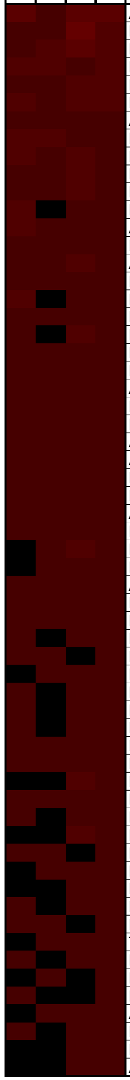
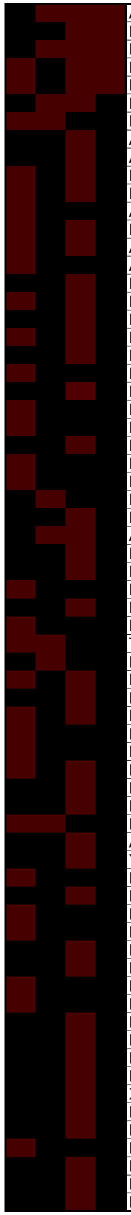
ANNEXOS

ANNEX 1.

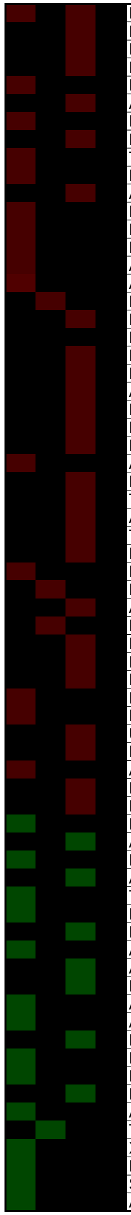
Taula resum dels 715 transcrits regulats almenys en un dels tres temps d’estimulació de la via CD40-CD40L en cèl·lules endotelials



log2ratio(M) 4h	log2ratio(M) 10h	log2ratio(M) 16h	log2ratio(M) all	Genbank Accession number (or Agilent probe ID)	Symbol	Name	Mean Fold Change 4h	Mean Fold Change 10h	Mean Fold Change 16h	Mean Fold Change all		
				AF086248	APLN	Apelin, AGTRL1 ligand	1.72	1.38	1.72	1.60		
				NM_002814	PSMD10	Proteasome (prosome, macropain) 26S subunit, non-ATPase, 10	1.38	1.34	1.84	1.51		
				BC019900	MGC39900	Hypothetical protein MGC39900	1.27	1.41	1.69	1.45		
				NM_000361	THBD	Thrombomodulin	1.48	1.44	1.37	1.43		
				NM_021992	TMSL8	Thymosin-like 8	1.34	1.37	1.50	1.40		
				BC047949	FAM102A	Family with sequence similarity 102, member A	1.45	1.29	1.47	1.40	5.00	🟥
				AK095258	ZNF185	Zinc finger protein 185 (LIM domain)	1.40	1.39	1.39	1.39	4.80	🟥
				NM_004490	GRB14	Growth factor receptor-bound protein 14	1.40	1.43	1.35	1.39	4.60	🟥
				NM_012094	PRDX5	Peroxiredoxin 5	1.50	1.23	1.42	1.38	4.40	🟥
				NM_152832	FAM89B	Family with sequence similarity 89, member B	1.26	1.30	1.47	1.34	4.20	🟥
				NM_002444	MSN	Moesin	1.34	1.22	1.44	1.33	4.00	🟥
				NM_001611	ACP5	Acid phosphatase 5, tartrate resistant	1.59	1.05	1.39	1.33	3.80	🟥
				AK097461	FLJ40142	FLJ40142 protein	1.41	1.31	1.23	1.31	3.60	🟥
				BC069216	LOC388610	Hypothetical LOC388610	1.38	1.26	1.30	1.31	3.40	🟥
				A_23_P66347	A_23_P66347	Unknown	1.22	1.30	1.42	1.31	3.20	🟥
				NM_015444	TMEM158	Transmembrane protein 158	1.31	1.38	1.22	1.30	3.00	🟥
				NM_003467	CXCR4	Chemokine (C-X-C motif) receptor 4	1.53	1.10	1.31	1.30	2.80	🟥
				NM_052970	HSPA12B	Heat shock 70kD protein 12B	1.28	1.28	1.36	1.30	2.60	🟥
				NM_017413	APLN	Apelin, AGTRL1 ligand	1.26	1.19	1.46	1.30	2.40	🟥
				NR_001296	NR_001296	trypsinogen C (TRY6) on chromosome 7	1.33	1.23	1.33	1.30	2.20	🟥
				NM_016445	PLEK2	Pleckstrin 2	1.27	1.28	1.33	1.29	2.00	🟥
				A_23_P111766	A_23_P111766	Unknown	1.32	1.31	1.25	1.29	1.80	🟥
				NM_002770	PRSS2	Protease, serine, 2 (trypsin 2)	1.30	1.28	1.29	1.29	1.60	🟥
				NM_016172	UBAC1	UBA domain containing 1	1.28	1.28	1.30	1.29	1.40	🟥
				AL834325	GAPVD1	GTPase activating protein and VPS9 domains 1	1.30	1.29	1.26	1.29	1.20	🟥
				AF074331	AF074331	PAPS synthetase-2 (PAPSS2) mRNA, complete cds	1.24	1.26	1.35	1.28	-1.20	🟩
				NM_033342	TRIM7	Tripartite motif-containing 7	1.29	1.26	1.29	1.28	-1.40	🟩
				NM_002997	SDC1	Syndecan 1	1.28	1.31	1.24	1.28	-1.60	🟩
				A_24_P913961	A_24_P913961	Unknown	1.26	1.23	1.33	1.27	-1.80	🟩
				NM_018090	NECAP2	NECAP endocytosis associated 2	1.22	1.20	1.38	1.27	-2.00	🟩
				NM_000304	PMP22	Peripheral myelin protein 22	1.12	1.29	1.41	1.27	-2.20	🟩
				NM_021229	NTN4	Netrin 4	1.20	1.25	1.34	1.26	-2.40	🟩
				A_32_P192842	A_32_P192842	Unknown	1.23	1.26	1.29	1.26	-2.60	🟩
				NM_002771	PRSS3	Protease, serine, 3 (mesotrypsin)	1.29	1.22	1.26	1.25	-2.80	🟩
				NM_002224	ITPR3	Inositol 1,4,5-triphosphate receptor, type 3	1.20	1.26	1.30	1.25	-3.00	🟩
				NM_080388	S100A16	S100 calcium binding protein A16	1.29	1.16	1.31	1.25	-3.20	🟩
				NM_000358	TGFBI	Transforming growth factor, beta-induced, 68kDa	1.30	1.29	1.16	1.25	-3.40	🟩
				BC028567	C1orf21	Chromosome 1 open reading frame 21	1.15	1.23	1.38	1.25	-3.60	🟩
				NM_014023	WDR37	WD repeat domain 37	1.20	1.20	1.35	1.25	-3.80	🟩
				NM_016307	PRRX2	Paired related homeobox 2	1.29	1.19	1.26	1.24	-4.00	🟩
				NM_004670	PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2	1.22	1.19	1.33	1.24	-4.20	🟩
				NM_000185	SERPIND1	Serpin peptidase inhibitor, clade D (heparin cofactor), member 1	1.25	1.27	1.21	1.24	-4.40	🟩
				NM_000024	ADRB2	Adrenergic, beta-2-, receptor, surface	1.27	1.20	1.25	1.24	-4.60	🟩
				NM_018003	UACA	Uveal autoantigen with coiled-coil domains and ankyrin repeats	1.13	1.15	1.46	1.24	-4.80	🟩
				BC007723	COX6A1	Cytochrome c oxidase subunit VIa polypeptide 1	1.21	1.20	1.30	1.24	-5.00	🟩
				NM_053056	CCND1	Cyclin D1	1.23	1.19	1.29	1.24		
				NM_006691	XLKD1	Extracellular link domain containing 1	1.19	1.12	1.41	1.24		
				NM_015894	STMN3	Stathmin-like 3	1.22	1.33	1.15	1.23		
				NM_139314	ANGPTL4	Angiopoietin-like 4	1.09	1.34	1.27	1.23		
				NM_174887	IFT20	Intraflagellar transport 20 homolog (Chlamydomonas)	1.19	1.18	1.32	1.23		
				NM_021254	C21orf59	Chromosome 21 open reading frame 59	1.27	1.17	1.24	1.23		
				NM_148965	TNFRSF25	Tumor necrosis factor receptor superfamily, member 25	1.24	1.29	1.15	1.23		
				THC1880115	THC1880115	Unknown	1.14	1.23	1.30	1.22		
				NM_032552	DAB2IP	DAB2 interacting protein	1.27	1.17	1.23	1.22		
				NM_000958	PTGER4	Prostaglandin E receptor 4 (subtype EP4)	1.19	1.28	1.19	1.22		
				NM_032717	MAG1	Lung cancer metastasis-associated protein	1.29	1.19	1.19	1.22		
				AB040955	KIAA1522	KIAA1522	1.17	1.23	1.25	1.22		
				NM_001666	ARHGAP4	Rho GTPase activating protein 4	1.22	1.19	1.24	1.22		
				NM_015913	TXNDC12	Thioredoxin domain containing 12 (endoplasmic reticulum)	1.16	1.15	1.33	1.21		
				AF295356	MSN	Moesin	1.15	1.20	1.29	1.21		

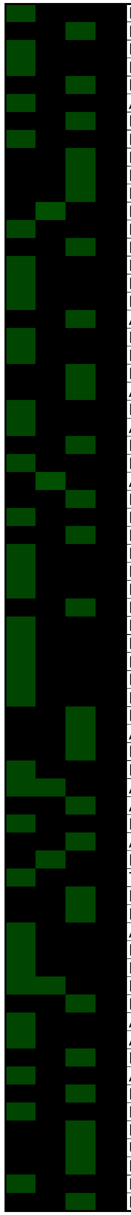


AB040954	GAPVD1	GTPase activating protein and VPS9 domains 1	1.11	1.30	1.22	1.21	
NM_173562	KCTD20	Potassium channel tetramerisation domain containing 20	1.19	1.14	1.29	1.21	
BC000737	RGS4	Regulator of G-protein signalling 4	1.13	1.29	1.21	1.21	
NM_020467	LOC57228	Small trans-membrane and glycosylated protein	1.22	1.19	1.20	1.20	
NM_006096	NDRG1	N-myc downstream regulated gene 1	1.31	1.09	1.22	1.20	
NM_016270	KLF2	Kruppel-like factor 2 (lung)	1.14	1.22	1.24	1.20	
BF129169	BF129169	Transcribed locus	1.29	1.21	1.10	1.20	
AK023754	HES2	Hairy and enhancer of split 2 (Drosophila)	1.20	1.18	1.22	1.20	
AF086249	ITGB1	Integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)	1.15	1.14	1.31	1.20	
NM_018688	BIN3	Bridging integrator 3	1.26	1.10	1.24	1.20	
NM_014762	DHCR24	24-dehydrocholesterol reductase	1.30	1.08	1.22	1.20	
AY049781	ENC1	Ectodermal-neural cortex (with BTB-like domain)	1.27	1.18	1.14	1.20	
NM_024292	UBL5	Ubiquitin-like 5	1.20	1.15	1.24	1.19	5.00
A_24_P803809	A_24_P803809	Unknown	1.23	1.14	1.22	1.19	4.80
AK075558	AK075558	cDNA PSEC0258 fis, clone NT2RP3003731	1.32	1.10	1.17	1.19	4.60
NM_003630	PEX3	Peroxisomal biogenesis factor 3	1.15	1.18	1.24	1.19	4.40
NM_007032	TRIOBP	TRIO and F-actin binding protein	1.20	1.12	1.24	1.19	4.20
NM_003713	PPAP2B	Phosphatidic acid phosphatase type 2B	1.14	1.14	1.27	1.18	4.00
NM_152407	GRPEL2	GrpE-like 2, mitochondrial (E. coli)	1.33	1.03	1.20	1.18	3.80
NM_033666	ITGB1	Integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)	1.15	1.11	1.30	1.18	3.60
NM_000693	ALDH1A3	Aldehyde dehydrogenase 1 family, member A3	1.23	1.18	1.14	1.18	3.40
NM_005358	LMO7	LIM domain 7	1.01	1.14	1.42	1.18	3.20
NM_020698	TMCC3	Transmembrane and coiled-coil domain family 3	1.23	1.16	1.14	1.18	3.00
NM_002863	PYGL	Phosphorylase, glycogen; liver (Hers disease, glycogen storage disease type VI)	1.20	1.13	1.20	1.18	2.80
NM_003565	ULK1	Unc-51-like kinase 1 (C. elegans)	1.16	1.10	1.27	1.18	2.60
NM_153631	HOXA3	Homeobox A3	1.34	1.11	1.09	1.17	2.40
NM_015140	TTLL12	Tubulin tyrosine ligase-like family, member 12	1.21	1.14	1.17	1.17	2.20
NM_001107	ACYP1	Acylphosphatase 1, erythrocyte (common) type	1.12	1.23	1.17	1.17	2.00
ENST00000308269	ENST00000308269	Unknown	1.03	1.19	1.31	1.17	1.80
AL834327	PNMA1	Paraneoplastic antigen MA1	1.10	1.21	1.21	1.17	1.60
NM_033667	ITGB1	Integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)	1.14	1.14	1.24	1.17	1.40
NM_005100	AKAP12	A kinase (PRKA) anchor protein (gravin) 12	1.17	1.13	1.22	1.17	1.20
BC033829	AKAP12	A kinase (PRKA) anchor protein (gravin) 12	1.27	1.12	1.13	1.17	-1.20
NM_000305	PON2	Paraoxonase 2	1.13	1.11	1.27	1.17	-1.40
NM_014059	C13orf15	Chromosome 13 open reading frame 15	1.24	1.08	1.20	1.17	-1.60
THC1822535	THC1822535	Unknown	1.25	1.23	1.04	1.17	-1.80
NM_003541	HIST1H4I	Histone cluster 1, H4i	1.17	1.22	1.12	1.17	-2.00
NM_024830	AYTL2	Acyltransferase like 2	1.20	1.07	1.24	1.17	-2.20
NM_001659	ARF3	ADP-ribosylation factor 3	1.16	1.13	1.21	1.17	-2.40
NM_002599	PDE2A	Phosphodiesterase 2A, cGMP-stimulated	1.21	1.05	1.26	1.17	-2.60
NM_001190	BCAT2	Branched chain aminotransferase 2, mitochondrial	1.22	1.19	1.10	1.17	-2.80
NM_013336	SEC61A1	Sec61 alpha 1 subunit (S. cerevisiae)	1.24	1.09	1.17	1.17	-3.00
NM_004877	GMFG	Glia maturation factor, gamma	1.26	1.01	1.24	1.16	-3.20
NM_001728	BSG	Basigin (Ok blood group)	1.15	1.11	1.23	1.16	-3.40
NM_012164	FBXW2	F-box and WD repeat domain containing 2	1.12	1.12	1.26	1.16	-3.60
BC010117	BCAN	Brevican	1.21	1.30	1.00	1.16	-3.80
AF144325	HPSE	Heparanase	1.17	1.08	1.25	1.16	-4.00
Y08686	SPTLC2	Serine palmitoyltransferase, long chain base subunit 2	1.12	1.14	1.22	1.16	-4.20
NM_000270	NP	Nucleoside phosphorylase	1.21	1.13	1.14	1.16	-4.40
NM_172240	WDR51B	WD repeat domain 51B	1.14	1.10	1.23	1.16	-4.60
M57765	IL11	Interleukin 11	1.23	1.18	1.07	1.16	-4.80
NM_030817	APOLD1	Apolipoprotein L domain containing 1	1.24	1.17	1.07	1.15	-5.00
NM_005064	CCL23	Chemokine (C-C motif) ligand 23	1.09	1.03	1.36	1.15	
NM_024785	FAM124B	Family with sequence similarity 124B	1.20	1.06	1.21	1.15	
NM_005397	PODXL	Podocalyxin-like	1.25	1.12	1.09	1.15	
NM_000273	GPR143	G protein-coupled receptor 143	1.22	1.07	1.17	1.15	
NM_138444	NM_138444	potassium channel tetramerisation domain containing 12 (KCTD12), mRNA	1.04	1.15	1.27	1.15	
BC007050	VAMP3	Vesicle-associated membrane protein 3 (cellubrevin)	1.20	1.05	1.20	1.15	
NM_003921	BCL10	B-cell CLL/lymphoma 10	1.10	1.09	1.25	1.15	
NM_000604	NM_000604	fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome) (FGFR1), transcript variant 1, mR	1.16	1.06	1.22	1.15	
XM_208234	XM_208234	similar to unactive progesterone receptor, 23 kD; likely ortholog of mouse telomerase binding protein, p23 (LOC28467	1.06	1.14	1.24	1.14	
NM_018326	GIMAP4	GTPase, IMAP family member 4	1.09	1.04	1.32	1.14	
BC036649	SEC23A	Sec23 homolog A (S. cerevisiae)	1.14	1.06	1.24	1.14	
NM_000683	ADRA2C	Adrenergic, alpha-2C-, receptor	1.22	1.06	1.14	1.14	
NM_002659	PLAUR	Plasminogen activator, urokinase receptor	1.10	1.12	1.20	1.14	
NM_006843	SDS	Serine dehydratase	1.17	1.02	1.24	1.14	
BC014851	LFNG	LFNG O-fucosylpeptide 3-beta-N-acetylglucosaminyltransferase	1.14	1.07	1.20	1.14	

