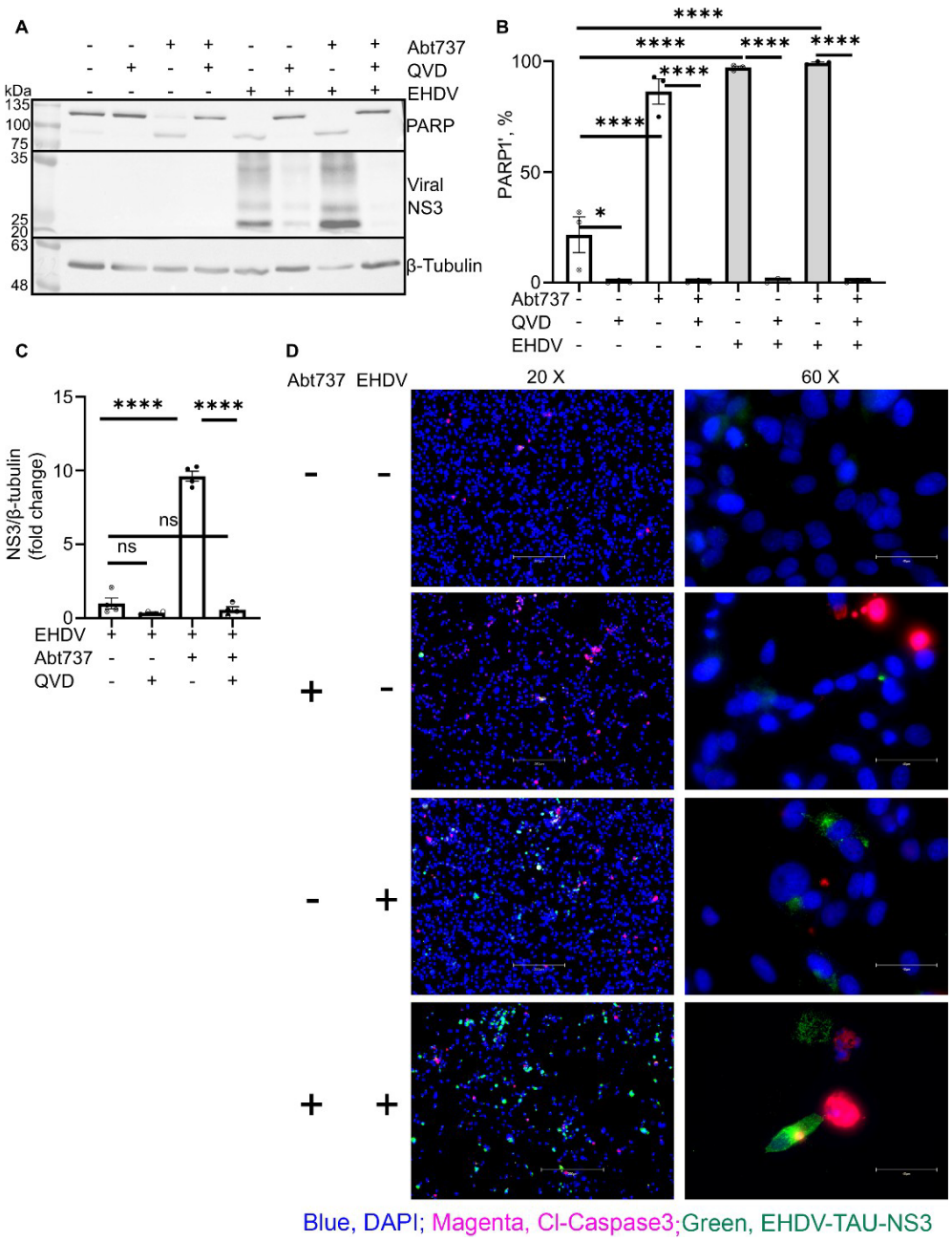
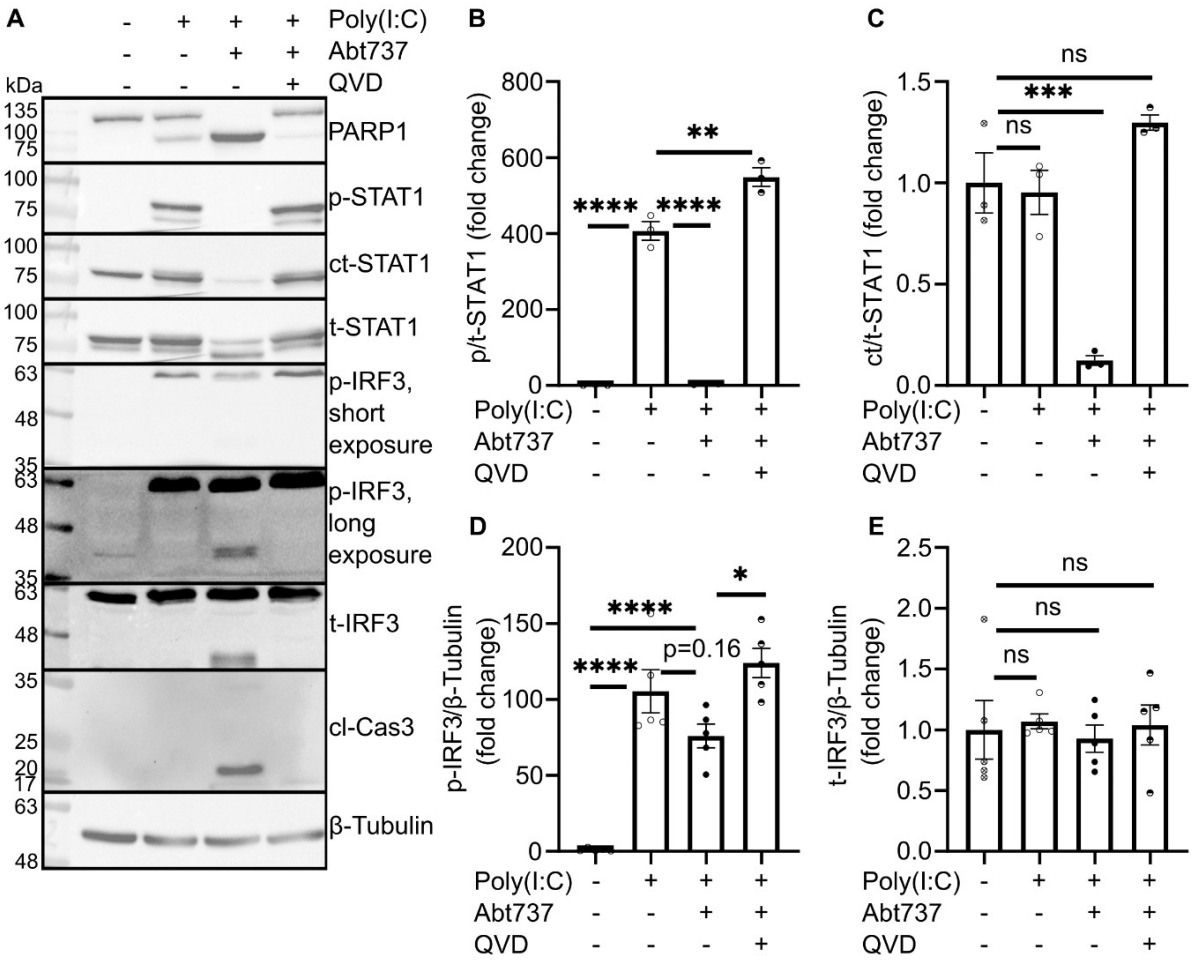
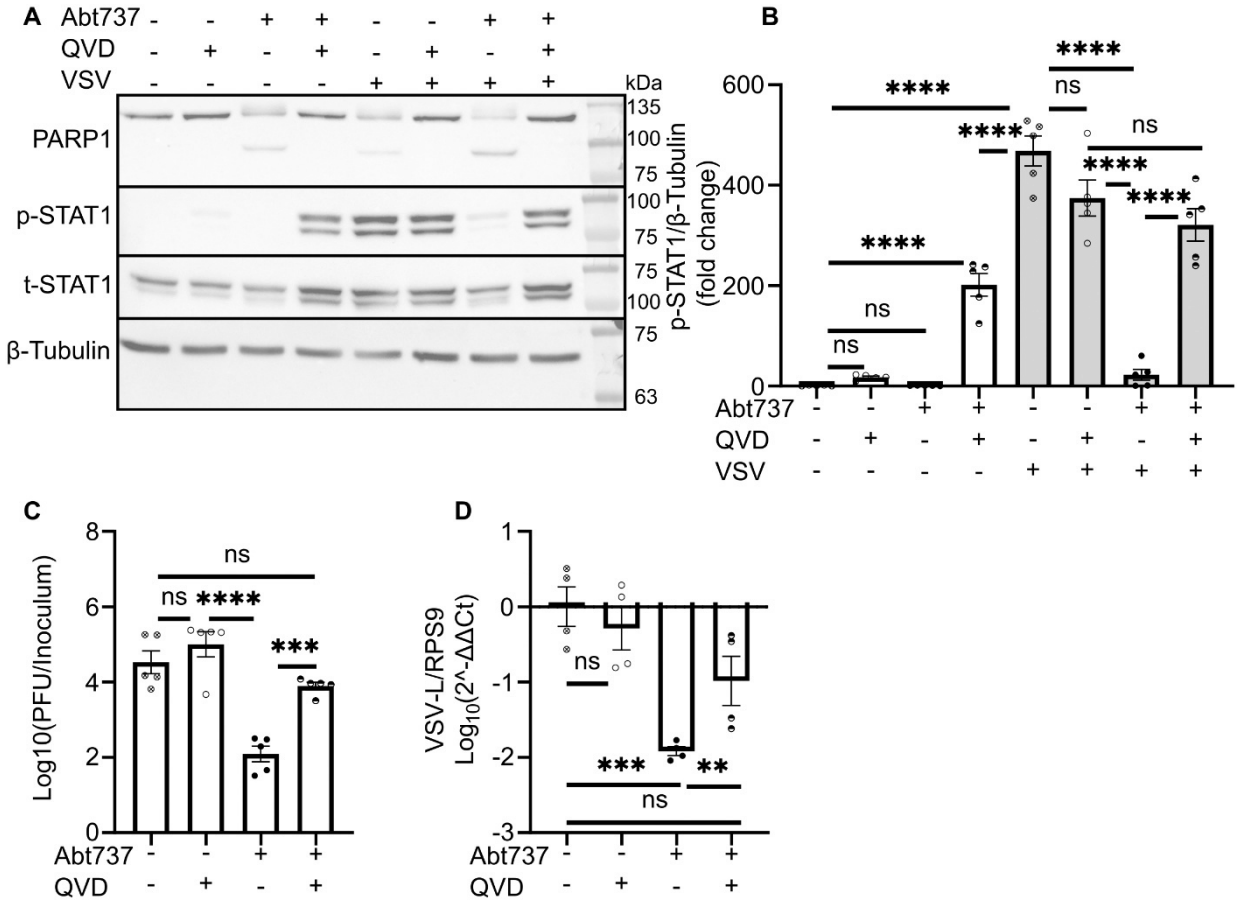


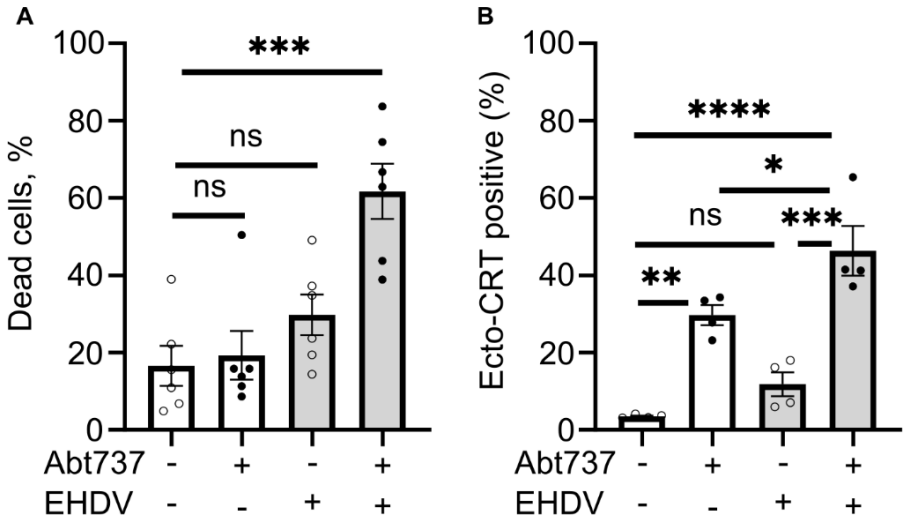
Supplementary Fig. 1. Abt737 activates caspases and increases expression of EHDV-TAU NS3 non-structural protein in UMUC3 cells, with dependence on caspase activity. UMUC3 cells were simultaneously treated, or not, with Abt737 (5 μM) and/or QVD-OPH (20 μM) and infected, or not, with EHDV-TAU (MOI=1.0), for 48h. (**A**) A representative immunoblot probed for the caspase substrate PARP1, the viral NS3 protein, and β-Tubulin (loading control). (**B**) The graphs show the mean ± SEM of the percentage of cleaved PARP1 relative to total PARP1. (**C**) The graph shows the mean ± SEM of the