Supplemental Data

An inhaled dose of budesonide induces genes involved in transcription and signaling in the human airways: Enhancement of anti- and pro-inflammatory effector genes

Richard Leigh, Mahmoud M. Mostafa, Elizabeth M. King, Christopher F. Rider, Suharsh Shah, Curtis Dumonceaux, Suzanne L. Traves, Andrew McWhae, Tyler Kolisnik, Cora Kooi, Donna M. Slater, Margaret M. Kelly, Mark Bieda, Anna Miller-Larsson, Robert Newton

Supplemental Results

Biopsy microarray analysis. Following chip scanning the CEL files generated by Affymetrix Expression Console software were analyzed by Partek Genomics Suite (v6.6). Data using ≥2 fold and ≤0.5 fold each with $P \leq 0.05$ provides 109 budesonide up-regulated probe sets and 35 repressed probe sets (Supplemental Table 3). However, the application of a 5% false discovery rate (FDR) reduced this to 72 and 11 probe sets respectively and these are plotted as a heat map (Supplemental Fig. 2). Application of the gene identification tool in DAVID, to remove redundant probes sets, pseudogenes, non-coding RNAs, or other non-gene annotations produced 46 up-regulated and 10 unique down-regulated genes by budesonide. Despite representing the most robustly increased probe sets, the heat map clearly indicates considerable variations between individuals and this, depending on the function of these genes, may have a significant bearing on the profile of responses by each individual to an ICS.

For the extended, lower stringency, gene list there were the 889 probe sets that showed ≥1.25-fold ($P \leq 0.05$) budesonide inducibility. Analysis using the DAVID gene ID tools identified 588 up-regulated genes (Supplemental Table 4).

Comparison of PCR and array data for individual probe sets. One feature of the microarray analysis, exemplified by FKBP5 and TSC22D3, was the range of fold inducibility shown for the different probe sets corresponding to each individual gene (Supplemental Table 5, Supplemental Fig. 4A). Thus the fold induction for the 6 probe sets corresponding to FKBP5 ranged from 13.41 ($P \leq 0.001$) down to 1.24 fold, which was not considered significant. By comparison, qPCR produced a significant induction of 15.69 fold. While reasons for this difference may be genuine, for example due to alternative mRNA splicing, and are not examined, this outcome has implications for downstream analyses. Of the induced genes tested by qPCR, 18 were induced ≥2 fold by inhaled budesonide (Supplemental Table 5). However, of these genes, only 14 had probe sets achieving the 2-fold threshold (Supplemental Table 5). This indicates the superior sensitivity of qPCR. Indeed, for the 18 genes with ≥2 fold inducibility by qPCR, there were a total of 68 probe sets of which 28 achieved ≥2 fold (Supplemental Table 5). Consequently, comparing the fold induction obtained by qPCR with the average fold for all probes sets for each gene produced a slope of 0.54 ($r^2 = 0.66$) (Supplemental Fig. 4B, left panel), yet using just the probe set with the highest fold induction for each target gene markedly improves the correlation with the qPCR data (slope = 0.77, $r^2 = 0.96$) (Supplemental Fig. 4B, right panel). Thus, consideration of the most highly induced probe set for each target gene, rather than averaging probe set values, provides the most appropriate representation of gene expression change. This approach is therefore taken for all analyses of the microarray data. Secondly, there were many probe sets with less than 2-fold induction, but which based on PCR data reflect real and significant changes in gene expression. Thus, while all 23 genes tested by qPCR showed significantly induced expression by inhaled budesonide, eight genes (CDKN1C, CEBPD, DUSP1, NKBKIA, RGS2, SLC45A1, TLR2 and ZFP36) revealed between 1 and 2 fold inducibility on the microarray with probe sets for SLC45A1 and ZFP36 failing to reach significance (Supplemental Table 5). This clearly confirms that the imposition of the 2 fold, 0.05 FDR criteria excludes much data that are genuine in these biopsy samples. Given the relative ease of later confirmation of genes of interest, an extended gene list based on the 889 probe sets showing >1.25 inducibility ($P < 0.05$) by budesonide inhalation was generated using the DAVID gene ID conversion tool to produce 588 individual identities (Supplemental Table 4).

Supplemental Tables

SUPPLEMENTAL TABLE 1
Gene symbols, names and description of genes analyzed by qPCR

HGNC Symbol	Common Symbol(s)	Brief description
ALOX15B	15-LOX-2	Arachidonate 15-lipoxygenase, type B, converts arachidonic acid to 15S-hydroperoxyeicosatetraenoic acid.
CD163	M130, MM130	Member of the scavenger receptor cysteine-rich superfamily. Found on monocytes and macrophage, CD163 is an acute phase factor involved in the clearance of haemoglobin/haptoglobin. May help protect from free-haemoglobine-mediated oxidated damage. CD163 may be an innate sensor for bacteria.
CEBPD	C/EBPδ	CCAAT/enhancer binding protein δ is a bZIP transcription factor that is involved in the regulation of immune and inflammatory responses.
CDKN1C	p57KIP2	Cyclin-dependent kinase inhibitor 1C inhibits G1 cyclin/Cdk complexes to negatively regulate cell cycle. Reported to interact with and inhibit JNK MAPKs (10, 11).
CNR1	CB1, CNR	Cannabinoid receptor 1 is a GPCR that inhibits adenylyl cyclase activity.
CXCR4	LAP3, LCR1	Chemokine (C-X-C motif) receptor 4 is a GPCR receptor for stromal cell-derived factor 1 (SDF1) (CXCL12)
DUSP1	MKP1	Dual-specificity phosphatase 1 / mitogen-activated protein kinase phosphastas 1 is up-regulated by inflammatory pathways and by glucocorticoids to dephosphorylate and, thereby inactivate, MAPK family members including ERK, p38 MAPK and JNK (12, 13).
FAM150B	PRO1097	Function unknown.
FKBP5	FKBP51	FK506 binding protein 5 is an immunophilin that interacts with the cytoplasmic Hsp90/nuclear hormone receptor complex to negatively regulate GR function (14-16).
IGF1	MGF	Insulin-like growth factor 1 (somatomedin C) is similar to insulin in function and mediates growth and development.
KLF9	BTEB	Krupple-like factor 9 is a GC box transcription factor.
LIFR	CD118	Leukemia inhibitor factor receptor alpha is a type I cytokine receptor that binds to gp130 to form a functional receptor complex. Mediates differentiation, proliferation and survival.
NFKBIA	IκBα	NFκB inhibitor alpha is an endogenous cytoplasmic inhibitor of the inflammatory transcription factor NF-κB.
PDK4		Pyruvate dehydrogenase kinase, isozyme 4. Involved in the regulation of glucose metabolism.
PER1	PER, RIGUI	Member of the Period family of genes. A transcription factor that is regulated in a circadian manner.
RGS1	1R20, BL34	Regulator of G-protein signaling (RGS) 1 is a GTPase-activating protein (GAP) for the Gα subunit of heterotrimeric G proteins. It is a $G_{i/o}$α-selective RGS that plays roles in regulating responses to chemokines (17, 18).
RGS2	RGS2	Regulator or G-protein signaling 2 is a GTPase-activating protein (GAP) for the Gα subunit of heterotrimeric G proteins. RSG2 is selective for Gqα and attenuates signaling by bronchonstrictor stimuli, including histamine, methacholine and U46619 (19, 20).
SLC45A1	DNB5	Solute carrier 45A1 is an integral membrane symporter categorized as a proton-associated sugar transporter that may show glucose transporter activity.

TFCP2L1	LBP9	Transcription factor CP2-like 1.
TLR2	TIL4, CD82	Toll-like receptor 2 plays a role in pathogen recognition and activation of innate immunity.
TSC22D3	GILZ	TSC22D3 is a leucine zipper protein believed to be a transcriptional regulator that negatively regulates inflammatory signaling to reduce NF-κB- and AP-1-dependent transcription (21, 22) (23, 24).
ZBTB16	PLZF	Zinc finger and BTB domain containing 16 is a transcription factor that interacts with HDACs and may play roles in transcriptional repression.
ZFP36	TTP	Zinc finger protein 36 / tristetraprolin is a RNA binding protein which regulates the mRNA decay of mRNAs via AUUUA motifs. Expression is up-regulated by inflammatory stimuli, such as IL1B, to provide feedback control (25, 26).

Information was taken from NCBI Gene and supplemented with the indicated references.

SUPPLEMANTAL TABLE 2

Clinical characteristics of study participants

Study ID #	Age	Gender	FVC Actual (l)	FEV_1 Actual (l)	FEV_1 % Pred	FEV_1/ FVC	Skin Test	Smoking History	MCh PC_{20}
01	40	M	5.96	4.77	113.0	0.80	negative	Non smoker	>16
02	34	M	6.43	4.84	107.3	0.75	negative	Non smoker	>16
03	27	M	6.22	4.53	95.8	0.73	negative	Non smoker	>16
04	28	M	5.56	4.65	100.0	0.84	negative	Non smoker	>16
05	49	M	5.85	4.28	101.9	0.73	negative	Non smoker	>16
06	38	M	6.00	5.26	122.9	0.88	negative	Non smoker	>16
07	27	M	5.43	4.41	91.7	0.81	negative	Non smoker	>16
08	32	M	5.08	3.8	89.4	0.75	negative	Non smoker	>16
09	22	M	3.57	3.11	89.1	0.87	negative	Non smoker	>16
10	26	M	4.68	3.72	83.6	0.79	negative	Non smoker	>16
11	24	M	6.87	5.91	105.0	0.86	negative	Non smoker	>16
12	30	M	6.48	4.9	105.8	0.76	negative	Non smoker	>16

FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second; MCh PC_{20}: Provocative Concentration (mg/ml) of methacholine causing a 20% fall in FEV_1.; Pred, predicted

SUPPLEMENTAL TABLE 3

Biopsy microarray data: Probe sets showing ≥2 fold, or ≤0.5 fold change ($P \leq 0.05$) following budesonide inhalation

Probe set ID	Entrez Gene	Gene Symbol	Gene Title	*P*-value (Bud/ Plac)	Fold (Bud/ Plac)
11743917_a_at	2289	FKBP5	FK506 binding protein 5	2.0E-13	13.41
11729371_a_at	7704	ZBTB16	zinc finger and BTB domain containing 16	1.7E-14	12.75
11739567_s_at	2289	FKBP5	FK506 binding protein 5	3.5E-17	12.47
11739565_a_at	2289	FKBP5	FK506 binding protein 5	1.2E-11	11.18
11726088_s_at	116154	PHACTR3	phosphatase and actin regulator 3	2.2E-09	8.38
11748099_a_at	116154	PHACTR3	phosphatase and actin regulator 3	5.5E-09	7.91
11728679_a_at	9332	CD163	CD163 molecule	4.4E-09	6.89
11746275_a_at	2289	FKBP5	FK506 binding protein 5	2.8E-08	6.52
11729445_at	285016	FAM150B	family with sequence similarity 150, member B	5.5E-07	5.89
11720161_at	10563	CXCL13	chemokine (C-X-C motif) ligand 13	7.0E-03	4.39
11717829_s_at	1831	TSC22D3	TSC22 domain family, member 3	1.0E-12	4.06
11739566_a_at	2289	FKBP5	FK506 binding protein 5	2.8E-06	3.94
11751415_a_at	1831	TSC22D3	TSC22 domain family, member 3	2.9E-07	3.83
11716974_a_at	5166	PDK4	pyruvate dehydrogenase kinase, isozyme 4	9.9E-12	3.62
11731461_x_at	1368	CPM	carboxypeptidase M	4.0E-06	3.60
11717168_a_at	5187	PER1	period circadian clock 1	1.3E-08	3.48
11717327_at	687	KLF9	Kruppel-like factor 9	2.7E-08	3.33
11721033_a_at	11170	FAM107A	family with sequence similarity 107, member A	2.3E-08	3.23
11756473_a_at	10659	CELF2	CUGBP, Elav-like family member 2	1.1E-09	3.16
11745144_a_at	26253	CLEC4E	C-type lectin domain family 4, member E	7.3E-06	3.16
11731460_at	1368	CPM	carboxypeptidase M	1.8E-07	3.15
11721032_s_at	11170	FAM107A	family with sequence similarity 107, member A	1.6E-08	3.12
11723464_s_at	10659	CELF2	CUGBP, Elav-like family member 2	7.2E-08	3.11
11728190_s_at	7852	CXCR4	chemokine (C-X-C motif) receptor 4	2.4E-04	3.10
11717326_at	687	KLF9	Kruppel-like factor 9	1.3E-09	3.08
11732871_a_at	158062	LCN6	lipocalin 6	5.7E-05	3.01
11730310_at	29842	TFCP2L1	transcription factor CP2-like 1	5.2E-07	3.00
11733262_a_at	10659	CELF2	CUGBP, Elav-like family member 2	1.1E-04	2.95
11729817_a_at	3479	IGF1	insulin-like growth factor 1 (somatomedin C)	1.9E-05	2.91
11720162_at	10563	CXCL13	chemokine (C-X-C motif) ligand 13	1.6E-02	2.81
11717830_a_at	1831	TSC22D3	TSC22 domain family, member 3	2.5E-03	2.77
11725722_at	29028	ATAD2	ATPase family, AAA domain containing 2	4.6E-09	2.75
11724157_x_at	6783	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	1.0E-03	2.73
11727015_s_at	5069	PAPPA	pregnancy-associated plasma protein A, pappalysin 1	1.7E-05	2.71
11758664_s_at	22836	RHOBTB3	Rho-related BTB domain containing 3	2.8E-05	2.71
11726210_at	28999	KLF15	Kruppel-like factor 15	5.1E-09	2.70
11722675_at	64344	HIF3A	hypoxia inducible factor 3, alpha subunit	9.6E-08	2.69
11751273_a_at	2857	GPR34	G protein-coupled receptor 34	7.0E-05	2.68
11724156_at	6783	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	7.7E-04	2.68
11726375_x_at	2857	GPR34	G protein-coupled receptor 34	8.2E-05	2.66
11728191_x_at	7852	CXCR4	chemokine (C-X-C motif) receptor 4	1.2E-03	2.66
11729818_s_at	3479	IGF1	insulin-like growth factor 1 (somatomedin C)	1.9E-04	2.65
11724155_at	6783	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	2.2E-03	2.64
11740522_a_at	7173	TPO	thyroid peroxidase	2.2E-04	2.63
11727715_at	8515	ITGA10	integrin, alpha 10	5.3E-05	2.59
11723465_a_at	10659	CELF2	CUGBP, Elav-like family member 2	1.7E-09	2.58
11728189_a_at	7852	CXCR4	chemokine (C-X-C motif) receptor 4	3.1E-03	2.57
11742193_a_at	1268	CNR1	cannabinoid receptor 1 (brain)	8.0E-05	2.55
11728397_at	4499	MT1M	metallothionein 1M	2.1E-07	2.50
11756888_a_at	29842	TFCP2L1	transcription factor CP2-like 1	3.1E-07	2.45

11724154_a_at	6783	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	1.6E-02	2.43
11730342_x_at	84174	SLA2	Src-like-adaptor 2	5.0E-04	2.41
11721388_a_at	5026	P2RX5	purinergic receptor P2X, ligand-gated ion channel, 5	1.6E-03	2.41
11725912_a_at	2066	ERBB4	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	5.5E-04	2.39
11728571_a_at	5334	PLCL1	phospholipase C-like 1	7.9E-04	2.39
11744436_a_at	11113 / 100302274	CIT /// MIR1178	citron (rho-interacting, serine/threonine kinase 21) /// microRNA 1178	7.8E-05	2.39
11733628_at	642938	FAM196A	family with sequence similarity 196, member A	7.3E-04	2.38
11761173_at	64344	HIF3A	hypoxia inducible factor 3, alpha subunit	5.7E-06	2.38
11761174_x_at	64344	HIF3A	hypoxia inducible factor 3, alpha subunit	5.7E-06	2.38
11758145_s_at	3977	LIFR	leukemia inhibitory factor receptor alpha	1.2E-04	2.37
11751570_a_at	51338	MS4A4A	membrane-spanning 4-domains, subfamily A, member 4A	2.4E-05	2.37
11731464_at	1368	CPM	carboxypeptidase M	1.1E-07	2.37
11742035_a_at	5334	PLCL1	phospholipase C-like 1	9.3E-04	2.35
11734619_x_at	247	ALOX15B	arachidonate 15-lipoxygenase, type B	2.7E-06	2.34
11727016_s_at	5069	PAPPA	pregnancy-associated plasma protein A, pappalysin 1	1.8E-05	2.34
11724954_s_at	4360	MRC1	mannose receptor, C type 1	4.7E-04	2.33
11728398_x_at	4499	MT1M	metallothionein 1M	3.3E-07	2.31
11726079_x_at	117248	GALNT15	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 15	4.6E-04	2.30
11744843_s_at	5069	PAPPA	pregnancy-associated plasma protein A, pappalysin 1	5.3E-06	2.28
11739094_a_at	7852	CXCR4	chemokine (C-X-C motif) receptor 4	4.5E-03	2.27
11723030_at	83716	CRISPLD2	cysteine-rich secretory protein LCCL domain containing 2	9.9E-05	2.26
11726131_a_at	5318	PKP2	plakophilin 2	4.7E-06	2.26
11720202_at	2766	GMPR	guanosine monophosphate reductase	2.0E-05	2.26
11756885_a_at	29028	ATAD2	ATPase family, AAA domain containing 2	2.4E-08	2.25
11720749_a_at	11185	INMT	indolethylamine N-methyltransferase	1.4E-03	2.25
11732699_a_at	5570	PKIB	protein kinase (cAMP-dependent, catalytic) inhibitor beta	2.0E-03	2.24
11733017_a_at	5295	PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	1.5E-06	2.24
11715659_s_at	54206	ERRFI1	ERBB receptor feedback inhibitor 1	6.3E-11	2.23
11729831_a_at	9073	CLDN8	claudin 8	9.6E-04	2.22
11723862_at	6529	SLC6A1	solute carrier family 6 (neurotransmitter transporter, GABA), member 1	3.9E-03	2.21
11754631_x_at	5295	PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	4.4E-06	2.21
11726080_a_at	117248	GALNT15	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 15	3.0E-03	2.19
11733187_a_at	3575	IL7R	interleukin 7 receptor	2.3E-04	2.19
11725071_at	79960	JADE1	Jade family PDH finger 1	1.6E-07	2.19
11757645_s_at	387758	FIBIN	fin bud initiation factor homolog (zebrafish)	4.1E-03	2.18
11742765_at	5996	RGS1	regulator of G-protein signaling 1	5.5E-03	2.17
11720339_at	387758	FIBIN	fin bud initiation factor homolog (zebrafish)	8.2E-04	2.17
11720300_a_at	6503	SLA	Src-like-adaptor	3.6E-04	2.17
11729832_s_at	9073	CLDN8	claudin 8	8.3E-04	2.16
11758120_s_at	3745	KCNB1	potassium voltage-gated channel, Shab-related subfamily, member 1	3.1E-04	2.16
11725072_at	79960	JADE1	Jade family PDH finger 1	2.0E-07	2.15
11732700_x_at	5570	PKIB	protein kinase (cAMP-dependent, catalytic) inhibitor beta	2.1E-03	2.13
11722615_s_at	8843 /// 338442	HCAR2 / HCAR3	hydroxycarboxylic acid receptor 2 / hydroxycarboxylic acid receptor 3	2.2E-07	2.12
11745893_s_at	10797	MTHFD2	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate c	1.1E-04	2.10
11728769_at	256435	ST6GALNAC3	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2	1.8E-03	2.08
11732588_at	3745	KCNB1	potassium voltage-gated channel, Shab-related subfamily, member 1	6.1E-04	2.08
11716455_at	22836	RHOBTB3	Rho-related BTB domain containing 3	9.4E-08	2.08
11725073_s_at	79960	PHF17	PHD finger protein 17	2.0E-09	2.07
11716457_x_at	22836	RHOBTB3	Rho-related BTB domain containing 3	1.0E-04	2.06

11726823_at	140	ADORA3	adenosine A3 receptor	8.1E-06	2.06
11717413_a_at	55062	WIPI1	WD repeat domain, phosphoinositide interacting 1	6.8E-09	2.06
11731112_at	27232	GNMT	glycine N-methyltransferase	1.6E-03	2.05
11753736_s_at	4498 / 4499 / 140851	MT1JP / MT1M / MT1P3	metallothionein 1J, pseudogene / metallothionein 1M / metallothionein 1 pseudogene	9.3E-06	2.03
11728653_at	3488	IGFBP5	insulin-like growth factor binding protein 5	6.8E-04	2.03
11727014_at	5069	PAPPA	pregnancy-associated plasma protein A, pappalysin 1	2.5E-03	2.03
11729444_a_at	6820	SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	5.0E-06	2.02
11751905_a_at	4811	NID1	nidogen 1	2.8E-03	2.01
11755663_s_at	2309 / 2310	FOXO3 / FOXO3B	forkhead box O3 / forkhead box O3B pseudogene	1.4E-03	2.01
11731762_s_at	6196	RPS6KA2	ribosomal protein S6 kinase, 90kDa, polypeptide 2	1.6E-09	2.00
11755742_a_at	131	ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	2.0E-02	0.50
11731903_at	50489	CD207	CD207 molecule, langerin	1.2E-06	0.50
11728771_a_at	22802	CLCA4	chloride channel accessory 4	1.8E-02	0.49
11723418_a_at	7447	VSNL1	visinin-like 1	2.2E-03	0.49
11749996_a_at	7447	VSNL1	visinin-like 1	2.6E-03	0.49
11742867_at	1004	CDH6	cadherin 6, type 2, K-cadherin (fetal kidney)	3.7E-03	0.49
11718743_a_at	6387	CXCL12	chemokine (C-X-C motif) ligand 12	1.1E-04	0.48
11719754_s_at	3557	IL1RN	interleukin 1 receptor antagonist	3.6E-02	0.48
11716523_at	6280	S100A9	S100 calcium binding protein A9	2.1E-02	0.48
11757583_s_at	9865	TRIL	TLR4 interactor with leucine-rich repeats	2.2E-05	0.48
11753131_x_at	4071	TM4SF1	transmembrane 4 L six family member 1	4.5E-04	0.47
11753129_a_at	4071	TM4SF1	transmembrane 4 L six family member 1	3.0E-04	0.46
11753130_at	4071	TM4SF1	transmembrane 4 L six family member 1	3.4E-04	0.46
11754410_s_at	187	APLNR	apelin receptor	1.3E-03	0.46
11719899_at	387763	C11orf96	chromosome 11 open reading frame 96	1.4E-02	0.43
11723048_at	1524	CX3CR1	chemokine (C-X3-C motif) receptor 1	8.2E-04	0.43
11757425_s_at	7412	VCAM1	vascular cell adhesion molecule 1	4.6E-03	0.43
11725905_a_at	1903	S1PR3	sphingosine-1-phosphate receptor 3	3.2E-02	0.43
11731776_at	6356	CCL11	chemokine (C-C motif) ligand 11	3.3E-03	0.43
11719675_a_at	7412	VCAM1	vascular cell adhesion molecule 1	5.3E-04	0.43
11730319_at	4982	TNFRSF11B	tumor necrosis factor receptor superfamily, member 11b	5.8E-05	0.43
11749997_x_at	7447	VSNL1	visinin-like 1	5.3E-03	0.43
11732901_a_at	9582 / 200315 / 100913187	APOBEC3A / APOBEC3A_B / APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A /// APOBEC3A and AP	2.5E-02	0.42
11728532_at	2205	FCER1A	Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide	7.8E-05	0.42
11751426_a_at	90865	IL33	interleukin 33	1.8E-02	0.41
11732902_x_at	9582	APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	2.2E-02	0.41
11743350_a_at	84419	C15orf48	chromosome 15 open reading frame 48	3.7E-02	0.40
11722792_a_at	187	APLNR	apelin receptor	3.3E-04	0.38
11729296_s_at	4322	MMP13	matrix metallopeptidase 13 (collagenase 3)	2.1E-04	0.38
11725584_at	3038	HAS3	hyaluronan synthase 3	2.1E-04	0.36
11720298_at	3627	CXCL10	chemokine (C-X-C motif) ligand 10	8.4E-03	0.35
11727906_at	4319	MMP10	matrix metallopeptidase 10 (stromelysin 2)	6.4E-05	0.34
11726316_at	6401	SELE	selectin E	2.5E-04	0.34
11729297_at	4322	MMP13	matrix metallopeptidase 13 (collagenase 3)	5.5E-05	0.28
11716384_at	6347	CCL2	chemokine (C-C motif) ligand 2	1.8E-05	0.27

RNA was prepared from biopsy samples taken 5-6h after placebo (Plac) or budesonide (1600µg) (Bud) inhalation. Total RNA was subjected to expression profiling using Affymetrix PrimeView microarrays. Analysis (n = 11 individuals) was performed with Partek Genomics Suite (Version 6.6) using robust multi-array averaging (RMA). Resultant fold expression and *P* values for all probe sets showing fold change ≥2 or ≤0.5 with $P \leq 0.05$ are listed.