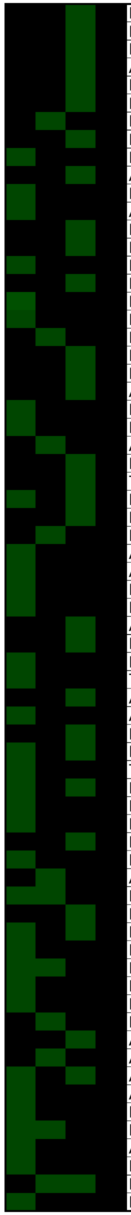


NM_003914	CCNA1	Cyclin A1	1.21	-1.03	1.24	1.13	
NM_016448	DTL	Denticleless homolog (Drosophila)	1.08	1.09	1.23	1.13	
NM_006601	PTGES3	Prostaglandin E synthase 3 (cytosolic)	1.04	1.05	1.32	1.13	
NM_004663	RAB11A	RAB11A, member RAS oncogene family	1.14	1.05	1.21	1.13	
NM_004727	SLC24A1	Solute carrier family 24 (sodium/potassium/calcium exchanger), member 1	1.21	1.03	1.16	1.13	
AL080111	NEK7	NIMA (never in mitosis gene a)-related kinase 7	1.04	1.16	1.20	1.13	
BU626228	PAICS	Phosphoribosylaminoimidazole carboxylase, phosphoribosylaminoimidazole succinocarboxamide synthetase	1.22	1.00	1.18	1.13	
NM_006504	PTPRE	Protein tyrosine phosphatase, receptor type, E	1.03	1.10	1.27	1.13	
THC1910219	THC1910219	Unknown	1.21	1.10	1.07	1.13	
NM_016089	ZNF589	Zinc finger protein 589	1.22	1.13	1.03	1.12	
A_24_P384196	A_24_P384196	Unknown	1.07	1.05	1.25	1.12	
NM_018976	SLC38A2	Solute carrier family 38, member 2	1.20	1.02	1.15	1.12	
NM_006107	CROP	Cisplatin resistance-associated overexpressed protein	1.24	1.11	1.02	1.12	5.00
NM_032744	C6orf105	Chromosome 6 open reading frame 105	1.21	1.10	1.05	1.12	4.80
AL713660	DKFZp667E0512	Hypothetical protein DKFZp667E0512	1.28	1.13	-1.04	1.12	4.60
A_24_P581311	A_24_P581311	Unknown	1.42	1.07	-1.11	1.11	4.40
NM_176870	MT1M	Metallothionein 1M	1.07	1.27	1.01	1.11	4.20
NM_004417	DUSP1	Dual specificity phosphatase 1	1.07	1.02	1.24	1.11	4.00
NM_000135	FANCA	Fanconi anemia, complementation group A	-1.00	1.18	1.16	1.11	3.80
NM_006391	IPO7	Importin 7	1.05	1.07	1.21	1.11	3.60
NM_006750	SNTB2	Syntrophin, beta 2 (dystrophin-associated protein A1, 59kDa, basic component 2)	1.01	1.08	1.22	1.10	3.40
AF318382	IGF2	Insulin-like growth factor 2 (somatomedin A)	1.06	1.04	1.21	1.10	3.20
ENST00000294662	ENST00000294662	Unknown	1.00	1.11	1.20	1.10	3.00
NM_145814	CACNG6	Calcium channel, voltage-dependent, gamma subunit 6	1.11	-1.02	1.22	1.10	2.80
NM_021777	ADAM28	ADAM metallopeptidase domain 28	-1.02	1.01	1.31	1.09	2.60
AK096589	RPL32P3	Ribosomal protein L32 pseudogene 3	1.21	1.11	-1.03	1.09	2.40
NM_018295	TMEM140	Transmembrane protein 140	1.02	-1.03	1.29	1.09	2.20
THC1993166	THC1993166	Unknown	-1.06	1.10	1.23	1.09	2.00
AK026443	ATP2B4	ATPase, Ca++ transporting, plasma membrane 4	1.05	1.01	1.21	1.08	1.80
THC1946694	THC1946694	Unknown	1.06	-1.01	1.21	1.08	1.60
NM_032333	C10orf58	Chromosome 10 open reading frame 58	1.04	1.01	1.20	1.08	1.40
NM_024681	KCTD17	Potassium channel tetramerisation domain containing 17	1.24	1.02	-1.02	1.07	1.20
NM_012242	DKK1	Dickkopf homolog 1 (Xenopus laevis)	-1.09	1.26	1.05	1.07	-1.20
AK091818	GIMAP1	GTPase, IMAP family member 1	1.03	-1.02	1.20	1.07	-1.40
NM_007281	SCRG1	Scrapie responsive protein 1	1.04	1.22	-1.05	1.06	-1.60
NM_145802	sep-06	Septin 6	1.04	-1.05	1.21	1.06	-1.80
NM_006136	CAPZA2	Capping protein (actin filament) muscle Z-line, alpha 2	-1.05	1.02	1.22	1.06	-2.00
NM_175571	GIMAP8	GTPase, IMAP family member 8	-1.00	-1.08	1.26	1.05	-2.20
NM_080927	DCBLD2	Discoidin, CUB and LCCL domain containing 2	1.20	1.06	-1.10	1.05	-2.40
NM_021939	FKBP10	FK506 binding protein 10, 65 kDa	1.22	1.04	-1.12	1.04	-2.60
U93703	GFRA2	GDNF family receptor alpha 2	-1.08	1.00	1.22	1.04	-2.80
NM_006758	U2AF1	U2 small nuclear RNA auxiliary factor 1	1.02	-1.10	1.20	1.04	-3.00
AK027240	EIF5	Eukaryotic translation initiation factor 5	1.21	-1.05	-1.06	1.03	-3.20
ENST00000311061	ENST00000311061	Unknown	-1.03	-1.12	1.21	1.02	-3.40
NM_153236	GIMAP7	GTPase, IMAP family member 7	-1.09	-1.09	1.22	1.01	-3.60
BC040880	C10orf114	Chromosome 10 open reading frame 114	-1.20	1.05	1.06	-1.03	-3.80
AK095791	AK095791	CDNA FLJ38472 fis, clone FEBRA2022148	-1.01	1.12	-1.25	-1.04	-4.00
NM_002658	PLAU	Plasminogen activator, urokinase	-1.21	-1.01	1.10	-1.04	-4.20
AK025245	KITLG	KIT ligand	1.03	1.05	-1.22	-1.04	-4.40
THC1954314	THC1954314	Unknown	-1.21	1.03	1.01	-1.05	-4.60
NM_032354	TMEM107	Transmembrane protein 107	-1.31	1.06	1.05	-1.06	-4.80
NM_005562	LAMC2	Laminin, gamma 2	1.04	-1.03	-1.21	-1.06	-5.00
A_24_P717262	A_24_P717262	Unknown	-1.21	-1.02	1.03	-1.06	
AK021804	AK021804	CDNA FLJ38472 fis, clone FEBRA2022148	-1.04	1.04	-1.22	-1.07	
NM_002840	PTPRF	Protein tyrosine phosphatase, receptor type, F	-1.04	1.03	-1.21	-1.07	
AB014735	ZNF588	Zinc finger protein 588	-1.20	-1.04	1.02	-1.07	
AK091618	ZNF92	Zinc finger protein 92	-1.23	-1.02	1.02	-1.07	
NM_016205	PDGFC	Platelet derived growth factor C	-1.05	1.04	-1.20	-1.07	
NM_001786	CDC2	Cell division cycle 2, G1 to S and G2 to M	-1.20	-1.10	1.07	-1.07	
BX647769	KIAA1641	KIAA1641	-1.21	1.01	-1.03	-1.07	
BC012029	LOC152573	Hypothetical protein BC012029	-1.10	1.07	-1.20	-1.07	
AK126842	FLJ44894	Similar to zinc finger protein 91	-1.20	-1.04	-1.01	-1.08	
THC1934423	THC1934423	Unknown	-1.06	-1.26	1.06	-1.08	
X52339	ZNF708	Zinc finger protein 708	-1.21	-1.04	-1.00	-1.08	
ENST00000330097	ENST00000330097	Zinc finger protein 208. [Source:SWISSPROT;Acc:O43345]	-1.21	-1.09	1.04	-1.08	
S69873	S69873	Mutant DNA polymerase beta	-1.21	1.02	-1.07	-1.08	
AY269786	ZNF493	Zinc finger protein 493	-1.21	-1.09	1.04	-1.08	

