

Supplemental data

Mechanisms of biased beta-arrestin mediated signaling  
downstream from the cannabinoid 1 receptor (CB1R)

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Molecular Pharmacology

**Supplementary material****Figure 1. Receptor expression levels**

(A) HEK293 cells expressing either SEP-CB1R or SEP-CB1R S426/430A were imaged live-cell confocal microscopy in the presence of 0.01% triton X-100 (S4A). Fluorescence from SEP molecules is restricted to neutral compartment. Triton X-100 was added to the imaging media before confocal imaging to neutralize any intracellular compartments (acidic) and reveal all intracellular receptor pools. (B) live HEK293 cells expressing either SEP-CB1R or SEP-CB1R S426/430A were harvested in PBS and surface fluorescence was analyzed using an imaged based cytometer. Cell count versus fluorescence was plotted and analyzed. No significant difference was observed between groups (insert) (n=2057 cells were analyzed expressing wild-type receptors and n=3547 were analyzed expressing the mutant receptor). (C) HEK cells transfected with either SEP-CB1R or SEP-CB1R S426A/S430A in the same conditions as those utilized in the manuscript, were lysed in RIPA buffer and total receptor expression levels was analyzed by western blots utilizing antibodies against GFP/SEP.

**Figure 2. beta-arrestin 1 and 2 expression knock-out by siRNAs.**

Representative western blot depicts isoform-specific knockdown of endogenous beta-arrestin 1 and 2 expression by siRNAs from HEK293 cells. Immunodetectable levels of GAPDH are shown as loading controls.

**Figure 3. Kinome antibody array analysis of CB1R activation.**

Dot blots evaluated by profiling phosphorylation of 43 human kinases. Lysates from untreated and agonist-treated (1  $\mu$ M WIN or 10  $\mu$ M 2-AG for 5 and 15 min) cells expressing the wild-type or S426A/S430A receptor were applied to a nitrocellulose membrane spotted with antibodies for 43 kinases along with control antibodies. Data are expressed as the fold change over basal level for each compound. The effect of beta-arrestin 1 knockdown (red) and PTX treatments are included.

**Figure 4. Receptor internalization kinetics and beta-arrestin recruitment**

(A) Receptor endocytosis was analyzed in HEK293 cells expressing either SEP-CB1R or SEP-CB1R S426/430A three days after transfection by TIRFM. 1 $\mu$ M WIN 55,212-2 was added and remained in the incubation media as indicated by the bar. Total surface fluorescence was analyzed in stable areas of the plasma membrane (n=7 and 10 for CB1R and CB1RS426/430A respectively, error bars represent SEM). (B) Beta-arrestin 1 recruitment was analyzed in HEK293 cells expressing beta-arrestin1-RFP with either SEP-CB1R or SEP-CB1R S426/430A. The addition of 1 $\mu$ M WIN 55,212-2 to the imaging media induced an increase in total average fluorescence proportional to the recruitment of beta-arrestin 1 (n=12 cells, 4 different experiments, errors represent SEM). (C) Beta-arrestin 2 recruitment was analyzed in HEK293 cells expressing beta-arrestin2-RFP with either SEP-CB1R or SEP-CB1R S426/430A. The addition of 1 $\mu$ M WIN 55,212-2 to the imaging media induced an increase in total average fluorescence proportional to the recruitment of beta-arrestin 2 (n=17 cells, 5 different experiments, errors represent SEM).

**Figure 5. mRNA transcripts controlled by WIN in the mutant receptor versus wild type receptor**

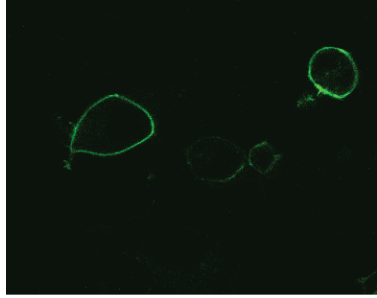
HEK293 cells expressing the HA-tagged rat wild-type or S426/430A mutant receptors were treated with 1  $\mu$ M WIN for 2 hrs. Differential expression was examined using DESeq2 (Bioconductor) at a 5% false discovery rate.

