YMTHE, Volume *29*

Supplemental Information

Plant-derived exosomal microRNAs

inhibit lung inflammation induced

by exosomes SARS-CoV-2 Nsp12

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Supplementary Data

Figure S1. Lung epithelial cells release exosomes containing the proteins of SARS-CoV-2.

(**A**) A549 cells transfected with pcDNA3-CoV-2-S-GFP. Visualization with confocal fluorescent microscopy; Scale bars, 20 μm. (**B**) Analysis of dot blot with anti-GFP antibody. (**C**) U937 cells treated with exosomes from A549 cells and cytokine analysis in the medium with ELISA. Data are representative of three independent experiments (error bars, SD).

Figure S2. Distribution of lung epithelial cell-released exosomes following intratracheal administration in mice.

(**A**) A representative fluorescent image of brain, lung, heart, liver, kidney, small intestine and large intestine from C57BL/6 mice receiving a single intratracheal administration of 10 mg DiR dye-labelled LLC1-derived exosome at 0 h, 1 h and 2 h (**left panel**); Image of serum after intratracheal administration (**right panel**). (**B, C**) Representative immunofluorescence in the lung from C57BL/6 mice receiving a single intratracheal administration of 10 mg PKH26-labelled LLC1-derived exosome at 24 h. Visualization of $F4/80^+$, $Gr\text{-}1^+$ (**B**) and $CD\text{-}11b^+$ (**C**) cells by confocal microscopy. Arrows in yellow indicated exosome/PKH26 taken up by $F4/80^+$ or $Gr\text{-}1^+$ cells; Scale bars, 20 μm. (**D**) ELISA analysis of TNFα, IL-1β and IL-6 in lung from C57BL/6 mice three days after inoculation of Vero E2 cells-derived exosomes containing Nsp12, Nsp13, or Nsp12/13 through intratracheal administration. (**E**) ELISA analysis of TNFα, IL-1β and IL-6 in serum from C57BL/6 mice three days after inoculation of LLC1-derived exosome containing Nsp12, Nsp13, or Nsp12/13 through intratracheal administration. (**F**) Exosomes from primary lung epithelial cells transfected with Nsp12 and Nsp13 plasmids and administrated to mice via intratracheal injection. ELISA analysis of TNFα, IL-1β and IL-6 in lung. Data are representative of three independent experiments (error bars, SD). *p <0.05 and **p < 0.01 (two-tailed t-test).

Figure S3. Nsp12/13 activate cytokines mediated by the NFκB pathway.

(**A**) Western blot analysis of the phosphorylation of MAPK (p38), ERK 1/2 (p44/42) and PI3K in lung macrophages of C57BL/6 mice (n=5) after intratracheal inoculation with exosomes from LLC1 cells transfected with Nsp12 and/or Nsp13 as well as aly-miR396a-5p. Data are representative of three independent experiments. (**B**) Pretreatment with p–IκBα inhibitor (Bay 11-7821, 10 mg/kg/d, body weight) (n=5) by intraperitoneal injection 3 days following intratracheal administration of exosomes. ELISA analysis of TNFα and IL-6 in lung macrophages. (**C**) Representative immunofluorescence in lung from C57BL/6 mice receiving Bay 11-7821 (10 mg/kg/d, body weight) (n=5) by intraperitoneal injection 3 days following a single intratracheal administration of 10 mg of exosomes with Nsp12/13 per day for three consecutive days. Visualization of TUNEL-GFP^{+} and EpCAM^{+} cells by confocal microscopy. Arrows in yellow indicated TUNEL^{+}EpCAM^{+} cells; Scale bars, 20 μm. (**D**) The exosome$^{Nsp12/13}$ and exosome$^{Nsp12/13+miR396a-5p}$ from LLC1 cells intratracheally injected into mice. The apoptotic bodies (ABs) were isolated from lung epithelial cells and quantified with FACS using forward scatter (FSC) and Annexin V-FITC staining. (**E**) ELISA analysis of cytokines in the lung of mice intratracheally injected with ABs at 1x10^{8}. Data are representative of three independent experiments (error bars, SD). *p < 0.05 and **p < 0.01 (two-tailed t-test).