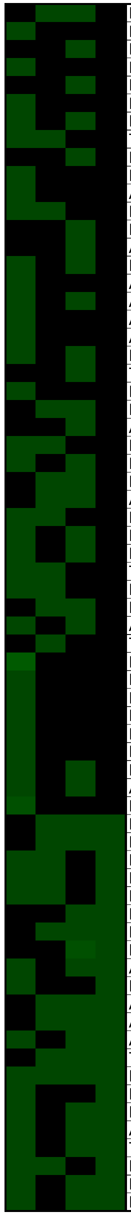
🟩	⬛	⬛	THC1991717	THC1991717	Unknown	-1.25	1.06	-1.07	-1.08		
⬛	⬛	🟩	AK092584	CYP2R1	Cytochrome P450, family 2, subfamily R, polypeptide 1	-1.02	-1.04	-1.20	-1.08		
⬛	⬛	🟩	NM_001924	GADD45A	Growth arrest and DNA-damage-inducible, alpha	-1.04	-1.03	-1.21	-1.09		
⬛	⬛	🟩	NM_017590	ZC3H7B	Zinc finger CCCH-type containing 7B	-1.00	1.06	-1.36	-1.09		
⬛	⬛	🟩	BC020847	LOC644246	Hypothetical protein LOC644246	-1.07	-1.00	-1.20	-1.09		
⬛	⬛	🟩	THC1946794	THC1946794	Unknown	-1.10	1.04	-1.22	-1.09		
⬛	⬛	🟩	A_24_P619891	A_24_P619891	Unknown	-1.03	-1.03	-1.22	-1.09		
🟩	⬛	⬛	A_24_P705136	A_24_P705136	Unknown	-1.23	-1.08	1.02	-1.09		
🟩	⬛	⬛	AK022681	C6orf62	Chromosome 6 open reading frame 62	-1.22	-1.04	-1.03	-1.09		
🟩	⬛	⬛	NM_080743	SRrp35	Serine-arginine repressor protein (35 kDa)	-1.25	1.03	-1.07	-1.09		
🟩	⬛	⬛	BC002646	JUN	Jun oncogene	-1.33	-1.01	1.04	-1.09		
⬛	⬛	🟩	NM_022755	IPPK	Inositol 1,3,4,5,6-pentakisphosphate 2-kinase	-1.04	-1.05	-1.20	-1.09		
🟩	⬛	⬛	NM_013283	MAT2B	Methionine adenosyltransferase II, beta	-1.20	-1.07	-1.01	-1.09	5.00	🟥
🟩	⬛	⬛	BX641010	TBL1XR1	Transducin (beta)-like 1X-linked receptor 1	-1.25	1.00	-1.05	-1.09	4.80	🟥
🟩	⬛	⬛	AL713796	LOC389831	Hypothetical gene supported by AL713796	-1.22	-1.07	-1.00	-1.09	4.60	🟥
🟩	⬛	⬛	ENST00000327446	ENST00000327446	Zinc finger protein 15 (Zinc finger protein KOX8) (Fragment). [Source:SWISSPROT;Acc:P17019]	-1.21	-1.08	-1.01	-1.10	4.40	🟥
🟩	⬛	⬛	A_32_P160186	A_32_P160186	Unknown	-1.21	1.01	-1.11	-1.10	4.20	🟥
⬛	⬛	🟩	NM_002317	LOX	Lysyl oxidase	-1.07	-1.01	-1.23	-1.10	4.00	🟥
🟩	⬛	⬛	AF256215	AF256215	cycle-like factor CLIF mRNA, complete cds	-1.21	1.01	-1.11	-1.10	3.80	🟥
⬛	⬛	🟩	NM_000421	KRT10	Keratin 10 (epidermolytic hyperkeratosis; keratosis palmaris et plantaris)	-1.13	1.07	-1.26	-1.10	3.60	🟥
🟩	⬛	⬛	THC1819164	THC1819164	Unknown	-1.27	1.06	-1.11	-1.10	3.40	🟥
🟩	⬛	⬛	ENST00000323012	ENST00000323012	Unknown	-1.20	-1.15	1.03	-1.10	3.20	🟥
🟩	⬛	⬛	AK021874	AK021874	CDNA FLJ11812 fis, clone HEMBA1006364	-1.30	-1.06	1.03	-1.10	3.00	🟥
🟩	⬛	⬛	NM_021818	SAV1	Salvador homolog 1 (Drosophila)	-1.21	1.01	-1.12	-1.10	2.80	🟥
🟩	⬛	⬛	AK091330	MCTP1	Multiple C2 domains, transmembrane 1	-1.27	-1.07	1.01	-1.10	2.60	🟥
🟩	⬛	⬛	AJ420516	LOC221710	Hypothetical protein LOC221710	-1.25	-1.01	-1.06	-1.10	2.40	🟥
🟩	⬛	⬛	A_32_P108203	A_32_P108203	Unknown	-1.20	-1.07	-1.04	-1.10	2.20	🟥
🟩	⬛	⬛	NM_014459	NM_014459	protocadherin 17 (PCDH17), mRNA	-1.23	-1.08	-1.02	-1.11	2.00	🟥
🟩	⬛	⬛	NM_005748	YAF2	YY1 associated factor 2	-1.21	-1.04	-1.08	-1.11	1.80	🟥
🟩	⬛	⬛	THC1924019	THC1924019	Unknown	-1.20	-1.05	-1.08	-1.11	1.60	🟥
⬛	⬛	🟩	NM_016462	TMEM14C	Transmembrane protein 14C	-1.14	1.03	-1.23	-1.11	1.40	🟥
⬛	⬛	🟩	NM_024524	NM_024524	ATPase family homolog up-regulated in senescence cells (AFURS1), mRNA	-1.13	1.01	-1.23	-1.11	1.20	🟥
⬛	⬛	🟩	NM_003204	NFE2L1	Nuclear factor (erythroid-derived 2)-like 1	-1.05	-1.07	-1.22	-1.11	-1.20	🟩
🟩	⬛	⬛	THC1866291	THC1866291	Unknown	-1.27	-1.06	-1.02	-1.11	-1.40	🟩
🟩	⬛	⬛	NM_001860	SLC31A2	Solute carrier family 31 (copper transporters), member 2	-1.21	-1.12	-1.01	-1.11	-1.60	🟩
🟩	⬛	⬛	BC033770	CHD9	Chromodomain helicase DNA binding protein 9	-1.21	-1.10	-1.04	-1.11	-1.80	🟩
🟩	⬛	⬛	AB040974	AB040974	mRNA for KIAA1541 protein, partial cds	-1.25	-1.01	-1.09	-1.11	-2.00	🟩
🟩	⬛	⬛	NM_016545	IER5	Immediate early response 5	-1.20	-1.06	-1.09	-1.11	-2.20	🟩
🟩	⬛	⬛	NM_002844	PTPRK	Protein tyrosine phosphatase, receptor type, K	-1.22	1.01	-1.15	-1.12	-2.40	🟩
⬛	🟩	⬛	AK093341	RP5-821D11.2	Meiosis defective 1	1.03	-1.22	-1.17	-1.12	-2.60	🟩
⬛	⬛	🟩	NM_007080	LSM6	LSM6 homolog, U6 small nuclear RNA associated (S. cerevisiae)	-1.10	-1.03	-1.22	-1.12	-2.80	🟩
⬛	⬛	🟩	NM_022480	KLHL25	Kelch-like 25 (Drosophila)	-1.09	-1.05	-1.20	-1.12	-3.00	🟩
⬛	⬛	🟩	THC1899140	THC1899140	Unknown	-1.14	1.05	-1.28	-1.12	-3.20	🟩
🟩	⬛	⬛	THC1881403	THC1881403	Unknown	-1.42	-1.05	1.07	-1.12	-3.40	🟩
⬛	⬛	🟩	AB007870	AB007870	KIAA0410 mRNA, partial cds	-1.15	-1.01	-1.21	-1.12	-3.60	🟩
⬛	⬛	🟩	AF316855	FLJ22795	Hypothetical protein FLJ22795	-1.09	-1.04	-1.24	-1.12	-3.80	🟩
🟩	⬛	⬛	BC030005	MCTP1	Multiple C2 domains, transmembrane 1	-1.24	-1.09	-1.04	-1.12	-4.00	🟩
🟩	⬛	⬛	NM_020169	LXN	Latexin	-1.22	-1.10	-1.05	-1.12	-4.20	🟩
🟩	⬛	⬛	NM_004064	CDKN1B	Cyclin-dependent kinase inhibitor 1B (p27, Kip1)	-1.21	-1.09	-1.07	-1.12	-4.40	🟩
🟩	⬛	⬛	NM_144996	ARL13B	ADP-ribosylation factor-like 13B	-1.20	-1.11	-1.06	-1.12	-4.60	🟩
🟩	⬛	⬛	NM_004180	TANK	TRAF family member-associated NFKB activator	-1.20	-1.07	-1.10	-1.12	-4.80	🟩
⬛	🟩	⬛	AK057437	PRRC1	Proline-rich coiled-coil 1	-1.06	-1.22	-1.09	-1.12	-5.00	🟩
🟩	⬛	⬛	A_32_P10623	A_32_P10623	Unknown	-1.24	-1.12	-1.02	-1.12		
⬛	⬛	🟩	NM_006516	SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	-1.16	-1.01	-1.20	-1.12		
🟩	⬛	⬛	AK024926	DDAH1	Dimethylarginine dimethylaminohydrolase 1	-1.24	1.01	-1.15	-1.12		
⬛	⬛	🟩	NM_024599	RHBDF2	Rhomboid 5 homolog 2 (Drosophila)	-1.09	-1.06	-1.21	-1.12		
🟩	⬛	⬛	A_24_P814872	A_24_P814872	Unknown	-1.20	-1.17	-1.01	-1.12		
⬛	🟩	⬛	NM_016306	DNAJB11	DnaJ (Hsp40) homolog, subfamily B, member 11	-1.06	-1.22	-1.10	-1.12		
⬛	⬛	🟩	NM_025163	PIGZ	Phosphatidylinositol glycan anchor biosynthesis, class Z	-1.15	-1.03	-1.20	-1.12		
⬛	⬛	🟩	A_24_P919605	A_24_P919605	Unknown	1.03	-1.07	-1.38	-1.13		
🟩	⬛	⬛	NR_001455	NR_001455	RNA, small nucleolar (LOC85391) on chromosome 11	-1.39	-1.01	-1.01	-1.13		
🟩	⬛	⬛	NM_138409	C6orf117	Chromosome 6 open reading frame 117	-1.22	-1.18	1.01	-1.13		
⬛	⬛	🟩	ENST00000325192	ENST00000325192	Unknown	-1.13	-1.04	-1.22	-1.13		
⬛	🟩	⬛	AB033114	MTUS1	Mitochondrial tumor suppressor 1	-1.12	-1.25	-1.02	-1.13		
⬛	⬛	🟩	NM_032483	PPAPDC1B	Phosphatidic acid phosphatase type 2 domain containing 1B	-1.11	-1.06	-1.22	-1.13		
⬛	⬛	🟩	A_32_P30898	A_32_P30898	Unknown	-1.08	-1.09	-1.22	-1.13		
🟩	⬛	⬛	AK022962	PBX1	Pre-B-cell leukemia homeobox 1	-1.26	-1.07	-1.06	-1.13		



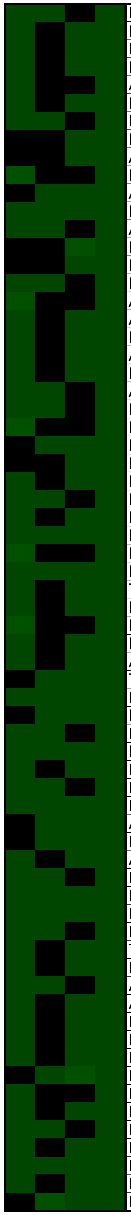
NM_006598	SLC12A7	Solute carrier family 12 (potassium/chloride transporters), member 7	-1.23	1.01	-1.18	-1.13	
NM_030627	CPEB4	Cytoplasmic polyadenylation element binding protein 4	-1.09	-1.03	-1.28	-1.13	
BC024020	TMEM49	Transmembrane protein 49	-1.29	-1.06	-1.05	-1.13	
NM_019058	DDIT4	DNA-damage-inducible transcript 4	-1.29	-1.01	-1.11	-1.13	
NM_015907	LAP3	Leucine aminopeptidase 3	-1.13	-1.06	-1.20	-1.13	
AL833005	AL833005	MRNA; cDNA DKFZp666D074 (from clone DKFZp666D074)	-1.30	-1.10	-1.00	-1.13	
NM_021149	COTL1	Coactosin-like 1 (Dictyostelium)	-1.04	-1.10	-1.27	-1.13	
NM_002353	TACSTD2	Tumor-associated calcium signal transducer 2	-1.22	-1.12	-1.06	-1.13	
NM_002182	IL1RAP	Interleukin 1 receptor accessory protein	-1.13	-1.05	-1.23	-1.13	
ENST00000299596	ENST00000299596	Unknown	-1.08	-1.11	-1.22	-1.13	
NM_016200	LSM8	LSM8 homolog, U6 small nuclear RNA associated (S. cerevisiae)	-1.12	-1.08	-1.20	-1.13	
BC037208	EP400	E1A binding protein p400	-1.03	-1.44	1.01	-1.13	
BC015439	ARL13B	ADP-ribosylation factor-like 13B	-1.27	-1.05	-1.10	-1.13	5.00
NM_031427	DNAL1	Dynein, axonemal, light chain 1	-1.12	-1.05	-1.24	-1.14	4.80
NM_145307	PLEKHK1	Pleckstrin homology domain containing, family K member 1	-1.22	-1.09	-1.10	-1.14	4.60
NM_005570	LMAN1	Lectin, mannose-binding, 1	-1.22	-1.04	-1.17	-1.14	4.40
NM_018101	CDCA8	Cell division cycle associated 8	-1.23	-1.11	-1.08	-1.14	4.20
AK095564	AK095564	CDNA FLJ38245 fis, clone FCBBF2007186	-1.14	-1.07	-1.21	-1.14	4.00
BC029749	PKN2	Protein kinase N2	-1.22	-1.12	-1.08	-1.14	3.80
NM_020453	ATP10D	ATPase, Class V, type 10D	-1.21	-1.09	-1.13	-1.14	3.60
NM_005429	VEGFC	Vascular endothelial growth factor C	-1.19	1.01	-1.26	-1.14	3.40
AK094088	ALDH1L2	Aldehyde dehydrogenase 1 family, member L2	-1.00	-1.19	-1.25	-1.14	3.20
NM_138555	KIF23	Kinesin family member 23	-1.23	-1.12	-1.08	-1.14	3.00
AB073737	GIPC2	GIPC PDZ domain containing family, member 2	-1.25	-1.15	-1.03	-1.14	2.80
BC012204	FNDC3B	Fibronectin type III domain containing 3B	-1.18	-1.05	-1.21	-1.14	2.60
NM_003662	PIR	Pirin (iron-binding nuclear protein)	-1.22	-1.09	-1.12	-1.14	2.40
AB037903	tAKR	Aldo-keto reductase, truncated	1.01	-1.57	1.04	-1.14	2.20
NM_002709	PPP1CB	Protein phosphatase 1, catalytic subunit, beta isoform	-1.19	-1.03	-1.21	-1.14	2.00
NM_014782	ARMCX2	Armadillo repeat containing, X-linked 2	-1.21	-1.12	-1.11	-1.14	1.80
NM_001550	IFRD1	Interferon-related developmental regulator 1	-1.16	-1.02	-1.26	-1.14	1.60
NM_019013	FAM64A	Family with sequence similarity 64, member A	-1.21	-1.05	-1.18	-1.14	1.40
NM_181836	TICAM2	Toll-like receptor adaptor molecule 2	-1.23	-1.13	-1.09	-1.15	1.20
NM_007315	STAT1	Signal transducer and activator of transcription 1, 91kDa	-1.23	-1.18	-1.04	-1.15	-1.20
NM_003376	VEGFA	Vascular endothelial growth factor A	-1.06	-1.12	-1.27	-1.15	-1.40
NM_000449	RFX5	Regulatory factor X, 5 (influences HLA class II expression)	-1.23	-1.10	-1.12	-1.15	-1.60
NM_030763	NSBP1	Nucleosomal binding protein 1	-1.24	-1.11	-1.09	-1.15	-1.80
BC018448	MALAT1	Metastasis associated lung adenocarcinoma transcript 1 (non-coding RNA)	-1.31	-1.14	-1.01	-1.15	-2.00
NM_022763	FNDC3B	Fibronectin type III domain containing 3B	-1.20	-1.09	-1.16	-1.15	-2.20
NM_018098	ECT2	Epithelial cell transforming sequence 2 oncogene	-1.27	-1.08	-1.10	-1.15	-2.40
NM_018357	LARP6	La ribonucleoprotein domain family, member 6	-1.14	-1.07	-1.24	-1.15	-2.60
AK027663	STC2	Stanniocalcin 2	-1.07	-1.10	-1.29	-1.15	-2.80
NM_016594	FKBP11	FK506 binding protein 11, 19 kDa	-1.17	-1.06	-1.23	-1.15	-3.00
NM_004289	NFE2L3	Nuclear factor (erythroid-derived 2)-like 3	-1.21	-1.05	-1.20	-1.15	-3.20
AF306679	ESCO2	Establishment of cohesion 1 homolog 2 (S. cerevisiae)	-1.23	-1.25	1.00	-1.15	-3.40
A_24_P234871	A_24_P234871	Unknown	-1.15	-1.07	-1.23	-1.15	-3.60
NM_153231	NM_153231	zinc finger protein 550 (ZNF550), mRNA	-1.23	-1.10	-1.12	-1.15	-3.80
AK002107	RAB3B	RAB3B, member RAS oncogene family	-1.14	-1.04	-1.28	-1.15	-4.00
NM_001777	CD47	CD47 molecule	-1.15	-1.21	-1.09	-1.15	-4.20
THC1952953	THC1952953	Unknown	-1.26	-1.07	-1.13	-1.15	-4.40
NM_005795	CALCRL	Calcitonin receptor-like	-1.16	-1.10	-1.20	-1.15	-4.60
BG178211	BG178211	Unknown	-1.12	-1.10	-1.25	-1.15	-4.80
AK091248	TBC1D8B	TBC1 domain family, member 8B (with GRAM domain)	-1.21	-1.17	-1.08	-1.15	-5.00
NM_006153	NCK1	NCK adaptor protein 1	-1.20	-1.16	-1.10	-1.15	
NM_014920	ICK	Intestinal cell (MAK-like) kinase	-1.21	-1.14	-1.12	-1.15	
NM_024669	ANKRD55	Ankyrin repeat domain 55	-1.21	-1.21	-1.06	-1.16	
NM_012385	NUPR1	Nuclear protein 1	-1.01	-1.20	-1.28	-1.16	
AL049265	IL6ST	Interleukin 6 signal transducer (gp130, oncostatin M receptor)	-1.21	-1.12	-1.14	-1.16	
A_32_P18147	A_32_P18147	Unknown	-1.23	-1.10	-1.14	-1.16	
NM_000214	JAG1	Jagged 1 (Alagille syndrome)	1.04	-1.19	-1.36	-1.16	
AY358623	LYPD6	LY6/PLAUR domain containing 6	-1.33	-1.05	-1.11	-1.16	
NM_004911	PDIA4	Protein disulfide isomerase family A, member 4	-1.05	-1.19	-1.25	-1.16	
NM_002716	PPP2R1B	Protein phosphatase 2 (formerly 2A), regulatory subunit A, beta isoform	-1.28	-1.07	-1.13	-1.16	
NM_052965	C1orf19	Chromosome 1 open reading frame 19	-1.16	-1.05	-1.28	-1.16	
U16307	GLIPR1	GLI pathogenesis-related 1 (glioma)	-1.09	-1.11	-1.27	-1.16	
NM_145714	ATXN2L	Ataxin 2-like	-1.14	-1.06	-1.29	-1.16	
NM_005534	IFNGR2	Interferon gamma receptor 2 (interferon gamma transducer 1)	-1.22	-1.12	-1.14	-1.16	
BC016285	PRKACB	Protein kinase, cAMP-dependent, catalytic, beta	-1.15	-1.07	-1.27	-1.16	