SUPPLEMENTAL TABLE 4

Biopsy microarray data – Induced genes: Genes corresponding to probes sets showing ≥1.25 fold (*P* ≤ 0.05) with inhaled budesonide are collected into functional groups

Fold	**Gene symbols**
1. Transcriptional control	
Positive regulator - DNA binding	
≥2	FOXO3, HIF3A, KLF9, KLF15, PER1, TFCP2L1
<2/≥1.5	AFF3, ASCL3, CEBPD, FHL5, FOSL2, FOXO1, IKZF1, KLF7, KLF13, PPARGC1A, TCF21, TFEB, TOX, TOX2
<1.5/≥1.25	ARNTL, ATF5, ATOH8, CAMTA1, CSRNP1, FOXN2, GLIS3, HAND2, IRX3, KLF2, KLF6, LMO2, MAFB, MYEF2, NFIA, NFIB, NFIC, NR2E3, PBX4, RORA, RUNX2, SCML4, SNAPC3, STOX1, TBX21, THRA, ZNF234, ZNF275, ZNF320, ZNF561, ZNF682, ZNF763, ZNF844
Negative regulator – DNA binding	
≥2	TSC22D3, ZBTB16
<2/≥1.5	ANKRA2, BATF, CREBRF, NFIL3, SPEN, ZBTB8A, ZBTB20, ZFHX3, ZNF652
<1.5/≥1.25	BCL6, CRY2, GZF1, KLHL24, ZBTB38, ZHX3, ZMYND8, ZNF57, ZNF157, ZNF331, ZNF540
Other regulator	
≥2	ATAD2, JADE1
<2/≥1.5	POU2AF1
<1.5/≥1.25	ATRX, ATXN7, CITED2, EID3, FAM120B, GREB1, HMGB2, NAP1L1, PHF8, PIAS1, SMARCD2, TOX3, TTF1, VGLL3
2. Membrane receptors	
GPCRs	
≥2	ADORA3, CNR1, CXCR4, GPR34, HCAR2/HCAR3
<2/≥1.5	ADCYAP1R1, C3AR1, F2R, GPR133
<1.5/≥1.25	ADRA2C, CMKLR1, FZD7, NMUR2, NPY2R, OR7A5
Cytokine, growth factor, and related receptors	
≥2	IL7R, LIFR
<2/≥1.5	FLT3, IL6R, PDGFRA
<1.5/≥1.25	CSF1R, CSF2RA, GFRA1, IL1R1, IL6ST, INSR, NTRK3, TGFBR3, TLR2
Other membrane receptors	
≥2	CD163, CLEC4E, ITGA10, MRC1, MS4A4A
<2/≥1.5	CD53, FCGR2B, FCRL5, GPIHBP1, KLRD1, MERTK, MSR1
<1.5/≥1.25	CD84, CD86, CD160, CD302, F3, HAVCR2, ITGA5, ITGB1, LAIR1, LDLRAD3, LILRA6, LILRB3, LY9, MS4A7, NKTR, OGFRL1, RTN4RL1, SIGLEC10, SLAMF6, ROR1, VSIG4
3. Signaling and regulation of signaling	
Kinase	
≥2	CIT, ERBB4, RPS6KA2
<2/≥1.5	BLK, CAMK2B, DGKG, IRAK3, PAK3, PTK2B, RPS6KA5, SIK1, TAOK1
<1.5/≥1.25	AKT3, DAPK1, FGR, HIPK2, LATS2, MAP3K6, MKNK2, NIM1K, PRKCA, SGK1, TXK, UHMK1, WNK1, ZAK
Phosphatase	
≥2	PHACTR3
<2/≥1.5	DUSP1, PTPN5
1.5>1.25	PPM1B, PPM1K, PTPDC1, PTPRG, PTPRM, TENC1
GTPase, GEF and GAP	
≥2	ERRFI1, RGS1, RHOBTB3
<2/≥1.5	ARHGAP10, FGD4, RAPGEF3, RHOU, SMAP2,
<1.5/≥1.25	ARHGAP6, ARHGAP19, ARHGAP26, ARHGEF10, ARL4A, DENND3, DENND6A, DOCK5, FAM13A, GIMAP1, IQGAP2, RAB3IP, RAB8B, RAB31, RAB40A, RHOB, RGS2, RRAGD, SRGAP1, SRGAP2, TBC1D2B, TRIO
Secreted factors (cytokines, growth factors)	
≥2	CXCL13, IGF1
<2/≥1.5	CTGF, INHBA, TNFSF4, SAA1

<1.5/≥1.25	BMP2, EBI3, IL16, NRTN
Other signaling	
≥2	CCND3, CELF2, CRISPLD2, FAM107A, KCNB1, FKBP5, IGFBP5, P2RX5, PIK3R1, PKIB, PKP2, PLCL1, SLA, SLA2, WIPI1
<2/≥1.5	AKAP13, APBA2, APOLD1, BIRC3, C10orf10, CYTIP, DDIT4, DISC1, EFHD1, ELMO1, FAIM, FAM134B, GADD45G, HOMER2, HOOK1, KIAA1033, MAP1B, NDRG4, NEDD4L, NPTX2, NRXN3, OSBPL1A, PDE4DIP, PIK3R5, PPP1R16B, PRR16, RASSF4, SRPX, SSR3, TACC1, TIPARP, TRIM35, UBE2H, USP53, VSTM2L, ZFAND5
<1.5/≥1.25	AKAP7, AKAP9, ANKHD1, APBB1, BAIAP2, BICC1, BNIP3, CABYR, CALCOCO2, CALD1, CCDC64, CDKN1C, CELF6, CEP350, CYFIP2, DEPTOR, EIF4EBP3, EMILIN3, FBXO31, FBXO32, FERMT2, FNBP1, FNBP1L, FNIP2, GADD45B, GCSAM, GMNN, HECTD2, HERC4, INHBB, IRS2, JAKMIP1, KCNK17, KLK14, LARP6, LDLRAD4, LGI1, LRRC16A, MAP1LC3C, MARVELD3, MCL1, METTL7A, MICAL1, MKLN1, MRO, MS4A6A, MTSS1, MTUS1, MYRIP, NANOS1, NDRG1, NFATC2IP, NFKBIA, NUDT16, PAGE4, PALD1, PLCB4, PNISR, PPP1CB, PRKAB1, PRPF38B, PTPLB, RBMS3, REPS2, RNPC3, RPH3AL, SECISBP2L, SESN1, SH3RF3, SLIT1, SLIT2, SNTG2, SORBS2, SPAG9, STOM, THEMIS2, THUMPD1, TOB1, TRIM52, TRPM2, TSKU, TSPYL2, UBE2D2, WASF2, WASF3, ZFR
4. Metabolic and metabolism	
≥2	ALOX15B, CPM, INMT, GALNT15, GMPR, GNMT, MT1M, MTHFD2, PAPPA, PDK4, SLC6A1, ST6GALNAC3, SULT2B1, SULT1E1, TPO
<2/≥1.5	AASS, ABCA6, ADAMTS1, AKR1C1, AOX1, ATP6V1C2, BCAT1, CHPT1, CHST4, DIO3, ECI2, ENPP1, GALNT18, HSD11B2, LPL, MAN1C1, MAOA, MATN3, MT1X, MT2A, NAMPT, NNMT, PFKFB2, SAMHD1, SLC16A12, SLC16A14, SLC19A2, SLC22A15, SLC26A2, SLCO2B1, SLCO4A1, SPTSSA, TAT, TBXAS1
<1.5/≥1.25	ACSL1, AKR1C2, ANPEP, ARG2, ARSK, AS3MT, ATP10A, CA4, CHKA, CHST11, CORIN, CTH, CYP27A1, DCXR, ENPP3, ETNK2, GBA3, GFOD1, GFPT2, GGT5, GLUL, GNPTAB, GPM6B, GXYLT1, GXYLT2, HK1, HS6ST3, LOX, LPIN1, MAMDC2, MFNG, MGEA5, MGLL, MPC2, MT1A, MT1E, MT1F, MT1H, NOX4, NT5DC3, PAPLN, PAPPA, PAPSS2, PDXK, PHKA1, PNMT, PRDX6, PRODH, SEC14L5, SLC16A10, SLC25A25, SLC29A2, SLC31A2, SLC38A1, SLC4A7, SLC7A8, SLCO3A1, SORD, SQLE, ST3GAL1, TP53I3,
5. Other function	
≥2	CLDN8, LCN6, NID1
<2/≥1.5	ADAMDEC1, C1QB, CEP70, CNST, LAMA2, LAMA3, ELN, LCN10, PRELP, RNASE6
<1.5/≥1.25	CEP162, COL4A3, EPB41L5, LAMB1, MAP1LC3B, MYBPC1, MYO10, N4BP2, NINJ2, PLIN2, RIF1, RMI1, RPL4, SEPP1, SERPINF2, SHROOM3, SPAG4, SNORD16, SNORD18A, SNORD18B, SNORD18C, TCHP
6. Function not assigned	
≥2	FAM150B, FAM196A, FIBIN
<2/≥1.5	ARRDC2, C1orf162, C1orf168, CCDC85A, FAM198A, FAM21A, FAM21C, FNDC3B, FNDC3B, LOC101060254, LOC653513, MEI1, PRR15L, SMIM3, TM6SF1, TMEM132C, TMEM204, TMTC1,
<1.5/≥1.25	ANKHD1-EIF4EBP3, ARMC12, BTNL9, C15orf43, C16orf45, C1orf21, C20orf197, C2orf72, CCDC152, CCDC68, CDV3, COBLL1, FAM102A, FAM105A, FAM111A, FAM126B, FAM153B, FAM169A, FAM177A1, FAM180A, FAM213A, FAM46C, FAM63B, FLVCR2, GATSL3, GOLGA2P10, IGSF21, LINC00341, LINC01588, LOC100128751, LONRF2, NKAPL, NXPE3, RANBP3L, RCSD1, RFTN2, RSBN1, SPDYE6, SPRYD7, TMEM108, TMEM192, TMEM61, TNFAIP8L3, WDYHV1, YPEL1, ZNF609

The 889 probe sets showing ≥1.25 fold induction (*P*≤0.05) by budesonide in the biopsy microarray analysis were analyzed by the DAVID gene ID conversion tool to produce 588 separate identities. Using gene ontology (GO) information and functional information from NCBI Gene, gene symbols were categorized into six general groups: 1, Transcriptional control; 2, Membrane receptors; 3, Signaling and regulation of signaling; 4, Metabolic and metabolism; 5, Other function; or 6, Function not assigned and further sub-divided as indicated. Gene symbols that are underlined were tested by qPCR.

SUPPLEMENTAL TABLE 5

Probe sets corresponding to the 23 genes validated by qPCR as being significantly induced by inhaled budesonide in the biopsy samples

Gene	**qPCR (Fold)**	**Array data (Fold for each probe set)**	**Average array (Fold)**
ALOX15B	249.6***	2.34***, 1.86***, 1.42**, 1.05, 0.99	1.53
CD163	10.53***	6.89***	6.89
CDKN1C	1.43**	1.45***, 1.41***, 1.36**, 1.29*	1.38
CEBPD	2.13***	1.82***, 1.76***, 1.75***, 1.63***, 1.60***	1.71
CNR1	4.03***	2.55***, 0.99	1.77
CXCR4	4.26***	3.10***, 2.66**, 2.57**, 2.27**	2.65
DUSP1	2.22**	1.78*, 1.44, 1.19, 1.05	1.37
FAM150B	9.12***	5.89***	5.89
FKBP5	15.69***	13.41***, 12.47***, 11.18***, 6.52***, 3.94***, 1.24	8.13
IGF1	4.38***	2.91***, 2.65***, 1.40**, 1.40*, 1.25	1.92
KLF9	3.65***	3.33***, 3.08***, 1.18, 1.08	2.17
LIFR	2.04***	2.37***, 1.81**, 1.76***, 1.64***, 1.29*	1.78
NFKBIA	1.60***	1.53***, 1.46***, 1.38**	1.46
PDK4	3.92***	3.62***, 1.68**	2.65
PER1	3.91***	3.48***, 1.09, 1.00	1.19
RGS1	4.20***	2.17**, 1.22	1.69
RGS2	1.91**	1.46*	1.46
SLC45A1	1.75**	1.13	1.13
TFCP2L1	4.92***	3.00***, 2.77**, 2.45***	2.45
TLR2	2.04**	1.35***, 1.25**, 1.24**	1.28
TSC22D3	5.39***	4.06***, 3.83***, 2.77**	3.55
ZBTB16	16.32***	12.75***	12.75
ZFP36	1.96***	1.35 (*P* = 0.052)	1.35

qPCR data for the indicated genes were taken from Figs 1 - 3 and are displayed as fold of placebo. Using the microarray data presented in Fig. 1A of the main manuscript, all probe sets corresponding to each of the indicated genes were identified and the fold induction for the individual probe sets provided. The relationship between qPCR and array data are plotted in Supplemental Fig. 4. Significance for qPCR and array data is as described in Figures 1 - 3 of the main manuscript. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

SUPPLEMENTAL TABLE 6

Functional annotation clustering of genes significantly increased by ≥2 fold (FDR 0.05) by budesonide inhalation in bronchial biopsies

GO terms	**Genes**
Annotation cluster 1	
Reg of cell migration (*), Reg of locomotion (*), Reg of cell motion (*)	CXCR4, IGF1, PIK3R1, ALOX15B
Annotation cluster 2	
Purinergic nucleotide receptor activity - G-protein coupled (*), Nucleotide receptor activity - G-protein coupled (**), Integral to plasma membrane (**), Intrinsic to plasma membrane (**), Purinergic nucleotide receptor activity (**), Nucleotide receptor activity (**), Plasma membrane part (*), Rhodopsin-like G protein-coupled receptors, GPCR, rhodopsin-like superfamily, 7TM GPCR, rhodopsin-like, Plasma membrane, Cell surface receptor linked signal, transduction, Intrinsic to membrane, Integral to membrane, G-protein coupled receptor protein signaling pathway	ITGA10, GPR34, LIFR, CXCR4, CD163, TPO, CNR1, HCAR2/HCAR3, ADORA3, TPO, PKP2, IL17R, ZBTB16, CPM, PIK3R1, PAPPA, CLEC4E, TSC22D3, MS4A4A
Annotation cluster 3	
mTOR signaling pathway (*), Progesterone-mediated oocyte maturation (*), Intracellular signaling cascade	RPS6KA2, IGF1, PIK3R1, KLF9, CXCR4, CNR1, CIT
Annotation cluster 4	
Cytokine binding (*), Cytokine-cytokine receptor interaction (*), cell morphogenesis, Cellular component morphogenesis	LIFR, CXCR4, IL7R,TPO, IL7R, TFCP2L1
Annotation cluster 5	
Apoptosis, Programmed cell death, Cell death, Death	TSC22D3, JADE1, ZBTB16, CXCR4, HCAR2, HCAR3
Annotation cluster 6	
Lymphocyte activation, Leukocyte activation, Cell activation	CXCR4, PIK3R1, IL7R
Annotation cluster 7	
Hemopoiesis, Hemopoietic or lymphoid organ development, Immune system development	CXCR4, PIK3R1, IL7R
Annotation cluster 8	
Small GTPase regulator activity, GTPase regulator activity, Nucleoside-triphosphatase regulator activity	ERRFI1, RHOBTB3, CIT
Annotation cluster 9	
Response to wounding, Inflammatory response, Defense response	CXCR4, CD163, IGF1, ADORA3
Annotation cluster 10	
Transition metal ion binding, Metal ion binding, Cation binding, Ion binding, Zinc ion binding	KLF9, KLF15, MT1JP, MT1P3, JADE1, ZBTB16, PAPPA, TPO, MT1M, CIT, CPM, ALOX15B, ITGA10, MTHFD2, GMPR, RPS6KA2
Annotation cluster 11	
+ve reg of apoptosis, +ve reg of programmed cell death, +ve reg of cell death, Reg of cell proliferation, Reg of apoptosis, Reg of programmed cell death, Reg of cell death	ZBTB16, HCAR2/HCAR3, ALOX15B, LIFR, IGF1
Annotation cluster 12	
Transcription factor activity, Reg of transcription, DNA-dependent, Reg of RNA metabolic process, Transcription regulator activity, Reg of transcription, -ve reg of transcription, Transcription, -ve reg of gene expression, -ve reg of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process, -ve reg of nitrogen compound metabolic process, -ve reg of macromolecule biosynthetic process, -ve reg of cellular biosynthetic process, Zinc finger, C2H2-type/integrase, DNA-binding, -ve reg of biosynthetic process, Zinc finger, C2H2-type, Reg of transcription from RNA polymerase II promoter, Zinc finger, C2H2-like, -ve reg of macromolecule metabolic process, ZnF_C2H2, DNA binding	KLF9, KLF15, TSC22D3, TFCP2L1, HIF3A, ATAD2, PER1, IGF1, JADE1, ZBTB16,

The 72 probe sets meeting the expression criteria (≥2 fold, FDR 0.05) were analyzed using the DAVID gene ID conversion tool to provide a list of 46 up-regulated genes. Functional annotation clustering was performed in DAVID using a medium stringency. This produced 15 annotation clusters of which the top 12 are shown. GO terms mapping to each cluster are listed along with the total genes within each cluster. GO terms that are significantly associated with the gene list are indicated. * $P \leq 0.05$, ** $P \leq 0.01$. Abbreviations: Reg = regulation, -ve = negative, +ve = positive.

SUPPLEMENTAL TABLE 7

Gene ontology (GO) terms used and not used in Fig. 2

1A. GO terms used in Figure 2A – Budesonide up-regulated genes (≥2 fold, *P*≤0.05)
Transcription: GO:0032583~regulation of gene-specific transcription; GO:0016481~negative regulation of transcription; GO:0010629~negative regulation of gene expression; GO:0045944~positive regulation of transcription from RNA polymerase II promoter**; GO:0010628~positive regulation of gene expression*; GO:0006357~regulation of transcription from RNA, polymerase II promoter**; GO:0045449~regulation of transcription *Signaling:* GO:0034097~response to cytokine stimulus*; GO:0001817~regulation of cytokine production; GO:0000165~MAPKKK cascade; GO:0033674~positive regulation of kinase activity; hsa04060:Cytokine-cytokine receptor interaction; GO:0009968~negative regulation of signal transduction*; GO:0007169~transmembrane receptor protein tyrosine kinase signaling pathway**; GO:0043549~regulation of kinase activity; GO:0007167~enzyme linked receptor protein signaling pathway**; GO:0007243~protein kinase cascade**; GO:0006468~protein amino acid phosphorylation**; GO:0007242~intracellular signaling cascade* *Metabolism:* GO:0010827~regulation of glucose transport*; GO:0010906~regulation of glucose metabolic process*; GO:0006109~regulation of carbohydrate metabolic process*; GO:0005996~monosaccharide metabolic process; GO:0051347~positive regulation of transferase activity; GO:0051050~positive regulation of transport*; GO:0051338~regulation of transferase activity; GO:0045934~negative regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process; GO:0010605~negative regulation of macromolecule metabolic process*; GO:0045935~positive regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process**; GO:0010604~positive regulation of macromolecule metabolic process* *Proliferation, apoptosis and death:* GO:0045786~negative regulation of cell cycle*; GO:0008361~regulation of cell size; GO:0045596~negative regulation of cell differentiation; GO:0045597~positive regulation of cell differentiation*; GO:0040008~regulation of growth; GO:0000902~cell morphogenesis; GO:0051726~regulation of cell cycle; GO:0008285~negative regulation of cell proliferation; GO:0008284~positive regulation of cell proliferation; GO:0009611~response to wounding; GO:0042981~regulation of apoptosis; GO:0042127~regulation of cell proliferation** *Defence and immune:* GO:0045321~leukocyte activation; GO:0002684~positive regulation of immune system process; GO:0006954~inflammatory response; GO:0006952~defense response; GO:0006955~immune response *Cell motion, migration:* GO:0030335~positive regulation of cell migration**; GO:0040017~positive regulation of locomotion***; GO:0030334~regulation of cell migration***; GO:0040012~regulation of locomotion***; GO:0006928~cell motion *Other:* hsa04960:Aldosterone-regulated sodium reabsorption**; hsa04910:Insulin signaling pathway; GO:0048545~response to steroid hormone stimulus; hsa04510:Focal adhesion; GO:0030036~actin cytoskeleton organization; GO:0031175~neuron projection development; GO:0001944~vasculature development; GO:0001501~skeletal system development; GO:0048666~neuron development; hsa05200:Pathways in cancer; GO:0051094~positive regulation of developmental process*; GO:0009725~response to hormone stimulus*
1B. GO terms not used in Figure 2A – Budesonide up-regulated genes (≥2 fold, *P*≤0.05)
GO:0035295~tube development; GO:0044057~regulation of system process; GO:0051240~positive regulation of multicellular organismal process; GO:0009719~response to endogenous stimulus; GO:0010035~response to inorganic substance*; GO:0044093~positive regulation of molecular function; GO:0048878~chemical homeostasis; GO:0030029~actin filament-based process; GO:0051270~regulation of cell motion***; GO:0010033~response to organic substance**; GO:0042592~homeostatic process; GO:0040007~growth; GO:0001558~regulation of cell growth; GO:0043068~positive regulation of programmed cell death; GO:0010942~positive regulation of cell death; GO:0012501~programmed cell death; GO:0043067~regulation of programmed cell death; GO:0010941~regulation of cell death; GO:0008219~cell death; GO:0016265~death; GO:0010558~negative regulation of macromolecule biosynthetic process**; GO:0031327~negative regulation of cellular biosynthetic process**; GO:0010557~positive regulation of macromolecule biosynthetic process**; GO:0031328~positive regulation of cellular biosynthetic process*; GO:0048584~positive regulation of response to stimulus; GO:0051174~regulation of phosphorus metabolic process*; GO:0019220~regulation of phosphate metabolic process*; GO:0006793~phosphorus metabolic process**; GO:0006366~transcription from RNA polymerase II promoter; GO:0045892~negative regulation of transcription, DNA-dependent; GO:0045893~positive regulation of transcription, DNA-dependent**; GO:0051252~regulation of RNA metabolic process; GO:0046324~regulation of glucose import*; GO:0051254~positive regulation of RNA metabolic process**; GO:0045941~positive regulation of transcription**; GO:0006355~regulation of transcription, DNA-dependent; GO:0050865~regulation of cell activation; GO:0045860~positive regulation of protein kinase activity; GO:0001775~cell activation; GO:0045859~regulation of protein kinase activity; GO:0042325~regulation of phosphorylation*; GO:0006796~phosphate metabolic process**; GO:0010648~negative regulation of cell communication*; GO:0010675~regulation of cellular carbohydrate metabolic process*; GO:0051172~negative

regulation of nitrogen compound metabolic process; GO:0009890~negative regulation of biosynthetic process**; GO:0051173~positive regulation of nitrogen compound metabolic process**; GO:0009891~positive regulation of biosynthetic process*; GO:0000904~cell morphogenesis involved in differentiation; GO:0032989~cellular component morphogenesis; GO:0008283~cell proliferation; GO:0006915~apoptosis; GO:0051249~regulation of lymphocyte activation; GO:0046649~lymphocyte activation; GO:0001568~blood vessel development;GO:0051272~positive regulation of cell motion**; GO:0006350~transcription; GO:0051253~negative regulation of RNA metabolic process; GO:0016310~phosphorylation**; GO:0031399~regulation of protein modification process; GO:0001932~regulation of protein amino acid phosphorylation; GO:0043065~positive regulation of apoptosis; GO:0002694~regulation of leukocyte activation; GO:0030030~cell projection organization; GO:0003006~reproductive developmental process; GO:0032535~regulation of cellular component size
2. GO terms associated with (*P*≤0.05) Budesonide down-regulated genes (≤0.5 fold, *P*≤0.05)
Transcription: No GO terms *Signaling:* GO:0007166~cell surface receptor linked signal transduction; GO:0007186~G-protein coupled receptor protein signaling pathway; GO:0032101~regulation of response to external stimulus; GO:0019932~second-messenger-mediated signaling; GO:0005125~cytokine activity***; GO:0008009~chemokine activity**; GO:0042379 ~chemokine receptor binding**; GO:0048019~receptor antagonist activity; GO:0030547~receptor inhibitor activity; GO:0030545~receptor regulator activity; hsa04060:Cytokine-cytokine receptor interaction**; hsa04062:Chemokine signaling pathway** *Metabolism:* GO:0030574~collagen catabolic process; GO:0032963~collagen metabolic process; GO:0044259~multicellular organismal macromolecule metabolic process; GO:0044236~multicellular organismal metabolic process; GO:0044243~multicellular organismal catabolic process *Proliferation, apoptosis and death:* GO:0008284~positive regulation of cell proliferation *Defence and immune:* GO:0009611~response to wounding***; GO:0006952~defense response***; GO:0006954~ inflammatory response***; GO:0006955~immune response; GO:0002684~positive regulation of immune system process *Cell motion, migration:* GO:0007155~cell adhesion**; GO:0022610~biological adhesion**; GO:0042330~taxis***; GO:0006935~chemotaxis***; GO:0007626~locomotory behavior**; GO:0016477~cell migration*; GO:0048870~cell motility*; GO:0051674~localization of cell*; GO:0006928~cell motion*; GO:0050900~leukocyte migration**; GO:0016337~cell-cell adhesion; GO:0050901~leukocyte tethering or rolling; GO:0045123~cellular extravasation GO:0007157~heterophilic cell adhesion; GO:0007159~leukocyte adhesion; GO:0030595~leukocyte chemotaxis; GO:0060326~cell chemotaxis *Other:* GO:0007610~behavior**; GO:0010033~response to organic substance*; GO:0006874~cellular calcium ion homeostasis*; GO:0055074~calcium ion homeostasis*; GO:0048545~response to steroid hormone stimulus*; GO:0006875~cellular metal ion homeostasis*; GO:0055065~metal ion homeostasis*; GO:0030005~cellular di-, tri-valent inorganic cation homeostasis; GO:0055066~di-, tri-valent inorganic cation homeostasis; GO:0030003~cellular cation homeostasis; GO:0055080~cation homeostasis; GO:0009725~response to hormone stimulus; GO:0006873 ~cellular ion homeostasis; GO:0055082~cellular chemical homeostasis; GO:0009719~response to endogenous stimulus; GO:0050801~ion homeostasis; GO:0019725~cellular homeostasis; GO:0048878~chemical homeostasis

The 889 probe sets showing ≥1.25 fold induction (*P*≤0.05) by budesonide (Supplemental Table 3) in the microarray analysis depicted in Fig. 2 were analyzed using the DAVID gene identity conversion tool. This produced 588 separate gene identities, which were analyzed using the DAVID functional annotation tool (default settings, medium stringency) and resulted in 647 GO terms containing at least 2 gene symbols each. Of these, 420 were significantly associated (*P*≤0.05) with the gene list and 235 corresponded to GO terms for biological process (GOTERM_BP_FAT) or KEGG (KEGG_PATHWAY). Selected terms used to generate Fig. 2A are listed above (Supplemental Table 7, part 1A). Significantly associated terms not used in Fig. 2A are listed (Supplemental Table 7, part 1B). Terms showing significant fold enrichment, Benjamini ≤0.05, ≤0.01 & ≤0.001, with budesonide inhalation are indicated (*, **, and *** respectively). An identical analysis was also performed on the 35 probe sets down-regulated ≤0.5 fold (*P*≤0.05) by inhaled budesonide. The 28 genes thus identified were subjected to functional annotation to give 107 GO terms that were significantly associated with the probe list. Of these 57 correspond to biological process (GOTERM_BP_FAT) or KEGG (KEGG_PATHWAY) or molecular function (GOTERM_MF_FAT) and are listed above (Supplemental Table 7, part 2). Selected terms are used in Figure 2C. Terms showing significant fold enrichment, Benjamini ≤0.05, ≤0.01 & ≤0.001, with budesonide are indicated (*, **, and *** respectively).

