUCY1B3
BAMBI
JUND
KRT23
IER2
SLBP
POLR3K
NP
PCNA
RRS1
KRT19
MDFIC
CD24
SF3B3
SLC27A2
MCM6
LEPR
LGALS3
FDFT1
POLD3
JUN
TALDO1
TLR5
PEG10
GMNN
MSH2
PRPF4
MSH6
GADD45B
FEN1
PKMYT1
UBPH
CCNE2
MAPRE2
ITPKC
MCM7