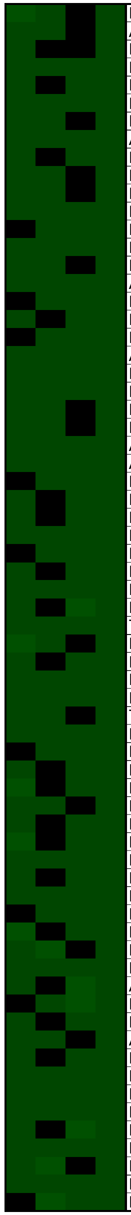
NM_032258	LOC729873	Similar to TBC1 domain family, member 3	-1.13	-1.14	-1.21	-1.16	
NM_025138	C13orf23	Chromosome 13 open reading frame 23	-1.09	-1.13	-1.26	-1.16	
NM_005065	SEL1L	Sel-1 suppressor of lin-12-like (C. elegans)	-1.10	-1.17	-1.21	-1.16	
AF078866	SURF4	Surfeit 4	-1.17	-1.09	-1.23	-1.16	
NM_170744	UNC5B	Unc-5 homolog B (C. elegans)	-1.18	-1.01	-1.31	-1.16	
NM_033280	SEC11C	SEC11 homolog C (S. cerevisiae)	-1.15	-1.09	-1.25	-1.16	
NM_004933	CDH15	Cadherin 15, M-cadherin (myotubule)	-1.04	-1.33	-1.14	-1.16	
NM_002589	PCDH7	Protocadherin 7	-1.19	-1.06	-1.23	-1.16	
NM_006329	FBLN5	Fibulin 5	-1.20	-1.10	-1.18	-1.16	
AK021919	AK021919	cDNA FLJ11857 fis, clone HEMBA1006807, moderately similar to mRNA for SPOP	-1.17	-1.07	-1.25	-1.16	
NM_004060	CCNG1	Cyclin G1	-1.23	-1.16	-1.10	-1.16	
AK074711	HHIP	Hedgehog interacting protein	-1.21	-1.14	-1.14	-1.16	
NM_004148	NINJ1	Ninjurin 1	-1.16	-1.10	-1.22	-1.16	5.00
ENST00000327887	ENST00000327887	Unknown	-1.05	-1.20	-1.25	-1.16	4.80
BM921275	GPR68	G protein-coupled receptor 68	-1.23	-1.12	-1.14	-1.16	4.60
NM_178547	ZBTB8OS	Zinc finger and BTB domain containing 8 opposite strand	-1.17	-1.06	-1.26	-1.16	4.40
NM_004233	CD83	CD83 molecule	-1.43	-1.08	-1.03	-1.16	4.20
NM_153607	LOC153222	Adult retina protein	-1.28	-1.09	-1.13	-1.16	4.00
NM_001166	BIRC2	Baculoviral IAP repeat-containing 2	-1.17	-1.20	-1.12	-1.16	3.80
NM_003489	NRIP1	Nuclear receptor interacting protein 1	-1.13	-1.15	-1.22	-1.16	3.60
NM_005038	PPID	Peptidylprolyl isomerase D (cyclophilin D)	-1.14	-1.11	-1.24	-1.17	3.40
AK027632	RP11-217H1.1	Implantation-associated protein	-1.19	-1.07	-1.24	-1.17	3.20
BC006322	ATF3	Activating transcription factor 3	-1.36	-1.06	-1.09	-1.17	3.00
BC031320	CHD2	Chromodomain helicase DNA binding protein 2	-1.20	-1.15	-1.15	-1.17	2.80
AL157482	FNDC3B	Fibronectin type III domain containing 3B	-1.15	-1.21	-1.14	-1.17	2.60
NM_006321	ARIH2	Ariadne homolog 2 (Drosophila)	-1.18	-1.07	-1.26	-1.17	2.40
THC1819195	THC1819195	Unknown	-1.20	-1.06	-1.26	-1.17	2.20
NM_133646	ZAK	Sterile alpha motif and leucine zipper containing kinase AZK	-1.25	-1.02	-1.25	-1.17	2.00
NM_015364	LY96	Lymphocyte antigen 96	-1.18	-1.12	-1.20	-1.17	1.80
NM_175709	CBX7	Chromobox homolog 7	-1.12	-1.22	-1.17	-1.17	1.60
AF038963	DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	-1.25	-1.13	-1.12	-1.17	1.40
AF279614	CIDEC	Cell death-inducing DFFA-like effector c	-1.26	-1.10	-1.14	-1.17	1.20
NM_000109	DMD	Dystrophin (muscular dystrophy, Duchenne and Becker types)	-1.32	-1.06	-1.14	-1.17	-1.20
NM_016619	PLAC8	Placenta-specific 8	-1.22	-1.13	-1.16	-1.17	-1.40
AB018289	KIAA0746	KIAA0746 protein	-1.10	-1.15	-1.26	-1.17	-1.60
NM_004748	CCPG1	Cell cycle progression 1	-1.19	-1.12	-1.20	-1.17	-1.80
BC029120	C12orf26	Chromosome 12 open reading frame 26	-1.30	-1.09	-1.13	-1.17	-2.00
THC1989996	THC1989996	Unknown	-1.25	-1.09	-1.17	-1.17	-2.20
AB075862	ABCA11	ATP-binding cassette, sub-family A (ABC1), member 11 (pseudogene)	-1.17	-1.11	-1.23	-1.17	-2.40
AK056185	LRRCC1	Leucine rich repeat and coiled-coil domain containing 1	-1.21	-1.14	-1.16	-1.17	-2.60
BC002742	LSM8	LSM8 homolog, U6 small nuclear RNA associated (S. cerevisiae)	-1.16	-1.11	-1.24	-1.17	-2.80
NM_006680	ME3	Malic enzyme 3, NADP(+)-dependent, mitochondrial	-1.21	-1.10	-1.20	-1.17	-3.00
THC1891147	THC1891147	Unknown	-1.27	-1.09	-1.16	-1.17	-3.20
NM_000056	BCKDHB	Branched chain keto acid dehydrogenase E1, beta polypeptide (maple syrup urine disease)	-1.21	-1.07	-1.24	-1.17	-3.40
BC007072	RP4-747L4.3	Hypothetical protein MGC12538	-1.23	-1.18	-1.11	-1.17	-3.60
NM_004428	EFNA1	Ephrin-A1	-1.27	-1.13	-1.12	-1.17	-3.80
NM_139169	TRUB1	TruB pseudouridine (psi) synthase homolog 1 (E. coli)	-1.16	-1.12	-1.24	-1.17	-4.00
NM_021023	CFHR1	Complement factor H-related 1	-1.28	-1.17	-1.08	-1.17	-4.20
AF086016	NRP1	Neuropilin 1	-1.14	-1.21	-1.16	-1.17	-4.40
BC044624	PBX1	Pre-B-cell leukemia homeobox 1	-1.27	-1.24	-1.03	-1.17	-4.60
NM_003338	UBE2D1	Ubiquitin-conjugating enzyme E2D 1 (UBC4/5 homolog, yeast)	-1.11	-1.18	-1.24	-1.17	-4.80
NM_003672	CDC14A	CDC14 cell division cycle 14 homolog A (S. cerevisiae)	-1.29	-1.01	-1.24	-1.18	-5.00
BC000951	SQSTM1	Sequestosome 1	-1.20	-1.18	-1.15	-1.18	
NM_030899	ZNF323	Zinc finger protein 323	-1.21	-1.25	-1.08	-1.18	
NM_004414	DSCR1	Down syndrome critical region gene 1	-1.29	-1.16	-1.09	-1.18	
NM_004616	TSPAN8	Tetraspanin 8	-1.32	-1.12	-1.10	-1.18	
NM_152748	KIAA1324L	KIAA1324-like	-1.15	-1.21	-1.17	-1.18	
AK074057	FLJ10357	Hypothetical protein FLJ10357	-1.16	-1.11	-1.26	-1.18	
AB014525	SETX	Senataxin	-1.14	-1.31	-1.10	-1.18	
AK023631	AK023631	CDNA FLJ13569 fis, clone PLACE1008369	-1.24	-1.04	-1.27	-1.18	
AK023743	FLJ31033	Hypothetical protein FLJ31033	-1.26	-1.17	-1.12	-1.18	
NM_003506	FZD6	Frizzled homolog 6 (Drosophila)	-1.25	-1.11	-1.17	-1.18	
NM_000044	AR	Androgen receptor (dihydrotestosterone receptor; testicular feminization; spinal and bulbar muscular atrophy; Kenned	-1.26	-1.22	-1.06	-1.18	
AB063116	NAV2	Neuron navigator 2	-1.21	-1.20	-1.13	-1.18	
NM_012338	TSPAN12	Tetraspanin 12	-1.21	-1.15	-1.17	-1.18	
NM_133631	ROBO1	Roundabout, axon guidance receptor, homolog 1 (Drosophila)	-1.06	-1.22	-1.26	-1.18	
NM_012198	GCA	Grancalcin, EF-hand calcium binding protein	-1.24	-1.16	-1.14	-1.18	



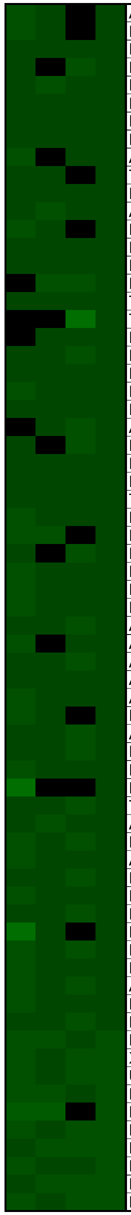
NM_017983	WIPI1	WD repeat domain, phosphoinositide interacting 1	-1.07	-1.26	-1.22	-1.18	
NM_007034	DNAJB4	DnaJ (Hsp40) homolog, subfamily B, member 4	-1.34	-1.12	-1.10	-1.18	
NM_000311	PRNP	Prion protein (p27-30) (Creutzfeldt-Jakob disease, Gerstmann-Strausler-Scheinker syndrome, fatal familial insomnia)	-1.08	-1.17	-1.30	-1.18	
NM_001321	CSRP2	Cysteine and glycine-rich protein 2	-1.28	-1.08	-1.20	-1.18	
NM_015714	G0S2	G0/G1switch 2	-1.13	-1.15	-1.28	-1.18	
NM_004926	ZFP36L1	Zinc finger protein 36, C3H type-like 1	-1.29	-1.14	-1.13	-1.18	
NM_003629	PIK3R3	Phosphoinositide-3-kinase, regulatory subunit 3 (p55, gamma)	-1.24	-1.08	-1.25	-1.19	
THC1965256	THC1965256	Unknown	-1.21	-1.22	-1.13	-1.19	
NM_006816	LMAN2	Lectin, mannose-binding 2	-1.16	-1.17	-1.23	-1.19	
BC047636	BC047636	Homo sapiens, clone IMAGE:5171705, mRNA	-1.23	-1.18	-1.15	-1.19	
A_24_P106166	A_24_P106166	Unknown	-1.21	-1.19	-1.17	-1.19	
NM_021800	DNAJC12	DnaJ (Hsp40) homolog, subfamily C, member 12	-1.23	-1.23	-1.11	-1.19	
NM_025144	ALPK1	Alpha-kinase 1	-1.18	-1.17	-1.21	-1.19	5.00
AK075342	C12orf39	Chromosome 12 open reading frame 39	-1.18	-1.12	-1.28	-1.19	4.80
BC022968	SLC7A14	Solute carrier family 7 (cationic amino acid transporter, y+ system), member 14	-1.27	-1.09	-1.21	-1.19	4.60
A_24_P192805	A_24_P192805	Unknown	-1.23	-1.16	-1.17	-1.19	4.40
A_24_P375076	A_24_P375076	Unknown	-1.23	-1.12	-1.22	-1.19	4.20
AK094603	AK094603	cDNA FLJ37284 fis, clone BRAMY2013590	-1.32	-1.09	-1.17	-1.19	4.00
AK074645	APOL6	Apolipoprotein L, 6	-1.21	-1.17	-1.20	-1.19	3.80
NM_003864	SAP30	Sin3A-associated protein, 30kDa	-1.22	-1.15	-1.21	-1.19	3.60
THC1857560	THC1857560	Unknown	-1.17	-1.13	-1.28	-1.19	3.40
NM_001914	CYB5A	Cytochrome b5 type A (microsomal)	-1.24	-1.14	-1.19	-1.19	3.20
BC001454	PCK2	Phosphoenolpyruvate carboxykinase 2 (mitochondrial)	-1.10	-1.21	-1.27	-1.19	3.00
AF090900	LIN7C	Lin-7 homolog C (C. elegans)	-1.20	-1.13	-1.26	-1.19	2.80
BC020718	CFI	Complement factor I	-1.24	-1.25	-1.09	-1.19	2.60
NM_016441	CRIM1	Cysteine rich transmembrane BMP regulator 1 (chordin-like)	-1.25	-1.08	-1.25	-1.19	2.40
NM_014751	MTSS1	Metastasis suppressor 1	-1.12	-1.20	-1.27	-1.19	2.20
AK056156	TMED10	Transmembrane emp24-like trafficking protein 10 (yeast)	-1.16	-1.21	-1.21	-1.19	2.00
NM_016613	C4orf18	Chromosome 4 open reading frame 18	-1.24	-1.22	-1.12	-1.19	1.80
NM_013956	NRG1	Neuregulin 1	-1.22	-1.08	-1.30	-1.20	1.60
NM_006527	SLBP	Stem-loop (histone) binding protein	-1.25	-1.13	-1.21	-1.20	1.40
THC1818601	THC1818601	Unknown	-1.25	-1.21	-1.13	-1.20	1.20
NM_018178	GOLPH3L	Golgi phosphoprotein 3-like	-1.26	-1.24	-1.09	-1.20	-1.20
BC011614	MTHFR	5,10-methylenetetrahydrofolate reductase (NADPH)	-1.13	-1.21	-1.25	-1.20	-1.40
A_32_P161327	A_32_P161327	Unknown	-1.22	-1.17	-1.20	-1.20	-1.60
THC1911551	THC1911551	Unknown	-1.17	-1.35	-1.09	-1.20	-1.80
NM_006732	FOSB	FBJ murine osteosarcoma viral oncogene homolog B	-1.63	-1.04	-1.01	-1.20	-2.00
NM_003272	GPR137B	G protein-coupled receptor 137B	-1.22	-1.17	-1.20	-1.20	-2.20
BC022055	BC022055	Homo sapiens, clone IMAGE:4690669, mRNA	-1.27	-1.19	-1.14	-1.20	-2.40
NM_022074	FAM111A	Family with sequence similarity 111, member A	-1.29	-1.12	-1.20	-1.20	-2.60
NM_006074	TRIM22	Tripartite motif-containing 22	-1.24	-1.17	-1.19	-1.20	-2.80
BC015869	EPAS1	Endothelial PAS domain protein 1	-1.22	-1.19	-1.18	-1.20	-3.00
NM_002127	HLA-G	HLA-G histocompatibility antigen, class I, G	-1.20	-1.16	-1.23	-1.20	-3.20
A_32_P200970	A_32_P200970	Unknown	-1.22	-1.13	-1.25	-1.20	-3.40
BC041955	BC041955	CDNA clone IMAGE:5301910	-1.50	-1.03	-1.11	-1.20	-3.60
NM_002210	ITGAV	Integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)	-1.11	-1.24	-1.26	-1.20	-3.80
NM_000155	GALT	Galactose-1-phosphate uridylyltransferase	-1.18	-1.22	-1.20	-1.20	-4.00
NM_138786	TM4SF18	Transmembrane 4 L six family member 18	-1.28	-1.25	-1.08	-1.20	-4.20
NM_005658	TRAF1	TNF receptor-associated factor 1	-1.20	-1.24	-1.16	-1.20	-4.40
NM_032636	PSRC1	Proline/serine-rich coiled-coil 1	-1.27	-1.23	-1.11	-1.20	-4.60
NM_172374	NUP62	Nucleoporin 62kDa	-1.16	-1.19	-1.26	-1.20	-4.80
NM_000235	LIPA	Lipase A, lysosomal acid, cholesterol esterase (Wolman disease)	-1.19	-1.21	-1.20	-1.20	-5.00
NM_022083	NM_022083	chromosome 1 open reading frame 24 (C1orf24), mRNA	-1.08	-1.15	-1.40	-1.20	
AK096664	ABCA5	ATP-binding cassette, sub-family A (ABC1), member 5	-1.21	-1.18	-1.22	-1.20	
NM_021999	ITM2B	Integral membrane protein 2B	-1.24	-1.18	-1.19	-1.20	
AK000854	VPS37C	Vacuolar protein sorting 37 homolog C (S. cerevisiae)	-1.16	-1.23	-1.23	-1.20	
AB071605	HUWE1	HECT, UBA and WWE domain containing 1	-1.17	-1.21	-1.24	-1.21	
AK091503	RPS6KB1	Ribosomal protein S6 kinase, 70kDa, polypeptide 1	-1.25	-1.12	-1.26	-1.21	
THC2002433	THC2002433	Unknown	-1.16	-1.22	-1.25	-1.21	
NM_017599	VEZT	Vezatin, adherens junctions transmembrane protein	-1.20	-1.20	-1.22	-1.21	
NM_014350	TNFAIP8	Tumor necrosis factor, alpha-induced protein 8	-1.39	-1.11	-1.14	-1.21	
NM_005194	CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	-1.24	-1.12	-1.28	-1.21	
A_24_P67748	A_24_P67748	Unknown	-1.29	-1.09	-1.25	-1.21	
THC1967781	THC1967781	Unknown	-1.24	-1.17	-1.23	-1.21	
BC040210	AKR1C2	Aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxyste	-1.30	-1.33	-1.03	-1.21	
NM_006948	STCH	Stress 70 protein chaperone, microsome-associated, 60kDa	-1.22	-1.14	-1.28	-1.21	
NM_199511	CCDC80	Coiled-coil domain containing 80	-1.26	-1.14	-1.24	-1.21	