SUPPLEMENTAL TABLE 8

Functional cluster analysis with the 588 budesonide up-regulated (≥1.25, *P*≤0.05) genes

Cluster 1	**Enrichment Score: 5.53**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0040012~regulation of locomotion	4.15	3.48E-08	ALOX15B, CITED2, CXCR4, ERBB4, F2R, F3, IGF1, IGFBP5, IL16, IL6R, IL6ST, INSR, IRS2, LAMA2, LAMA3, LAMB1, PDGFRA, PIK3R1, PRKCA, PTK2B, PTPRM, SLIT2, SPAG9, TGFBR3	3.98	8.39E-05
GO:0030334~regulation of cell migration	3.63	3.35E-07	ALOX15B, CITED2, CXCR4, ERBB4, F2R, F3, IGF1, IGFBP5, IL6R, IL6ST, INSR, IRS2, LAMA2, LAMA3, LAMB1, PDGFRA, PIK3R1, PTK2B, PTPRM, SPAG9, TGFBR3	3.96	4.04E-04
GO:0040017~positive regulation of locomotion	2.76	3.66E-07	ERBB4, F2R, F3, IGF1, IL16, IL6R, IL6ST, INSR, IRS2, LAMB1, PDGFRA, PIK3R1, PRKCA, PTK2B, SLIT2, SPAG9	5.20	2.94E-04
GO:0051270~regulation of cell motion	3.80	7.03E-07	ALOX15B, BCL6, CITED2, CXCR4, ERBB4, F2R, F3, IGF1, IGFBP5, IL6R, IL6ST, INSR, IRS2, LAMA2, LAMA3, LAMB1, PDGFRA, PIK3R1, PTK2B, PTPRM, SPAG9, TGFBR3	3.63	4.23E-04
GO:0051272~positive regulation of cell motion	2.42	1.12E-05	BCL6, ERBB4, F2R, F3, IGF1, IL6R, IL6ST, INSR, IRS2, LAMB1, PDGFRA, PIK3R1, PTK2B, SPAG9	4.55	0.0026938
GO:0030335~positive regulation of cell migration	2.25	2.06E-05	ERBB4, F2R, F3, IGF1, IL6R, IL6ST, INSR, IRS2, LAMB1, PDGFRA, PIK3R1, PTK2B, SPAG9	4.65	0.0032989
GO:0008284~positive regulation of cell proliferation	4.32	0.003	BCL6, CD86, EBI3, ERBB4, F2R, F3, FLT3, FOSL2, HIPK2, IGF1, IL6R, IL6ST, INSR, IRS2, ITGB1, LAMB1, LIFR, NAMPT, NAP1L1, PDGFRA, PPP1CB, PRKCA, PTK2B, RUNX2, TNFSF4	1.92	0.1180929
Cluster 2	**Enrichment Score: 5.47**				
Term	**%**	***P***		**Fold**	**Benjamini**
PIRSF002564:metallothionein	1.21	2.86E-07	MT1A, MT1E, MT1F, MT1H, MT1JP, MT1M, MT1P3, MT1X, MT2A	21.01	7.44E-05
IPR018064:Metallothionein, vertebrate, metal binding site	1.21	3.17E-07	MT1A, MT1E, MT1F, MT1H, MT1JP, MT1M, MT1P3, MT1X, MT2A	20.83	2.72E-04
IPR000006:Metallothionein, vertebrate	1.21	6.17E-07	MT1A, MT1E, MT1F, MT1H, MT1JP, MT1M, MT1P3, MT1X, MT2A	19.09	2.65E-04
IPR003019:Metallothionein superfamily, eukaryotic	1.21	6.17E-07	MT1A, MT1E, MT1F, MT1H, MT1JP, MT1M, MT1P3, MT1X, MT2A	19.09	2.65E-04
GO:0046870~cadmium ion binding	1.04	6.94E-06	MT1A, MT1E, MT1F, MT1H, MT1JP, MT1M, MT1P3, MT1X	18.86	0.0047356
GO:0005507~copper ion binding	1.38	0.006	LOX, MT1A, MT1E, MT1F, MT1H, MT1JP, MT1M, MT1P3, MT1X, SLC31A2	3.64	0.3170694
Cluster 3	**Enrichment Score: 3.61**				
Term	**%**	***P***		**Fold**	**Benjamini**
IPR017441:Protein kinase, ATP binding site	5.87	4.06E-06	AKAP9, AKT3, BLK, CAMK2B, CIT, CSF1R, DAPK1, ERBB4, FGR, FLT3, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA, PRKCA, PTK2B, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO, TXK, UHMK1, WNK1, ZAK	2.45	0.0011636
IPR000719:Protein kinase, core	5.87	1.05E-05	AKAP9, AKT3, BLK, CAMK2B, CIT, CSF1R, DAPK1, ERBB4, FGR, FLT3, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA, PRKCA, PTK2B, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO, TXK, UHMK1, WNK1, ZAK	2.34	0.0022478
IPR008266:Tyrosine protein kinase, active site	2.07	1.77E-4	BLK, CSF1R, ERBB4, FGR, FLT3, INSR, MERTK, NTRK3, PDGFRA, PTK2B, ROR1, TXK	4.05	0.0251222
IPR001245:Tyrosine protein kinase	2.25	2.58E-4	BLK, CSF1R, ERBB4, FGR, FLT3, INSR, MERTK, NTRK3, PDGFRA, PTK2B, ROR1, TXK, ZAK	3.61	0.0312315
SM00219:TyrKc	2.25	7.38E-4	BLK, CSF1R, ERBB4, FGR, FLT3, INSR, MERTK, NTRK3, PDGFRA, PTK2B, ROR1, TXK, ZAK	3.19	0.0683906
GO:0004714~transmembrane receptor protein tyrosine kinase activity	1.38	0.005	CSF1R, ERBB4, FLT3, INSR, MERTK, NTRK3, PDGFRA, ROR1	3.75	0.3000027
GO:0004713~protein tyrosine kinase activity	2.25	0.007	BLK, CSF1R, ERBB4, FGR, FLT3, INSR, MERTK, NTRK3, PDGFRA, PTK2B, ROR1, TXK, ZAK	2.46	0.2971148
Cluster 4	**Enrichment Score: 3.46**				
Term	**%**	***P***		Fold	Benjamini
GO:0051254~positive regulation of	6.04	8.48E-06	APBB1, ARNTL, ATXN7, BMP2, CITED2, CSRNP1, ERCC6, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, KLF13, KLF15, KLF6,	2.32	0.002269

RNA metabolic process			KLF7, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PIAS1, PPARGC1A, RORA, RUNX2, TCF21, TFEB, THRA, TTF1, ZBTB38		
GO:0045935~positive regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	7.08	1.38E-05	APBB1, ARNTL, ATXN7, BMP2, CD86, CITED2, CSRNP1, ERCC6, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, INSR, KLF13, KLF15, KLF2, KLF6, KLF7, MAFB, MGEA5, NFIB, NFIC, NFKBIA, NR2E3, PDGFRA, PIAS1, PPARGC1A, RORA, RUNX2, TBX21, TCF21, TFEB, THRA, TTF1, ZBTB38	2.09	0.0030251
GO:0045944~positive regulation of transcription from RNA polymerase II promoter	5.01	1.63E-05	APBB1, ARNTL, ATXN7, BMP2, CITED2, CSRNP1, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, KLF13, KLF6, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PPARGC1A, RORA, RUNX2, TFEB, THRA, TTF1, ZBTB38	2.49	0.0030236
GO:0045893~positive regulation of transcription, DNA-dependent	5.87	1.76E-05	APBB1, ARNTL, ATXN7, BMP2, CITED2, CSRNP1, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, KLF13, KLF15, KLF6, KLF7, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PIAS1, PPARGC1A, RORA, RUNX2, TCF21, TFEB, THRA, TTF1, ZBTB38	2.27	0.0030343
GO:0051173~positive regulation of nitrogen compound metabolic process	7.08	2.85E-05	APBB1, ARNTL, ATXN7, BMP2, CD86, CITED2, CSRNP1, ERCC6, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, INSR, KLF13, KLF15, KLF2, KLF6, KLF7, MAFB, MGEA5, NFIB, NFIC, NFKBIA, NR2E3, PDGFRA, PIAS1, PPARGC1A, RORA, RUNX2, TBX21, TCF21, TFEB, THRA, TTF1, ZBTB38	2.03	0.0036155
GO:0010557~positive regulation of macromolecule biosynthetic process	7.08	4.03E-05	APBB1, ARNTL, ATXN7, BMP2, CD86, CITED2, CSRNP1, EBI3, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, INSR, IRS2, KLF13, KLF15, KLF2, KLF6, KLF7, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PDGFRA, PIAS1, PPARGC1A, PTK2B, RORA, RUNX2, TCF21, TFEB, THRA, TTF1, ZBTB38	2.00	0.0048431
GO:0006357~regulation of transcription from RNA polymerase II promoter	7.60	4.45E-05	APBB1, ARNTL, ASCL3, ATF5, ATXN7, BCL6, BMP2, CDKN1C, CITED2, CSRNP1, FOSL2, FOXO1, FOXO3, FOXO3B, GLIS3, GZF1, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, KLF13, KLF6, KLF7, KLF9, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PPARGC1A, RORA, RUNX2, SIK1, SLA2, SMARCD2, SPEN, TFCP2L1, TFEB, THRA, TTF1, ZBTB38, ZFHX3, ZNF157	1.93	0.005101
GO:0045941~positive regulation of transcription	6.22	9.30E-05	APBB1, ARNTL, ATXN7, BMP2, CD86, CITED2, CSRNP1, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, KLF13, KLF15, KLF2, KLF6, KLF7, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PIAS1, PPARGC1A, RORA, RUNX2, TCF21, TFEB, THRA, TTF1, ZBTB38	2.03	0.0089283
GO:0031328~positive regulation of cellular biosynthetic process	7.08	1.10E-4	APBB1, ARNTL, ATXN7, BMP2, CD86, CITED2, CSRNP1, EBI3, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, INSR, IRS2, KLF13, KLF15, KLF2, KLF6, KLF7, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PDGFRA, PIAS1, PPARGC1A, PTK2B, RORA, RUNX2, TCF21, TFEB, THRA, TTF1, ZBTB38	1.91	0.0101749
GO:0010604~positive regulation of macromolecule metabolic process	8.29	1.25E-4	APBB1, ARNTL, ATXN7, BMP2, CCND3, CD86, CITED2, CSRNP1, EBI3, ERCC6, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, IL6R, IL6ST, INHBA, INSR, IRS2, KLF13, KLF15, KLF2, KLF6, KLF7, MAFB, MGEA5, NFIB, NFIC, NFKBIA, NR2E3, PDGFRA, PIAS1, PPARGC1A, PRKCA, PTK2B, RORA, RUNX2, TBX21, TCF21, TFEB, THRA, TTF1, ZBTB38	1.78	0.0107249
GO:0009891~positive regulation of biosynthetic process	7.08	1.50E-4	APBB1, ARNTL, ATXN7, BMP2, CD86, CITED2, CSRNP1, EBI3, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, INSR, IRS2, KLF13, KLF15, KLF2, KLF6, KLF7, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PDGFRA, PIAS1, PPARGC1A, PTK2B, RORA, RUNX2, TCF21, TFEB, THRA, TTF1, ZBTB38	1.88	0.0123974
GO:0010628~positive regulation of gene expression	6.22	1.65E-4	APBB1, ARNTL, ATXN7, BMP2, CD86, CITED2, CSRNP1, F2R, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, KLF13, KLF15, KLF2, KLF6, KLF7, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PIAS1, PPARGC1A, RORA, RUNX2, TCF21, TFEB, THRA, TTF1, ZBTB38	1.97	0.0123702
GO:0006355~regulation of transcription, DNA-dependent	13.47	0.002	APBB1, ARNTL, ASCL3, ATF5, ATRX, ATXN7, BATF, BCL6, BMP2, CDKN1C, CEBPD, CITED2, CREBRF, CSRNP1, ERCC6, F2R, FOSL2, FOXN2, FOXO1, FOXO3, FOXO3B, GLIS3, GZF1, HAND2, HIF3A, HIPK2, HMGB2, IGF1, IKZF1, INHBA, INSR, IRX3, KLF13, KLF15, KLF6, KLF7, KLF9, MAFB, NFATC2IP, NFIA, NFIB, NFIC, NFIL3, NFKBIA, NR2E3, PBX4, PER1, PIAS1, PPARGC1A, RORA, RPS6KA5, RUNX2, SIK1, SLA2, SMARCD2, SPEN, TBX21, TCF21, TFCP2L1, TFEB, THRA, TNFSF4, TSC22D3, TTF1, ZBTB16, ZBTB38, ZFHX3, ZHX3, ZNF157, ZNF234, ZNF275, ZNF320, ZNF331, ZNF540, ZNF561, ZNF57, ZNF682, ZNF763, ZNF844	1.40	0.0801575
GO:0051252~regulation of RNA metabolic process	13.64	0.002	APBB1, ARNTL, ASCL3, ATF5, ATRX, ATXN7, BATF, BCL6, BMP2, CDKN1C, CEBPD, CELF6, CITED2, CREBRF, CSRNP1, ERCC6, F2R, FOSL2, FOXN2, FOXO1, FOXO3, FOXO3B, GLIS3, GZF1, HAND2, HIF3A, HIPK2, HMGB2, IGF1, IKZF1, INHBA, INSR, IRX3, KLF13, KLF15, KLF6, KLF7, KLF9, MAFB, NFATC2IP, NFIA, NFIB, NFIC, NFIL3, NFKBIA, NR2E3, PBX4, PER1, PIAS1, PPARGC1A, RORA, RPS6KA5, RUNX2, SIK1, SLA2, SMARCD2, SPEN, TBX21, TCF21, TFCP2L1, TFEB, THRA, TNFSF4, TSC22D3, TTF1, ZBTB16, ZBTB38, ZFHX3, ZHX3, ZNF157, ZNF234, ZNF275, ZNF320, ZNF331, ZNF540, ZNF561, ZNF57, ZNF682, ZNF763, ZNF844	1.39	0.0911902
GO:0003700~transcription factor activity	7.94	0.007	ARNTL, ATAD2, ATF5, BATF, BCL6, CEBPD, CITED2, CREBRF, CSRNP1, FOSL2, FOXN2, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIF3A, HMGB2, IKZF1, IRX3, KLF15, KLF2, KLF6, KLF7, KLF9, MAFB, MYEF2, NFIA, NFIB, NFIC, NFIL3, NR2E3, PBX4,	1.48	0.2910864

			RORA, RUNX2, SPEN, TBX21, TCF21, TFCP2L1, TFEB, THRA, TSC22D3, ZBTB16, ZBTB38, ZFHX3, ZHX3, ZNF157		
GO:0045449~regulation of transcription	17.62	0.010	AFF3, APBB1, ARNTL, ASCL3, ATAD2, ATF5, ATOH8, ATRX, ATXN7, BATF, BCL6, BMP2, CAMTA1, CD86, CDKN1C, CEBPD, CITED2, CREBRF, CRY2, CSRNP1, EID3, ERCC6, F2R, FAM120B, FOSL2, FOXN2, FOXO1, FOXO3, FOXO3B, GLIS3, GZF1, HAND2, HIF3A, HIPK2, HMGB2, IGF1, IKZF1, IL16, INHBA, INSR, IRAK3, IRX3, JADE1, KLF13, KLF15, KLF2, KLF6, KLF7, KLF9, MAFB, NFATC2IP, NFIA, NFIB, NFIC, NFIL3, NFKBIA, NR2E3, PBX4, PER1, PIAS1, POU2AF1, PPARGC1A, PRR15L, RORA, RPS6KA5, RUNX2, SCML4, SIK1, SLA2, SMARCD2, SNAPC3, SPEN, TBX21, TCF21, TFCP2L1, TFEB, TGFBR3, THRA, TLR2, TNFSF4, TOX2, TSC22D3, TSPYL2, TTF1, VGLL3, ZBTB16, ZBTB20, ZBTB38, ZBTB8A, ZFHX3, ZHX3, ZNF157, ZNF234, ZNF275, ZNF320, ZNF331, ZNF540, ZNF561, ZNF57, ZNF652, ZNF682, ZNF763, ZNF844	1.25	0.2210508
GO:0030528~transcription regulator activity	11.05	0.014	ARNTL, ASCL3, ATAD2, ATF5, ATOH8, BATF, BCL6, BMP2, CAMTA1, CD86, CDKN1C, CEBPD, CITED2, CREBRF, CSRNP1, ERCC6, FHL5, FOSL2, FOXN2, FOXO1, FOXO3, FOXO3B, GLIS3, HAND2, HIF3A, HIPK2, HMGB2, IKZF1, IRX3, KLF13, KLF15, KLF2, KLF6, KLF7, KLF9, MAFB, MYEF2, NFIA, NFIB, NFIC, NFIL3, NR2E3, PBX4, PIAS1, POU2AF1, PPARGC1A, RORA, RUNX2, SIK1, SMARCD2, SPEN, TBX21, TCF21, TFCP2L1, TFEB, THRA, TOB1, TSC22D3, TTF1, VGLL3, ZBTB16, ZBTB38, ZFHX3, ZHX3, ZNF157	1.33	0.436208
GO:0006350~transcription	13.82	0.044	AFF3, APBB1, ARNTL, ASCL3, ATAD2, ATF5, ATOH8, ATXN7, BATF, BCL6, CAMTA1, CEBPD, CITED2, CRY2, CSRNP1, EID3, ERCC6, FAM120B, FOXN2, FOXO1, FOXO3, FOXO3B, GLIS3, GZF1, HAND2, HIF3A, HIPK2, IKZF1, IL16, JADE1, KLF13, KLF15, KLF2, KLF6, KLF7, KLF9, MAFB, MYEF2, NFIA, NFIB, NFIC, NFIL3, NR2E3, PBX4, PER1, PIAS1, POU2AF1, PPARGC1A, RORA, RUNX2, SCML4, SMARCD2, SNAPC3, SPEN, TBX21, TCF21, TFCP2L1, TFEB, THRA, TOX2, TSPYL2, TTF1, VGLL3, ZBTB16, ZBTB20, ZBTB38, ZBTB8A, ZFHX3, ZHX3, ZNF157, ZNF234, ZNF275, ZNF320, ZNF331, ZNF540, ZNF561, ZNF57, ZNF652, ZNF682, ZNF763, ZNF844	1.21	0.4553421
GO:0003677~DNA binding	13.82	0.274	AFF3, ARNTL, ASCL3, ATAD2, ATF5, ATOH8, ATRX, BATF, BCL6, CEBPD, CITED2, CREBRF, CSRNP1, ERCC6, FOSL2, FOXN2, FOXO1, FOXO3, FOXO3B, GLIS3, GZF1, HAND2, HIF3A, HMGB2, IKZF1, IRX3, KLF13, KLF15, KLF2, KLF6, KLF7, KLF9, LMO2, MAFB, MYEF2, NFIA, NFIB, NFIC, NFIL3, NR2E3, PBX4, PIAS1, POU2AF1, PPARGC1A, RORA, RUNX2, SCML4, SNAPC3, SPEN, STOX1, TBX21, TCF21, TFCP2L1, TFEB, THRA, TOX, TOX2, TOX3, TSC22D3, TSPYL2, TTF1, ZBTB16, ZBTB20, ZBTB38, ZBTB8A, ZFAND5, ZFHX3, ZFR, ZHX3, ZNF157, ZNF234, ZNF275, ZNF320, ZNF331, ZNF540, ZNF561, ZNF57, ZNF652, ZNF682, ZNF763, ZNF844	1.08	0.9096808
Cluster 5	**Enrichment Score: 2.89**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0019955~cytokine binding	2.07	6.77E-4	CMKLR1, CSF1R, CSF2RA, CXCR4, EBI3, GFRA1, IL1R1, IL6R, IL6ST, IL7R, LIFR, TGFBR3	3.46	0.143049
GO:0004896~cytokine receptor activity	1.38	0.002	CSF2RA, EBI3, GFRA1, IL1R1, IL6R, IL6ST, IL7R, LIFR	4.57	0.205317
GO:0019838~growth factor binding	1.90	0.002	CTGF, IGFBP5, IL1R1, IL6R, IL6ST, IL7R, INSR, LIFR, NTRK3, PDGFRA, TGFBR3	3.29	0.1881942
Cluster 6	**Enrichment Score: 2.73**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0006468~protein amino acid phosphorylation	7.77	2.35E-06	ADRA2C, AKAP9, AKT3, BLK, BMP2, CAMK2B, CIT, CSF1R, CXCR4, DAPK1, ERBB4, ERCC6, F2R, FGD4, FGR, FLT3, GADD45B, GADD45G, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA, PDK4, PRKCA, PTK2B, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, SPAG9, TAOK1, TGFBR3, TRIO, TXK, UHMK1, WNK1, ZAK	2.15	0.0011307
GO:0006796~phosphate metabolic process	10.02	3.12E-06	ADRA2C, AKAP9, AKT3, ATP6V1C2, BLK, BMP2, CAMK2B, CIT, CSF1R, CXCR4, DAPK1, DUSP1, ENPP1, ENPP3, ERBB4, ERCC6, F2R, FGD4, FGR, FLT3, GADD45B, GADD45G, GNPTAB, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA, PDK4, PIK3R1, PPM1B, PPM1K, PPP1CB, PRKCA, PTK2B, PTPDC1, PTPN5, PTPRG, PTPRM, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, SPAG9, TAOK1, TGFBR3, TRIO, TXK, UHMK1, WNK1, ZAK	1.90	0.0012524
GO:0006793~phosphorus metabolic process	10.02	3.12E-06	ADRA2C, AKAP9, AKT3, ATP6V1C2, BLK, BMP2, CAMK2B, CIT, CSF1R, CXCR4, DAPK1, DUSP1, ENPP1, ENPP3, ERBB4, ERCC6, F2R, FGD4, FGR, FLT3, GADD45B, GADD45G, GNPTAB, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA, PDK4, PIK3R1, PPM1B, PPM1K, PPP1CB, PRKCA, PTK2B, PTPDC1, PTPN5, PTPRG, PTPRM, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, SPAG9, TAOK1, TGFBR3, TRIO, TXK, UHMK1, WNK1, ZAK	1.90	0.0012524
IPR017441:Protein kinase, ATP binding site	5.87	4.06E-06	AKAP9, AKT3, BLK, CAMK2B, CIT, CSF1R, DAPK1, ERBB4, FGR, FLT3, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA, PRKCA, PTK2B, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO, TXK, UHMK1, WNK1, ZAK	2.45	0.0011636
IPR000719:Protein kinase, core	5.87	1.05E-05	AKAP9, AKT3, BLK, CAMK2B, CIT, CSF1R, DAPK1, ERBB4, FGR, FLT3, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA, PRKCA, PTK2B, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO, TXK, UHMK1, WNK1, ZAK	2.34	0.0022478
GO:0016310~phosphorylation	8.29	2.32E-05	ADRA2C, AKAP9, AKT3, ATP6V1C2, BLK, BMP2, CAMK2B, CIT, CSF1R, CXCR4, DAPK1, ERBB4, ERCC6, F2R, FGD4, FGR, FLT3, GADD45B, GADD45G, GNPTAB, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA,	1.91	0.0032855