Figure S4. Purification and characterization of ginger-derived nanovesicles (GNVs).

(**A**) Sucrose-banded particles GELNs from ginger juice. The GELNs were isolated from ginger juice using a sucrose gradient (8, 30, 45, and 60% sucrose in 20 mM Tri-Cl, pH 7.2). Particles from the band between 8% and 30% sucrose were used for preparation of nanoparticles. (**B**) GNVs generated with the lipids extracted from GELNs. Size distribution of GNVs using a NanoSight NS300 (Westborough, MA) with a flow speed at 0.03 mL per min. (**C**) Quantification of GNV yield (*n* = 3) by weight of lipid from the GELN. Data are representative of three independent experiments (error bars, SD). (**D**) A representative electron microscopy image of GNVs. Scale bars, 200 nm. (**E**) A representative fluorescence image of lung (left panel) and small intestine (right panel) from C57BL/6 mice receiving a single intratracheal administration of 10 mg DiR dye-labelled GNVs at 0 h, 1 h, 12 h, 24 h and 72 h; Image of serum after intratracheal administration (right panel). n = 5 per group. Data are representative of three independent experiments (error bars, SD).

Figure S5. GNVs reduce the induction of cytokines activated by LPS in lung.

(**A**) Representative immunofluorescence in lung from C57BL/6 mice receiving a single intratracheal administration of 10 mg PKH26- labelled GNVs at 24 h. Visualization of F4/80$^+$ and EpCAM$^+$ cells by confocal microscopy. Arrows in yellow indicated GNVs/PKH26 taken up by F4/80$^+$ or EpCAM cells; Scale bars, 20 μm. (**B**) ELISA analysis of cytokines in lung from C57BL/6 mice receiving a single intratracheal administration of 1x10^8 GNVs, grapefruit-derived nanovesicles (GFNVs), gold nanoparticles (NP) and 5 µg of LPS at 12 h. (**C**) GNVs generated with additional PA, PC and PE. FACS analysis of GNVs/PKH26 taken up by A549 cells (**Top panel**). Quantification of percentage of exosome/PKH26$^+$ in A549 cells (**bottom panel**). (**D**) ELISA analysis of cytokines in lung treated with LPS (1 mg/kg) via intra-venous and potential vesicles for therapeutic delivery by Gold nanoparticles (NP), GNVs and grapefruit nanovesicles

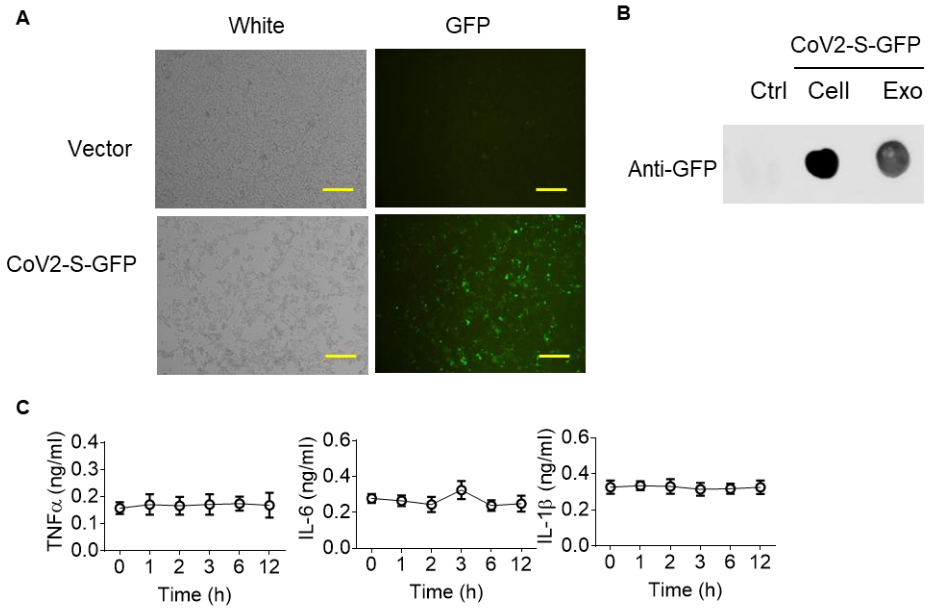
(GFNVs). (**E**) Serum aspartate transaminase (AST) and alanine transaminase (ALT) levels of C57BL/6 mice with various concentrations of GNVs by intratracheal administration. (**F**) Evaluation of A549 cell proliferation and cytotoxicity of GNVs with various concentrations indicated in the graph using a luminescence ATP monitoring system. n = 5 per group. *p<0.05 and **p<0.01 (two-tailed t-test). NS: not significant. Data are representative of three independent experiments (error bars, SD).