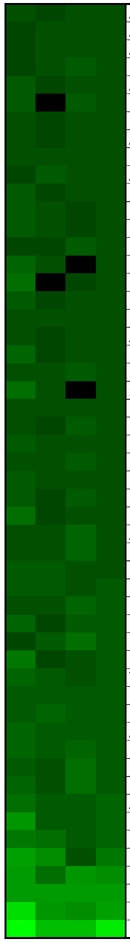
NM_000636	SOD2	Superoxide dismutase 2, mitochondrial	-1.22	-1.22	-1.19	-1.21	
NM_004199	P4HA2	Procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide II	-1.26	-1.12	-1.26	-1.21	
BC001663	BC001663	ribosomal protein L31, mRNA (cDNA clone IMAGE:2823904), partial cds	-1.22	-1.17	-1.25	-1.21	
NM_005054	RGPD5	RANBP2-like and GRIP domain containing 5	-1.25	-1.10	-1.30	-1.21	
AK130366	AK130366	CDNA FLJ26856 fis, clone PRS08123	-1.26	-1.19	-1.19	-1.21	
NM_015328	KIAA0828	Adenosylhomocysteinase 3	-1.29	-1.16	-1.20	-1.21	
NM_152270	SLFN11	Schlafen family member 11	-1.29	-1.21	-1.15	-1.21	
BC000232	REEP5	Receptor accessory protein 5	-1.19	-1.19	-1.26	-1.21	
AK021543	AK021543	CDNA FLJ11481 fis, clone HEMBA1001803	-1.20	-1.15	-1.31	-1.21	
BC018597	BC018597	Homo sapiens, clone IMAGE:3869276, mRNA	-1.40	-1.12	-1.14	-1.22	
AB023187	FNDC3A	Fibronectin type III domain containing 3A	-1.15	-1.26	-1.24	-1.22	
NM_015429	ABI3BP	ABI gene family, member 3 (NESH) binding protein	-1.21	-1.22	-1.21	-1.22	
AK021606	AK021606	CDNA FLJ11544 fis, clone HEMBA1002826	-1.27	-1.21	-1.16	-1.22	5.00
NM_000935	PLOD2	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	-1.10	-1.15	-1.42	-1.22	4.80
NM_006636	MTHFD2	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	-1.14	-1.19	-1.33	-1.22	4.60
NM_001773	CD34	CD34 molecule	-1.32	-1.25	-1.10	-1.22	4.40
A_32_P44932	A_32_P44932	Unknown	-1.53	1.01	-1.19	-1.22	4.20
AY008274	FBXW7	F-box and WD repeat domain containing 7	-1.25	-1.18	-1.22	-1.22	4.00
NM_000416	IFNGR1	Interferon gamma receptor 1	-1.29	-1.09	-1.28	-1.22	3.80
A_24_P552987	A_24_P552987	Unknown	-1.24	-1.18	-1.23	-1.22	3.60
NM_005776	CNIH	Cornichon homolog (Drosophila)	-1.24	-1.11	-1.32	-1.22	3.40
AF161542	CYLD	Cylindromatosis (turban tumor syndrome)	-1.28	-1.21	-1.17	-1.22	3.20
BU739448	MGP	Matrix Gla protein	-1.28	-1.25	-1.14	-1.22	3.00
NM_001547	IFIT2	Interferon-induced protein with tetratricopeptide repeats 2	-1.40	-1.20	-1.08	-1.22	2.80
NM_012173	FBXO25	F-box protein 25	-1.15	-1.29	-1.23	-1.22	2.60
NM_003715	VDP	Vesicle docking protein p115	-1.20	-1.19	-1.28	-1.22	2.40
NM_015285	WDR7	WD repeat domain 7	-1.23	-1.20	-1.23	-1.22	2.20
NM_002646	PIK3C2B	Phosphoinositide-3-kinase, class 2, beta polypeptide	-1.27	-1.23	-1.17	-1.22	2.00
NM_152271	LONRF1	LON peptidase N-terminal domain and ring finger 1	-1.21	-1.18	-1.28	-1.22	1.80
NM_006263	PSME1	Proteasome (prosome, macropain) activator subunit 1 (PA28 alpha)	-1.22	-1.24	-1.20	-1.22	1.60
NM_030952	NUAK2	NUAK family, SNF1-like kinase, 2	-1.41	-1.13	-1.15	-1.22	1.40
NM_015691	WWC3	WWC family member 3	-1.21	-1.20	-1.26	-1.22	1.20
THC1807843	THC1807843	Unknown	-1.29	-1.13	-1.26	-1.22	-1.20
NM_033161	SURF4	Surfeit 4	-1.21	-1.13	-1.34	-1.23	-1.40
NM_005195	CEBPD	CCAAT/enhancer binding protein (C/EBP), delta	-1.49	-1.11	-1.11	-1.23	-1.60
NM_006595	API5	Apoptosis inhibitor 5	-1.25	-1.19	-1.24	-1.23	-1.80
AK057669	PURB	Purine-rich element binding protein B	-1.24	-1.12	-1.33	-1.23	-2.00
THC1922938	THC1922938	Unknown	-1.20	-1.23	-1.26	-1.23	-2.20
NM_004120	GBP2	Guanylate binding protein 2, interferon-inducible	-1.25	-1.21	-1.22	-1.23	-2.40
NM_020739	CCPG1	Cell cycle progression 1	-1.17	-1.25	-1.27	-1.23	-2.60
NM_007021	C10orf10	Chromosome 10 open reading frame 10	-1.32	-1.34	-1.04	-1.23	-2.80
NM_014331	SLC7A11	Solute carrier family 7, (cationic amino acid transporter, y+ system) member 11	-1.25	-1.21	-1.23	-1.23	-3.00
NM_005595	NFIA	Nuclear factor I/A	-1.23	-1.17	-1.28	-1.23	-3.20
NM_032501	ACSS1	Acyl-CoA synthetase short-chain family member 1	-1.24	-1.27	-1.18	-1.23	-3.40
NM_016108	AIG1	Androgen-induced 1	-1.22	-1.27	-1.20	-1.23	-3.60
A_24_P217063	A_24_P217063	Unknown	-1.18	-1.22	-1.29	-1.23	-3.80
NM_001172	ARG2	Arginase, type II	-1.16	-1.21	-1.33	-1.23	-4.00
A_32_P149416	A_32_P149416	Unknown	-1.25	-1.15	-1.31	-1.23	-4.20
NM_002229	JUNB	Jun B proto-oncogene	-1.24	-1.31	-1.15	-1.23	-4.40
NM_152996	ST6GALNAC3	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 3	-1.23	-1.22	-1.25	-1.23	-4.60
NM_018672	ABCA5	ATP-binding cassette, sub-family A (ABC1), member 5	-1.24	-1.20	-1.26	-1.24	-4.80
NM_002185	IL7R	Interleukin 7 receptor	-1.25	-1.27	-1.19	-1.24	-5.00
THC1999547	THC1999547	Unknown	-1.24	-1.18	-1.28	-1.24	
NM_181531	BTN2A2	Butyrophilin, subfamily 2, member A2	-1.26	-1.19	-1.26	-1.24	
AL137464	FLJ20035	Hypothetical protein FLJ20035	-1.34	-1.25	-1.13	-1.24	
A_24_P802562	A_24_P802562	Unknown	-1.24	-1.16	-1.32	-1.24	
NM_006169	NNMT	Nicotinamide N-methyltransferase	-1.30	-1.19	-1.23	-1.24	
NM_014033	METTL7A	Methyltransferase like 7A	-1.34	-1.18	-1.21	-1.24	
NM_014417	BBC3	BCL2 binding component 3	-1.24	-1.15	-1.34	-1.24	
NM_000600	IL6	Interleukin 6 (interferon, beta 2)	-1.09	-1.24	-1.41	-1.24	
NM_006290	TNFAIP3	Tumor necrosis factor, alpha-induced protein 3	-1.37	-1.17	-1.20	-1.24	
NM_004083	DDIT3	DNA-damage-inducible transcript 3	-1.35	-1.14	-1.24	-1.24	
NM_020130	C8orf4	Chromosome 8 open reading frame 4	-1.36	-1.21	-1.17	-1.24	
NM_005502	ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	-1.34	-1.18	-1.21	-1.24	
NM_006813	PNRC1	Proline-rich nuclear receptor coactivator 1	-1.22	-1.27	-1.24	-1.24	
BC027332	TMEM157	Transmembrane protein 157	-1.22	-1.18	-1.33	-1.24	
NM_003706	PLA2G4C	Phospholipase A2, group IVC (cytosolic, calcium-independent)	-1.03	-1.46	-1.28	-1.24	



NM_003855	IL18R1	Interleukin 18 receptor 1	-1.41	-1.23	-1.11	-1.24	
AK057702	ZNF323	Zinc finger protein 323	-1.29	-1.28	-1.17	-1.24	
NM_178445	CCRL1	Chemokine (C-C motif) receptor-like 1	-1.40	-1.16	-1.19	-1.24	
NM_004031	IRF7	Interferon regulatory factor 7	-1.25	-1.22	-1.27	-1.25	
NM_016047	SF3B14	Splicing factor 3B, 14 kDa subunit	-1.22	-1.15	-1.38	-1.25	
NM_013257	SGK3	Serum/glucocorticoid regulated kinase family, member 3	-1.22	-1.27	-1.24	-1.25	
NM_017631	FLJ20035	Hypothetical protein FLJ20035	-1.33	-1.26	-1.15	-1.25	
AL833655	AL833655	CDNA clone IMAGE:5216666	-1.24	-1.28	-1.22	-1.25	
NM_006307	SRPX	Sushi-repeat-containing protein, X-linked	-1.32	-1.10	-1.34	-1.25	
NM_012328	DNAJB9	DnaJ (Hsp40) homolog, subfamily B, member 9	-1.26	-1.34	-1.15	-1.25	
NM_022473	ZFP106	Zinc finger protein 106 homolog (mouse)	-1.25	-1.32	-1.18	-1.25	
NM_005087	FXR1	Fragile X mental retardation, autosomal homolog 1	-1.27	-1.21	-1.27	-1.25	
NM_021158	TRIB3	Tribbles homolog 3 (Drosophila)	-1.08	-1.30	-1.39	-1.25	5.00
M11886	HLA-C	Major histocompatibility complex, class I, C	-1.25	-1.24	-1.25	-1.25	4.80
NM_004354	CCNG2	Cyclin G2	-1.27	-1.30	-1.18	-1.25	4.60
AF188611	HSPA5	Heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	-1.20	-1.22	-1.33	-1.25	4.40
NM_021237	SELK	Selenoprotein K	-1.19	-1.23	-1.34	-1.25	4.20
NM_014079	KLF15	Kruppel-like factor 15	-1.24	-1.16	-1.36	-1.25	4.00
NM_003820	TNFRSF14	Tumor necrosis factor receptor superfamily, member 14 (herpesvirus entry mediator)	-1.16	-1.29	-1.31	-1.25	3.80
AF217518	AF217518	uncharacterized bone marrow protein BM042 mRNA, complete cds	-1.20	-1.26	-1.29	-1.25	3.60
BC041925	SLC7A11	Solute carrier family 7, (cationic amino acid transporter, y+ system) member 11	-1.25	-1.23	-1.27	-1.25	3.40
BC035496	CITED4	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 4	-1.33	-1.22	-1.21	-1.25	3.20
NM_031458	PARP9	Poly (ADP-ribose) polymerase family, member 9	-1.34	-1.24	-1.18	-1.25	3.00
NM_021137	TNFAIP1	Tumor necrosis factor, alpha-induced protein 1 (endothelial)	-1.35	-1.21	-1.20	-1.25	2.80
AK091799	XAF1	XIAP associated factor-1	-1.26	-1.28	-1.22	-1.25	2.60
AB051464	KLHL15	Kelch-like 15 (Drosophila)	-1.21	-1.21	-1.34	-1.25	2.40
BC028068	JAK3	Janus kinase 3 (a protein tyrosine kinase, leukocyte)	-1.16	-1.29	-1.32	-1.25	2.20
NM_004687	MTMR4	Myotubularin related protein 4	-1.24	-1.16	-1.37	-1.25	2.00
NM_139312	YME1L1	YME1-like 1 (S. cerevisiae)	-1.27	-1.12	-1.39	-1.26	1.80
BC031860	TMEM170	Transmembrane protein 170	-1.28	-1.24	-1.25	-1.26	1.60
BC014203	FAM101B	Family with sequence similarity 101, member B	-1.19	-1.25	-1.34	-1.26	1.40
NM_014154	ARMC8	Armadillo repeat containing 8	-1.39	-1.18	-1.22	-1.26	1.20
NM_052889	COP1	Caspase-1 dominant-negative inhibitor pseudo-ICE	-1.30	-1.27	-1.22	-1.26	-1.20
NM_078476	BTN2A1	Butyrophilin, subfamily 2, member A1	-1.23	-1.11	-1.47	-1.26	-1.40
THC1953505	THC1953505	Unknown	-1.27	-1.21	-1.30	-1.26	-1.60
NM_003407	ZFP36	Zinc finger protein 36, C3H type, homolog (mouse)	-1.53	-1.30	-1.01	-1.26	-1.80
BC015887	WSB2	WD repeat and SOCS box-containing 2	-1.29	-1.19	-1.30	-1.26	-2.00
BC035582	TRIM22	Tripartite motif-containing 22	-1.28	-1.22	-1.29	-1.26	-2.20
NM_023005	NM_023005	bromodomain adjacent to zinc finger domain, 1B (BAZ1B), transcript variant 1, mRNA	-1.26	-1.27	-1.25	-1.26	-2.40
THC1877698	THC1877698	Unknown	-1.32	-1.35	-1.13	-1.26	-2.60
NM_004530	MMP2	Matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	-1.20	-1.31	-1.27	-1.26	-2.80
NM_058179	PSAT1	Phosphoserine aminotransferase 1	-1.16	-1.29	-1.34	-1.26	-3.00
BX538293	SLC7A11	Solute carrier family 7, (cationic amino acid transporter, y+ system) member 11	-1.39	-1.18	-1.22	-1.26	-3.20
NM_003821	RIPK2	Receptor-interacting serine-threonine kinase 2	-1.42	-1.16	-1.23	-1.26	-3.40
NM_173216	ST6GAL1	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	-1.24	-1.37	-1.19	-1.26	-3.60
NM_006851	GLIPR1	GLI pathogenesis-related 1 (glioma)	-1.25	-1.17	-1.39	-1.27	-3.80
BM989848	BM989848	Transcribed locus, moderately similar to NP_001003680.1 receptor isoform 3 [Homo sapiens]	-1.48	-1.11	-1.24	-1.27	-4.00
BC001500	PRCP	Prolylcarboxypeptidase (angiotensinase C)	-1.23	-1.31	-1.26	-1.27	-4.20
NM_016096	ZNF706	Zinc finger protein 706	-1.29	-1.15	-1.36	-1.27	-4.40
NM_005610	RBBP4	Retinoblastoma binding protein 4	-1.22	-1.30	-1.28	-1.27	-4.60
NM_001902	CTH	Cystathionase (cystathionine gamma-lyase)	-1.13	-1.33	-1.36	-1.27	-4.80
NM_014685	HERPUD1	Homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	-1.44	-1.13	-1.26	-1.27	-5.00
NM_003810	TNFSF10	Tumor necrosis factor (ligand) superfamily, member 10	-1.29	-1.41	-1.12	-1.27	
NM_000918	P4HB	Procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), beta polypeptide	-1.21	-1.27	-1.34	-1.27	
AK025431	RELL1	Receptor expressed in lymphoid tissues like 1	-1.24	-1.10	-1.52	-1.27	
BC036402	MXD1	MAX dimerization protein 1	-1.15	-1.24	-1.45	-1.27	
NM_016442	ARTS-1	Type 1 tumor necrosis factor receptor shedding aminopeptidase regulator	-1.32	-1.17	-1.35	-1.28	
AL133118	AL133118	MRNA; cDNA DKFZp586N0121 (from clone DKFZp586N0121)	-1.40	-1.32	-1.14	-1.28	
NM_005178	BCL3	B-cell CLL/lymphoma 3	-1.35	-1.16	-1.35	-1.28	
NM_020801	ARRDC3	Arrestin domain containing 3	-1.34	-1.22	-1.29	-1.28	
ENST00000324460	ENST00000324460	Unknown	-1.22	-1.27	-1.36	-1.28	
NM_015932	POMP	Proteasome maturation protein	-1.28	-1.24	-1.34	-1.29	
NM_014398	LAMP3	Lysosomal-associated membrane protein 3	-1.21	-1.17	-1.51	-1.29	
NM_006729	DIAPH2	Diaphanous homolog 2 (Drosophila)	-1.29	-1.27	-1.30	-1.29	
NM_002423	MMP7	Matrix metallopeptidase 7 (matrilysin, uterine)	-1.31	-1.42	-1.15	-1.29	
NM_004556	NFKBIE	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon	-1.28	-1.27	-1.33	-1.29	
NM_170672	RASGRP3	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	-1.13	-1.53	-1.24	-1.29	