**Figure 6. mRNA transcripts exclusively controlled by WIN in the mutant versus untreated mutant receptor**

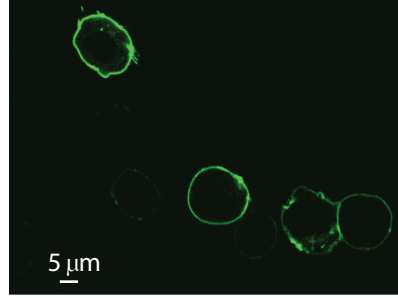
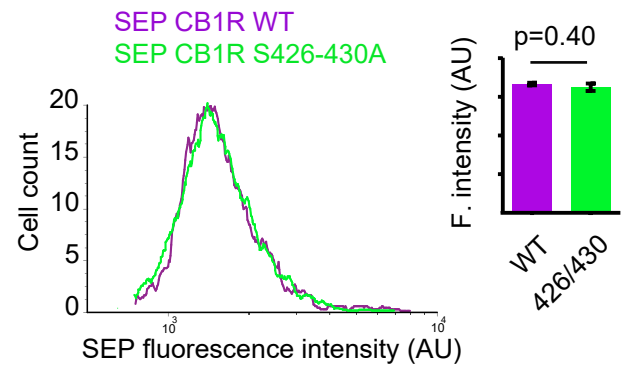
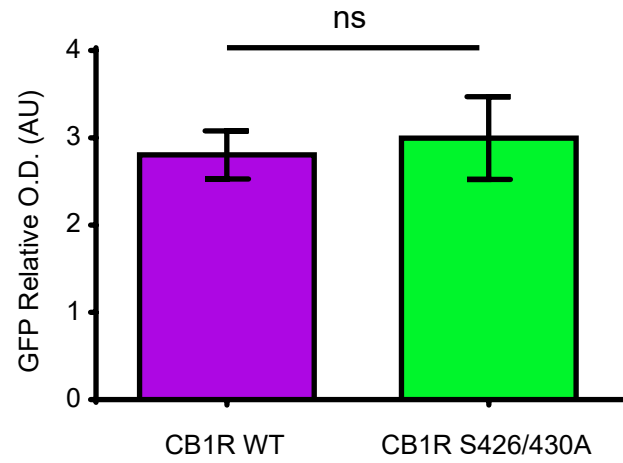
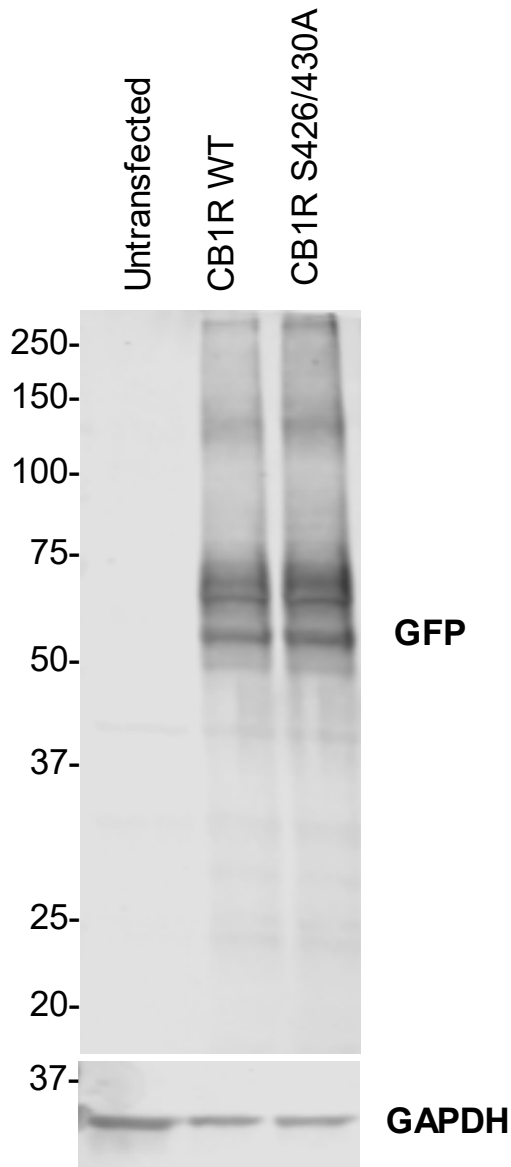
HEK293 cells expressing the HA-tagged rat wild-type or S426/430A mutant receptors were treated with 1  $\mu$ M WIN for 2 hrs. Transcripts specifically regulated by WIN in the mutant receptor versus the wild-type receptor are depicted.