ratio of NS3/β-tubulin in the EHDV-TAU-infected conditions. N = 3 (**B**) or 4 (**C**), ****, p <0.0001, *, p <0.05. (**D**) UMUC3 cells cultured on glass coverslips were treated, or not, with Abt737 (5 μM), and infected (or not) with EHDV-TAU (MOI=0.2) for 72 h. Following fixation and permeabilization, cells were stained with mouse anti-EHDV-TAU-NS3 (green), rabbit anti-cleaved caspase-3 (Cl-Caspase3, magenta) and DAPI (Blue). Micrographs depict typical fields at 20x magnification (left, Bar, 150 μm) or 60x magnification (right, Bar, 40 μm).



Supplementary Fig. 2 Abt737 induces caspase-mediated inhibition of STAT1 and IRF3 in poly(I:C)-stimulated T24 cells. T24 cells were pre-treated, or not, with Abt737 (5 μM) or Abt-737 + QVD-OPH (20μM) for 24 hours. After pretreatment, the cells were transfected with 4 μg of Poly(I:C) for 2.5 hours. (**A**) Representative immunoblots (n=5). Note two exposures (short and long) of the same p-IRF3 gel. (**B-E**) The graphs show the average ± SEM of the indicated ratios of densitometry signals. ****,p<0.0001,***,p<0.001,**,p<0.01,*,p<0.05.



Supplementary Fig. 3 Abt737 inhibits VSVΔ51M infection. T24 cells were treated, or not, with Abt737 (5 μM), and/or QVD-OPH (20 μM) and infected, or not, with oncolytic VSVΔ51M virus (VSV, MOI=1.0, 24 h). **(A)** Representative immunoblots. **(B)** The graph shows the average ± SEM of the p-STAT1-to-β-Tubulin densitometry ratio (n=5). **(C)** The graph shows the mean ± SEM of the Log10 transformation of the ratio of PFU/inoculum. **(D)** The graph shows the mean ± SEM of the Log10 transformation of fold-change in the viral VSV-L mRNA normalized to RPS9 relative to naïve cells. ****, p <0.0001, ***, p <0.001, **, p <0.01.



Supplementary Fig. 4 Abt737 + EHDV-TAU combination enhances cell death and ecto-CRT exposure in UMUC3 cells. UMUC3 cells were treated, or not, with Abt737 (5 μM) and infected, or not, with EHDV-TAU (MOI=0.2). After 72h, cells were collected and either stained with an amine-reactive viability dye (**A**) or surface-stained with an anti-CRT antibody (**B**). The graphs show the mean ± SEM percentage of dead cells (**A**) or the percentage of cells positive for ecto-CRT (**B**). ****, p <0.0001, ***, p <0.001, **, p <0.01, *, p <0.05.