			PDK4, PIK3R1, PRKCA, PTK2B, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, SPAG9, TAOK1, TGFBR3, TRIO, TXK, UHMK1, WNK1, ZAK		
GO:0004672~protein kinase activity	6.74	4.73E-05	AKAP13, AKAP9, AKT3, BLK, CAMK2B, CCND3, CIT, CSF1R, DAPK1, ERBB4, FGR, FLT3, HIPK2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, NIM1K, NTRK3, PAK3, PDGFRA, PDK4, PHKA1, PRKCA, PTK2B, ROR1, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TGFBR3, TRIO, TXK, UHMK1, WNK1, ZAK	2.02	0.0160494
GO:0004674~protein serine/threonine kinase activity	4.49	0.003	AKAP13, AKAP9, AKT3, CAMK2B, CCND3, CIT, DAPK1, HIPK2, IRAK3, LATS2, MAP3K6, MKNK2, NIM1K, PAK3, PHKA1, PRKCA, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TGFBR3, TRIO, UHMK1, WNK1, ZAK	1.90	0.2040827
IPR008271:Serine/threonine protein kinase, active site	3.80	0.003	AKAP9, AKT3, CAMK2B, CIT, DAPK1, HIPK2, IRAK3, LATS2, MAP3K6, MKNK2, NIM1K, PAK3, PRKCA, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO, UHMK1, WNK1, ZAK	2.03	0.2065896
IPR002290:Serine/threonine protein kinase	2.94	0.006	AKT3, CAMK2B, CIT, DAPK1, HIPK2, LATS2, MAP3K6, MKNK2, NIM1K, PAK3, PRKCA, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO	2.15	0.3123145
IPR017442:Serine/threonine protein kinase-related	3.63	0.007	AKAP9, AKT3, CAMK2B, CIT, DAPK1, HIPK2, IRAK3, LATS2, MAP3K6, MKNK2, NIM1K, PAK3, PRKCA, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO, UHMK1, WNK1	1.91	0.3242472
SM00220:S_TKc	2.94	0.017	AKT3, CAMK2B, CIT, DAPK1, HIPK2, LATS2, MAP3K6, MKNK2, NIM1K, PAK3, PRKCA, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO	1.90	0.427538
GO:0001883~purine nucleoside binding	10.88	0.054	ABCA6, ACSL1, AKAP9, AKT3, AOX1, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CHKA, CIT, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GLUL, HIPK2, HK1, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYO10, N4BP2, NIM1K, NOX4, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PRKCA, PRR15L, PTK2B, RAPGEF3, RHOB, RHOBTB3, ROR1, RPS6KA2, RPS6KA5, RUNX2, SGK1, SIK1, SQLE, TAOK1, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.24	0.7326692
GO:0030554~adenyl nucleotide binding	10.71	0.057	ABCA6, ACSL1, AKAP9, AKT3, AOX1, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CHKA, CIT, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GLUL, HIPK2, HK1, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYO10, N4BP2, NIM1K, NOX4, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PRKCA, PRR15L, PTK2B, RAPGEF3, RHOBTB3, ROR1, RPS6KA2, RPS6KA5, RUNX2, SGK1, SIK1, SQLE, TAOK1, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.24	0.7060824
GO:0001882~nucleoside binding	10.88	0.062	ABCA6, ACSL1, AKAP9, AKT3, AOX1, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CHKA, CIT, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GLUL, HIPK2, HK1, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYO10, N4BP2, NIM1K, NOX4, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PRKCA, PRR15L, PTK2B, RAPGEF3, RHOB, RHOBTB3, ROR1, RPS6KA2, RPS6KA5, RUNX2, SGK1, SIK1, SQLE, TAOK1, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.23	0.7109499
GO:0032559~adenyl ribonucleotide binding	10.19	0.062	ABCA6, ACSL1, AKAP9, AKT3, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CHKA, CIT, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GLUL, HIPK2, HK1, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYO10, N4BP2, NIM1K, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PRKCA, PRR15L, PTK2B, RAPGEF3, RHOBTB3, ROR1, RPS6KA2, RPS6KA5, RUNX2, SGK1, SIK1, TAOK1, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.24	0.7022977
GO:0005524~ATP binding	10.02	0.068	ABCA6, ACSL1, AKAP9, AKT3, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CHKA, CIT, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GLUL, HIPK2, HK1, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYO10, N4BP2, NIM1K, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PRKCA, PRR15L, PTK2B, RHOBTB3, ROR1, RPS6KA2, RPS6KA5, RUNX2, SGK1, SIK1, TAOK1, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.23	0.699918
GO:0017076~purine nucleotide binding	12.44	0.088	ABCA6, ACSL1, AKAP9, AKT3, AOX1, ARL4A, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CHKA, CIT, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GIMAP1, GLUL, HCAR2, HCAR3, HIPK2, HK1, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYO10, N4BP2, NIM1K, NMUR2, NOX4, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PRKCA, PRR15L, PTK2B, RAB31, RAB40A, RAB8B, RAPGEF3, RHOB, RHOBTB3, RHOU, ROR1, RPS6KA2, RPS6KA5, RRAGD, RUNX2, SGK1, SIK1, SQLE, TAOK1, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.18	0.7476594
GO:0000166~nucleotide binding	14.34	0.090	ABCA6, ACSL1, AKAP9, AKT3, AOX1, ARL4A, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CELF2, CELF6, CHKA, CIT, CRY2, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GIMAP1, GLUL, HCAR2, HCAR3, HIPK2, HK1, HSD11B2, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYEF2, MYO10, N4BP2, NIM1K, NMUR2, NOX4, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PPARGC1A, PRKCA, PRR15L, PTK2B, RAB31, RAB40A, RAB8B, RAPGEF3, RBMS3, RHOB, RHOBTB3, RHOU, RNPC3, ROR1, RPS6KA2, RPS6KA5, RRAGD, RUNX2, SGK1, SIK1, SORD, SPEN, SQLE, TAOK1, TP53I3, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.16	0.7464741
GO:0032553~ribonucleotide binding	11.92	0.096	ABCA6, ACSL1, AKAP9, AKT3, ARL4A, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CHKA, CIT, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GIMAP1, GLUL, HCAR2, HCAR3, HIPK2, HK1, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYO10, N4BP2, NIM1K, NMUR2, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PRKCA, PRR15L, PTK2B, RAB31, RAB40A, RAB8B, RAPGEF3, RHOB, RHOBTB3, RHOU, ROR1, RPS6KA2, RPS6KA5, RRAGD, RUNX2, SGK1, SIK1, TAOK1, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.18	0.7539376

GO:0032555~purine ribonucleotide binding	11.92	0.096	ABCA6, ACSL1, AKAP9, AKT3, ARL4A, ATAD2, ATP10A, ATRX, BLK, CAMK2B, CHKA, CIT, CSF1R, DAPK1, DGKG, ENPP1, ERBB4, ERCC6, ETNK2, FGR, FLT3, GIMAP1, GLUL, HCAR2, HCAR3, HIPK2, HK1, INSR, IRAK3, LATS2, MAP3K6, MERTK, MKNK2, MYO10, N4BP2, NIM1K, NMUR2, NTRK3, P2RX5, PAK3, PAPSS2, PDGFRA, PDK4, PDXK, PFKFB2, PRKCA, PRR15L, PTK2B, RAB31, RAB40A, RAB8B, RAPGEF3, RHOB, RHOBTB3, RHOU, ROR1, RPS6KA2, RPS6KA5, RRAGD, RUNX2, SGK1, SIK1, TAOK1, TRIO, TXK, UBE2D2, UBE2H, UHMK1, WNK1, ZAK	1.18	0.7539376
Cluster 7	**Enrichment Score: 2.72**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0010558~negative regulation of macromolecule biosynthetic process	6.39	2.16E-05	ANKHD1, ANKHD1-EIF4EBP3, APBB1, BCL6, BMP2, CDKN1C, CITED2, EIF4EBP3, ENPP1, GLIS3, GMNN, GZF1, HIPK2, HMGB2, IGFBP5, IKZF1, IL6R, INHBA, INHBB, MGEA5, NFIC, NR2E3, PER1, PRKCA, PRR15L, RUNX2, SIK1, SLA2, SPEN, TCF21, TFCP2L1, THRA, TNFSF4, TSPYL2, TTF1, ZBTB16, ZFHX3, ZHX3, ZNF157	2.15	0.0032453
GO:0009890~negative regulation of biosynthetic process	6.56	2.52E-05	ANKHD1, ANKHD1-EIF4EBP3, APBB1, BCL6, BMP2, CDKN1C, CITED2, EIF4EBP3, ENPP1, GIMAP1, GLIS3, GMNN, GZF1, HIPK2, HMGB2, IGFBP5, IKZF1, IL6R, INHBA, INHBB, MGEA5, NFIC, NR2E3, PER1, PRKCA, PRR15L, RUNX2, SIK1, SLA2, SPEN, TCF21, TFCP2L1, THRA, TNFSF4, TSPYL2, TTF1, ZBTB16, ZFHX3, ZHX3, ZNF157	2.11	0.0033638
GO:0006357~regulation of transcription from RNA polymerase II promoter	7.60	4.45E-05	APBB1, ARNTL, ASCL3, ATF5, ATXN7, BCL6, BMP2, CDKN1C, CITED2, CSRNP1, FOSL2, FOXO1, FOXO3, FOXO3B, GLIS3, GZF1, HAND2, HIPK2, HMGB2, IGF1, IKZF1, INHBA, KLF13, KLF6, KLF7, KLF9, MAFB, NFIB, NFIC, NFKBIA, NR2E3, PPARGC1A, RORA, RUNX2, SIK1, SLA2, SMARCD2, SPEN, TFCP2L1, TFEB, THRA, TTF1, ZBTB38, ZFHX3, ZNF157	1.93	0.005101
GO:0031327~negative regulation of cellular biosynthetic process	6.22	8.30E-05	ANKHD1, ANKHD1-EIF4EBP3, BCL6, BMP2, CDKN1C, CITED2, EIF4EBP3, ENPP1, GIMAP1, GLIS3, GMNN, GZF1, HIPK2, HMGB2, IGFBP5, IKZF1, INHBA, INHBB, MGEA5, NFIC, NR2E3, PER1, PRKCA, PRR15L, RUNX2, SIK1, SLA2, SPEN, TCF21, TFCP2L1, THRA, TNFSF4, TSPYL2, TTF1, ZBTB16, ZFHX3, ZHX3, ZNF157	2.04	0.0083062
GO:0010605~negative regulation of macromolecule metabolic process	6.91	8.55E-4	ANKHD1, ANKHD1-EIF4EBP3, APBB1, BCL6, BMP2, BNIP3, CDKN1C, CITED2, EIF4EBP3, ENPP1, GLIS3, GMNN, GZF1, HIPK2, HMGB2, IGFBP5, IKZF1, IL6R, INHBA, INHBB, INSR, IRAK3, MGEA5, NFIC, NR2E3, PER1, PRKCA, PRR15L, RUNX2, SIK1, SLA2, SPEN, TCF21, TFCP2L1, THRA, TNFSF4, TSPYL2, TTF1, ZBTB16, ZFHX3, ZHX3, ZNF157	1.73	0.0448267
GO:0051172~negative regulation of nitrogen compound metabolic process	5.01	0.004	BCL6, BMP2, CDKN1C, CITED2, GIMAP1, GLIS3, GMNN, GZF1, HIPK2, HMGB2, IKZF1, NFIC, NR2E3, PER1, PRR15L, RUNX2, SIK1, SLA2, SPEN, TCF21, TFCP2L1, THRA, TNFSF4, TSPYL2, TTF1, ZBTB16, ZFHX3, ZHX3, ZNF157	1.78	0.1326702
GO:0045934~negative regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	4.84	0.006	BCL6, BMP2, CDKN1C, CITED2, GLIS3, GMNN, GZF1, HIPK2, HMGB2, IKZF1, NFIC, NR2E3, PER1, PRR15L, RUNX2, SIK1, SLA2, SPEN, TCF21, TFCP2L1, THRA, TNFSF4, TSPYL2, TTF1, ZBTB16, ZFHX3, ZHX3, ZNF157	1.74	0.1704511
GO:0010629~negative regulation of gene expression	4.66	0.009	BCL6, BMP2, BNIP3, CDKN1C, CITED2, GLIS3, GZF1, HIPK2, HMGB2, IKZF1, INSR, NFIC, NR2E3, PER1, PRR15L, RUNX2, SIK1, SLA2, SPEN, TCF21, TFCP2L1, THRA, TNFSF4, ZBTB16, ZFHX3, ZHX3, ZNF157	1.71	0.209036
GO:0016481~negative regulation of transcription	4.32	0.010	BCL6, BMP2, CDKN1C, CITED2, GLIS3, GZF1, HIPK2, HMGB2, IKZF1, NFIC, NR2E3, PER1, PRR15L, RUNX2, SIK1, SLA2, SPEN, TCF21, TFCP2L1, THRA, TNFSF4, ZBTB16, ZFHX3, ZHX3, ZNF157	1.73	0.2208939
GO:0045892~negative regulation of transcription, DNA-dependent	3.45	0.017	BCL6, BMP2, CDKN1C, CITED2, GLIS3, GZF1, HIPK2, IKZF1, NFIC, NR2E3, SIK1, SLA2, SPEN, TCF21, TFCP2L1, TNFSF4, ZBTB16, ZFHX3, ZHX3, ZNF157	1.79	0.2866933
GO:0051253~negative regulation of RNA metabolic process	3.45	0.020	BCL6, BMP2, CDKN1C, CITED2, GLIS3, GZF1, HIPK2, IKZF1, NFIC, NR2E3, SIK1, SLA2, SPEN, TCF21, TFCP2L1, TNFSF4, ZBTB16, ZFHX3, ZHX3, ZNF157	1.76	0.3155051
GO:0016564~transcription repressor activity	2.94	0.045	ATF5, BCL6, BMP2, CDKN1C, CITED2, HIPK2, HMGB2, IKZF1, NFIL3, PIAS1, SIK1, SPEN, TFCP2L1, THRA, TOB1, ZBTB16, ZFHX3	1.69	0.715361
GO:0000122~negative regulation of transcription from RNA polymerase II promoter	2.42	0.076	BCL6, CDKN1C, CITED2, GLIS3, GZF1, HIPK2, IKZF1, NFIC, NR2E3, SIK1, SLA2, TFCP2L1, ZFHX3, ZNF157	1.68	0.5572789
Cluster 8	**Enrichment Score: 2.63**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0010033~response to organic substance	7.43	7.81E-05	ACSL1, BAIAP2, C1QB, CA4, CALCOCO2, COL4A3, DUSP1, ENPP1, ERBB4, F2R, FOXO1, GLUL, HMGB2, HSD11B2, IL1R1, IL6R, IL6ST, INSR, IRAK3, IRS2, LATS2, LIFR, LOX, LPIN1, MAP1B, MCL1, MGEA5, NFKBIA, NMUR2, PDGFRA, PFKFB2, PIK3R1, PLIN2, PRKCA, PTK2B, SERPINF2, SLC6A1, SQLE, TAT, TG, TGFBR3, THRA, TLR2	1.90	0.0081559

GO:0009725~response to hormone stimulus	4.32	5.63E-4	BAIAP2, C1QB, CA4, DUSP1, ENPP1, ERBB4, FOXO1, HMGB2, HSD11B2, IL6R, INSR, IRS2, LATS2, LOX, LPIN1, MAP1B, MGEA5, PDGFRA, PIK3R1, PRKCA, PTK2B, SLC6A1, TAT, TGFBR3, THRA	2.17	0.034223
GO:0009719~response to endogenous stimulus	4.32	0.002	BAIAP2, C1QB, CA4, DUSP1, ENPP1, ERBB4, FOXO1, HMGB2, HSD11B2, IL6R, INSR, IRS2, LATS2, LOX, LPIN1, MAP1B, MGEA5, PDGFRA, PIK3R1, PRKCA, PTK2B, SLC6A1, TAT, TGFBR3, THRA	1.96	0.0952617
GO:0048545~response to steroid hormone stimulus	2.59	0.003	C1QB, CA4, DUSP1, ERBB4, HMGB2, HSD11B2, IL6R, INSR, LOX, MAP1B, MGEA5, PDGFRA, PRKCA, SLC6A1, TAT	2.49	0.1169206
GO:0043434~response to peptide hormone stimulus	1.90	0.023	BAIAP2, ENPP1, FOXO1, HSD11B2, IL6R, INSR, IRS2, LPIN1, MAP1B, PIK3R1, PRKCA	2.27	0.3345707
GO:0032870~cellular response to hormone stimulus	1.73	0.024	BAIAP2, DUSP1, ENPP1, FOXO1, INSR, IRS2, LATS2, LPIN1, PIK3R1, THRA	2.39	0.338967
Cluster 9	**Enrichment Score: 2.57**				
Term	**%**	***P***		**Fold**	**Benjamini**
PIRSF000384:PNMTase	0.52	0.003	INMT, NNMT, PNMT	33.02	0.2927969
PIRSF000384:phenylethanolamine N-methyltransferase	0.52	0.003	INMT, NNMT, PNMT	33.02	0.2927969
IPR000940:Methyltransferase, NNMT/PNMT/TEMT	0.52	0.003	INMT, NNMT, PNMT	32.73	0.209369
Cluster 10	**Enrichment Score: 2.47**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0031226~intrinsic to plasma membrane	9.67	0.001	ADCYAP1R1, ADORA3, ADRA2C, ANPEP, C3AR1, CD160, CD163, CD302, CD84, CMKLR1, CNR1, CORIN, CSF1R, CSF2RA, CXCR4, ENPP3, F2R, F3, FLT3, GPIHBP1, GPR34, HCAR2, HCAR3, IL1R1, IL6R, IL6ST, INSR, ITGA10, ITGA5, ITGB1, KCNB1, LIFR, LILRB3, MERTK, MRC1, MSR1, NINJ2, NPY2R, NRXN3, NTRK3, P2RX5, PDGFRA, PTPRG, PTPRM, ROR1, RTN4RL1, SLC26A2, SLC29A2, SLC31A2, SLC6A1, SLC7A8, STOM, TGFBR3, TLR2, TNFSF4, TPO, TRPM2	1.53	0.1244671
GO:0044459~plasma membrane part	15.20	0.003	ADCYAP1R1, ADORA3, ADRA2C, AKAP7, ANPEP, ARHGAP26, C3AR1, CA4, CD160, CD163, CD302, CD84, CD86, CLDN8, CMKLR1, CNR1, CORIN, CSF1R, CSF2RA, CXCR4, CYFIP2, ENPP1, ENPP3, EPB41L5, ERBB4, F2R, F3, FERMT2, FLT3, FNBP1, FNBP1L, GPIHBP1, GPR34, HCAR2, HCAR3, HOMER2, IL1R1, IL6R, IL6ST, IL7R, INSR, ITGA10, ITGA5, ITGB1, KCNB1, KLRD1, LAMA3, LAMB1, LIFR, LILRB3, MAOA, MERTK, MRC1, MSR1, NINJ2, NOX4, NPY2R, NRXN3, NTRK3, P2RX5, PDGFRA, PHKA1, PKP2, PTK2B, PTPRG, PTPRM, RAB31, RAB40A, RAB8B, RHOU, ROR1, RTN4RL1, SCNN1A, SHROOM3, SLC16A10, SLC26A2, SLC29A2, SLC31A2, SLC6A1, SLC7A8, SNTG2, STOM, TENC1, TGFBR3, TLR2, TMEM204, TNFSF4, TPO, TRPM2	1.33	0.2273889
GO:0005887~integral to plasma membrane	8.98	0.005	ADCYAP1R1, ADORA3, ADRA2C, ANPEP, C3AR1, CD163, CD302, CD84, CMKLR1, CNR1, CORIN, CSF1R, CSF2RA, CXCR4, ENPP3, F2R, FLT3, GPR34, HCAR2, HCAR3, IL1R1, IL6R, IL6ST, INSR, ITGA10, ITGA5, ITGB1, KCNB1, LIFR, LILRB3, MERTK, MRC1, MSR1, NINJ2, NPY2R, NRXN3, NTRK3, P2RX5, PDGFRA, PTPRG, PTPRM, ROR1, SLC26A2, SLC29A2, SLC31A2, SLC6A1, SLC7A8, STOM, TGFBR3, TLR2, TNFSF4, TPO, TRPM2	1.46	0.198527
GO:0005886~plasma membrane	23.66	0.006	ACSL1, ADCYAP1R1, ADORA3, ADRA2C, AKAP7, ANPEP, APBA2, APBB1, APOLD1, ARHGAP10, ARHGAP26, BAIAP2, C3AR1, CA4, CALD1, CD160, CD163, CD302, CD53, CD84, CD86, CLDN8, CMKLR1, CNR1, CORIN, CPM, CSF1R, CSF2RA, CTGF, CXCR4, CYFIP2, DIO3, EBI3, ELMO1, ENPP1, ENPP3, EPB41L5, ERBB4, F2R, F3, FCGR2B, FCRL5, FERMT2, FLT3, FLVCR2, FNBP1, FNBP1L, FZD7, GFRA1, GGT5, GPIHBP1, GPR133, GPR34, HCAR2, HCAR3, HOMER2, IL1R1, IL6R, IL6ST, IL7R, INSR, IRS2, ITGA10, ITGA5, ITGB1, KCNB1, KLRD1, LAIR1, LAMA2, LAMA3, LAMB1, LDLRAD4, LIFR, LILRB3, LPL, MAOA, MAP1B, MERTK, MRC1, MSR1, MTUS1, NDRG1, NFIA, NINJ2, NMUR2, NOX4, NPY2R, NRXN3, NTRK3, OR7A5, P2RX5, PDGFRA, PHKA1, PKP2, PLIN2, PPP1R16B, PRKCA, PTK2B, PTPRG, PTPRM, RAB31, RAB40A, RAB8B, RFTN2, RGS1, RHOB, RHOU, ROR1, RTN4RL1, SCNN1A, SGK1, SHROOM3, SIGLEC10, SLA2, SLAMF6, SLC16A10, SLC16A12, SLC16A14, SLC19A2, SLC26A2, SLC29A2, SLC31A2, SLC38A1, SLC4A7, SLC6A1, SLC7A8, SLIT2, SNTG2, STOM, TENC1, TGFBR3, TLR2, TMEM204, TNFSF4, TPO, TRPM2, VSIG4, ZBTB16	1.21	0.1996784
Cluster 11	**Enrichment Score: 2.33**				
Term	**%**	***P***		**Fold**	**Benjamini**
hsa05222:Small cell lung cancer	1.73	0.002	AKT3, BIRC3, ITGB1, LAMA2, LAMA3, LAMB1, NFKBIA, PIAS1, PIK3R1, PIK3R5	3.38	0.1672441
hsa04510:Focal adhesion	2.76	0.004	AKT3, BIRC3, CCND3, IGF1, ITGA10, ITGA5, ITGB1, LAMA2, LAMA3, LAMB1, PAK3, PDGFRA, PIK3R1, PIK3R5, PPP1CB, PRKCA	2.26	0.1893609
hsa05200:Pathways in cancer	3.63	0.010	AKT3, BIRC3, BMP2, CSF1R, CSF2RA, DAPK1, FLT3, FOXO1, FZD7, IGF1, ITGB1, LAMA2, LAMA3, LAMB1, NFKBIA, PDGFRA, PIAS1, PIK3R1, PIK3R5, PRKCA, ZBTB16	1.82	0.1703425
Cluster 12	**Enrichment Score: 2.32**				
Term	**%**	***P***		**Fold**	**Benjamini**