**A**

CB1R WT

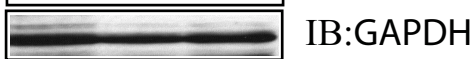
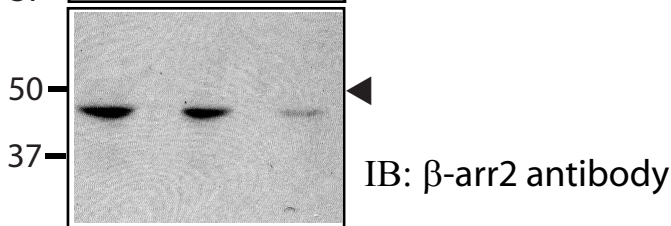
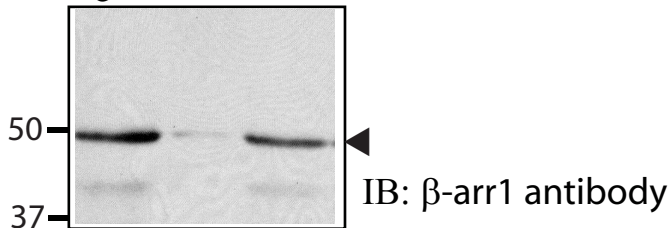


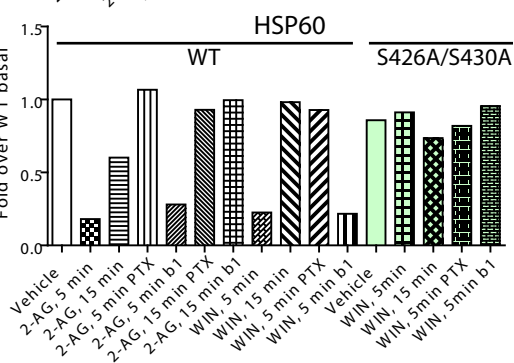
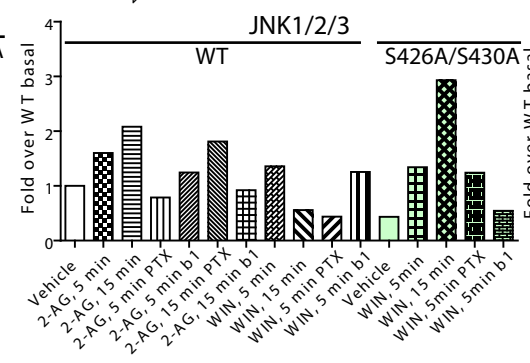
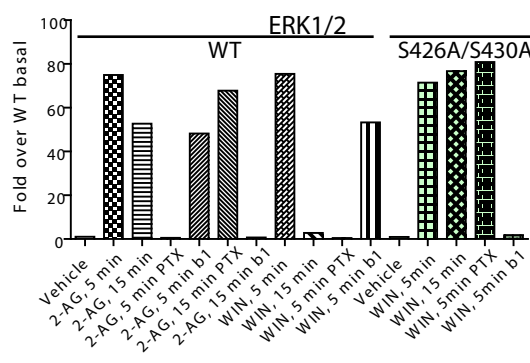
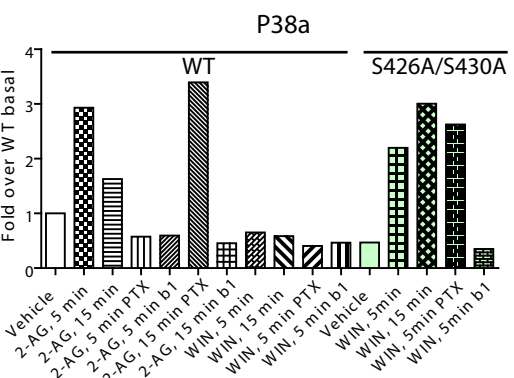