RandomlySelectedGenes	RandomlySelectedGenes	RandomlySelectedGenes	RandomlySelectedGenes	Response tovirus (GO0009615)	Response tovirus (GO0009615)	Response tovirus (GO0009615)	Response tovirus (GO0009615)
AARSD1	EXOC6	NFIL3	SPATA4	ABCC9	GATA3	MOV10	TBK1
ABCB9	FAM217B	NFKBIA	SRPRA	ABCF3	GBF1	MST1R	TBX21
ABHD1	FAM237A	NLGN1	SRRM5	ACTA2	GBP2	MTOR	TGFB1
ABHD17C	FAM89A	NMUR1	SSPN	ADAR	GBP4	MUL1	TICAM1
ACBD6	FBN3	NOP2	SSR4P1	AGBL4	GBP5	MX1	TICAM2
ACE2	FBXO31	NOXRED1	ST8SIA5	AGBL5	GBP7	MX2	TLR3
ACP4	FBXO6	NPAS4	STARD7-AS1	AICDA	GLI2	MYD88	TLR7
ACSL6	FBXO8	NRP2	STOX1	AIM2	GPAM	NCBP1	TLR8
ADAM3A	FEZF1	NUBP1	SUN1	AKAP1	GPR108	NCBP3	TLR9
ADRA1D	FGD3	NUMA1	SWI5	AP1S1	GPR146	NCK1	TMEM120A
AIFM1	FHDC1	OR10Q1	SYT2	APOB	GSDME	NCR1	TNF
AKR1B10	FKBP3	OR1A2	TBC1D3C	APOBEC1	GTF2F1	NDUFAF4	TNFSF4
AKR1C8	FKBP9P1	OR2T8	TCTA	ARF1	HCFC2	NFKB1	TOMM70
ANAPC15	FOXN4	OR4F5	TCTN1	ARIH2	HEATR9	NLRC5	TPT1
ANXA10	FUCA1	OR56B4	TENT5C	ARMC5	HES1	NLRP3	TRAF3
ARFGEF3	GABARAPL2	OR5AN1	TERF1	ATAD3A	HIF1A	NLRP6	TRAF3IP1
ARHGAP30	GAGE1	OR5B3	TET1	ATF2	HMGA2	NMB	TRAF3IP2
ARID1B	GAS2	OR6C3	TIMM17B	ATG12	HSP90AA1	NMBR	TRAF3IP3
ARMC10	GCK	OSBPL5	TINCR	ATG14	HSPB1	NMI	TRAF6
ASAH1	GDAP1	OTUD1	TJP3	ATG16L1	HTRA1	NPC2	TREML4
ASPH	GDF2	OVCH2	TMEM165	ATG5	HYAL1	NTSC2	TREX1
ATG4C	GGTLC1	P4HA3	TMPRSS15	ATG7	HYAL2	NTSC3A	TRIM11
AZIN2	GGTLC2	PA2G4P4	TPS3BP2	AUP1	HYAL3	OAS2	TRIM13
BDKRB1	GLYCTK	PABIR2	TPH2	BATF3	IFI44	OAS3	TRIM15
BEX1	GPR156	PASD1	TRA2A	BAX	IFI44L	OASL	TRIM21
BFAR	GPR88	PDE11A	TRIM16	BCL2	IFIH1	ODC1	TRIM25
BFSP1	GPT2	PDE4A	TRIM64	BCL2L1	IFIT1	OPRK1	TRIM26
C11ORF96	GTF2H1	PDGFRL	TRIP10	BCL3	IFIT2	OTUD4	TRIM27
C12ORF50	H2AC12	PFDN1	TRPC4	BECN1	IFIT3	PARP9	TRIM28
C18ORF21	H3C7	PGLYRP2	TSHZ1	BNIP3	IFITM1	PCBP2	TRIM31
C19ORF48P	HAP1	PGP	TSPAN7	BNIP3L	IFITM2	PDE12	TRIM32
C19ORF53	HBBP1	PHF5A	TSPYL5	BST2	IFITM3	PENK	TRIM35
C1ORF122	HCFC1	PHLDA1	TSR1	C1QBP	IFNA1	PHB1	TRIM38
C1ORF94	HDAC8	PI4KB	TSSK3	CALR	IFNA13	PHB2	TRIM41