Figure S6. GNVs efficiently deliver miRNA to lung through intratracheal injection. (**A**) 10 µg of aly-miR396a-5p packed with 200 µmol GNVs using ultrasonication. The capacity of aly-miR396a-5p GELNs and GNVs using qPCR. (**B**) qPCR analysis of aly-miR396a-5p in A549 cells transfected with aly-miR396a-5p GNV compared to RNAiMAX and PEI. (**C**) 10 µg of aly-miR396a-5p packed into GNVs and gold NPs following intratracheal administration of C57BL/6 mice. After 48 h, qPCR analysis of aly-miR396a-5p distribution in various parts of the lung. (**D**) qPCR analysis expression of Nsp12 and spike (S) protein in lung after administration of viral plasmid CoV-2-Nsp12-2xStrep and pcDNA3-CoV-2-S, as well as GNVs packing aly-miR396a-5p and rlcv-miR-rL1-28 or appropriate mutant RNA, respectively by intratracheal injection. *p<0.05 and **p<0.01 (two-tailed t-test). Data are representative of three independent experiments (error bars, SD).

Figure S7. Nsp12/13 reduce growth factors and CXCL family assessed by protein array.

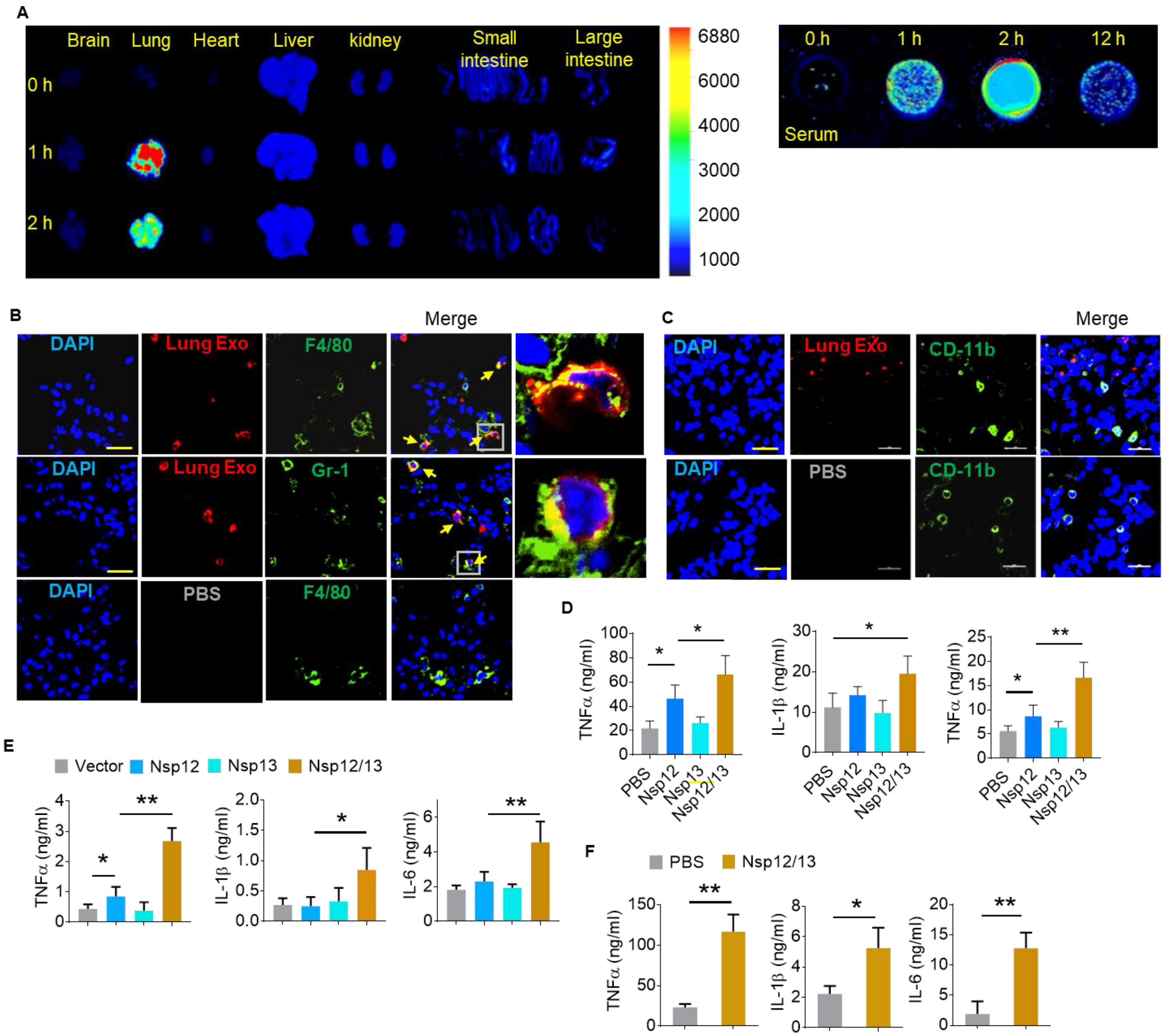
Quantification of relative intensity of the selected cytokines involving cell growth factor **(A)** and chemokine (C-X- C motif) ligand (CXCL) **(B)** shown in a cytokine array in **Fig. 3E.** *p<0.05 and **p<0.01 (two-tailed t-test).

Figure S1



97
98

Figure S2



A
Brain
Lung
Heart
Liver
kidney
Small intestine
Large intestine
0 h
1 h
2 h
6880
6000
4000
3000
2000
1000
0 h
1 h
2 h
12 h
Serum
B
DAPI
Lung Exo
F4/80
Merge
Gr-1
PBS
C
CD-11b
D
TNFα (ng/ml)
IL-1β (ng/ml)
PBS
Nsp12
Nsp13
Nsp12/13
E
Vector
IL-6 (ng/ml)
F