GO:0009611~response to wounding	5.18	0.003	ADORA3, AOX1, BMP2, C1QB, C3AR1, CD163, CD302, CHST4, CTGF, CXCL13, CXCR4, F2R, F3, IGF1, IL6R, ITGA5, KLF6, LOX, MAP1B, MGLL, NINJ2, NOX4, PAPSS2, PDGFRA, RTN4RL1, SAA1, SERPINF2, TLR2, TNFSF4, VSIG4	1.80	0.1072997
GO:0006952~defense response	5.53	0.006	ADORA3, AOX1, BMP2, BNIP3, C1QB, C3AR1, CALCOCO2, CD160, CD163, CD302, CD84, CHST4, CXCL13, CXCR4, F2R, F3, FGR, IL1R1, IL6R, INHBA, INHBB, ITGB1, LILRB3, MGLL, NOX4, RNASE6, SAA1, SAMHD1, SERPINF2, TLR2, TNFSF4, VSIG4	1.66	0.1743949
GO:0006954~inflammatory response	3.45	0.007	ADORA3, AOX1, BMP2, C1QB, C3AR1, CD163, CD302, CHST4, CXCL13, CXCR4, F2R, F3, IL6R, MGLL, NOX4, SAA1, SERPINF2, TLR2, TNFSF4, VSIG4	1.96	0.1850373
Cluster 13	**Enrichment Score: 2.27**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0005912~adherens junction	2.59	2.33E-4	ARHGAP26, EPB41L5, FERMT2, ITGA5, ITGB1, LAMA3, NOX4, NPY2R, PKP2, PTK2B, PTPRM, RHOU, SHROOM3, TENC1, TMEM204	3.22	0.0728512
GO:0070161~anchoring junction	2.59	6.72E-14	ARHGAP26, EPB41L5, FERMT2, ITGA5, ITGB1, LAMA3, NOX4, NPY2R, PKP2, PTK2B, PTPRM, RHOU, SHROOM3, TENC1, TMEM204	2.90	0.1034194
GO:0005925~focal adhesion	1.73	0.003	ARHGAP26, FERMT2, ITGA5, ITGB1, LAMA3, NOX4, NPY2R, PTK2B, RHOU, TENC1	3.26	0.2033434
GO:0005924~cell-substrate adherens junction	1.73	0.005	ARHGAP26, FERMT2, ITGA5, ITGB1, LAMA3, NOX4, NPY2R, PTK2B, RHOU, TENC1	3.14	0.1893378
GO:0030055~cell-substrate junction	1.73	0.006	ARHGAP26, FERMT2, ITGA5, ITGB1, LAMA3, NOX4, NPY2R, PTK2B, RHOU, TENC1	2.97	0.1898816
GO:0016323~basolateral plasma membrane	2.25	0.019	ARHGAP26, ENPP1, ERBB4, FERMT2, ITGA5, ITGB1, LAMA3, NOX4, NPY2R, PTK2B, RHOU, SLC16A10, TENC1	2.13	0.3451429
GO:0030054~cell junction	3.11	0.391	ARHGAP26, CLDN8, CYFIP2, EPB41L5, FERMT2, HOMER2, ITGA5, ITGB1, LAMA3, NOX4, NPY2R, PKP2, PTK2B, PTPRM, RHOU, SHROOM3, TENC1, TMEM204	1.16	0.9440095
Cluster 14	**Enrichment Score: 2.21**				
Term	**%**	***P***		**Fold**	**Benjamini**
IPR017892:Protein kinase, C-terminal	1.21	0.001	AKT3, CIT, LATS2, PRKCA, RPS6KA2, RPS6KA5, SGK1	5.73	0.1249849
IPR002290:Serine/threonine protein kinase	2.94	0.006	AKT3, CAMK2B, CIT, DAPK1, HIPK2, LATS2, MAP3K6, MKNK2, NIM1K, PAK3, PRKCA, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO	2.15	0.3123145
IPR000961:AGC-kinase, C-terminal	1.21	0.006	AKT3, CIT, LATS2, PRKCA, RPS6KA2, RPS6KA5, SGK1	4.17	0.3074952
SM00133:S_TK_X	1.21	0.011	AKT3, CIT, LATS2, PRKCA, RPS6KA2, RPS6KA5, SGK1	3.68	0.3514453
SM00220:S_TKc	2.94	0.017	AKT3, CAMK2B, CIT, DAPK1, HIPK2, LATS2, MAP3K6, MKNK2, NIM1K, PAK3, PRKCA, RPS6KA2, RPS6KA5, SGK1, SIK1, TAOK1, TRIO	1.90	0.427538
Cluster 15	**Enrichment Score: 2.08**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0019899~enzyme binding	5.18	0.003	AKAP7, ARG2, ARHGAP6, CABYR, CCND3, F3, FGD4, FLT3, FOXO3, FOXO3B, IL6R, INSR, IRS2, LAMB1, MYRIP, NFKBIA, PAK3, PFKFB2, PIAS1, PIK3R1, PPP1CB, PPP1R16B, PRKAB1, PTK2B, RAB3IP, RHOBTB3, RPH3AL, SERPINF2, SPAG9, TAOK1, ZFHX3	1.80	0.2185249
GO:0019900~kinase binding	2.25	0.012	AKAP7, CABYR, CCND3, FLT3, FOXO3, FOXO3B, INSR, IRS2, PFKFB2, PPP1CB, PRKAB1, PTK2B, SPAG9, TAOK1	2.28	0.3982653
GO:0019901~protein kinase binding	1.90	0.019	AKAP7, CABYR, CCND3, FOXO3, FOXO3B, INSR, IRS2, PPP1CB, PRKAB1, PTK2B, SPAG9, TAOK1	2.35	0.4940658
Cluster 16	**Enrichment Score: 2.00**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0004714~transmembrane receptor protein tyrosine kinase activity	1.38	0.005	CSF1R, ERBB4, FLT3, INSR, MERTK, NTRK3, PDGFRA, ROR1	3.75	0.3000027
PIRSF000615:tyrosine-protein kinase, CSF-1/PDGF receptor type	0.52	0.008	CSF1R, FLT3, PDGFRA	19.81	0.4266923
PIRSF000615:TyrPK_CSF1-R	0.52	0.008	CSF1R, FLT3, PDGFRA	19.81	0.4266923
IPR016243:Tyrosine-protein kinase, CSF-1/PDGF receptor	0.52	0.009	CSF1R, FLT3, PDGFRA	19.64	0.3582599
IPR001824:Receptor tyrosine kinase, class III, conserved site	0.52	0.029	CSF1R, FLT3, PDGFRA	10.91	0.636454
Cluster 17	**Enrichment Score: 1.99**				
Term	**%**	***P***		**Fold**	**Benjamini**

GO:0004896~cytokine receptor activity	1.38	0.002	CSF2RA, EBI3, GFRA1, IL1R1, IL6R, IL6ST, IL7R, LIFR	4.57	0.205317
GO:0070120~ciliary neurotrophic factor-mediated signaling pathway	0.52	0.009	IL6R, IL6ST, LIFR	19.10	0.2091599
GO:0019221~cytokine-mediated signaling pathway	1.04	0.068	IL1R1, IL6R, IL6ST, IRAK3, KLF6, LIFR	2.73	0.5374786
Cluster 18	**Enrichment Score: 1.89**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0007243~protein kinase cascade	5.01	1.55E-05	ADRA2C, BLK, CXCR4, DAPK1, ERCC6, F2R, FGD4, GADD45B, GADD45G, IL6ST, INSR, LATS2, MAP3K6, MKNK2, NFKBIA, NRTN, PIAS1, PIK3R1, PRKCA, PTK2B, RPS6KA2, RPS6KA5, SIK1, SPAG9, TGFBR3, TLR2, TXK, WNK1, ZAK	2.49	0.0031177
GO:0042325~regulation of phosphorylation	5.35	1.57E-4	ADRA2C, ATXN7, BMP2, CCND3, CDKN1C, CXCR4, DEPTOR, DGKG, ENPP1, ERCC6, F2R, FGD4, GADD45B, GADD45G, IGF1, IL6R, IL6ST, INHBA, INSR, IRAK3, LATS2, MAP3K6, PFKFB2, PKIB, PPP1CB, PRKCA, PTK2B, RAPGEF3, SPAG9, TSPYL2, ZAK	2.12	0.0121166
GO:0051174~regulation of phosphorus metabolic process	5.35	3.06E-4	ADRA2C, ATXN7, BMP2, CCND3, CDKN1C, CXCR4, DEPTOR, DGKG, ENPP1, ERCC6, F2R, FGD4, GADD45B, GADD45G, IGF1, IL6R, IL6ST, INHBA, INSR, IRAK3, LATS2, MAP3K6, PFKFB2, PKIB, PPP1CB, PRKCA, PTK2B, RAPGEF3, SPAG9, TSPYL2, ZAK	2.03	0.0203186
GO:0019220~regulation of phosphate metabolic process	5.35	3.06E-4	ADRA2C, ATXN7, BMP2, CCND3, CDKN1C, CXCR4, DEPTOR, DGKG, ENPP1, ERCC6, F2R, FGD4, GADD45B, GADD45G, IGF1, IL6R, IL6ST, INHBA, INSR, IRAK3, LATS2, MAP3K6, PFKFB2, PKIB, PPP1CB, PRKCA, PTK2B, RAPGEF3, SPAG9, TSPYL2, ZAK	2.03	0.0203186
GO:0043549~regulation of kinase activity	3.97	0.002	ADRA2C, CCND3, CDKN1C, CXCR4, DEPTOR, DGKG, ERCC6, F2R, FGD4, GADD45B, GADD45G, INSR, IRAK3, LATS2, MAP3K6, PFKFB2, PKIB, PPP1CB, PRKCA, PTK2B, SPAG9, TSPYL2, ZAK	2.05	0.091102
GO:0045859~regulation of protein kinase activity	3.80	0.003	ADRA2C, CCND3, CDKN1C, CXCR4, DEPTOR, DGKG, ERCC6, F2R, FGD4, GADD45B, GADD45G, INSR, IRAK3, LATS2, MAP3K6, PKIB, PPP1CB, PRKCA, PTK2B, SPAG9, TSPYL2, ZAK	2.03	0.1184377
GO:0051338~regulation of transferase activity	3.97	0.003	ADRA2C, CCND3, CDKN1C, CXCR4, DEPTOR, DGKG, ERCC6, F2R, FGD4, GADD45B, GADD45G, INSR, IRAK3, LATS2, MAP3K6, PFKFB2, PKIB, PPP1CB, PRKCA, PTK2B, SPAG9, TSPYL2, ZAK	1.97	0.1243774
GO:0000165~MAPKKK cascade	2.42	0.005	ADRA2C, CXCR4, ERCC6, F2R, FGD4, GADD45B, GADD45G, INSR, MAP3K6, NRTN, PRKCA, PTK2B, SPAG9, ZAK	2.42	0.1614951
GO:0033674~positive regulation of kinase activity	2.76	0.006	ADRA2C, CCND3, CXCR4, DGKG, ERCC6, F2R, FGD4, GADD45B, GADD45G, INSR, MAP3K6, PFKFB2, PPP1CB, PTK2B, SPAG9, ZAK	2.20	0.1755893
GO:0000186~activation of MAPKK activity	0.86	0.007	ERCC6, F2R, GADD45B, GADD45G, ZAK	6.37	0.1878801
GO:0051347~positive regulation of transferase activity	2.76	0.009	ADRA2C, CCND3, CXCR4, DGKG, ERCC6, F2R, FGD4, GADD45B, GADD45G, INSR, MAP3K6, PFKFB2, PPP1CB, PTK2B, SPAG9, ZAK	2.12	0.2080321
GO:0045860~positive regulation of protein kinase activity	2.59	0.011	ADRA2C, CCND3, CXCR4, DGKG, ERCC6, F2R, FGD4, GADD45B, GADD45G, INSR, MAP3K6, PPP1CB, PTK2B, SPAG9, ZAK	2.14	0.2233342
GO:0043405~regulation of MAP kinase activity	1.90	0.013	ADRA2C, CXCR4, ERCC6, FGD4, INSR, IRAK3, MAP3K6, PRKCA, PTK2B, SPAG9, ZAK	2.48	0.2524778
GO:0000187~activation of MAPK activity	1.38	0.014	ADRA2C, CXCR4, ERCC6, FGD4, INSR, MAP3K6, SPAG9, ZAK	3.11	0.2606802
GO:0043406~positive regulation of MAP kinase activity	1.55	0.015	ADRA2C, CXCR4, ERCC6, FGD4, INSR, MAP3K6, PTK2B, SPAG9, ZAK	2.81	0.2635496
GO:0043507~positive regulation of JUN kinase activity	0.86	0.017	ERCC6, FGD4, MAP3K6, PTK2B, ZAK	4.97	0.2848393
GO:0043408~regulation of MAPKKK cascade	1.55	0.021	ERCC6, F2R, FGD4, HIPK2, IL6R, INSR, MAP3K6, PTK2B, ZAK	2.63	0.3216015
GO:0043506~regulation of JUN kinase activity	0.86	0.029	ERCC6, FGD4, MAP3K6, PTK2B, ZAK	4.30	0.370244
GO:0007257~activation of JUN kinase activity	0.69	0.047	ERCC6, FGD4, MAP3K6, ZAK	4.90	0.4596867
GO:0044093~positive regulation of molecular function	4.66	0.048	ADCYAP1R1, ADORA3, ADRA2C, ARHGAP6, CALD1, CCND3, COL4A3, CXCR4, DGKG, ERCC6, F2R, F3, FGD4, GADD45B, GADD45G, HIPK2, INSR, IRAK3, MAP3K6, NMUR2, PFKFB2, PPP1CB, PTK2B, SPAG9, TGFBR3, TLR2, ZAK	1.47	0.4656015

GO:0046328~regulation of JNK cascade	1.04	0.053	ERCC6, FGD4, HIPK2, MAP3K6, PTK2B, ZAK	2.94	0.4811419
GO:0070302~regulation of stress-activated protein kinase signaling pathway	1.04	0.065	ERCC6, FGD4, HIPK2, MAP3K6, PTK2B, ZAK	2.77	0.5258098
GO:0032147~activation of protein kinase activity	1.38	0.067	DGKG, ERCC6, F2R, GADD45B, GADD45G, INSR, PTK2B, ZAK	2.23	0.5345401
GO:0080135~regulation of cellular response to stress	1.21	0.105	ERCC6, FGD4, HIPK2, MAP3K6, NTRK3, PTK2B, ZAK	2.16	0.6298038
GO:0043085~positive regulation of catalytic activity	3.80	0.143	ADCYAP1R1, ADORA3, ADRA2C, ARHGAP6, CCND3, COL4A3, CXCR4, DGKG, ERCC6, F2R, F3, FGD4, GADD45B, GADD45G, INSR, MAP3K6, NMUR2, PFKFB2, PPP1CB, PTK2B, SPAG9, ZAK	1.35	0.7112606
GO:0010627~regulation of protein kinase cascade	2.07	0.160	ERCC6, F2R, F3, FGD4, HIPK2, IGF1, IL6R, IL6ST, INSR, MAP3K6, PTK2B, ZAK	1.53	0.7330273
GO:0007254~JNK cascade	0.69	0.282	ERCC6, FGD4, MAP3K6, ZAK	2.16	0.8660435
GO:0031098~stress-activated protein kinase signaling pathway	0.69	0.316	ERCC6, FGD4, MAP3K6, ZAK	2.02	0.8942503
GO:0042770~DNA damage response, signal transduction	0.69	0.461	ERCC6, FBXO31, HIPK2, ZAK	1.59	0.9592314
Cluster 19	**Enrichment Score: 1.86**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0004896~cytokine receptor activity	1.38	0.002	CSF2RA, EBI3, GFRA1, IL1R1, IL6R, IL6ST, IL7R, LIFR	4.57	0.205317
IPR008957:Fibronectin, type III-like fold	2.25	0.011	CSF2RA, EBI3, F3, FNDC3B, IL6R, IL6ST, IL7R, INSR, LIFR, MERTK, MYBPC1, PTPRG, PTPRM	2.31	0.3920326
IPR003961:Fibronectin, type III	2.07	0.032	CSF2RA, EBI3, FNDC3B, IL6R, IL6ST, IL7R, INSR, LIFR, MERTK, MYBPC1, PTPRG, PTPRM	2.07	0.6537001
SM00060:FN3	2.07	0.064	CSF2RA, EBI3, FNDC3B, IL6R, IL6ST, IL7R, INSR, LIFR, MERTK, MYBPC1, PTPRG, PTPRM	1.83	0.6857741
Cluster 20	**Enrichment Score: 1.79**				
Term	**%**	***P***		**Fold**	**Benjamini**
GO:0030036~actin cytoskeleton organization	2.76	0.005	ARHGAP26, ARHGAP6, BCL6, CALD1, ELMO1, ELN, FERMT2, FGD4, ITGB1, LPIN1, MTSS1, PTK2B, RHOU, SHROOM3, WASF2, WASF3	2.25	0.1579872
GO:0030029~actin filament-based process	2.76	0.009	ARHGAP26, ARHGAP6, BCL6, CALD1, ELMO1, ELN, FERMT2, FGD4, ITGB1, LPIN1, MTSS1, PTK2B, RHOU, SHROOM3, WASF2, WASF3	2.11	0.2106697
GO:0007010~cytoskeleton organization	3.45	0.094	ARHGAP10, ARHGAP26, ARHGAP6, BCL6, CALD1, ELMO1, ELN, FERMT2, FGD4, HOOK1, ITGB1, LPIN1, MAP1B, MICAL1, MTSS1, PTK2B, RHOU, SHROOM3, WASF2, WASF3	1.46	0.6046078

The 889 probe sets showing ≥1.25 fold ($P \leq 0.05$) induction by budesonide in the biopsy microarray analysis were analyzed using the DAVID gene ID conversion tool to produce 588 separate identities that were used for functional annotation clustering in DAVID (default settings, medium stringency). This returned 183 clusters of which those with the highest 20 enrichment scores are shown. % = percentage of the gene list with associated probability (*P*). Fold = fold enrichment with the associated Benjamini score.

SUPPLEMENTAL TABLE 9

Primary human bronchial epithelial cell microarray data: Probes sets showing ≥2 fold, or ≤0.5 fold change (*P*≤0.05) following 6 h of *in vitro* budesonide treatment

Probe set ID	Entrez Gene	Gene Symbol	Gene Title	*P*-value (Bud/ Plac)	Fold (Bud/ Plac)
11751415_a_at	1831	TSC22D3	TSC22 domain family, member 3	2.9E-11	14.88
11743917_a_at	2289	FKBP5	FK506 binding protein 5	1.2E-12	13.43
11717829_s_at	1831	TSC22D3	TSC22 domain family, member 3	1.2E-11	12.51
11739567_s_at	2289	FKBP5	FK506 binding protein 5	1.1E-11	12.44
11739565_a_at	2289	FKBP5	FK506 binding protein 5	1.8E-11	10.12
11748099_a_at	116154	PHACTR3	phosphatase and actin regulator 3	9.7E-09	9.70
11726088_s_at	116154	PHACTR3	phosphatase and actin regulator 3	7.3E-09	9.33
11729371_a_at	7704	ZBTB16	zinc finger and BTB domain containing 16	1.6E-07	8.44
11736273_a_at	7097	TLR2	toll-like receptor 2	1.0E-07	8.07
11754833_a_at	7097	TLR2	toll-like receptor 2	2.0E-07	7.86
11746275_a_at	2289	FKBP5	FK506 binding protein 5	4.0E-10	7.07
11716974_a_at	5166	PDK4	pyruvate dehydrogenase kinase, isozyme 4	2.2E-02	6.34
11728201_at	4015	LOX	lysyl oxidase	1.1E-03	5.78
11717830_a_at	1831	TSC22D3	TSC22 domain family, member 3	4.0E-08	5.76
11723222_s_at	9499	MYOT	myotilin	4.6E-07	5.76
11740995_x_at	2752	GLUL	glutamate-ammonia ligase	5.5E-08	5.57
11742816_a_at	10144	FAM13A	family with sequence similarity 13, member A	3.3E-05	5.41
11744337_a_at	2752	GLUL	glutamate-ammonia ligase	3.1E-07	5.31
11717168_a_at	5187	PER1	period circadian clock 1	9.6E-09	5.21
11728055_at	2690	GHR	growth hormone receptor	5.1E-07	4.92
11718876_at	92737	DNER	delta/notch-like EGF repeat containing	3.2E-04	4.89
11717326_at	687	KLF9	Kruppel-like factor 9	7.0E-10	4.78
11730310_at	29842	TFCP2L1	transcription factor CP2-like 1	2.7E-05	4.53
11728200_a_at	4015	LOX	lysyl oxidase	2.2E-03	4.25
11744779_a_at	10144	FAM13A	family with sequence similarity 13, member A	1.6E-04	4.18
11758995_at	4015	LOX	lysyl oxidase	5.1E-03	4.16
11755138_s_at	158586	ZXDB	zinc finger, X-linked, duplicated B	6.3E-09	4.10
11733044_at	6542	SLC7A2	solute carrier family 7 (cationic amino acid transporter, y+ system), member 2	1.8E-06	4.06
11724157_x_at	6783	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	5.4E-03	3.99
11737088_at	7092	TLL1	tolloid-like 1	9.5E-03	3.92
11725521_x_at	2752	GLUL	glutamate-ammonia ligase	4.6E-07	3.84
11720139_a_at	128434	VSTM2L	V-set and transmembrane domain containing 2 like	6.7E-07	3.78
11717327_at	687	KLF9	Kruppel-like factor 9	6.3E-05	3.77
11724156_at	6783	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	7.1E-03	3.74
11723803_a_at	54209	TREM2	triggering receptor expressed on myeloid cells 2	4.6E-04	3.72
11739566_a_at	2289	FKBP5	FK506 binding protein 5	1.9E-08	3.70
11715757_a_at	5997	RGS2	regulator of G-protein signaling 2, 24kDa	1.4E-03	3.69
11721625_s_at	2752	GLUL	glutamate-ammonia ligase	6.9E-06	3.60
11745612_a_at	54209	TREM2	triggering receptor expressed on myeloid cells 2	3.0E-04	3.57
11731973_at	6340	SCNN1G	sodium channel, non-voltage-gated 1, gamma subunit	2.6E-05	3.35
11739539_a_at	5295	PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	1.7E-07	3.35
11750970_a_at	4015	LOX	lysyl oxidase	3.8E-03	3.31
11755020_a_at	283537	SLC46A3	solute carrier family 46, member 3	1.8E-02	3.29
11724155_at	6783	SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	5.4E-03	3.26
11721895_x_at	2619	GAS1	growth arrest-specific 1	7.9E-03	3.16
11756888_a_at	29842	TFCP2L1	transcription factor CP2-like 1	1.5E-04	3.13
11754595_s_at	1836	SLC26A2	solute carrier family 26 (sulfate transporter), member 2	2.5E-04	2.97
11733019_a_at	5295	PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	8.7E-05	2.95