CAMK2A	HDGFL1	PIH1D2	TTC9B	CARD9	IFNA2	PIM2	TRIM44
CAMSAP3	HDGFL2	PLCD3	UGT3A1	CASP1	IFNA4	PLA2G10	TRIM5
CAPN1	HEATR5B	PLCG2	UMODL1	CCL19	IFNA5	PLSCR1	TRIM52
CARD10	HECW1	POLD3	UQCRFS1	CCL5	IFNA6	PMAIP1	TRIM55
CARD8	HIPK2	POM121L12	USP33	CCT5	IFNA7	PML	TRIM56
CASKIN2	HOXC9	PPP1R1B	VPS33A	CD207	IFNAR1	POLR3B	TRIM6
CASTOR1	HSD17B2	PRAC1	VPS9D1	CD2AP	IFNAR2	POLR3C	TRIM65
CCDC102B	IGF1	PRAMEF6	WASHC3	CD37	IFNB1	POLR3D	TRIM7
CCDC140	IL2ORA	PRDM16-DT	WDR74	CD40	IFNE	POLR3E	TRIM8
CCDC168	IMPDH2	PTCRA	ZBTB20	CD86	IFNG	POLR3F	TSPAN32
CCDC82	INSR	PWAR5	ZBTB9	CD8A	IFNGR1	POLR3G	TTC4
CCNP	ITGA10	PWWP2B	ZFYVE28	CDK6	IFNGR2	POLR3H	UAP1
CCR9	ITPR2	QRICH1	ZNF275	CFL1	IFNK	POLR3K	UBE2F
CDA	IYD	RAPGEF3	ZNF471	CGAS	IFNL2	POU2AF1	UBE2N
CDC14B	KCNE4	RBM12	ZNF542P	CHMP3	IFNL3	POU2F2	UBE2W
CDCA7	KCTD1	RBP4	ZNF592	CHRM2	IFNLR1	PPM1B	UBL7
CDH10	KISS1R	RCOR2	ZNF605	CHUK	IKBKE	PQBP1	UFL1
CDH18	KLHDC9	REM2	ZNF702P	CLPB	IL10RB	PRF1	UNC13D
CEACAM8	KLHL12	REP15		CLU	IL12A	PRKRA	USP18
CEP131	KLRF1	RGS17		CNOT7	IL12B	PSMA2	USP20
CEP250	KPNA1	RHOG		CR2	IL12RB1	PTPN22	USP27X
CES5A	LILRA1	RIPPLY2		CRCP	IL15	PTPRC	USP29
CHAT	LILRA4	RNF168		CREBBP	IL17RA	PYCARD	USP38
CISH	LINC00235	RNGTT		CREBZF	IL1B	RAB2B	USP44
CLHC1	LINC00623	RNPEP		CUL1	IL21	RB1CC1	VAMP8
CLSTN1	LINC01106	RPE65		CUL5	IL23A	RELA	VAPB
CLYBL	LINC01226	RPL13AP6		CXADR	IL23R	RHEB	VWCE
CMKLR2	LINC01551	RPL15		CXCL10	IL27	RIGI	WDFY4
CNOT8	LOC728989	RPS19BP1		CXCL9	IL33	RIOK3	XPR1
COL8A1	LORICRIN	RPS26P11		DDIT4	IL4	RIPK3	YJU2B
COMTD1	LRATD2	RSPRY1		DDX1	IL6	RNASE6	ZBP1
CPM	LRRC1	RUSF1		DDX17	ILF3	RNASEL	ZC3H12A
CPN1	LRRN3	S100A16		DDX21	ILRUN	RNF135	ZC3HAV1
CRIP3	LTV1	S1PR1		DDX3X	IRAK3	RNF185	ZCCHC3
CSNK1E	LYZ	SACM1L		DDX41	IRF1	RNF216	ZDHHC1
CT45A2	LYZL6	SAXO1		DDX56	IRF2	RNF26	ZDHHC11
CTAGE11P	MACROD2	SCAND2P		DDX60	IRF3	RNF7	ZMPSTE24
CTH	MAGEB4	SCCPDH		DHX15	IRF5	RPS15A	ZMYND11
CYB561A3	MAML2	SCN1B		DHX16	IRF7	RRP1B	ZNFX1