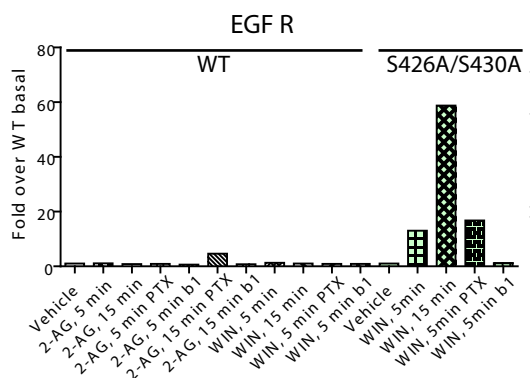
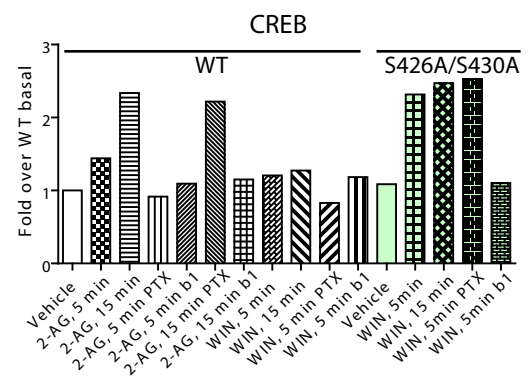
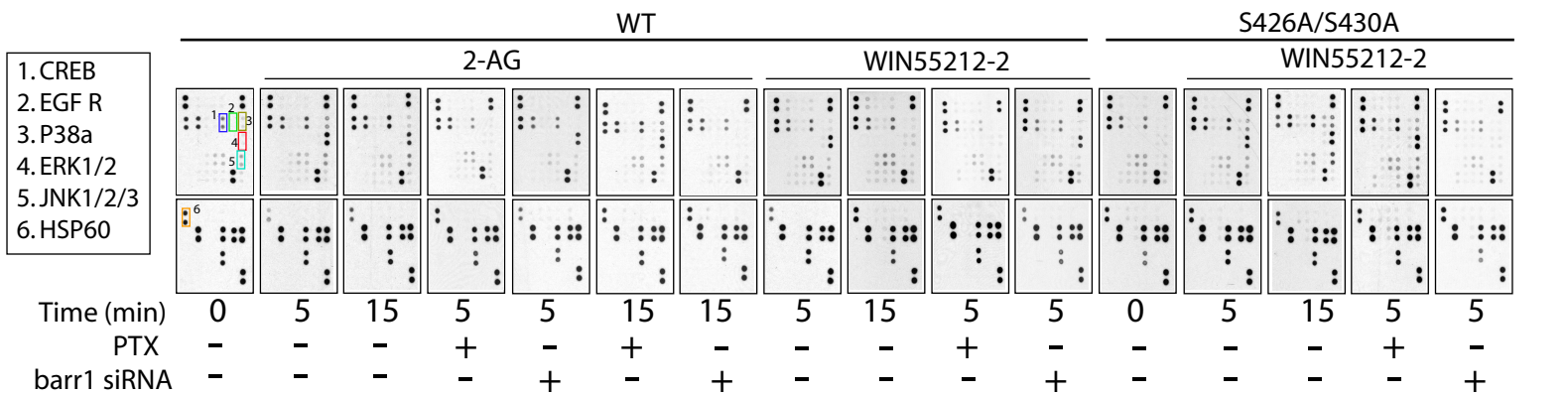
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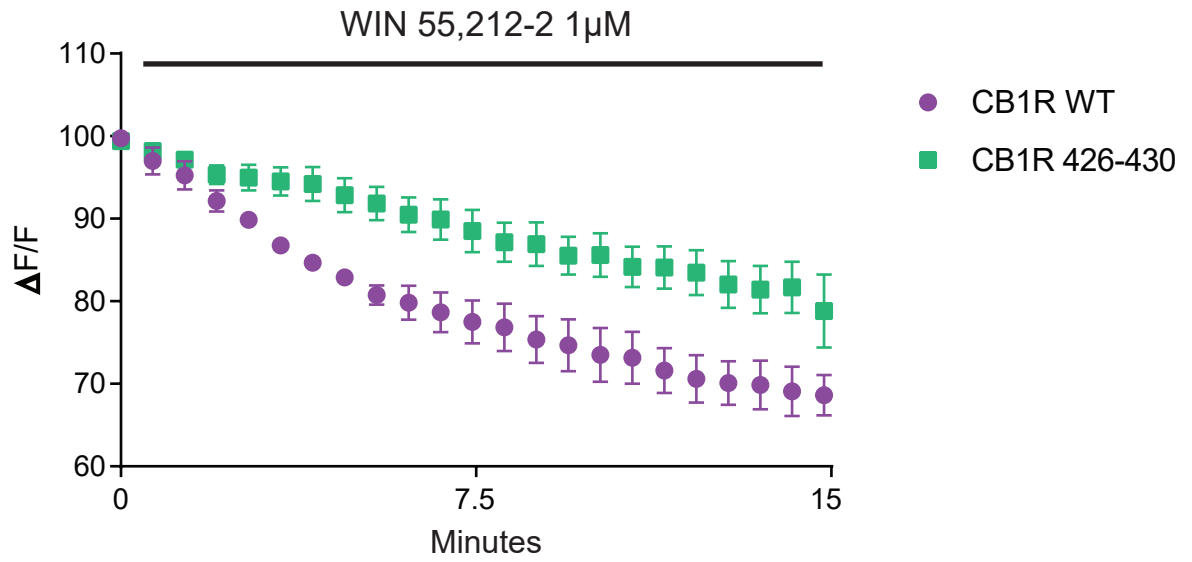
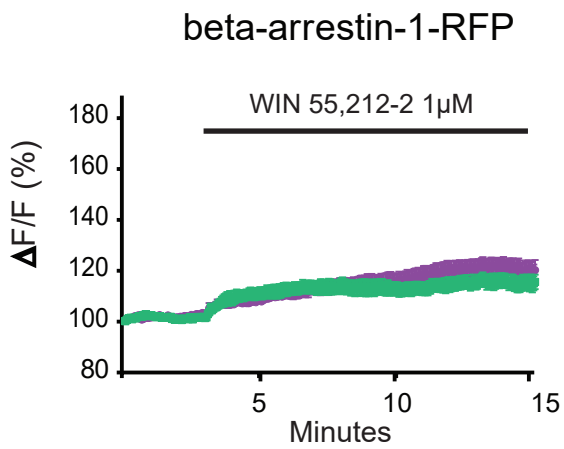
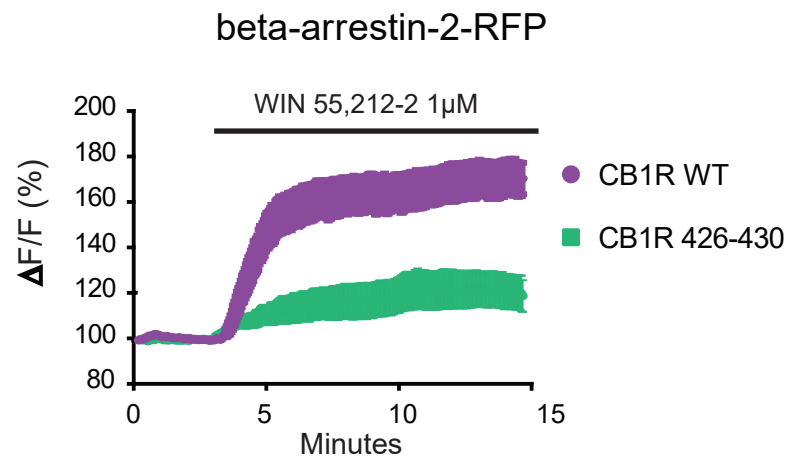
**B****C**