11717912_s_at	9547	CXCL14	chemokine (C-X-C motif) ligand 14	3.7E-03	2.93
11755450_a_at	57507	ZNF608	zinc finger protein 608	3.6E-04	2.93
11727284_at	23316	CUX2	cut-like homeobox 2	1.8E-04	2.91
11720746_s_at	604	BCL6	B-cell CLL/lymphoma 6	2.1E-04	2.91
11749685_a_at	10144	FAM13A	family with sequence similarity 13, member A	1.6E-03	2.87
11726113_a_at	115572	FAM46B	family with sequence similarity 46, member B	4.6E-05	2.86
11756059_a_at	9547	CXCL14	chemokine (C-X-C motif) ligand 14	4.5E-03	2.83
11736001_s_at	1634	DCN	decorin	2.0E-02	2.83
11718651_at	83857	TMTC1	transmembrane and tetratricopeptide repeat containing 1	3.9E-02	2.79
11726894_a_at	11213	IRAK3	interleukin-1 receptor-associated kinase 3	7.3E-04	2.76
11733042_at	6542	SLC7A2	solute carrier family 7 (cationic amino acid transporter, y+ system), member 2	7.6E-03	2.74
11726114_at	115572	FAM46B	family with sequence similarity 46, member B	9.1E-06	2.73
11735271_a_at	2650	GCNT1	glucosaminyl (N-acetyl) transferase 1, core 2	9.0E-03	2.73
11730195_at	23541	SEC14L2	SEC14-like 2 (S. cerevisiae)	1.4E-04	2.73
11720106_a_at	1836	SLC26A2	solute carrier family 26 (sulfate transporter), member 2	1.5E-02	2.71
11752184_a_at	57507	ZNF608	zinc finger protein 608	1.7E-04	2.70
11721572_at	387695	C10orf99	chromosome 10 open reading frame 99	9.8E-03	2.69
11739315_at	3791	KDR	kinase insert domain receptor (a type III receptor tyrosine kinase)	5.9E-03	2.69
11728825_at	388610	TRNP1	TMF1-regulated nuclear protein 1	5.3E-06	2.68
11730593_at	387700	SLC16A12	solute carrier family 16, member 12 (monocarboxylic acid transporter 12)	2.5E-02	2.68
11720745_a_at	604	BCL6	B-cell CLL/lymphoma 6	1.7E-04	2.66
11717440_a_at	2059	EPS8	epidermal growth factor receptor pathway substrate 8	1.2E-04	2.62
11724997_a_at	942	CD86	CD86 molecule	1.5E-02	2.58
11759525_at	4616	GADD45B	growth arrest and DNA-damage-inducible, beta	5.6E-05	2.57
11715766_a_at	1843	DUSP1	dual specificity phosphatase 1	5.1E-03	2.57
11719899_at	387763	C11orf96	chromosome 11 open reading frame 96	1.3E-02	2.56
11736375_a_at	942	CD86	CD86 molecule	2.3E-02	2.54
11763337_a_at	26468	LHX6	LIM homeobox 6	1.7E-03	2.52
11752993_a_at	1843	DUSP1	dual specificity phosphatase 1	7.6E-03	2.48
11718012_at	8660	IRS2	insulin receptor substrate 2	5.7E-05	2.47
11725512_a_at	55089	SLC38A4	solute carrier family 38, member 4	1.9E-05	2.45
11750749_a_at	604	BCL6	B-cell CLL/lymphoma 6	9.0E-04	2.43
11737087_at	7092	TLL1	tolloid-like 1	9.9E-03	2.40
11728523_a_at	4610	MYCL1	v-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)	1.5E-03	2.39
11757865_a_at	4616	GADD45B	growth arrest and DNA-damage-inducible, beta	9.5E-05	2.39
11755403_a_at	83539	CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9	1.3E-03	2.38
11718780_a_at	23635	SSBP2	single-stranded DNA binding protein 2	3.0E-06	2.38
11719408_a_at	28996	HIPK2	homeodomain interacting protein kinase 2	1.4E-04	2.38
11736581_a_at	2650	GCNT1	glucosaminyl (N-acetyl) transferase 1, core 2	9.0E-03	2.38
11754631_x_at	5295	PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	1.2E-02	2.37
11720967_a_at	29899	GPSM2	G-protein signaling modulator 2	9.5E-06	2.37
11733139_a_at	10124	ARL4A	ADP-ribosylation factor-like 4A	5.3E-04	2.35
11732521_a_at	83539	CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9	2.1E-03	2.33
11739230_a_at	10124	ARL4A	ADP-ribosylation factor-like 4A	1.6E-03	2.33
11740994_a_at	2752	GLUL	glutamate-ammonia ligase	5.6E-05	2.32
11746856_a_at	5054	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), me	3.8E-02	2.31
11724394_at	343990	KIAA1211L	KIAA1211-like	4.0E-03	2.30
11754183_s_at	3149	HMGB3	high mobility group box 3	4.6E-04	2.29
11753047_a_at	441024	MTHFD2L	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2-like	5.2E-03	2.29
11715659_s_at	54206	ERRFI1	ERBB receptor feedback inhibitor 1	4.4E-05	2.28
11722783_at	94234	FOXQ1	forkhead box Q1	4.5E-03	2.28
11756387_x_at	10124	ARL4A	ADP-ribosylation factor-like 4A	9.6E-04	2.28

11759322_at	604	BCL6	B-cell CLL/lymphoma 6	1.9E-04	2.27
11741001_s_at	10144	FAM13A	family with sequence similarity 13, member A	1.8E-03	2.27
11722852_s_at	330	BIRC3	baculoviral IAP repeat containing 3	2.6E-03	2.26
11720520_s_at	9659 /// 728802 /// 100996724 /// 100996761 /// 101060291 /// 101060344 /// 101060353 /	LOC100996724 /// LOC100996761 /// LOC101060291 /// LOC101060344 /// LOC101060353 /// LOC101060463 /// LOC101060582 /// LOC728802 /// PDE4DIP	myomegalin-like /// myomegalin-like /// myomegalin-like /// uncharacterized LOC10106034	1.6E-04	2.25
11730194_a_at	23541	SEC14L2	SEC14-like 2 (S. cerevisiae)	4.7E-05	2.23
11728826_s_at	388610	TRNP1	TMF1-regulated nuclear protein 1	1.2E-05	2.23
11719527_a_at	146330	FBXL16	F-box and leucine-rich repeat protein 16	2.1E-02	2.23
11749481_a_at	23087	TRIM35	tripartite motif containing 35	5.6E-05	2.22
11733017_a_at	5295	PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	2.4E-02	2.22
11715636_a_at	5054	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), me	3.7E-02	2.21
11718013_at	8660	IRS2	insulin receptor substrate 2	6.3E-03	2.21
11742813_at	57556	SEMA6A	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	4.1E-03	2.20
11724998_a_at	942	CD86	CD86 molecule	1.9E-03	2.20
11744229_a_at	65997	RASL11B	RAS-like, family 11, member B	1.4E-02	2.20
11743136_x_at	1052	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	2.4E-07	2.19
11725268_s_at	79633	FAT4	FAT atypical cadherin 4	9.5E-04	2.19
11733140_s_at	10124	ARL4A	ADP-ribosylation factor-like 4A	1.2E-03	2.19
11728829_at	3625	INHBB	inhibin, beta B	8.4E-03	2.18
11734164_a_at	26084	ARHGEF26	Rho guanine nucleotide exchange factor (GEF) 26	2.7E-03	2.18
11746140_a_at	26084	ARHGEF26	Rho guanine nucleotide exchange factor (GEF) 26	2.7E-03	2.18
11724961_a_at	9901	SRGAP3	SLIT-ROBO Rho GTPase activating protein 3	3.9E-07	2.17
11740964_a_at	441024	MTHFD2L	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2-like	1.3E-03	2.17
11750770_a_at	2729	GCLC	glutamate-cysteine ligase, catalytic subunit	2.2E-04	2.17
11719409_a_at	28996	HIPK2	homeodomain interacting protein kinase 2	1.9E-07	2.16
11718781_s_at	23635	SSBP2	single-stranded DNA binding protein 2	1.1E-04	2.14
11735309_a_at	4610	MYCL1	v-myc myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (avian)	2.0E-03	2.14
11719676_s_at	4128	MAOA	monoamine oxidase A	3.4E-06	2.14
11726896_a_at	11213	IRAK3	interleukin-1 receptor-associated kinase 3	1.7E-02	2.13
11719410_s_at	28996	HIPK2	homeodomain interacting protein kinase 2	2.8E-08	2.12
11729218_a_at	2729	GCLC	glutamate-cysteine ligase, catalytic subunit	4.7E-04	2.11
11723343_at	23087	TRIM35	tripartite motif containing 35	8.7E-08	2.11
11720565_a_at	89797	NAV2	neuron navigator 2	3.0E-04	2.11
11758028_s_at	94234	FOXQ1	forkhead box Q1	1.9E-03	2.10
11724931_a_at	10461	MERTK	c-mer proto-oncogene tyrosine kinase	4.9E-02	2.10
11757312_x_at	5054	SERPINE1	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), me	3.8E-02	2.09
11763714_a_at	23635	SSBP2	single-stranded DNA binding protein 2	2.9E-05	2.09
11728921_at	83992	CTTNBP2	cortactin binding protein 2	4.7E-02	2.07
11719736_s_at	54463	FAM134B	family with sequence similarity 134, member B	1.6E-02	2.07
11742768_a_at	23767	FLRT3	fibronectin leucine rich transmembrane protein 3	8.0E-05	2.06

11734619_x_at	247	ALOX15B	arachidonate 15-lipoxygenase, type B	1.3E-02	2.06
11722850_a_at	330	BIRC3	baculoviral IAP repeat containing 3	9.0E-03	2.05
11723344_at	23087	TRIM35	tripartite motif containing 35	1.2E-07	2.05
11735270_a_at	2650	GCNT1	glucosaminyl (N-acetyl) transferase 1, core 2	3.1E-02	2.03
11731465_a_at	1075	CTSC	cathepsin C	1.0E-03	2.03
11743626_s_at	55366	LGR4	leucine-rich repeat containing G protein-coupled receptor 4	3.5E-06	2.03
11721983_a_at	55022	PID1	phosphotyrosine interaction domain containing 1	1.6E-02	2.02
11746658_a_at	942	CD86	CD86 molecule	1.6E-02	2.02
11727552_at	2535	FZD2	frizzled family receptor 2	2.6E-03	2.01
11754931_a_at	2729	GCLC	glutamate-cysteine ligase, catalytic subunit	2.3E-04	2.01
11739518_a_at	23767	FLRT3	fibronectin leucine rich transmembrane protein 3	1.0E-04	2.00
11736382_at	90874	ZNF697	zinc finger protein 697	1.5E-03	0.50
11734339_at	5453	POU3F1	POU class 3 homeobox 1	1.5E-04	0.50
11718577_s_at	10276	NET1	neuroepithelial cell transforming 1	2.6E-04	0.50
11720760_x_at	10625	IVNS1ABP	influenza virus NS1A binding protein	4.9E-02	0.50
11739768_a_at	5791	PTPRE	protein tyrosine phosphatase, receptor type, E	8.9E-03	0.50
11755562_a_at	2863	GPR39	G protein-coupled receptor 39	1.3E-04	0.50
11749997_x_at	7447	VSNL1	visinin-like 1	5.2E-03	0.50
11743434_a_at	50515	CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	1.1E-04	0.49
11723418_a_at	7447	VSNL1	visinin-like 1	8.7E-03	0.49
11722547_a_at	3096	HIVEP1	human immunodeficiency virus type I enhancer binding protein 1	7.4E-03	0.49
11754114_a_at	2919	CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	4.3E-02	0.49
11726703_a_at	8915	BCL10	B-cell CLL/lymphoma 10	1.5E-04	0.49
11754344_s_at	81848	SPRY4	sprouty homolog 4 (Drosophila)	2.7E-02	0.49
11716151_a_at	56937	PMEPA1	prostate transmembrane protein, androgen induced 1	1.1E-02	0.49
11729574_at	8507	ENC1	ectodermal-neural cortex 1 (with BTB domain)	6.2E-03	0.49
11730390_at	10371	SEMA3A	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	7.7E-04	0.49
11732454_at	3772	KCNJ15	potassium inwardly-rectifying channel, subfamily J, member 15	8.4E-03	0.48
11743596_a_at	5791	PTPRE	protein tyrosine phosphatase, receptor type, E	5.0E-03	0.48
11728161_at	7476	WNT7A	wingless-type MMTV integration site family, member 7A	4.1E-06	0.48
11718940_a_at	7128	TNFAIP3	tumor necrosis factor, alpha-induced protein 3	3.9E-03	0.48
11732180_a_at	5724	PTAFR	platelet-activating factor receptor	9.6E-05	0.48
11723820_a_at	64750	SMURF2	SMAD specific E3 ubiquitin protein ligase 2	1.0E-05	0.48
11758583_s_at	201799	TMEM154	transmembrane protein 154	5.4E-04	0.48
11743063_x_at	5329	PLAUR	plasminogen activator, urokinase receptor	1.2E-03	0.48
11753988_a_at	10253	SPRY2	sprouty homolog 2 (Drosophila)	2.2E-02	0.48
11758050_s_at	5998	RGS3	regulator of G-protein signaling 3	2.8E-03	0.48
11718201_at	23462	HEY1	hairy/enhancer-of-split related with YRPW motif 1	1.5E-03	0.48
11715306_s_at	374 /// 727738	AREG /// AREGB	amphiregulin /// amphiregulin B	2.5E-03	0.48
11733214_a_at	162394	SLFN5	schlafen family member 5	5.4E-05	0.48
11749996_a_at	7447	VSNL1	visinin-like 1	7.5E-03	0.48
11751656_a_at	201799	TMEM154	transmembrane protein 154	3.9E-04	0.48
11746862_x_at	79642	ARSJ	arylsulfatase family, member J	8.6E-06	0.47
11723592_at	84230	LRRC8C	leucine rich repeat containing 8 family, member C	9.3E-03	0.47
11730363_a_at	3269	HRH1	histamine receptor H1	3.5E-02	0.47
11738219_s_at	127534	GJB4	gap junction protein, beta 4, 30.3kDa	1.3E-03	0.47
11763314_s_at	10123	ARL4C	ADP-ribosylation factor-like 4C	6.6E-03	0.47
11734825_at	161742	SPRED1	sprouty-related, EVH1 domain containing 1	1.5E-02	0.47
11720825_s_at	182	JAG1	jagged 1	9.3E-03	0.47
11739046_s_at	79812	MMRN2	multimerin 2	8.1E-03	0.47
11742468_at	644943	RASSF10	Ras association (RalGDS/AF-6) domain family (N-terminal) member 10	2.2E-06	0.47
11748382_a_at	64750	SMURF2	SMAD specific E3 ubiquitin protein ligase 2	1.2E-02	0.47
11724686_x_at	3455	IFNAR2	interferon (alpha, beta and omega) receptor 2	8.4E-04	0.47

11731096_at	80326	WNT10A	wingless-type MMTV integration site family, member 10A	6.2E-03	0.47
11722654_s_at	9263	STK17A	serine/threonine kinase 17a	2.1E-03	0.47
11724551_x_at	55529	TMEM55A	transmembrane protein 55A	2.6E-03	0.47
11739654_at	8797	TNFRSF10A	tumor necrosis factor receptor superfamily, member 10a	9.7E-03	0.46
11720759_s_at	10625	IVNS1ABP	influenza virus NS1A binding protein	2.9E-02	0.46
11717656_a_at	200734	SPRED2	sprouty-related, EVH1 domain containing 2	9.5E-04	0.46
11759497_at	50515	CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	1.2E-04	0.46
11722548_at	3096	HIVEP1	human immunodeficiency virus type I enhancer binding protein 1	2.0E-03	0.46
11727814_at	84959	UBASH3B	ubiquitin associated and SH3 domain containing B	8.1E-04	0.46
11754026_a_at	3576	IL8	interleukin 8	5.9E-03	0.46
11723147_a_at	89795	NAV3	neuron navigator 3	1.0E-02	0.46
11748409_a_at	26030	PLEKHG3	pleckstrin homology domain containing, family G (with RhoGef domain) member 3	1.6E-03	0.45
11716162_at	81606	LBH	limb bud and heart development	7.1E-03	0.45
11715950_a_at	115207	KCTD12	potassium channel tetramerisation domain containing 12	1.9E-02	0.45
11717409_at	10019	SH2B3	SH2B adaptor protein 3	1.6E-02	0.45
11729099_a_at	3556	IL1RAP	interleukin 1 receptor accessory protein	6.8E-04	0.45
11725371_s_at	7422	VEGFA	vascular endothelial growth factor A	1.2E-02	0.44
11732240_a_at	84189	SLITRK6	SLIT and NTRK-like family, member 6	2.9E-03	0.44
11733240_at	3656	IRAK2	interleukin-1 receptor-associated kinase 2	6.0E-03	0.44
11743617_at	3673	ITGA2	integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)	6.0E-03	0.44
11727215_a_at	3084	NRG1	neuregulin 1	1.3E-02	0.44
11756842_x_at	221468	TMEM217	transmembrane protein 217	2.2E-04	0.44
11731246_s_at	56256	SERTAD4	SERTA domain containing 4	1.8E-03	0.44
11731603_at	201799	TMEM154	transmembrane protein 154	3.9E-04	0.44
11746863_x_at	79642	ARSJ	arylsulfatase family, member J	1.5E-04	0.44
11740736_x_at	79905	TMC7	transmembrane channel-like 7	7.0E-05	0.44
11732712_a_at	10468	FST	follistatin	3.8E-02	0.44
11718576_s_at	10276	NET1	neuroepithelial cell transforming 1	1.5E-04	0.44
11750154_a_at	5998	RGS3	regulator of G-protein signaling 3	2.4E-03	0.44
11741056_a_at	136	ADORA2B	adenosine A2b receptor	3.1E-02	0.44
11725372_x_at	7422	VEGFA	vascular endothelial growth factor A	1.6E-02	0.43
11753008_a_at	56300	IL36G	interleukin 36, gamma	1.6E-02	0.43
11741964_s_at	7422	VEGFA	vascular endothelial growth factor A	2.3E-02	0.43
11731602_at	201799	TMEM154	transmembrane protein 154	2.9E-04	0.43
11749155_a_at	10276	NET1	neuroepithelial cell transforming 1	1.0E-04	0.43
11716733_at	3659	IRF1	interferon regulatory factor 1	6.7E-04	0.43
11723591_at	84230	LRRC8C	leucine rich repeat containing 8 family, member C	3.8E-03	0.43
11750740_a_at	8869	ST3GAL5	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	8.3E-03	0.43
11718084_a_at	4067	LYN	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	6.0E-04	0.42
11734827_at	161742	SPRED1	sprouty-related, EVH1 domain containing 1	1.1E-02	0.42
11726909_at	79413	ZBED2	zinc finger, BED-type containing 2	3.9E-02	0.42
11734824_at	161742	SPRED1	sprouty-related, EVH1 domain containing 1	2.4E-02	0.42
11737413_at	84953	MICALCL	MICAL C-terminal like	3.7E-03	0.42
11736686_a_at	2250	FGF5	fibroblast growth factor 5	7.4E-05	0.42
11725367_at	389792	IER5L	immediate early response 5-like	1.2E-04	0.42
11726158_at	139886	SPIN4	spindlin family, member 4	5.1E-03	0.42
11757853_s_at	117581	TWIST2	twist basic helix-loop-helix transcription factor 2	1.1E-04	0.42
11718295_a_at	10509	SEMA4B	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmi	4.1E-04	0.42
11732877_a_at	1591	CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	3.8E-03	0.42
11746931_a_at	3624	INHBA	inhibin, beta A	8.8E-03	0.41
11724032_a_at	10468	FST	follistatin	3.3E-02	0.41
11751739_a_at	5791	PTPRE	protein tyrosine phosphatase, receptor type, E	1.1E-02	0.40
11725469_at	9388	LIPG	lipase, endothelial	1.2E-03	0.40

11736685_a_at	2250	FGF5	fibroblast growth factor 5	2.5E-04	0.40
11715951_s_at	115207	KCTD12	potassium channel tetramerisation domain containing 12	3.2E-02	0.40
11716161_s_at	81606	LBH	limb bud and heart development	3.3E-04	0.40
11733852_at	112399	EGLN3	egl nine homolog 3 (C. elegans)	2.4E-02	0.40
11731897_a_at	5744	PTHLH	parathyroid hormone-like hormone	2.9E-02	0.40
11725198_at	3552	IL1A	interleukin 1, alpha	2.2E-02	0.40
11759549_a_at	9645	MICAL2	microtubule associated monooxygenase, calponin and LIM domain containing 2	2.3E-03	0.39
11730465_at	3759	KCNJ2	potassium inwardly-rectifying channel, subfamily J, member 2	1.3E-02	0.39
11718085_s_at	4067	LYN	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	1.6E-03	0.39
11752387_a_at	2113	ETS1	v-ets erythroblastosis virus E26 oncogene homolog 1 (avian)	3.8E-02	0.39
11736047_a_at	118429	ANTXR2	anthrax toxin receptor 2	8.7E-03	0.39
11718296_a_at	10509	SEMA4B	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmi	4.1E-03	0.38
11728141_at	387914	SHISA2	shisa homolog 2 (Xenopus laevis)	2.7E-02	0.38
11754119_a_at	5328	PLAU	plasminogen activator, urokinase	3.9E-03	0.38
11720447_s_at	6662	SOX9	SRY (sex determining region Y)-box 9	3.4E-03	0.38
11754394_a_at	8871	SYNJ2	synaptojanin 2	3.2E-04	0.38
11732514_s_at	4067	LYN	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	7.1E-04	0.38
11726572_a_at	8482	SEMA7A	semaphorin 7A, GPI membrane anchor (John Milton Hagen blood group)	3.8E-05	0.38
11727690_at	3589	IL11	interleukin 11	2.3E-03	0.38
11759155_a_at	162514	TRPV3	transient receptor potential cation channel, subfamily V, member 3	3.4E-04	0.38
11736687_a_at	2250	FGF5	fibroblast growth factor 5	3.4E-04	0.38
11740245_a_at	5744	PTHLH	parathyroid hormone-like hormone	3.3E-02	0.38
11725280_a_at	56978	PRDM8	PR domain containing 8	9.0E-03	0.38
11734826_s_at	161742	SPRED1	sprouty-related, EVH1 domain containing 1	4.2E-03	0.38
11720823_at	182	JAG1	jagged 1	1.4E-03	0.37
11736813_at	80380	PDCD1LG2	programmed cell death 1 ligand 2	2.6E-03	0.37
11755648_a_at	9645	MICAL2	microtubule associated monooxygenase, calponin and LIM domain containing 2	3.3E-03	0.37
11715947_a_at	115207	KCTD12	potassium channel tetramerisation domain containing 12	2.3E-04	0.37
11717886_a_at	5328	PLAU	plasminogen activator, urokinase	9.6E-03	0.37
11736048_at	118429	ANTXR2	anthrax toxin receptor 2	4.7E-03	0.36
11751994_s_at	182	JAG1	jagged 1	2.1E-03	0.36
11738053_x_at	5329	PLAUR	plasminogen activator, urokinase receptor	7.6E-04	0.36
11719916_at	3553	IL1B	interleukin 1, beta	1.4E-04	0.36
11759496_at	50515	CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	1.9E-03	0.36
11724948_at	163732	CITED4	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 4	2.9E-04	0.36
11716160_at	81606	LBH	limb bud and heart development	5.6E-05	0.35
11757940_at	5228	PGF	placental growth factor	2.2E-05	0.35
11754176_a_at	11009	IL24	interleukin 24	1.8E-02	0.35
11744128_x_at	2920	CXCL2	chemokine (C-X-C motif) ligand 2	1.0E-02	0.35
11732158_a_at	9510	ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	5.4E-05	0.35
11739767_a_at	5791	PTPRE	protein tyrosine phosphatase, receptor type, E	4.6E-03	0.35
11744005_at	7262	PHLDA2	pleckstrin homology-like domain, family A, member 2	7.5E-05	0.35
11732713_at	10468	FST	follistatin	4.0E-02	0.34
11760574_x_at	8061	FOSL1	FOS-like antigen 1	3.8E-03	0.33
11743841_at	257068	PLCXD2	phosphatidylinositol-specific phospholipase C, X domain containing 2	6.5E-04	0.33
11732331_s_at	10123	ARL4C	ADP-ribosylation factor-like 4C	1.0E-03	0.33
11754662_s_at	9510	ADAMTS1	ADAM metallopeptidase with thrombospondin type 1 motif, 1	4.3E-04	0.33
11731834_a_at	11009	IL24	interleukin 24	2.9E-02	0.33
11736688_x_at	2250	FGF5	fibroblast growth factor 5	7.7E-05	0.33
11751993_a_at	182	JAG1	jagged 1	9.5E-04	0.32
11721306_at	22822	PHLDA1	pleckstrin homology-like domain, family A, member 1	1.9E-03	0.31

11736247_x_at	347902	AMIGO2	adhesion molecule with Ig-like domain 2	6.9E-04	0.30
11717154_a_at	5328	PLAU	plasminogen activator, urokinase	3.3E-03	0.30
11754313_s_at	10123	ARL4C	ADP-ribosylation factor-like 4C	1.0E-03	0.29
11758216_s_at	6662	SOX9	SRY (sex determining region Y)-box 9	3.4E-04	0.29
11732181_x_at	5724	PTAFR	platelet-activating factor receptor	5.2E-06	0.29
11736246_a_at	347902	AMIGO2	adhesion molecule with Ig-like domain 2	3.7E-04	0.29
11755252_a_at	347902	AMIGO2	adhesion molecule with Ig-like domain 2	1.1E-03	0.29
11718841_s_at	3576	IL8	interleukin 8	3.6E-03	0.28
11733913_at	9957	HS3ST1	heparan sulfate (glucosamine) 3-O-sulfotransferase 1	3.6E-03	0.28
11737334_a_at	347902	AMIGO2	adhesion molecule with Ig-like domain 2	4.6E-04	0.27
11752515_a_at	4953	ODC1	ornithine decarboxylase 1	5.6E-03	0.27
11719586_a_at	29114	TAGLN3	transgelin 3	1.5E-04	0.27
11724036_a_at	5743	PTGS2	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	2.9E-02	0.27
11730029_a_at	144455	E2F7	E2F transcription factor 7	4.6E-03	0.26
11754074_s_at	50486	G0S2	G0/G1switch 2	5.2E-03	0.26
11724478_s_at	8061	FOSL1	FOS-like antigen 1	9.7E-03	0.26
11758222_s_at	6574	SLC20A1	solute carrier family 20 (phosphate transporter), member 1	1.5E-03	0.25
11720448_at	6662	SOX9	SRY (sex determining region Y)-box 9	1.3E-05	0.25
11720062_s_at	8870	IER3	immediate early response 3	2.6E-04	0.24
11731496_at	3624	INHBA	inhibin, beta A	2.3E-03	0.24
11736342_at	1960	EGR3	early growth response 3	6.5E-05	0.24
11719366_s_at	2919	CXCL1	chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	4.2E-03	0.23
11764263_s_at	162514	TRPV3	transient receptor potential cation channel, subfamily V, member 3	7.2E-04	0.23
11744162_a_at	1846	DUSP4	dual specificity phosphatase 4	7.0E-04	0.21
11744618_a_at	1848	DUSP6	dual specificity phosphatase 6	1.9E-02	0.20
11721308_at	22822	PHLDA1	pleckstrin homology-like domain, family A, member 1	1.8E-04	0.19
11722049_a_at	1848	DUSP6	dual specificity phosphatase 6	1.6E-02	0.19
11755981_a_at	1839	HBEGF	heparin-binding EGF-like growth factor	5.0E-06	0.17
11741980_a_at	1848	DUSP6	dual specificity phosphatase 6	1.7E-02	0.16
11744435_a_at	1848	DUSP6	dual specificity phosphatase 6	1.9E-02	0.16
11721305_a_at	22822	PHLDA1	pleckstrin homology-like domain, family A, member 1	3.9E-04	0.14
11719898_s_at	1839	HBEGF	heparin-binding EGF-like growth factor	1.2E-04	0.14
11725584_at	3038	HAS3	hyaluronan synthase 3	2.0E-05	0.13
11744219_at	50486	G0S2	G0/G1switch 2	4.7E-03	0.12
11721307_at	22822	PHLDA1	pleckstrin homology-like domain, family A, member 1	2.0E-04	0.10

Human bronchial epithelial cells were either not treated or treated with 0.1 μM budesonide (Bud) prior to harvesting at 6 h. Total RNA was subjected to expression profiling using Affymetrix PrimeView microarrays. Analysis (n = 6 independent donors) was performed with Partek Genomics Suite (Version 6.6). Resultant fold expression and *P* values for all probe sets showing fold ≥ 2 or ≤ 0.5 with $P \leq 0.05$ are listed.