AK097204	SAMD9L	Sterile alpha motif domain containing 9-like	-1.41	-1.28	-1.19	-1.29	
BC032663	PMAIP1	Phorbol-12-myristate-13-acetate-induced protein 1	-1.40	-1.31	-1.17	-1.29	
NM_002800	PSMB9	Proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	-1.26	-1.29	-1.32	-1.29	
NM_003589	CUL4A	Cullin 4A	-1.33	-1.15	-1.42	-1.29	
NM_021945	C6orf85	Chromosome 6 open reading frame 85	-1.22	-1.47	-1.21	-1.29	
M21963	HLA-C	Major histocompatibility complex, class I, C	-1.27	-1.32	-1.30	-1.29	
NM_000204	CFI	Complement factor I	-1.33	-1.33	-1.23	-1.29	
NM_002113	CFH	Complement factor H	-1.35	-1.25	-1.29	-1.30	
AB051549	ZFHX2	Zinc finger homeobox 2	-1.46	-1.18	-1.27	-1.30	
THC1921239	THC1921239	Unknown	-1.40	-1.33	-1.17	-1.30	
NM_004688	NMI	N-myc (and STAT) interactor	-1.32	-1.28	-1.29	-1.30	
AF352781	CXCL11	Chemokine (C-X-C motif) ligand 11	-1.27	-1.41	-1.22	-1.30	
NM_016242	EMCN	Endomucin	-1.41	-1.35	-1.16	-1.30	5.00
NM_138455	CTHRC1	Collagen triple helix repeat containing 1	-1.20	-1.40	-1.31	-1.30	4.80
NM_021133	RNASEL	Ribonuclease L (2',5'-oligoisoadenylate synthetase-dependent)	-1.27	-1.27	-1.37	-1.30	4.60
NM_002425	MMP10	Matrix metallopeptidase 10 (stromelysin 2)	1.01	-1.48	-1.52	-1.30	4.40
THC1934501	THC1934501	Unknown	-1.36	-1.20	-1.36	-1.30	4.20
THC1926688	THC1926688	Unknown	-1.01	-1.02	-2.15	-1.30	4.00
NM_058172	ANTXR2	Anthrax toxin receptor 2	-1.17	-1.38	-1.37	-1.30	3.80
NM_002056	GFPT1	Glutamine-fructose-6-phosphate transaminase 1	-1.27	-1.24	-1.41	-1.30	3.60
M27396	ASNS	Asparagine synthetase	-1.29	-1.29	-1.33	-1.31	3.40
NM_015170	SULF1	Sulfatase 1	-1.43	-1.30	-1.22	-1.31	3.20
NM_000963	PTGS2	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	-1.22	-1.35	-1.38	-1.32	3.00
A_23_P421323	A_23_P421323	Unknown	-1.17	-1.31	-1.49	-1.32	2.80
NM_015508	TIPARP	TCDD-inducible poly(ADP-ribose) polymerase	-1.39	-1.17	-1.42	-1.32	2.60
NM_000867	HTR2B	5-hydroxytryptamine (serotonin) receptor 2B	-1.25	-1.38	-1.34	-1.32	2.40
NM_024119	LGP2	Likely ortholog of mouse D11lgp2	-1.27	-1.38	-1.32	-1.32	2.20
THC1968370	THC1968370	Unknown	-1.27	-1.35	-1.36	-1.32	2.00
NM_002053	GBP1	Guanylate binding protein 1, interferon-inducible, 67kDa	-1.46	-1.23	-1.30	-1.33	1.80
NM_000900	MGP	Matrix Gla protein	-1.44	-1.41	-1.15	-1.33	1.60
BC013734	PTGS2	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	-1.30	-1.18	-1.52	-1.33	1.40
ENST00000332484	ENST00000332484	Unknown	-1.44	-1.27	-1.29	-1.33	1.20
NM_003739	AKR1C3	Aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II)	-1.43	-1.33	-1.25	-1.33	-1.20
NM_145640	APOL3	Apolipoprotein L, 3	-1.41	-1.39	-1.23	-1.34	-1.40
AJ004914	TMED10	Transmembrane emp24-like trafficking protein 10 (yeast)	-1.36	-1.26	-1.42	-1.35	-1.60
AK001823	GBP3	Guanylate binding protein 3	-1.51	-1.20	-1.35	-1.35	-1.80
AK074954	TBC1D1	TBC1 (tre-2/USP6, BUB2, cdc16) domain family, member 1	-1.34	-1.27	-1.45	-1.35	-2.00
AK097398	NUCB2	Nucleobindin 2	-1.32	-1.36	-1.38	-1.35	-2.20
AF113212	RGS5	Regulator of G-protein signalling 5	-1.41	-1.29	-1.35	-1.35	-2.40
NM_015660	GIMAP2	GTPase, IMAP family member 2	-1.55	-1.37	-1.17	-1.35	-2.60
AL110170	RPL22L1	Ribosomal protein L22-like 1	-1.32	-1.21	-1.55	-1.36	-2.80
NM_018981	DNAJC10	DnaJ (Hsp40) homolog, subfamily C, member 10	-1.32	-1.35	-1.40	-1.36	-3.00
NM_020311	CXCR7	Chemokine (C-X-C motif) receptor 7	-1.54	-1.24	-1.31	-1.36	-3.20
NM_000758	CSF2	Colony stimulating factor 2 (granulocyte-macrophage)	-2.07	-1.04	-1.17	-1.36	-3.40
THC1811158	THC1811158	Unknown	-1.32	-1.32	-1.45	-1.36	-3.60
AK001770	PARP14	Poly (ADP-ribose) polymerase family, member 14	-1.39	-1.42	-1.28	-1.36	-3.80
NM_013417	IARS	Isoleucyl-tRNA synthetase	-1.44	-1.25	-1.41	-1.37	-4.00
AF116660	AF116660	PRO1430 mRNA, complete cds	-1.47	-1.32	-1.32	-1.37	-4.20
NM_138459	NUS1	Nuclear undecaprenyl pyrophosphate synthase 1 homolog (S. cerevisiae)	-1.39	-1.29	-1.44	-1.37	-4.40
NM_017523	XAF1	XIAP associated factor-1	-1.51	-1.31	-1.31	-1.37	-4.60
NM_006827	TMED10	Transmembrane emp24-like trafficking protein 10 (yeast)	-1.38	-1.31	-1.46	-1.38	-4.80
NM_005252	FOS	V-fos FBJ murine osteosarcoma viral oncogene homolog	-2.13	-1.21	-1.02	-1.38	-5.00
NM_173515	CNKSR3	CNKSR family member 3	-1.53	-1.23	-1.41	-1.38	
NM_005824	LRRC17	Leucine rich repeat containing 17	-1.53	-1.37	-1.27	-1.39	
AK025800	NUPL1	Nucleoporin like 1	-1.46	-1.32	-1.40	-1.39	
NM_002341	LTB	Lymphotoxin beta (TNF superfamily, member 3)	-1.45	-1.39	-1.35	-1.40	
NM_016584	IL23A	Interleukin 23, alpha subunit p19	-1.28	-1.39	-1.55	-1.40	
NM_007047	BTN3A2	Butyrophilin, subfamily 3, member A2	-1.46	-1.41	-1.35	-1.41	
XM_371762	XM_371762	similar to Proteasome activator complex subunit 2 (Proteasome activator 28-beta subunit) (PA28beta) (PA28b) (Activa	-1.43	-1.31	-1.48	-1.41	
U90143	BTN3A2	Butyrophilin, subfamily 3, member A2	-1.43	-1.38	-1.42	-1.41	
NM_052941	GBP4	Guanylate binding protein 4	-1.46	-1.47	-1.31	-1.41	
NM_001964	EGR1	Early growth response 1	-1.80	-1.65	1.05	-1.41	
NM_005420	SULT1E1	Sulfotransferase family 1E, estrogen-preferring, member 1	-1.53	-1.25	-1.48	-1.41	
NM_013231	FLRT2	Fibronectin leucine rich transmembrane protein 2	-1.30	-1.55	-1.42	-1.42	
NM_003004	SECTM1	Secreted and transmembrane 1	-1.53	-1.38	-1.35	-1.42	
NM_003265	TLR3	Toll-like receptor 3	-1.39	-1.45	-1.42	-1.42	
NM_002818	PSME2	Proteasome (prosome, macropain) activator subunit 2 (PA28 beta)	-1.43	-1.35	-1.48	-1.42	



AB007963	ATPAF1	ATP synthase mitochondrial F1 complex assembly factor 1	-1.45	-1.37	-1.45	-1.42		
AK131073	PAPLN	Papilin, proteoglycan-like sulfated glycoprotein	-1.27	-1.51	-1.52	-1.43		
AF169676	FLRT2	Fibronectin leucine rich transmembrane protein 2	-1.35	-1.43	-1.51	-1.43		
NM_052966	FAM129A	Family with sequence similarity 129, member A	-1.28	-1.45	-1.60	-1.44		
AL359062	AL359062	MRNA full length insert cDNA clone EUROIMAGE 1913076	-1.65	-1.25	-1.45	-1.45		
NM_001511	CXCL1	Chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha)	-1.62	-1.16	-1.61	-1.45		
NM_000593	TAP1	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	-1.53	-1.27	-1.57	-1.45		
AK098422	AK098422	CDNA FLJ25556 fis, clone JTH02629	-1.55	-1.33	-1.49	-1.45		
NM_153377	LRIG3	Leucine-rich repeats and immunoglobulin-like domains 3	-1.52	-1.41	-1.46	-1.46		
A_23_P8812	A_23_P8812	Unknown	-1.27	-1.65	-1.51	-1.47		
NM_138397	NM_138397	hypothetical protein BC012317 (LOC93082), mRNA	-1.61	-1.36	-1.46	-1.47		
BC018149	IL15	Interleukin 15	-1.65	-1.48	-1.31	-1.48		
NM_181782	NCOA7	Nuclear receptor coactivator 7	-1.64	-1.43	-1.37	-1.48	5.00	🟥
BC008810	LOC196264	Hypothetical protein LOC196264	-1.39	-1.37	-1.70	-1.48	4.80	🟥
NM_002522	NPTX1	Neuronal pentraxin I	-1.98	-1.56	-1.06	-1.48	4.60	🟥
NM_006291	TNFAIP2	Tumor necrosis factor, alpha-induced protein 2	-2.18	-1.18	-1.27	-1.49	4.40	🟥
NM_018284	GBP3	Guanylate binding protein 3	-1.65	-1.29	-1.56	-1.49	4.20	🟥
NM_005347	HSPA5	Heat shock 70kDa protein 5 (glucose-regulated protein, 78kDa)	-1.41	-1.48	-1.60	-1.49	4.00	🟥
AK094583	LOC339745	Hypothetical protein LOC339745	-1.60	-1.34	-1.58	-1.50	3.80	🟥
NM_002089	CXCL2	Chemokine (C-X-C motif) ligand 2	-1.83	-1.29	-1.45	-1.51	3.60	🟥
NM_024569	MPZL1	Myelin protein zero-like 1	-1.42	-1.44	-1.68	-1.51	3.40	🟥
X72308	X72308	mRNA for monocyte chemotactic protein-3 (MCP-3)	-2.05	-1.50	-1.13	-1.51	3.20	🟥
NM_138639	BCL2L12	BCL2-like 12 (proline rich)	-1.53	-1.49	-1.53	-1.51	3.00	🟥
NM_012142	CCNDBP1	Cyclin D-type binding-protein 1	-1.56	-1.40	-1.60	-1.52	2.80	🟥
NM_002199	IRF2	Interferon regulatory factor 2	-1.65	-1.46	-1.48	-1.53	2.60	🟥
BC028013	RELB	V-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-ce	-1.55	-1.43	-1.69	-1.55	2.40	🟥
BC014259	TIFA	TRAF-interacting protein with a forkhead-associated domain	-1.66	-1.48	-1.55	-1.56	2.20	🟥
NM_012106	ARL2BP	ADP-ribosylation factor-like 2 binding protein	-1.69	-1.27	-1.78	-1.56	2.00	🟥
NM_002090	CXCL3	Chemokine (C-X-C motif) ligand 3	-2.11	-1.30	-1.43	-1.58	1.80	🟥
AF369952	NDUFC2	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14.5kDa	-1.50	-1.44	-1.84	-1.58	1.60	🟥
NM_139313	YME1L1	YME1-like 1 (S. cerevisiae)	-1.54	-1.41	-1.83	-1.59	1.40	🟥
NM_033292	CASP1	Caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	-1.63	-1.65	-1.49	-1.59	1.20	🟥
NM_002183	IL3RA	Interleukin 3 receptor, alpha (low affinity)	-1.61	-1.68	-1.57	-1.62	-1.20	🟩
NM_018639	WSB2	WD repeat and SOCS box-containing 2	-1.57	-1.47	-1.85	-1.62	-1.40	🟩
NM_020529	NFKBIA	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	-1.93	-1.38	-1.69	-1.65	-1.60	🟩
NM_006398	UBD	Ubiquitin D	-1.36	-1.74	-2.03	-1.69	-1.80	🟩
NM_004591	CCL20	Chemokine (C-C motif) ligand 20	-2.30	-1.34	-1.56	-1.69	-2.00	🟩
THC1880502	THC1880502	Unknown	-1.89	-1.64	-1.57	-1.69	-2.20	🟩
NM_148919	PSMB8	Proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	-1.67	-1.73	-1.73	-1.71	-2.40	🟩
NM_005409	CXCL11	Chemokine (C-X-C motif) ligand 11	-1.61	-1.97	-1.63	-1.73	-2.60	🟩
AK056293	IFIH1	Interferon induced with helicase C domain 1	-1.82	-1.66	-1.72	-1.73	-2.80	🟩
NM_032012	C9orf5	Chromosome 9 open reading frame 5	-1.83	-1.61	-1.84	-1.76	-3.00	🟩
NM_003139	SRPR	Signal recognition particle receptor ('docking protein')	-1.73	-1.53	-2.05	-1.76	-3.20	🟩
NM_000584	IL8	Interleukin 8	-1.82	-1.56	-2.01	-1.79	-3.40	🟩
AK090468	TRAF1	TNF receptor-associated factor 1	-2.04	-1.68	-1.75	-1.81	-3.60	🟩
NM_001781	CD69	CD69 molecule	-2.81	-1.63	-1.62	-1.95	-3.80	🟩
NM_000201	ICAM1	Intercellular adhesion molecule 1 (CD54), human rhinovirus receptor	-2.20	-2.05	-1.76	-2.00	-4.00	🟩
NM_002996	CX3CL1	Chemokine (C-X3-C motif) ligand 1	-3.24	-2.64	-1.51	-2.35	-4.20	🟩
NM_001165	BIRC3	Baculoviral IAP repeat-containing 3	-3.16	-2.12	-2.96	-2.71	-4.40	🟩
NM_002982	CCL2	Chemokine (C-C motif) ligand 2	-3.08	-3.11	-3.15	-3.11	-4.60	🟩
NM_001078	VCAM1	Vascular cell adhesion molecule 1	-4.54	-2.84	-2.63	-3.24	-4.80	🟩
NM_000450	SELE	Selectin E (endothelial adhesion molecule 1)	-6.40	-4.15	-4.08	-4.77	-5.00	🟩