siRNA knock down

Control  $\beta$ -arr1  $\beta$ -arr2





**A****B****C**

# Supplemental Figure 5

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-0.348570161	PTP4A1	ENSG00000112245.7
-0.34902443	GMPPB	ENSG00000173540.10
-0.350797342	SLC1A4	ENSG00000115902.8
-0.356424127	TMEM39A	ENSG00000176142.10
-0.359046881	HSPB8	ENSG00000152137.4
-0.360359278	SEL1L	ENSG00000071537.11
-0.361714337	ITPRIP	ENSG00000148841.13
-0.361974844	OSTC	ENSG00000198856.10
-0.362706649	HSPA8	ENSG00000109971.11
-0.365919808	NUCB2	ENSG00000070081.13
-0.36595	DNAJC3	ENSG00000102580.12
-0.371779481	ERO1LB	ENSG00000086619.11
-0.384984283	PTGS2	ENSG00000073756.9
-0.391000798	DNAJB1	ENSG00000132002.5
-0.391330944	SSR4	ENSG00000180879.11
-0.395350403	VIMP	ENSG00000131871.12
-0.39656917	ANKRD1	ENSG00000148677.6
-0.39735974	GMPPA	ENSG00000144591.15
-0.400791201	PMEPA1	ENSG00000124225.13
-0.406232375	MAFK	ENSG00000198517.7
-0.435433076	NEDD9	ENSG00000111859.14
-0.440001553	PPIB	ENSG00000166794.4
-0.448176554	SERP1	ENSG00000120742.8
-0.450211621	SSR3	ENSG00000114850.4
-0.452550826	MBNL2	ENSG00000139793.16
-0.455320795	NANS	ENSG00000095380.10
-0.457716612	TRIM5	ENSG00000132256.16
-0.478469369	FOSB	ENSG00000125740.11
-0.479545955	EIF4A1	ENSG00000161960.12
-0.482983957	HSP90B1	ENSG00000166598.10
-0.48576515	PDIA5	ENSG00000065485.15
-0.489120583	ELL2	ENSG00000118985.12
-0.517195973	MANF	ENSG00000145050.13
-0.518875854	HSPA1B	ENSG00000204388.6
-0.522001206	FKBP2	ENSG00000173486.10
-0.528596848	DNAJB11	ENSG00000090520.8
-0.539390751	SLC2A3	ENSG00000059804.13
-0.540893845	FICD	ENSG00000198855.4
-0.568562201	CHAC1	ENSG00000128965.9
-0.581409315	SELK	ENSG00000113811.8
-0.582739686	TRIB3	ENSG00000101255.8
-0.588586026	CDK2AP2	ENSG00000167797.5
-0.6028449	HYOU1	ENSG00000149428.16
-0.602964399	PDIA4	ENSG00000155660.8
-0.606225909	HSPA1A	ENSG00000204389.9
-0.62371381	PPAPDC1B	ENSG00000147535.14
-0.62853397	WIPI1	ENSG00000070540.10
-0.64184692	GLIPR1	ENSG00000139278.7
-0.649215685	DERL3	ENSG00000099958.12
-0.651474292	HERPUD1	ENSG00000051108.12
-0.651964524	HSPA5	ENSG00000044574.7
-0.679393234	HID1	ENSG00000167861.13
-0.690259591	DNAJB9	ENSG00000128590.4