SUPPLEMENTAL TABLE 10

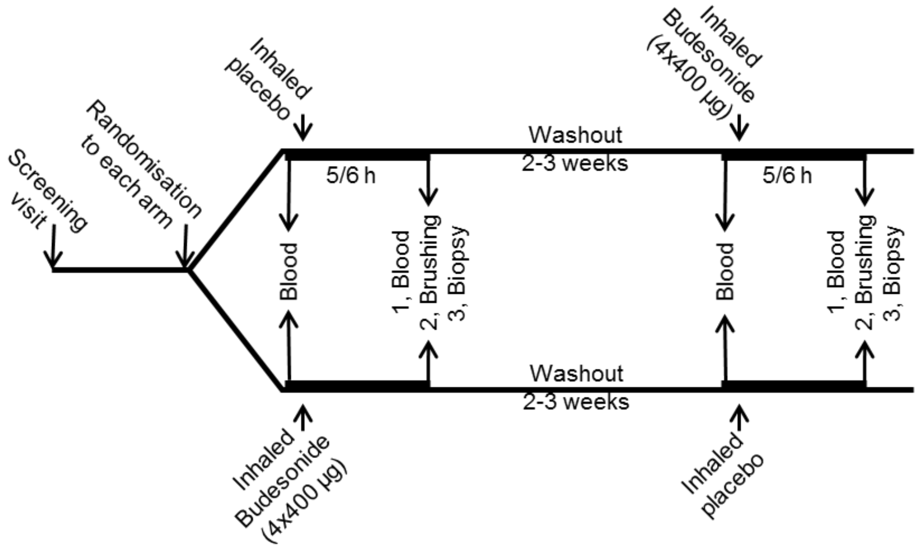
Primary human bronchial epithelial cell microarray data: Functional grouping of genes showing ≥2 or ≤0.5 fold change (*P*≤0.05) following 6h *in vitro* budesonide treatment

A. Up-regulated genes (>2 fold)	
A1. Transcriptional control	
Positive regulator - DNA binding	
≥2	CEBPD, CUX2, FOXQ1, KLF9, LHX6, MYCL1, PER1, TFCP2L1, TRNP1
Negative regulator – DNA binding	
≥2	BCL6, TSC22D3, ZBTB16
Other regulator	
≥2	HGMB3
A2. Membrane receptors	
GPCRs	
≥2	FZD2, LGR4
Cytokine, growth factor, and related receptors	
≥2	GHR, KDR, MERTK, TLR2
Other membrane receptors	
≥2	CD86, FLRT3, SEMA6A, TREM2
A3. Signaling and regulation of signaling	
Kinase	
≥2	HIPK2, IRAK3,
Phosphatase	
≥2	DUSP1, PHACTR3
GTPase, GEF and GAP	
≥2	ARHGEF26, ARL4A, ERRFI1, FAM13A, GPSM2, RASL11B, RGS2, SRGAP3
Secreted factors (cytokines, growth factors)	
≥2	C10orf99, CXCL14, INHBB, VSTM2L
Other signaling	
≥2	BIRC3, DNER, EPS8, FAT4, FBXL16, FKBP5, GADD45B, GAS1, IRS2, PDE4DIP, PID1, PIK3R1,TMTC1
A4. Metabolic and metabolism	
≥2	ALOX15B, CHST9, CTSC, DCN, GCLC, GCNT1, GLUL, LOX, MAOA, MTHFD2L, PDK4, SEC14L2, SLC16A12, SLC26A2, SLC38A4, SLC46A3, SLC7A2, SULT1E1, TLL1
A5. Other function	
≥2	MYOT, NAV2, SCNN1G, SERPINE1, SSBP2
A6. Function not assigned	
≥2	C11orf96,CTTNBP2, FAM134B, FAM46B, KIAA1211L, TRIM35, ZNF608, ZXDB
B. Down-regulated genes (<0.5 fold)	
B1. Transcriptional control	
Positive regulator - DNA binding	
≥2	E2F7, EGR3, ETS1, FOSL1, IRF1, LBH, POU3F1, SOX9
Negative regulator – DNA binding	
≥2	HEY1, HIVEP1, TWIST2
Other regulator	
≥2	CITED4, PRDM8
B2. Membrane receptors	
GPCRs	
≥2	ADORA2B, GPR39, HRH1, PTAFR
Cytokine, growth factor, and related receptors	
≥2	IFNAR2, IL1RAP, SLITRK6, TNFRSF10A
Other membrane receptors	
≥2	ANTXR2, ITGA2, NRG1
B3. Signaling and regulation of signaling	
Kinase	
≥2	IRAK2, LYN, STK17A

Phosphatase	
≥2	DUSP4, DUSP6, PTPRE, UBASH3B
GTPase, GEF and GAP	
≥2	ARL4C, NET1, PLEKHG3, RGS3
Secreted factors (cytokines, growth factors)	
≥2	AREG, CXCL1, CXCL2, FGF5, FST, HBEGF, IL11, IL1A, IL1B, IL24, IL36G, IL8, INHBA, PGF, PTHLH, SEMA3A, VEGFA, WNT10A, WNT7A
Other signaling	
≥2	AMIGO2, BCL10, EGLN3, ENC1, IER3, IVNS1ABP, JAG1, KCNJ15, KCNJ2, KCTD12, LRRC8C, MICAL2, MICALCL, PDCD1LG2, PHLDA1, PHLDA2, PLAUR, PMEPA1, RASSF10, SEMA4B, SEMA7A, SERTAD4, SH2B3, SHISA2, SLFN5, SMURF2, SPRED1, SPRED2, SPRY2, SPRY4, TMC7, TNFAIP3, TRPV3, VSNL1
B4. Metabolic and metabolism	
≥2	ADAMTS1, ARSJ, CHST11, CYP24A1, G0S2, HAS3, LIPG, ODC1, PLAU, PLCXD2, PTGS2, SLC20A1, ST3GAL5, SYNJ2, TMEM55A
B5. Other function	
≥2	GJB4, HS3ST1, MMRN2, NAV3
B6. Function not assigned	
≥2	IER5L, SPIN4, TAGLN3, TMEM154, TMEM217, ZBED2, ZNF697

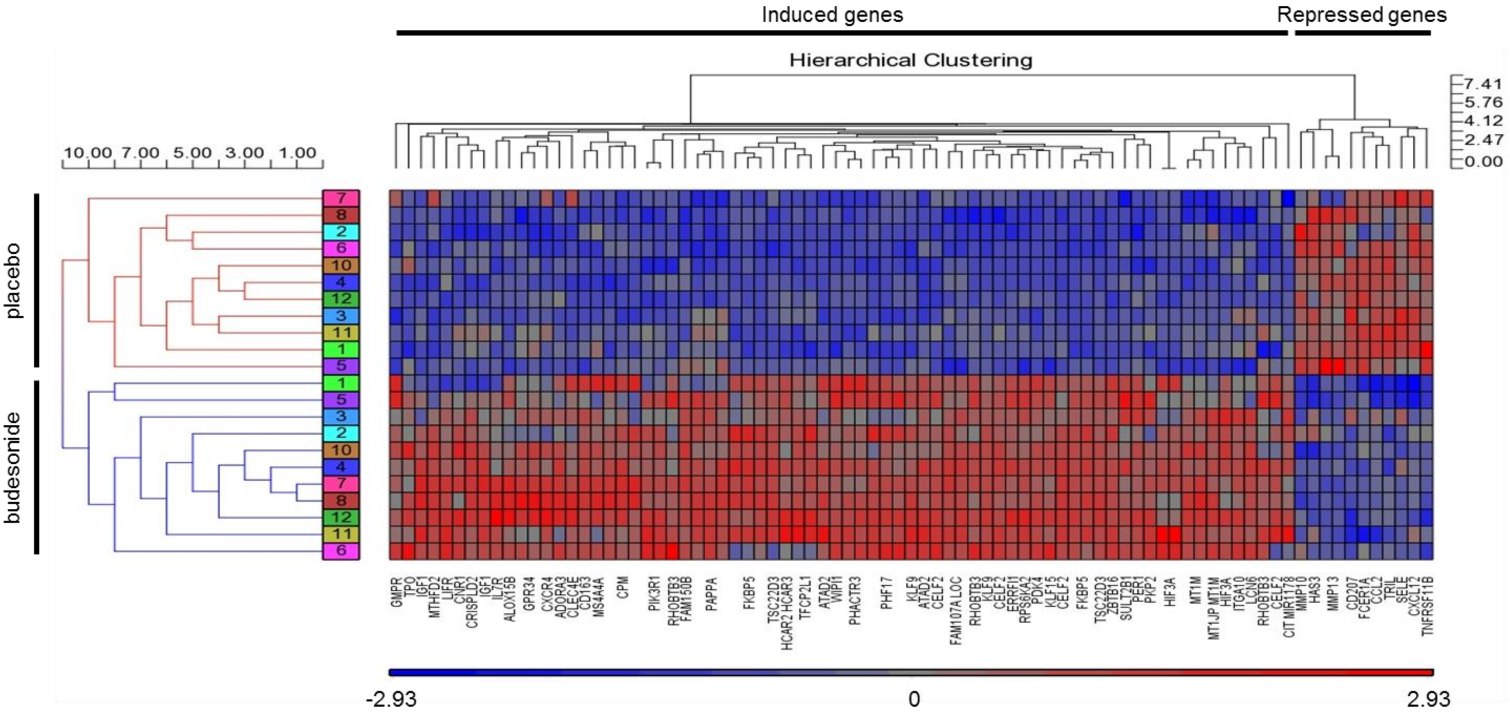
HBE cells were either not treated or treated with 0.1 μM budesonide (Bud) prior to harvesting at 6 h. Total RNA was subjected to expression profiling using Affymetrix PrimeView microarrays. Analysis (n = 6 independent donors) was performed with Partek Genomics Suite (Version 6.6). Resultant fold expression and *P* values for all probe sets showing ≥2 or ≤0.5 fold (*P*≤0.05) were analyzed using the DAVID gene ID conversion tool to produce individual gene identities. Using gene ontology (GO) information and functional information from NCBI Gene, gene symbols were categorized into six general groups: 1, Transcriptional control; 2, Membrane receptors; 3, Signaling and regulation of signaling; 4, Metabolic and metabolism; 5, Other function; or 6, Function not assigned and further sub-divided as indicated. Genes subjected to qPCR validation are underlined.

Supplemental Figures

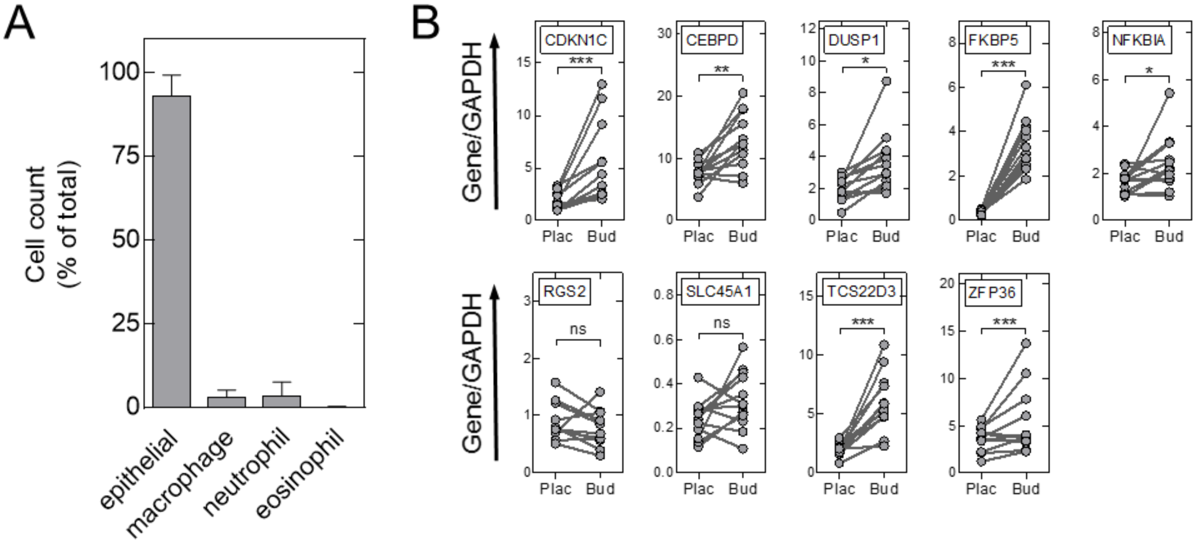


	Screening visit	Visit 1	Visit 2
Brief history/physical examination	X		
Spirometry	X	X	X
Methacholine challenge	X		
Skin prick test	X		
Blood		X	X
Administration of study drug/placebo ~07h.00		X	X
Bronchoscopy 5 – 6 h later		X	X
Bronchial brushing		X	X
Endobronchial biopsy		X	X

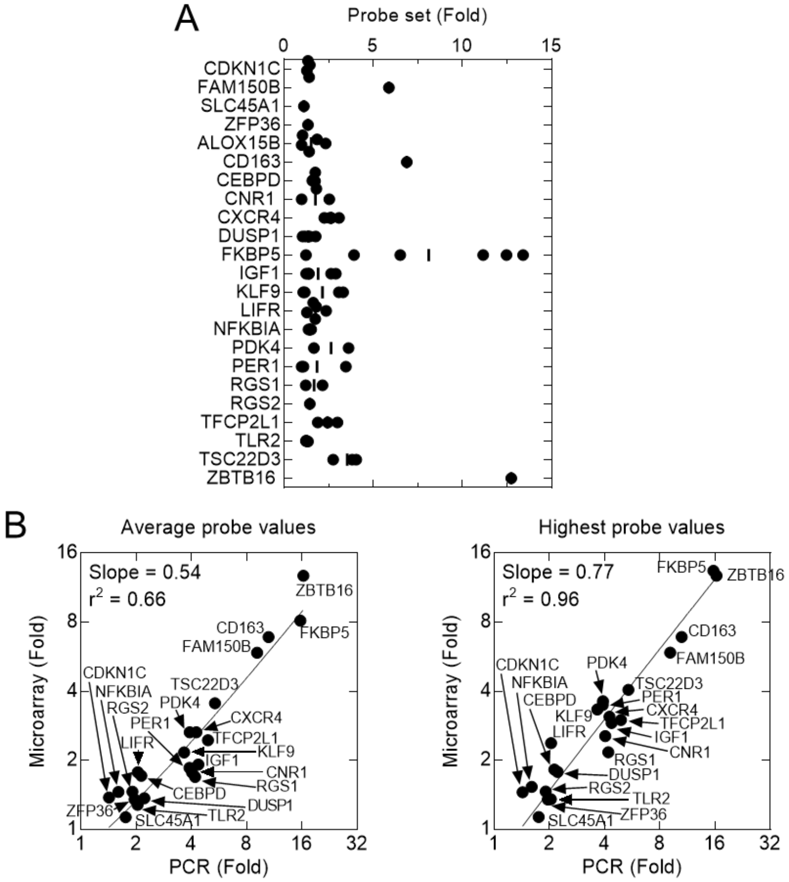
Supplemental Fig. 1. Study design: overview and procedures conducted at each visit. Following screening, the study participants were each randomized to receive either inhaled placebo followed by inhaled budesonide, or inhaled budesonide followed by inhaled placebo. Each treatment intervention was separated by a 2–3 week washout period. Randomization was performed by research pharmacy personnel, not otherwise associated with the study.



Supplemental Fig. 2. Heat map of budesonide-modulated genes showing ≥2 or ≤0.5 fold change with 5% false discovery rate (FDR). Biopsy RNA was subjected to expression profiling using Affymetrix PrimeView microarrays. Analysis (n = 11 individuals) was performed with Partek Genomics Suite (v6.6). Probe sets with fold ≥2 or ≤0.5 fold change and FDR corrected *P* values of ≤ 0.05 are portrayed as a heat map. The visualisation was generated by standardizing the selected probes to a mean of 0 and a standard deviation of 1 followed by hierarchical clustering.

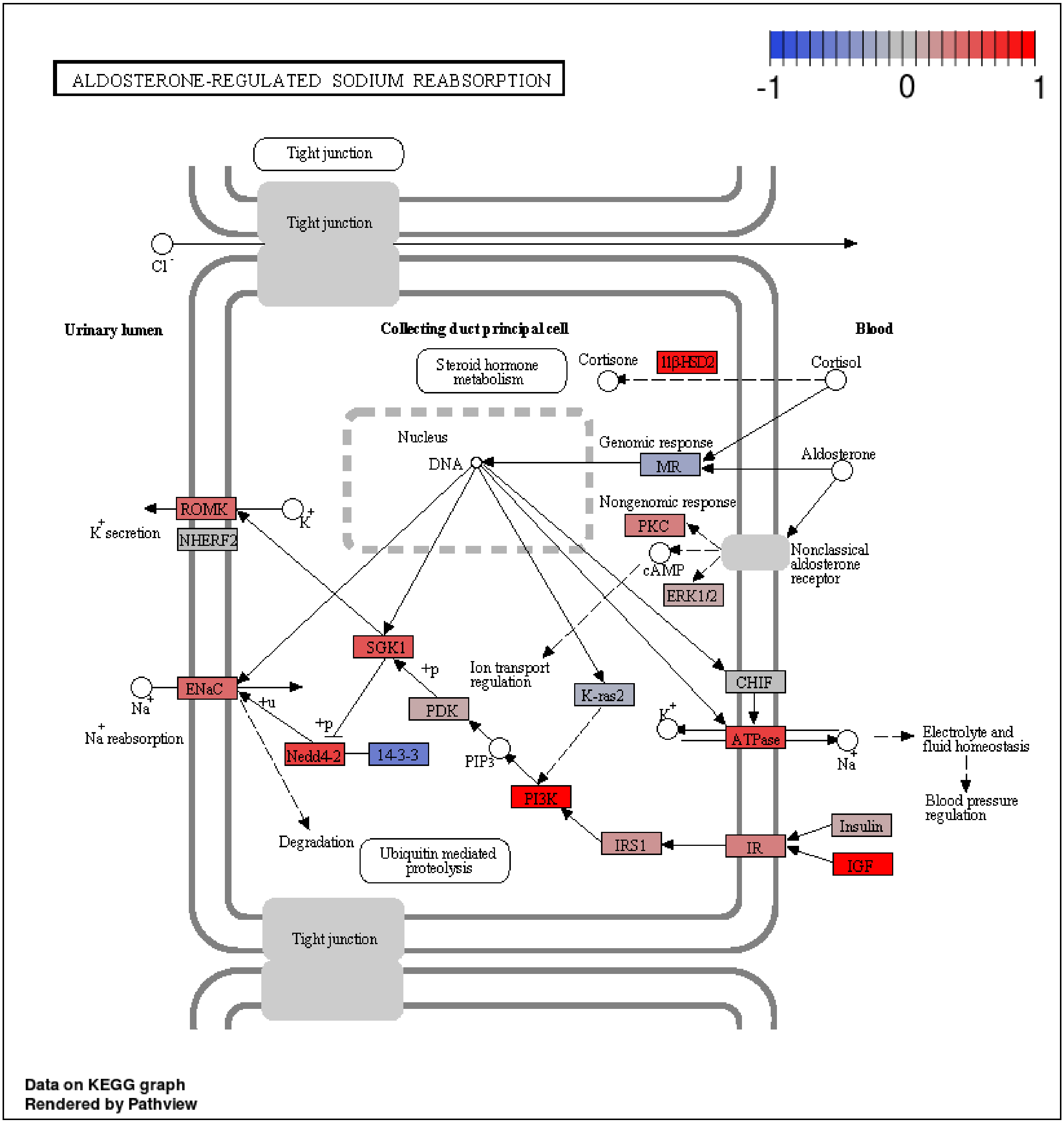


Supplemental Fig. 3. Differential cell counts and gene expression in bronchial brushings. (A) Recovered cells were collected into PBS prior to cytospining onto slides and differential cell counting. Data on brushed cells from 4 individuals are plotted as percentages of the total cells counted. Data are presented as means ±SE. (B) RNA was extracted from the recovered cells and following cDNA synthesis, qPCR for the indicated genes and GAPDH was performed. Data from the 12 individuals are expressed as the gene of interest/GAPDH and are plotted (in arbitrary units) as means ±SE. Significance was assessed by Wilcoxon signed rank test. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$.

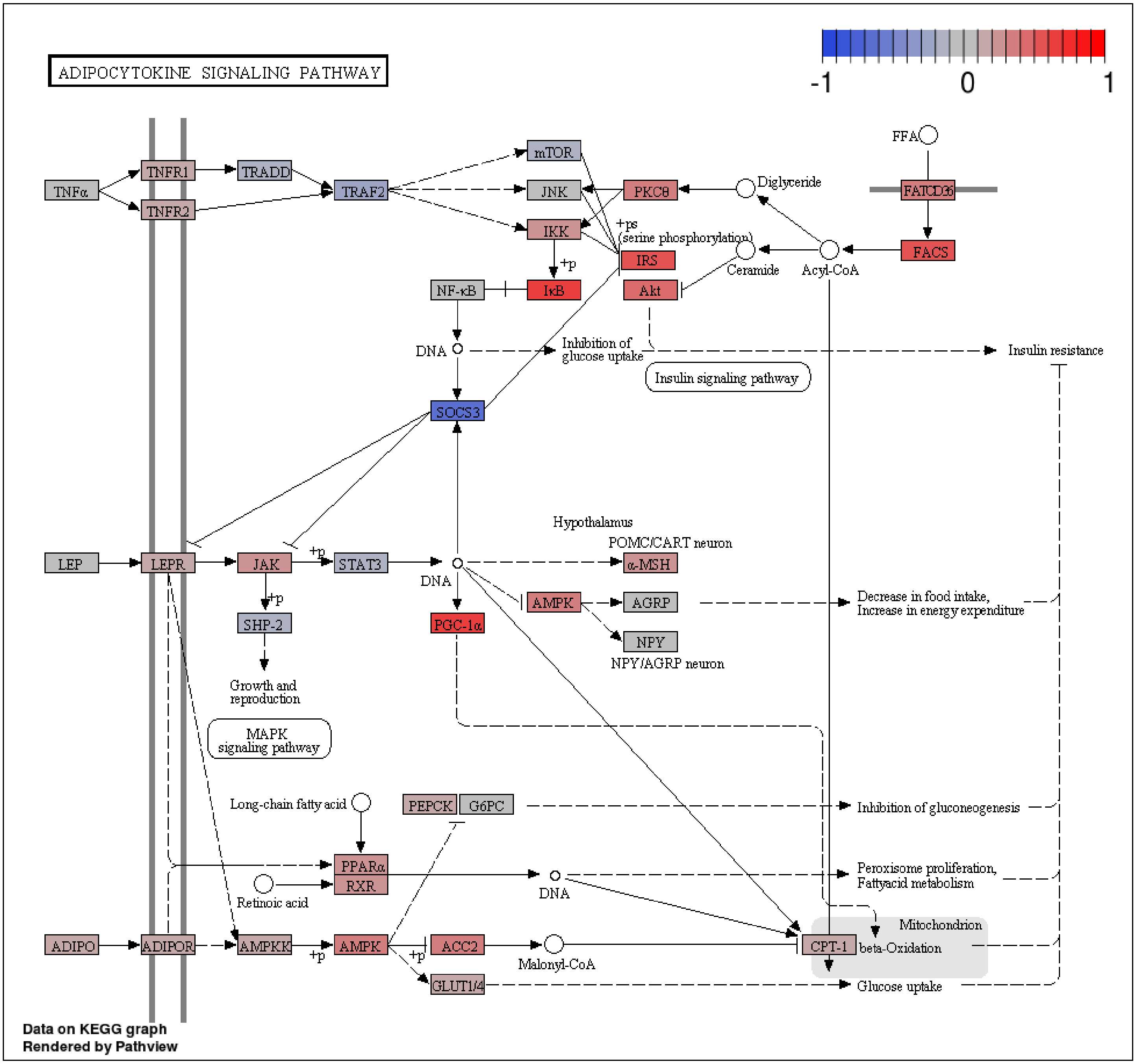


Supplemental Fig. 4. Comparison of biopsy microarray data with qPCR analysis of budesonide-induced genes. (A) Of the genes analyzed by qPCR in Figs. 1-3 in the main paper, many corresponded to multiple microarray probe sets (Supplemental Table 5). The values for each of these probe sets are plotted as fold for each gene. (B) Left panel - The average fold for all probe sets for each gene (y axis) is plotted against the fold obtained by qPCR (x axis). Right panel – Probe sets with the maximum fold for each gene (y axis) are plotted against the fold obtained by PCR (x axis). Slope and r^2 values are provided.