Figure S3

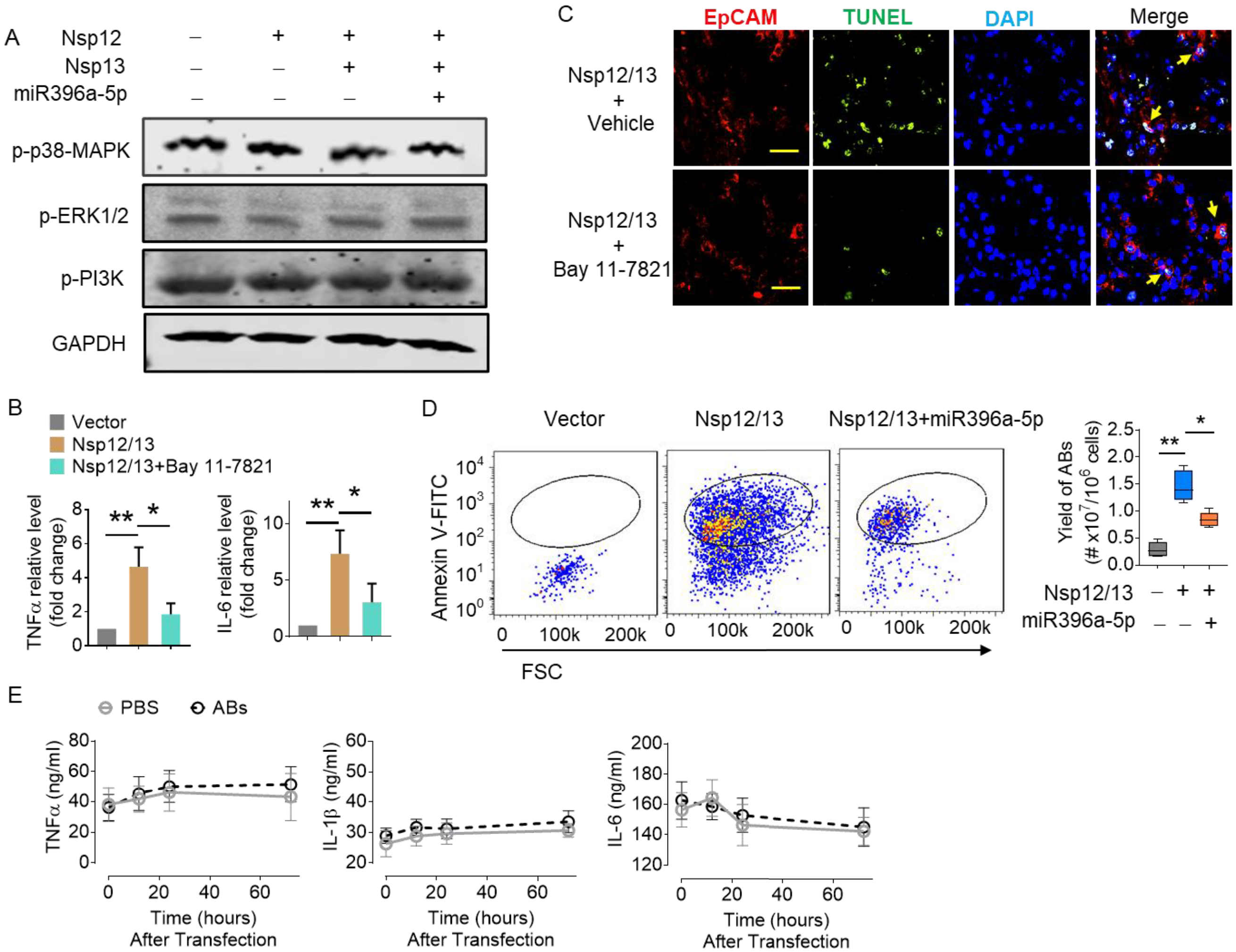

A
Nsp12
Nsp13
miR396a-5p
p-p38-MAPK
p-ERK1/2
p-PI3K
GAPDH
B
Vector
Nsp12/13
Nsp12/13+Bay 11-7821
TNFα relative level (fold change)
IL-6 relative level (fold change)
C
EpCAM
TUNEL
DAPI
Merge
Nsp12/13 + Vehicle
Nsp12/13 + Bay 11-7821
D
Vector
Nsp12/13
Nsp12/13+miR396a-5p
Annexin V-FITC
FSC
Yield of ABs (# x10^7/10^6 cells)
Nsp12/13
miR396a-5p
E
PBS
ABs
TNFα (ng/ml)
IL-1β (ng/ml)
IL-6 (ng/ml)
Time (hours) After Transfection