CYP24A1	MANSC1	SCOC		DHX36	IRGM	RSAD2	
CYP2D7	MAP4K5	SCRN2		DHX58	ISG15	RTP4	
CYP4X1	MATK	SEC23A		DHX9	ISG20	SAMHD1	
CYP7A1	MDC1	SEMA4F		DICER1	ITCH	SAP30BP	
DAB2	MDH1	SEMA5B		DTX3L	ITGAX	SELENOK	
DAZAP1	MEN1	SERP1		DTX4	ITGB6	SENP7	
DCAF15	MERTK	SGCD		DUOX2	ITGB8	SERINC3	
DCAF7	METTL3	SGK3		DUS2	IVNS1ABP	SERINC5	
DCTN6	METTL4	SGPP1		EEF1G	KCNJ8	SERTAD3	
DENND2B	MIPOL1	SHROOM3		EIF2AK2	KCTD9	SETD2	
DIP2C-AS1	MIR443S-2HG	SLC13A1		EIF2AK4	LCN2	SHFL	
DNAJC18	MKX	SLC22A18AS		EIF5A	LGALS8	SIN3A	
DNAJC28	MOB3A	SLC26A2		ELMOD2	LGALS9	SKP2	
DOK5	MRGPRG-AS1	SLC31A1		EPG5	LSM14A	SLC38A8	
DTL	MRPL36	SLC35B1		ERCC6	LYSET	SMAD3	
DUX4L6	MRPL55	SLC49A4		EXOSC4	LYST	SMARCA5	
EAF1	MSN	SLC50A1		EXOSC5	MAP3K14	SMPD1	
ECT2	MTF1	SLITRK2		EXT1	MAPK11	SMURF1	
EDN2	MUCL3	SLN		F2RL1	MAPK14	SPN	
EEF1B2	MYCBPAP	SMAGP		FADD	MARCHF2	SPON2	
EIF1AD	MYO18A	SNORA59B		FGL2	MAVS	STAT1	
EIF3L	MYOM3	SNORD15B		FLT3	MBL2	STAT2	
EIF4G3	MYT1L	SNORD22		FMR1	MID2	STING1	
ENOPH1	NAA80	SNW1		FOXP3	MLKL	STMN1	
ENY2	NCS1	SOX11		G3BP1	MMP12	TAGAP	
EPHA8	NEU3	SP3		GARIN5A	MORC3	TARBP2	

Supplementary Table 1. List of genes involved in expression analyses in Figure1

List of primers		
Gene	**Forward Primer**	**Reverse Primer**
RPS9	5′CGGAGACCCTTCGAGAAATCT3'	5′GCCCATACTCGCCGATCA3'
IFN-β	5′CTTCTCCACTACAGCTCTTT3'	5′CTGTCCTTGAGGCAGTATTC3'
IRF1	5′CCTCCACCTCTGAAGCTACAAC3'	5′CCATCCACGTTTGTTGGCTG3'
Apo-L3	5′CTTTCTGCTGCACATATTGCTCC3'	5′CTTTCTGCTGCACATATTCGTCC3'
IFITM3	5′CGCCTACTCCGTGAAGTCTA3'	5′CCATAGGCCTGGAAGATCAGC3'
TRIM22	5′TGCCTTCACTCTTCTCCCCT3'	5′GCTCCCTTGGCTTCCTTCTG3'
NS3	5′ATAAGCCAGCGGATTGACCA3'	5′ACTCATCCTCACCGCCTCAT3'
VSV-L	5′TGATACAGTACAATTATTTTGGGAC3'	5′GAGACTTTCTGTTACGGGATCTGG3'
IL6	5′CATCCTCGACGGCATCTCAG3'	5′TCACCAGGCAAGTCTCCTCAT3'
CCL13	5′GGTTGCTGTCTCTAAGCCCC3'	5′ATGCTCTCAACCCCTGGGAA3'
CD163	5′GACAGCGGCTTGCAGTTTC3'	5′CTGAAATCAGCTGACTCATGGGA3'

Supplementary Table 2. List of Primers Employed in Study