-0.70882547 CRELD2	ENSG00000184164.12
-0.733025061 SDF2L1	ENSG00000128228.4
-0.784240922 SEC24D	ENSG00000150961.12
-0.845014629 ACTBL2	ENSG00000169067.3
-0.889839799 CYR61	ENSG00000142871.13
-0.983024239 KRT17	ENSG00000128422.13
-1.156678504 TAC1	ENSG00000006128.9
-1.212235778 NR4A3	ENSG00000119508.15
-1.244382511 NR4A2	ENSG00000153234.11
-1.2919287 CTGF	ENSG00000118523.5
-1.71379434 NR4A1	ENSG00000123358.17
-3.30547802 GH1	ENSG00000259384.4

## Supplemental figure 6

Exclusive transcripts controlled by beta-arrestins

ENSEMBL Gene	Abbr name	log2fold change	Fold change
ENSG00000128965.9	CHAC1	-0.57	0.67
ENSG00000173486.10	FKBP2	-0.52	0.70
ENSG00000161960.12	EIF4A1	-0.48	0.72
ENSG00000149257.11	SERPINH1	-0.45	0.73
ENSG00000124225.13	PMEPA1	-0.4	0.76
ENSG00000180879.11	SSR4	-0.39	0.76
ENSG00000276023.2	DUSP14	-0.29	0.82
ENSG00000168280.14	KIF5C	-0.28	0.82
ENSG00000118363.9	SPCS2	-0.28	0.82
ENSG00000068912.11	ERLEC1	-0.26	0.84
ENSG00000070495.12	JMJD6	-0.25	0.84
ENSG00000117500.10	TMED5	-0.24	0.85
ENSG00000169976.6	SF3B5	-0.23	0.85
ENSG00000112715.18	VEGFA	-0.2	0.87
ENSG00000167996.13	FTH1	-0.18	0.88
ENSG00000140988.13	RPS2	-0.18	0.88
ENSG00000204387.10	C6orf48	-0.176	0.89
ENSG00000180398.9	MCFD2	-0.17	0.89
ENSG00000134294.11	SLC38A2	-0.17	0.89
ENSG00000167881.12	SRP68	-0.16	0.90
ENSG00000138326.16	RPS24	-0.16	0.90
ENSG00000164111.12	ANXA5	-0.15	0.90
ENSG00000182199.8	SHMT2	-0.145	0.90
ENSG00000108298.7	RPL19	-0.13	0.91
ENSG00000124422.9	USP22	0.14	1.10
ENSG00000116984.10	MTR	0.17	1.13
ENSG00000148730.6	EIF4EBP2	0.19	1.14
ENSG00000242498.5	ARPIN	0.235	1.18
ENSG00000153048.8	CARHSP1	0.24	1.18
ENSG00000100350.12	FOXRED2	0.28	1.21
ENSG00000135547.6	HEY2	0.3	1.23
ENSG00000092931.9	MFSD11	0.33	1.26
ENSG00000081189.11	MEF2C	0.33	1.26
ENSG00000167740.7	CYB5D2	0.38	1.30
ENSG00000119669.4	IRF2BPL	0.5	1.41