ANNEX 2.

Article:

“RNAi-mediated silencing of CD40 prevents leukocyte adhesion on CD154-activated endothelial cells”.

Pluvinet R, Petriz J, Torras J, Herrero I, Cruzado J.M, Grinyo J.M, and Aran J.M. 2004.
Blood; 104(12):3642-6.

Brief report

RNAi-mediated silencing of CD40 prevents leukocyte adhesion on CD154-activated endothelial cells

Raquel Pluvinet, Jordi Pétriz, Joan Torras, Inmaculada Herrero-Fresneda, Josep M. Cruzado, Josep M. Grinyó, and Josep M. Aran

The CD40-CD154 dyad has a central role in the development of immune-inflammatory processes. Therefore, disruption of CD40 signaling has the potential to be therapeutically useful in a number of disease indications, including autoimmune syndromes, atherosclerosis, and allograft rejection. Blocking antibodies to CD154 have been successfully employed in experimental animal models, and recently in clinical trials, to prevent or treat these immunologically induced diseases. However, the thrombotic events observed in some of these studies raise important issues regarding future use of anti-CD154 antibodies in humans. In this study, we demonstrate that a small interfering RNA (siRNA) can effectively reduce the surface expression of the human CD40 costimulatory receptor. Moreover, by rendering endothelial cells unresponsive to CD154$^+$ Jurkat cell–mediated activation through RNA interference, induction of endothelial cell-adhesion molecule expression and leukocyte adhesion is prevented in vitro. Thus, anti-CD40 siRNA may become a safe and effective therapeutic option for interfering with CD40-CD154–mediated acute or chronic immune-inflammatory conditions. (Blood. 2004;104:3642-3646)

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Introduction

The 48 kD type I transmembrane glycoprotein CD40 (tumor necrosis factor receptor 5 [TNFR5]) holds a spectrum of signaling activities. Activation of endothelial cells via CD40-CD154 interaction triggers proinflammatory cytokine and chemokine production; matrix metalloproteinase and tissue factor expression; an increased density of leukocyte adhesion molecules CD62E, CD106, and CD54; and thrombomodulin down-regulation.[1-7] These events play an important role in the promotion of extravasation and accumulation of activated T cells at the sites of inflammation. Interruption of CD40 signaling is, thus, being considered as a potential pharmacologic target for therapy. Indeed, preclinical studies in several animal models have shown that blockade of the CD40-CD154 pathway by antibodies to CD154 can prevent or treat a variety of autoimmune diseases, vascular disease, and allograft rejection without inducing generalized immune suppression.[8] Remarkably, a recent clinical trial has demonstrated that passive administration of a humanized monoclonal antibody (mAb) specific for CD154 ameliorates disease in systemic lupus erythematosus (SLE) patients.[9,10] However, the association of anti-CD154 mAb therapy with thromboembolic complications in human and nonhuman primates has provoked concern, leading to a halt in all clinical studies using anti-CD154 antibodies.[10-12] Thus, the development of alternative approaches to abrogate CD40-CD154 signaling seems mandatory for an effective and safer prevention or treatment of human immune-inflammatory disorders.

RNA interference (RNAi) mediated by small interfering RNAs (siRNAs), a type of posttranscriptional gene silencing, is revolutionizing the field of functional genomics owing to its powerful, sequence-specific capability to knock down gene expression and shows great promise for therapeutic applications.[13] In this study, we demonstrate that efficient blockade of the CD40-CD154 signaling by RNAi-mediated silencing of human CD40 expression on vascular endothelial cells leads to inhibition of CD62E, CD106, and CD54 expression and to a concomitant reduction of leukocyte adherence on these cells. This suggests an effective and potentially therapeutic anti-inflammatory effect mediated by anti-CD40 siRNA in the human endothelium.

Study design

The siRNA duplexes targeting the human CD40 mRNA (GenBank accession no. X60592.1) were designed according to previously described guidelines.[14] For the initial screening of the most effective siRNA duplexes, the 21-nucleotide (21-nt) RNAs were synthesized by in vitro transcription (Silencer siRNA Construction Kit; Ambion, Austin, TX). Further experiments were performed with the use of the most efficient siRNA-2–duplex chemically synthesized (Qiagen, Hilden, Germany), with 2′-deoxythymidines instead of uridine residues in the 3′ overhangs to enhance nuclease resistance.

ECV-304 cells (American Type Culture Collection [ATCC], Manassas, VA) (CRL 1998) were seeded in 6-well culture plates at a density of 1 × 10^5

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cells per well 16 to 18 hours prior to RNAi treatment. Transfection of siRNAs was performed by means of the cationic lipid OligofectAMINE in OptiMEM medium (Invitrogen, San Diego, CA), according to the manufacturer's instructions. Exponentially growing human umbilical vein endothelial cells (HUVECs) (Advancell, Barcelona, Spain) (4×10^5 cells per well in 6-well culture plates) underwent lipid-mediated transfection with the use of Targefect (Targeting Systems, Santee, CA), as recommended by the manufacturer. Two consecutive rounds of transfection with siRNA were performed to ensure maximum CD40 silencing on these primary cells.

RNA from siRNA-transfected cells was isolated and reverse transcribed (3 μg DNAse I–treated RNA per sample) by means of the RNeasy RNA Isolation and Omniscript RT kits (Qiagen). Quantification of CD40 mRNA levels was performed by real-time polymerase chain reaction (PCR) with the use of the LightCycler technology (Roche Molecular Biochemicals, Indianapolis, IN) and the human CD40-specific primers: CD40-forward (CD40-f) (5′-CAGCCAGGACAGAAACTGGTGAGT-3′) and CD40-reverse (CD40-r) (5′-CTTCTTCACAGGTGCAGATGGTGTC-3′). All samples were normalized with the use of the following primer set for the constitutively expressed human cyclophilin gene: Cyph-f (5′-CTCCTTTGAGCTGTTTGCAG-3′) and Cyph-r (5′-CACCACATGCTTGCCATCC-3′). PCR amplifications were performed in a 20 μL vol containing 2 μL ready-to-use reaction mix, 10 × DNA Master SYBR Green I (Roche Molecular Biochemicals); $MgCl_2$ (3 mM for CD40 amplification; 4 mM for cyclophilin amplification); 0.15 μM each primer; 5% dimethyl sulfoxide (DMSO); and 75 ng cDNA as template. The amplification program used an initial denaturation at 95°C for 10 minutes, followed by 45 cycles: 95°C for 1 second; 64°C for 5 seconds; 72°C for 10 seconds.

Immunoblotting for human CD40 detection was performed with a monoclonal antibody (H-10; 1:1000 dilution) (Santa Cruz Biotechnology, Santa Cruz, CA). Membranes were reprobed with rabbit polyclonal antiactin antibody (1:2000 dilution) (Sigma-Aldrich, St Louis, MO).

Indirect immunofluorescence staining for cell adhesion molecule (CAM) expression included anti–intercellular adhesion molecule 1 (anti–ICAM-1), CD54 (HA58); anti–vascular cell adhesion molecule 1 (anti–VCAM-1), CD106 (51-10C9); and anti–E-selectin, CD62E (68-5H11) (all from BD Pharmingen, San Diego, CA).

Adhesion of calcein acetoxymethyl ester (calcein AM)–loaded HL-60 leukemia cells (ATCC CCL 240) to endothelial cells was performed essentially as previously described.[4]

Table 1. Sequence composition and target localization within the human CD40 mRNA of the siRNAs (siRNA-1 through siRNA-8) designed to screen for effective CD40 gene silencing

siRNA anti-hCD40	hDC40 mRNA targeted region*	Sequence
siRNA-1	173-193	5′-UGCCUUCCUUGCGGUGAAAUU-3′ 3′-UUACGGAAGGAACGCCACUUU-5′
siRNA-2	192-212	5′-GCGAAUUCCUAGACACCUGUU-3′ 3′-UUCGCUUAAGGAUCUGUGGAC-5′
siRNA-3	479-499	5′-UGUCACCCUUGGACAAGCUUU-3′ 3′-UUACAGUGGGAACCUGUUCGU-5′
siRNA-4	709-729	5′-UUUUCCCGACGAUCUUCCUUU-3′ 3′-UUAAAAGGGCUGCUAGAAGGA-5′
siRNA-5	62-82	5′-CCACCCACUGCAUGCAGAGUU-3′ 3′-UUGGUGGGUGACGUACGUCUC-3′
siRNA-6	137-157	5′-CUGGUGAGUGACUGCACAGUU-3′ 3′-UUGACCACUCACUGACGUGUC-5′
siRNA-7	214-234	5′-CAGAGAGACACACUGCCACUU-3′ 3′-UUGUCUCUCUGUGUGACGGUG-5′
siRNA-8	242-262	5′-UACUGCGACCCCAACCUAGUU-3′ 3′-UUAUGACGCUGGGGUUGGAUC-5′
msiRNA-2	192-212	5′-GCGAAUUCGAUCUCACCUGUU-3′ 3′-UUCGCUUAAGCUAGAGUGGAC-5′
siRNA-C	—	5′-ACUACAAGACUCGUGACCAUU-3′ 3′-UUUGAUGUUCUGAGCACUGGU-5′

Selected sequences were of the type $AA(N_{19})UU$ (N, any nucleotide) and were submitted to a basic local alignment search tool (BLAST)[15] search against the human genome sequence to ensure gene specificity. The siRNA-C, with a scrambled sequence, was used as control for the initial screening on ECV-304 cells. The mismatched siRNA-2 (msiRNA-2), whose sequence was identical to that siRNA-2 except for the underlined 5-nt mismatch mutated by transversion, was used as control in the endothelial cell assays. The 21 nucleotide RNA sequences displayed in each row are arranged by complementary homology yielding the corresponding siRNA duplexes, with 2 unpaired uridine nucleotides at the 3′ end of each strand.

— indicates absence of homology with respect to the hCD40 mRNA sequence.

*Numbers indicate the position of the targeted region within the hCD40 mRNA sequence from ATG initiation codon.

Results and discussion

Selection and characterization of effective anti-CD40 siRNAs

Eight siRNAs were designed and generated by in vitro transcription to target-defined positions within the coding region of the human CD40 mRNA (Table 1). The potencies of the 8 siRNAs relative to a randomized control siRNA were compared both at the posttranscriptional level by real-time RT-PCR and at the translational level by Western immunoblotting (Figure 1A). The fluorescence ratios of target CD40 mRNA level to endogenous cyclophilin mRNA level in the presence of 100 nM siRNA duplexes revealed that 3 of the 8 siRNAs tested (siRNA-2, siRNA-6, and siRNA-8) were capable of specifically and significantly reducing the basal expression of CD40 in the ECV-304 cells. However, siRNA-2 was the most active inhibitor, showing a nearly 9-fold reduction of the CD40-cyclophilin mRNA ratio with respect to that shown by treatment with both the control siRNA (siRNA-C) and the inactive siRNAs. To better discriminate the effect of the different siRNAs on the CD40 protein level, we performed the screening over ECV-304 cells activated through TNF-α and IFN-γ, which up-regulated CD40 expression. It is noteworthy that siRNA-2 was confirmed as the most potent CD40 silencer capable of reducing CD40 receptor expression below its basal level on cytokine-activated ECV-304 cells, giving an overall inhibition of 85% to 90% at 48 hours, which correlates with that observed at the posttranscriptional level. Certainly, a dose-response assay corroborated the potency of siRNA-2 (50% inhibitory concentration [IC_{50}], approximately 5 nM) in ECV-304 cells (Figure 1B). In terms of local target accessibility, the superior efficiency of the siRNA-2 over alternative siRNA designs may reflect its targeting toward a stable internal loop within the secondary structure of the CD40 mRNA, determined by suboptimal folding (Figure 1D). It is being progressively recognized that the activity of siRNAs, similar to that of antisense oligonucleotides, is affected by the secondary structure of the target mRNA.[17,18] Interestingly, recent comparisons of the effectiveness of antisense oligonucleotides and siRNAs, both in cell culture and in vivo, suggest a superior efficiency and inhibitory persistence of the siRNAs.[19,20] Moreover, siRNAs are highly effective without any chemical modifications, resulting in a dramatically lower toxicity profile compared with antisense oligomers.