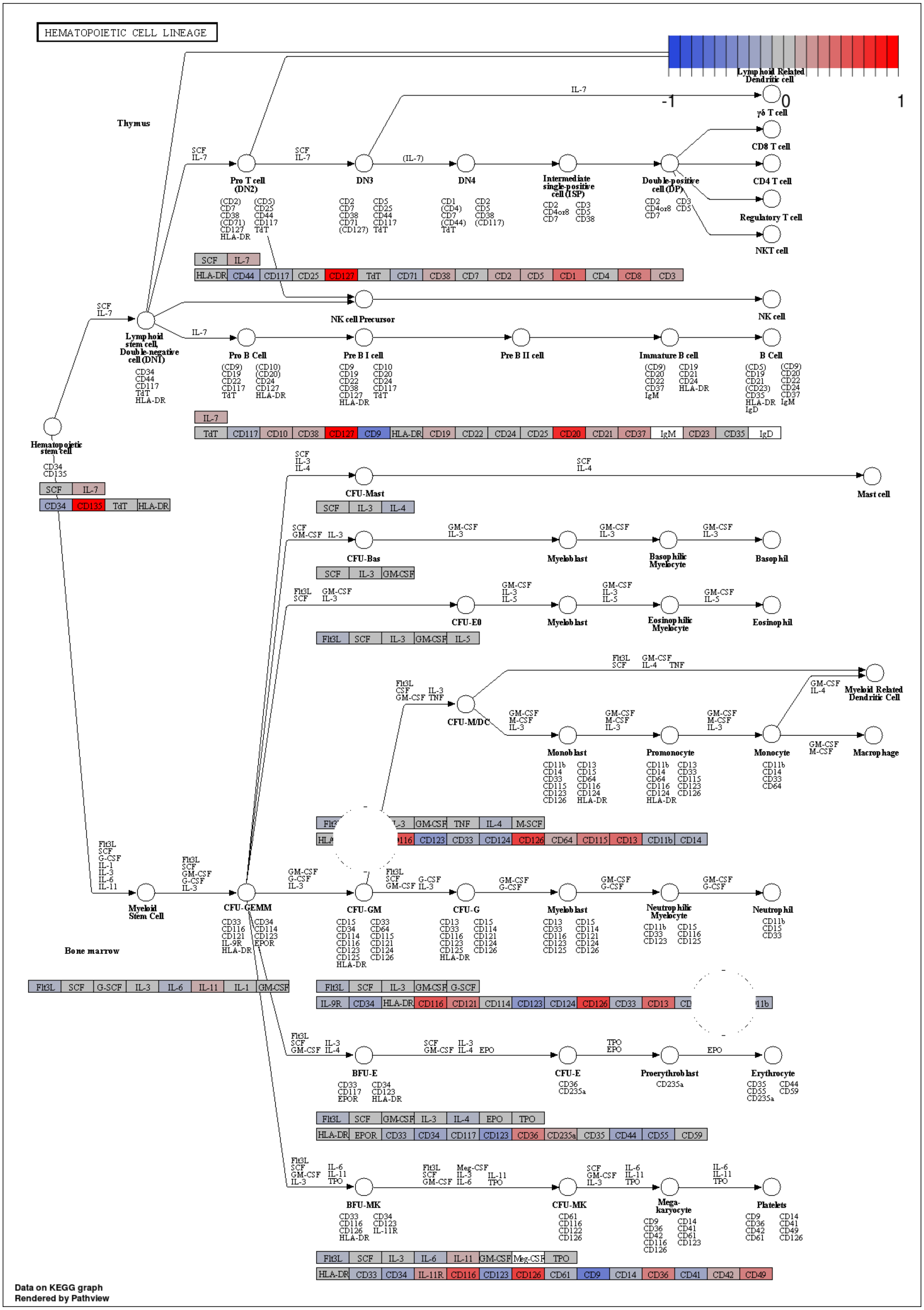
Supplemental Fig. 5. Pathway analysis showing selected pathways from the top 10 pathways most significantly associated with the microarray data. Color key shows log fold.
A. Aldosterone-regulated sodium reabsorption



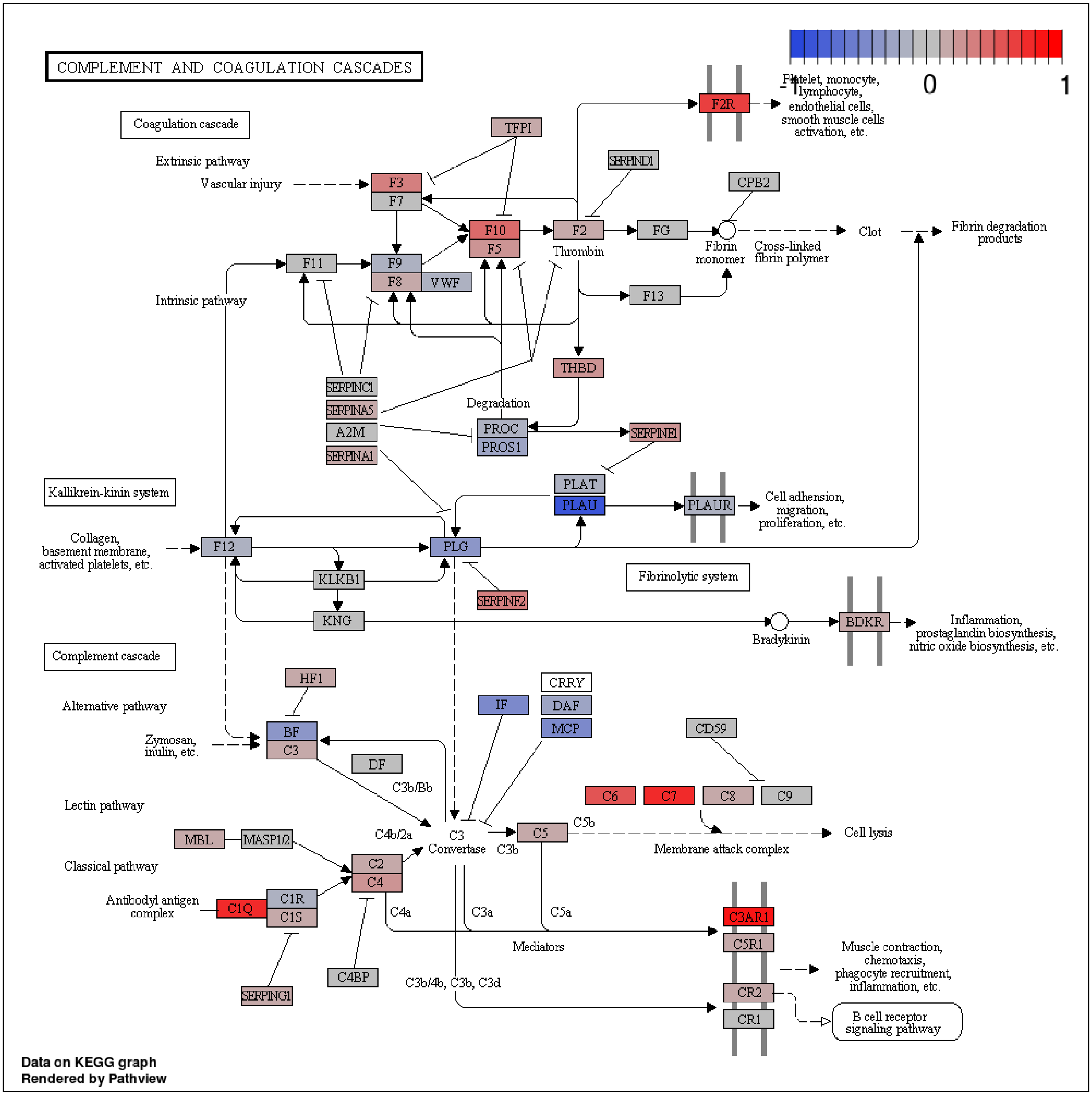
B. Adipocytokine signaling pathway



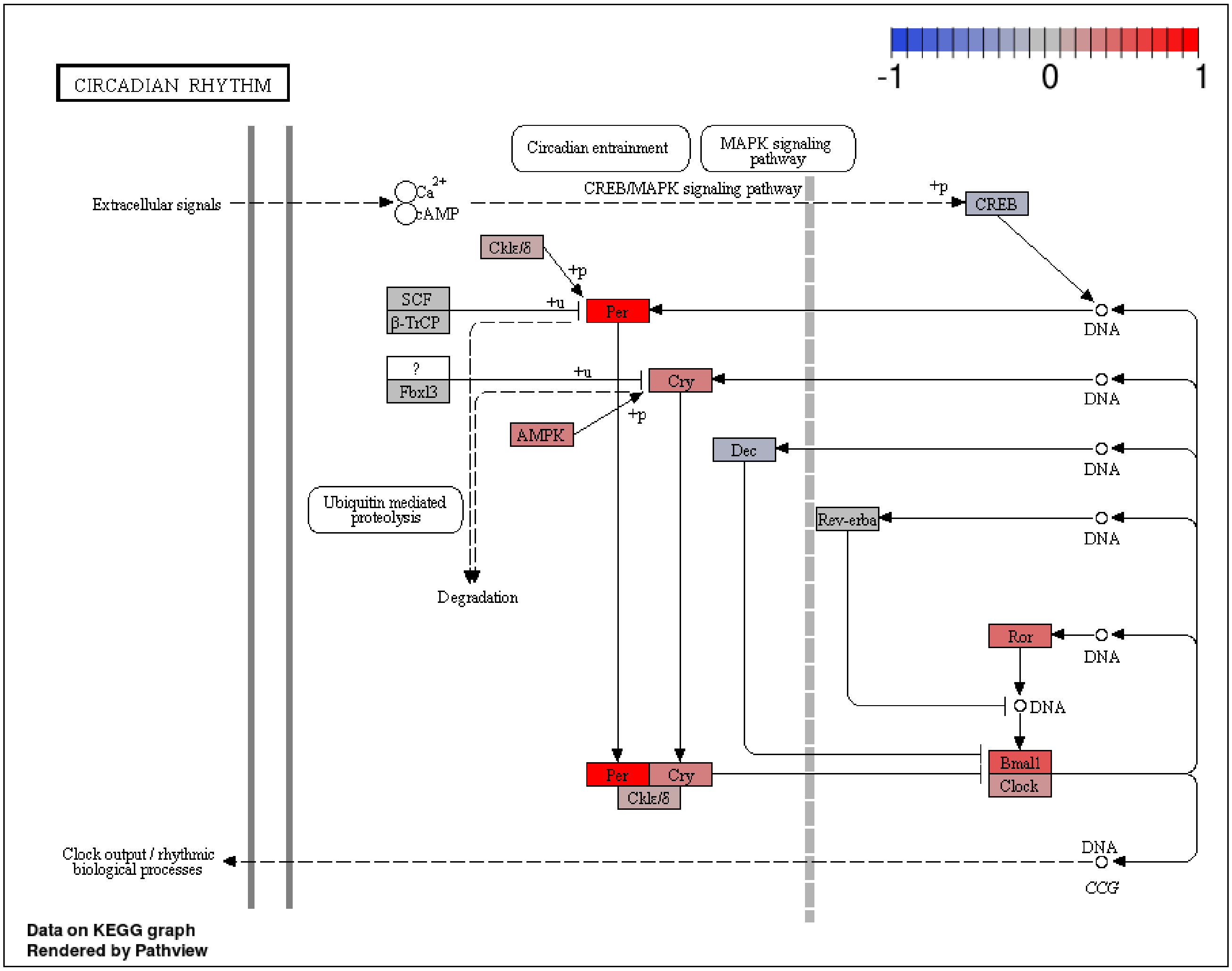
C. Hematopoietic cell lineage



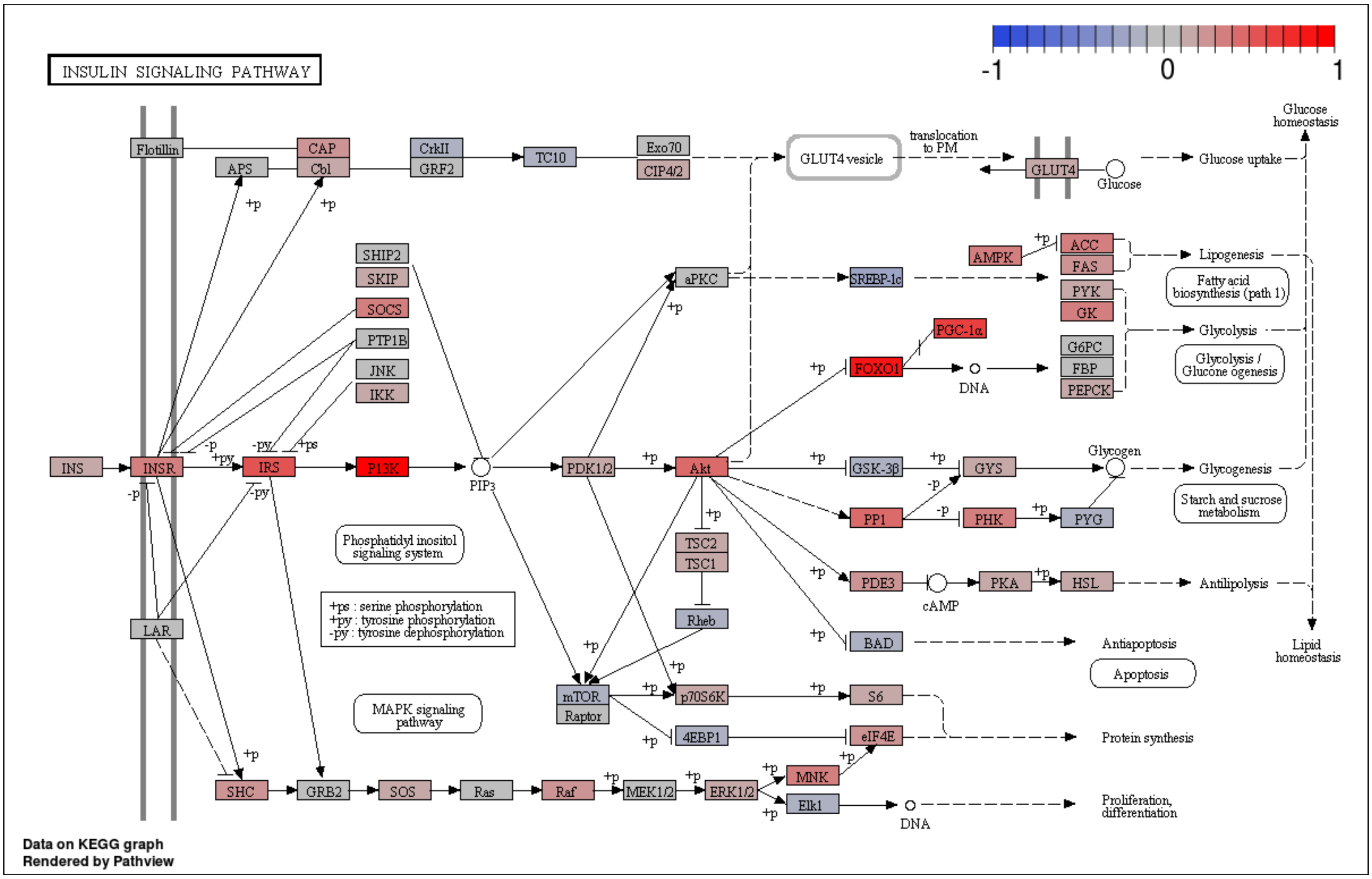
D. Complement and coagulation cascades



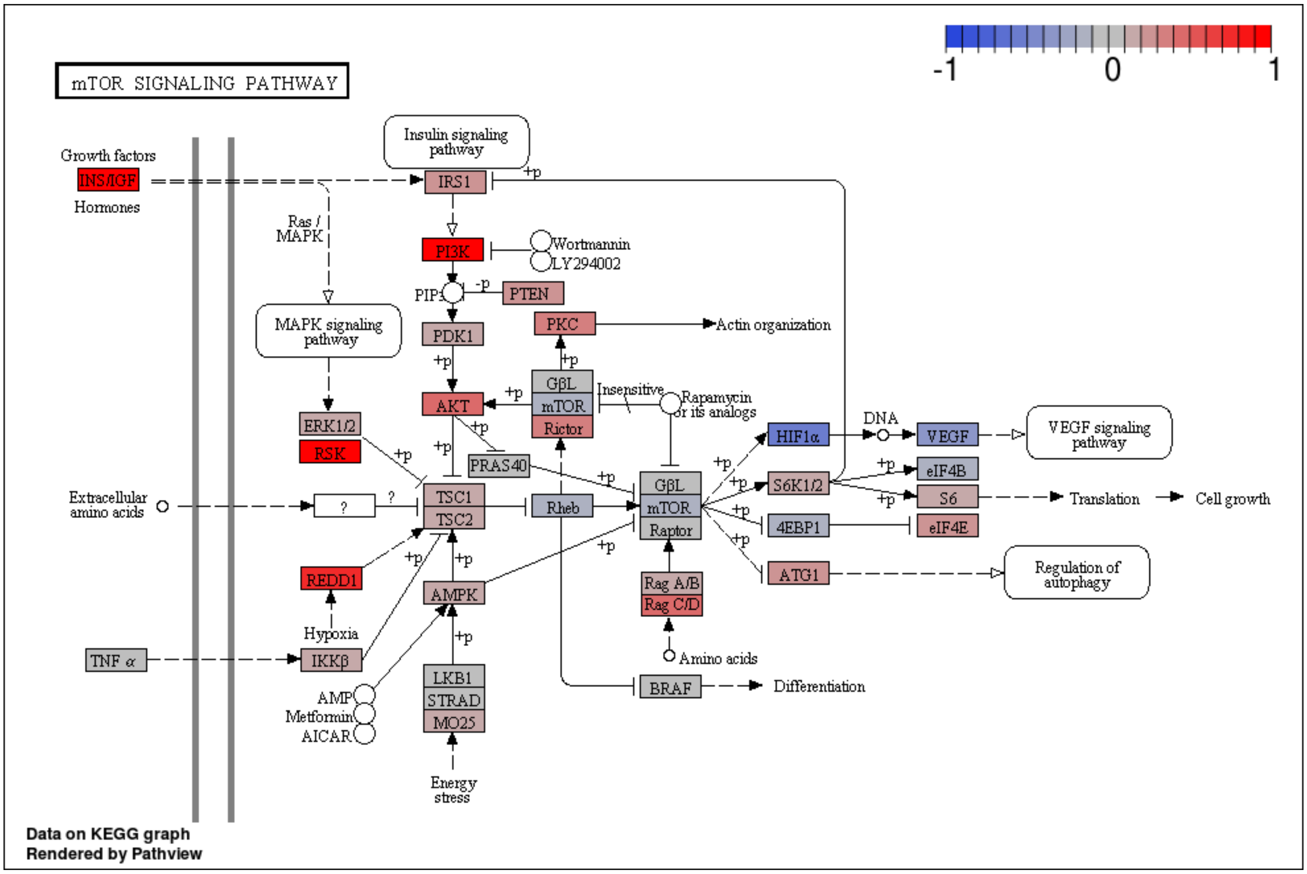
E. Circadian rhythm

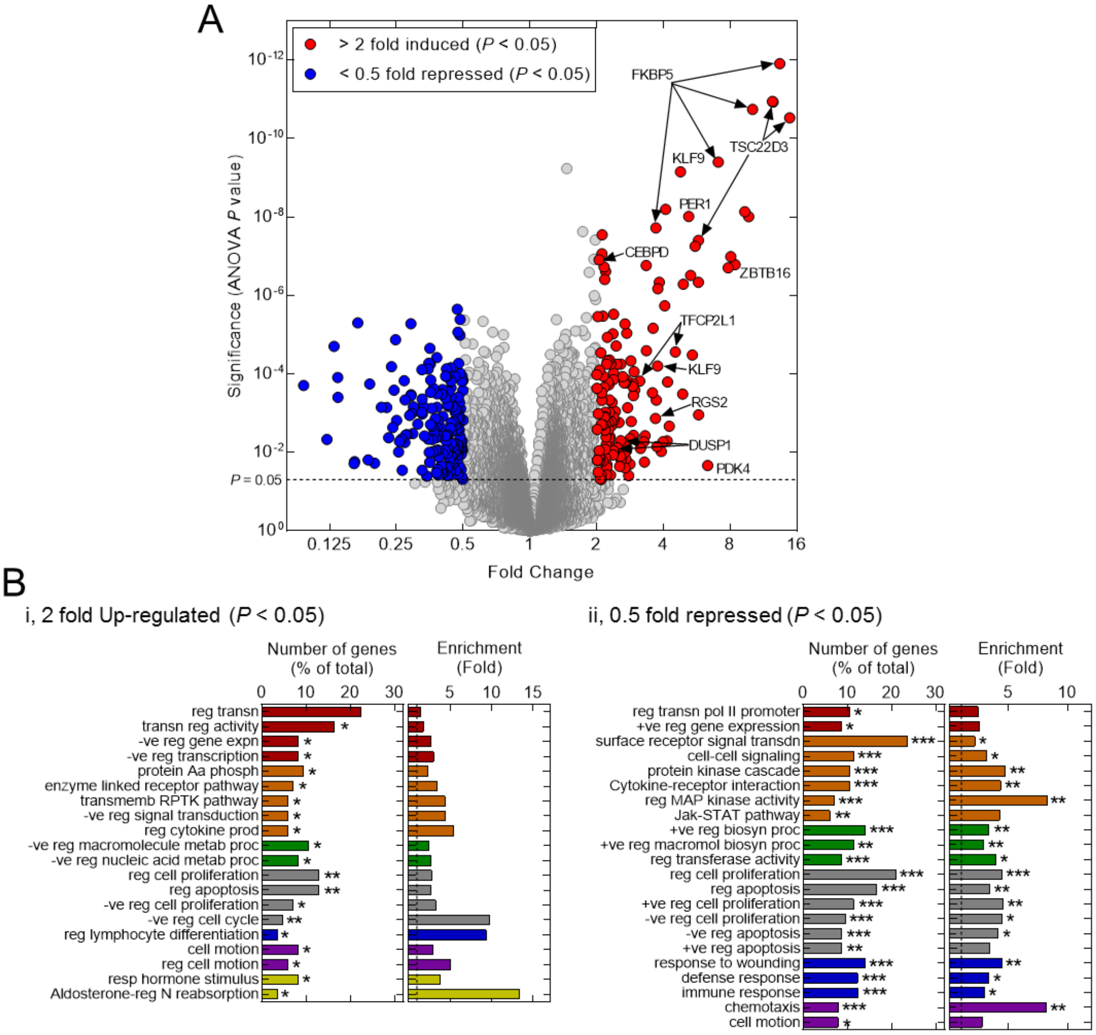


F. Insulin signaling pathway



G. mTOR signaling pathway





Supplemental Fig. 6. Microarray and gene ontology analysis of primary human bronchial epithelial cells treated with budesonide. (A) Microarray analysis of primary HBE cells. Primary HBE cells, grown from 6 of the 12 individuals recruited into the main study and who had not received budesonide inhalation, were not treated or treated with budesonide (0.1 µM). RNA was prepared and microarray analysis performed using Affymetrix Primeview arrays. Analysis was performed with Partek Genomics Suite (v6.6) using robust multi-array averaging (RMA) and resultant fold expression and *P* values used to generate a volcano plot (Supplemental Fig. 2). (B) GO analysis of biological process. Budesonide-induced and -repressed probe sets meeting the criteria; i, ≥2 fold, *P*≤0.05, or ii, ≤0.5 fold, *P*≤0.05 were analyzed using the DAVID gene ID conversion tool to give: i, 84 up-regulated and ii, 114 down-regulated genes, respectively (Supplemental Table 10). Each gene list was analyzed by DAVID functional annotation, which produced gene clusters (≥2 genes/cluster) corresponding to 99 and 194 GO annotation terms respectively. GO terms corresponding to biological process (GOTERM_BP_FAT and KEGG_PATHWAY) were extracted. Selected terms are plotted with the numbers of genes (as a percentage of total) for each term along with the fold enrichment for each term. Abbreviations are as used in Figure 2 of the main manuscript.