Figure S4

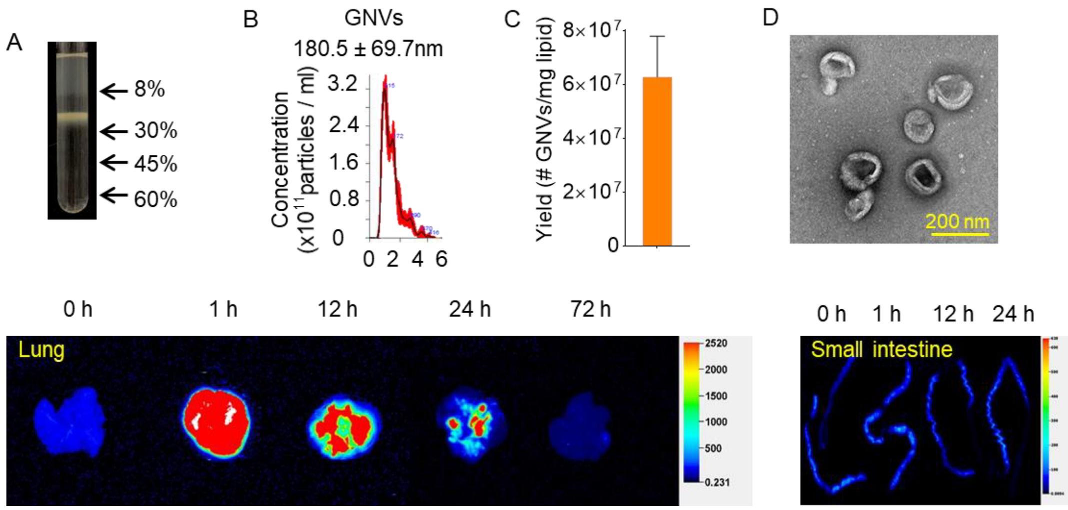
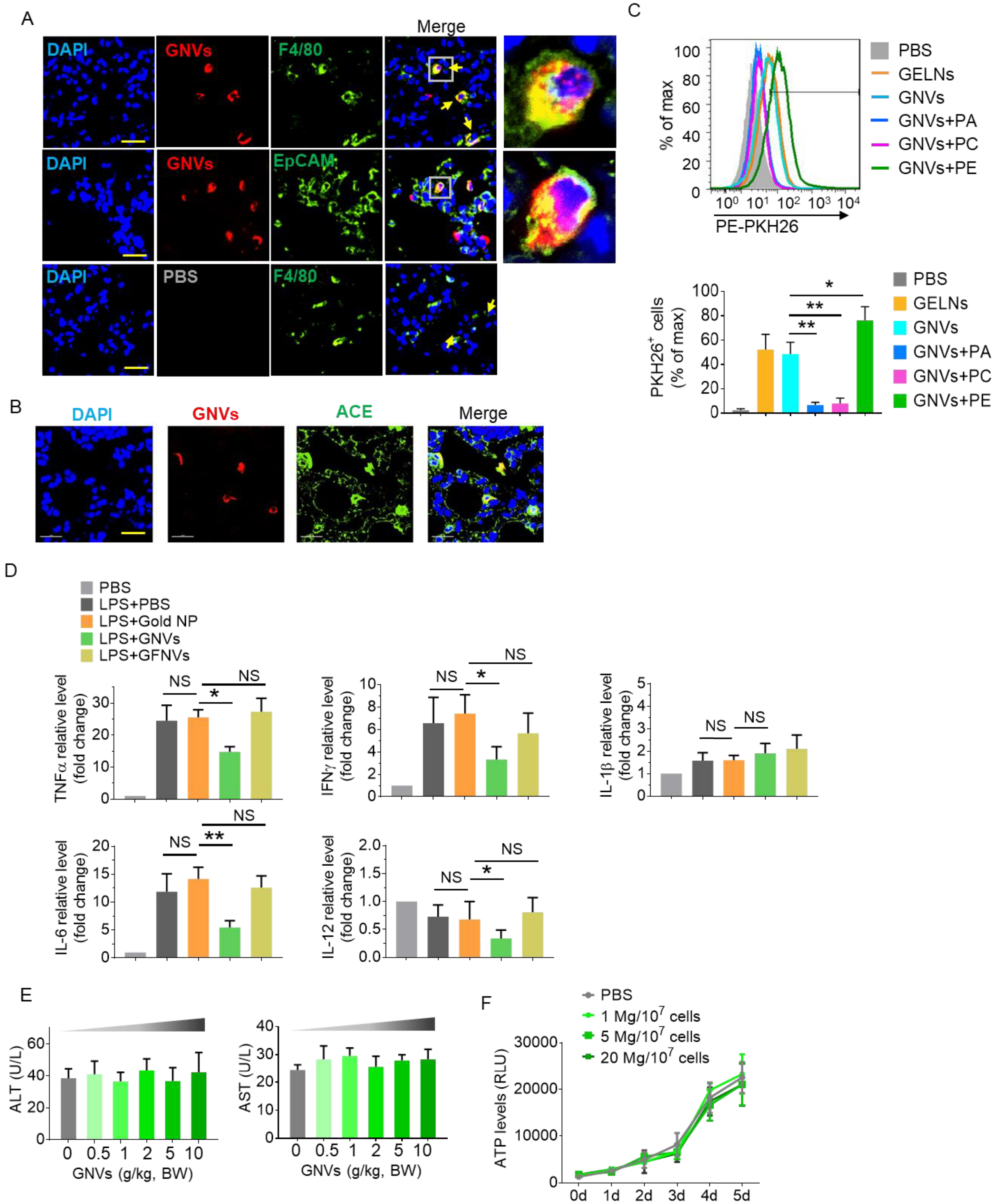