Efficient blockade of CD40-CD154 signaling by anti-CD40 siRNA-2 mitigates proinflammatory events on human endothelial cells

CD40 receptor silencing by siRNA-2 in HUVECs was further recognized by immunoblotting (Figure 1C). Careful optimization of cationic lipid–mediated transfection of cyanine 3 (Cy3)–labeled siRNAs on these cells yielded efficiencies in the range of 50% determined by fluorescence microscopy, with an acceptable toxicity (data not shown). This correlates with the moderate effect of

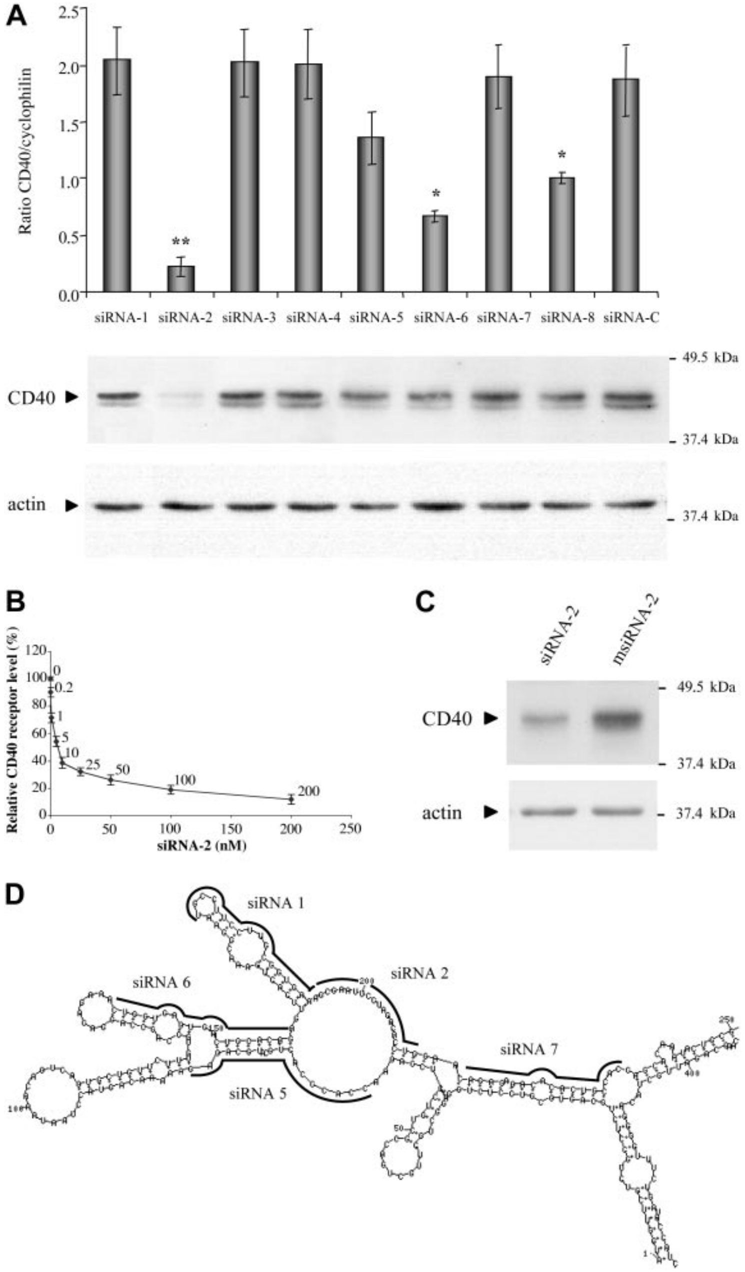

Figure 1. RNAi-mediated silencing of endogenous human CD40 expression. (A) Screening for effective siRNA inhibitors of endogenous CD40 expression. ECV-304 cells were transfected for 4 hours with 100 nM of the siRNAs as indicated in "Study Design." Total cellular RNA was extracted 48 hours after transfection and analyzed by real-time semiquantitative reverse-transcription PCR (RT-PCR). Human CD40 mRNA expression levels were assessed relative to the constitutively expressed cyclophilin gene (ratio of CD40 to cyclophilin mRNA). Data are presented as means and standard error of the mean (SEM) for 3 independent experiments (**$P < .01$, *$P < .05$, versus siRNA-C). The lower parts of panel A depict the evaluation of CD40 silencing at the protein level. The siRNA-transfected ECV-304 cells were stimulated with proinflammatory cytokines TNF-α (100 U/mL) and interferon-γ (IFN-γ) (1000 U/mL) 24 hours prior to protein extraction and Western immunoblotting, performed 48 hours after transfection. (B) Potency of siRNA-2. ECV-304 cells were stimulated as previously described and transfected with the indicated concentration of siRNA-2, and the CD40 receptor levels relative to the β-actin protein levels were determined by Western immunoblotting and densitometry by means of Phoretix 10 software (Nonlinear Dynamics, Newcastle upon Tyne, United Kingdom). Data are shown as means and SEM from 2 independent assays. (C) Specific inhibition by siRNA-2 of CD40 expression on human endothelial cells. HUVECs were lipofected for 2 hours with 100 nM siRNA-2 or its corresponding siRNA control, msiRNA-2, complexed with Targefect as described in "Study Design," and activated with TNF-α (100 U/mL) and IFN-γ (1000 U/mL) 16 hours prior to protein extraction. Representative Western immunoblotting was performed 48 hours after transfection. The housekeeping β-actin protein was included in the Western analyses to normalize for equal loading of the gel lanes. Relative mobility of molecular weight markers is shown in kilodaltons. (D) Predicted secondary structure of human CD40 mRNA. The predicted secondary structure of CD40 mRNA (residues 1-250 from the coding region are displayed) was determined by means of the suboptimal folding program of Michael Zucker, Mfold,[16] based on the energy minimization method. The targeting locations from 5 of the 8 designed siRNAs are indicated over the optimal lowest free energy structure.

siRNA-2, a 45% inhibition of endogenous CD40 receptor expression, detected in TNF-α/IFN-γ–activated HUVECs.

A major step of the immune-mediated inflammatory process, endothelial cell activation via CD40-CD154 interaction, leads to induction of cell surface adhesion molecule expression, which orchestrates the egress of inflammatory cells from the vessel lumen.[4-6] Thus, we investigated whether siRNA-2 could interfere with the CD40-CD154 activation pathway in HUVECs. We assessed the specific silencing effect of siRNA-2, compared with its corresponding mismatched control msiRNA-2, analyzing by flow cytometry both CAM expression and leukocyte adhesion in CD154-activated endothelial cells (Figure 2). The siRNA-2–treated, but not control msiRNA-2–treated, HUVECs showed a strong reduction of CAM expression when activated via CD154 (Figure 2A). Moreover, direct evaluation of leukocyte adhesion on CD154-activated HUVECs using HL-60 cells, which express the ligands for all 3 adhesion molecules ICAM-1, VCAM-1, and E-selectin, demonstrated that pretreatment with siRNA-2, but not with msiRNA-2, reduced leukocyte adherence by 87% (Figure 2B-C). Furthermore, the anti-CD40 siRNA-2 had no effect on either CAM expression (data not shown) or leukocyte adhesion induced by TNF-α–mediated HUVEC activation (Figure 2B), demonstrating its inability to interfere with the family member CD120 (TNF-α receptor), and hence its pathway specificity.

A recently completed preclinical trial has demonstrated the safety and efficacy of an siRNA therapeutic agent against vascular endothelial growth factor in a validated primate model of age-related macular degeneration.[21] The anti-CD40 siRNA is expected to have significant advantages over alternative approaches for CD40-CD154 costimulatory pathway blockade based on ligand/receptor binding, such as anti-CD40 or anti-CD154 antibodies, or the soluble CD40 form CD40Ig.[22] By activating the enzymatic RNAi mechanism, one anti-CD40

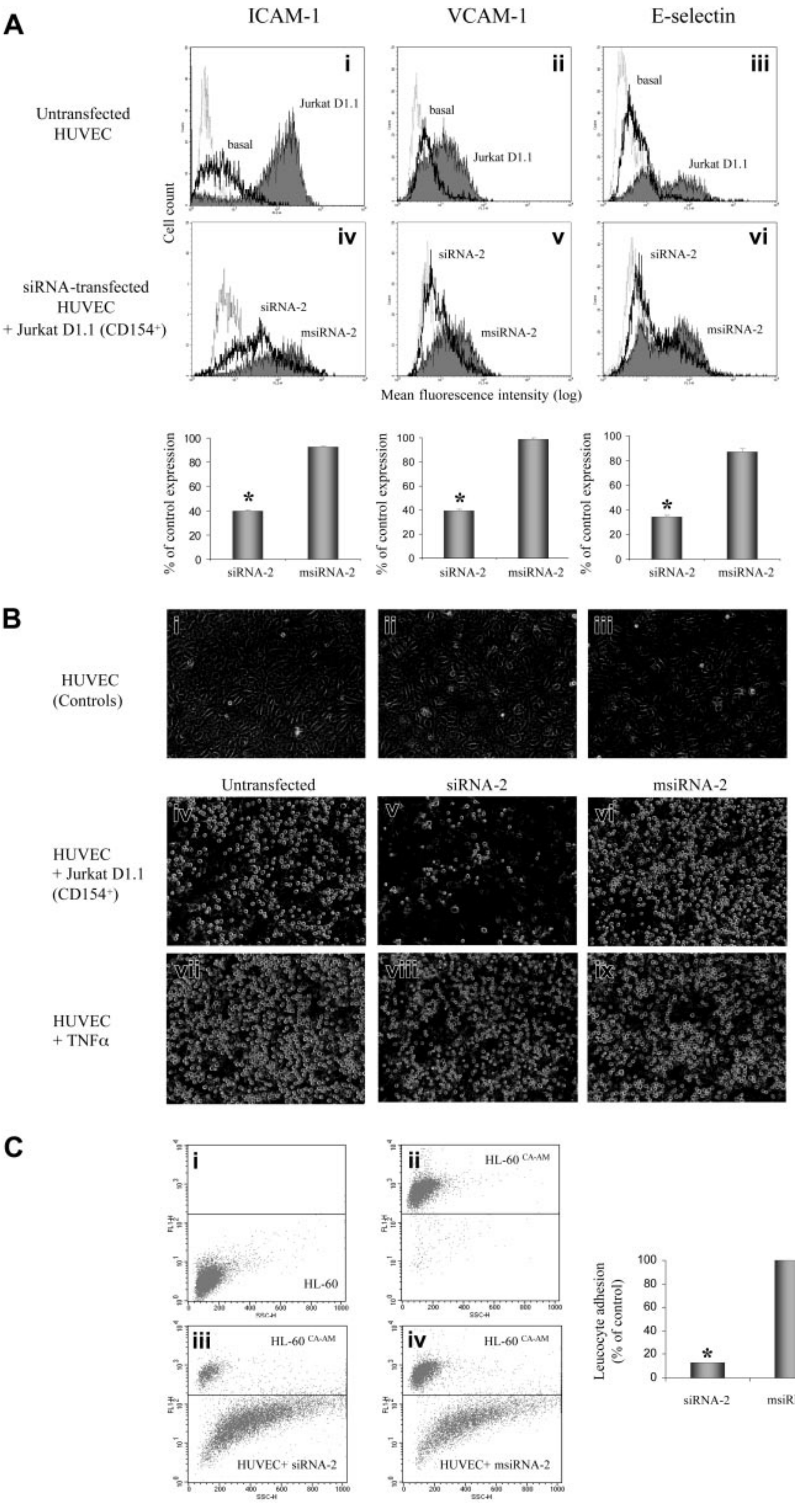

Figure 2. Effect of CD40 gene silencing by siRNA-2 on HUVEC leukocyte adhesion. CD40 gene silencing by siRNA-2 prevents CD154-mediated induction of leukocyte adhesion in human endothelial cells. (A) RNAi-mediated inhibition of CAM expression on CD154-activated endothelial cells. HUVECs, either untransfected or transfected for 2 hours with 100 nM siRNA-2 or msiRNA-2 as indicated in "Study Design," were activated by coincubation with Jurkat D1.1 (CD154$^+$) cells (ATCC CRL 1095; a Jurkat T cell subclone that constitutively expresses CD154) at a T/EC ratio of 5:1 at 6 hours (E-selectin) or 16 hours (ICAM-1 and VCAM-1) prior to analysis. At 48 hours after transfection, the cocultures were washed extensively with warm phosphate-buffered saline (PBS) to release the attached Jurkat D1.1 cells from the HUVEC monolayer. The endothelial cells were analyzed for CAM expression in the MoFlo flow cytometer (DakoCytomation, Fort Collins, CO) and were readily distinguished from residual T cells by light scatter. In i-iii, solid-line histograms represent basal CAM expression from untreated HUVECs, and filled histograms represent CAM expression from D1.1 (CD154$^+$)–stimulated, untreated HUVECs. In iv-vi, solid-line histograms represent CAM expression from D1.1 (CD154$^+$)–stimulated, siRNA-2–transfected HUVECs, and filled histograms represent CAM expression from D1.1 (CD154$^+$)–stimulated, msiRNA-2–transfected HUVECs. Dotted-line histograms display the corresponding immunoglobulin G (IgG) isotype-matching controls in each panel. Bar diagrams quantify the percentage of CAM expression after siRNA treatment, calculated as follows: ((CAM expression for siRNA–treated, D1.1 (CD154$^+$)–induced cells) − (basal CAM expression)) / ((D1.1 (CD154$^+$)–induced CAM expression) − (basal CAM expression)) × 100. CAM expression data are the mean fluorescence intensity (MFI) values of the corresponding histograms from 3 independent experiments (*$P < .05$, versus msiRNA-2). (B) RNAi-mediated inhibition of leukocyte adhesion on CD154-activated, but not in TNF-α–activated, endothelial cells. HUVECs, either untransfected or transfected for 2 hours with 100 nM siRNA-2 or msiRNA-2 as indicated in "Study Design," were activated either by coculture with Jurkat D1.1 (CD154$^+$) cells at a T/EC ratio of 5:1 (iv-vi), or by incubation with TNF-α (300 U/mL) (vii-ix) at 16 hours prior to the assay. At 48 hours after transfection, the cocultures were washed extensively with warm PBS to release the attached Jurkat D1.1 cells from the HUVEC monolayer, which was further coincubated with HL-60 cells for 30 minutes (2×10^6 cells per well from 6-well plate, in 2 mL endothelial cell culture medium). Supernatant aspiration plus 2 rounds of brief washing with PBS removed nonadherent cells. Shown are phase-contrast microscopic images of PBS-washed, adherent cells taken at × 40 magnification. The images were acquired as monochromatic JPEG files using a SPOT camera and SPOT 3.2.4 software (Diagnostic Instruments, Sterling Heights, MI) mounted on an Olympus IX-70 inverted microscope (Olympus America, Melville, NY) and linked to an iMac G4 Apple computer (Apple Computers, Cupertino, CA). Controls refer to untreated HUVEC monolayer (i); untreated HUVECs coincubated with HL-60 cells (ii); untreated Jurkat D1.1 (CD154$^+$)–activated HUVECs (iii). (C) To quantify the percentage of leukocyte adhesion to siRNA-2–transfected HUVECs, the same assay as in panel B was performed with the use of calcein AM–loaded HL-60 cells (5 μM calcein AM for 60 minutes at 37°C). Finally, attached cells were harvested by mild trypsinization and the ratio of adherent, fluorescence-labeled HL-60 cells to unlabeled endothelial cells was determined by flow cytometry after counting 10 000 events per sample. Shown are density plots corresponding to the following: unlabeled HL-60 cells (i); calcein AM–loaded HL-60 cells (ii); calcein AM–loaded HL-60 cells plus siRNA-2–transfected HUVEC mix (iii); calcein AM–loaded HL-60 cells plus msiRNA-2–transfected HUVEC mix (iv), all from one representative assay. The mean ratio obtained from msiRNA-2–treated HUVECs was assigned a 100% adhesion. Data are from 5 independent experiments (*$P < .05$, versus msiRNA-2).

siRNA can destroy hundreds of targeted CD40 mRNAs, which will result in the silencing of potentially thousands of CD40 protein receptors. Conversely, systemic administration of therapeutic antibodies or recombinant protein fusions may induce undesired immune responses against the foreign protein by the host or result in serious side effects such as thromboembolism.[10,23] The precise mechanism leading to the prothrombotic effects of anti-CD154 antibodies is not known, although it has been related either to inhibition of CD154-β_3 platelet integrin interaction[24] or to their direct interaction with platelet Fc receptors. The anti-CD40 siRNA may become instrumental for discarding the involvement of CD40 signaling in anti-CD154 antibody-mediated thromboembolism. In all, targeted delivery of anti-CD40 siRNA to specific CD40-expressing cells should avert these unwanted effects while exerting a powerful upstream down-regulation of the CD40 pathway.

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