A
8%
30%
45%
60%
B
GNVs
180.5 ± 69.7nm
Concentration (x10^11 particles / ml)
3.2
2.4
1.6
0.8
0
0 2 4 6
C
Yield (# GNVs/mg lipid)
8×10^7
6×10^7
4×10^7
2×10^7
0
D
200 nm
E
0 h
1 h
12 h
24 h
72 h
Lung
2520
2000
1500
1000
500
0.231
0 h
1 h
12 h
24 h
Small intestine

Figure S5



105

Figure S6

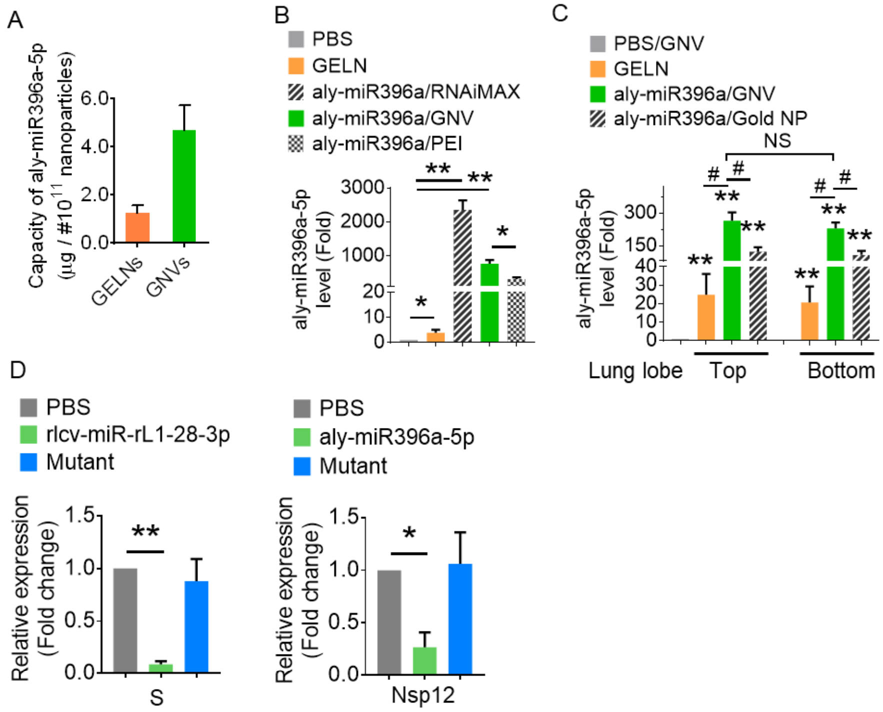


Figure S7

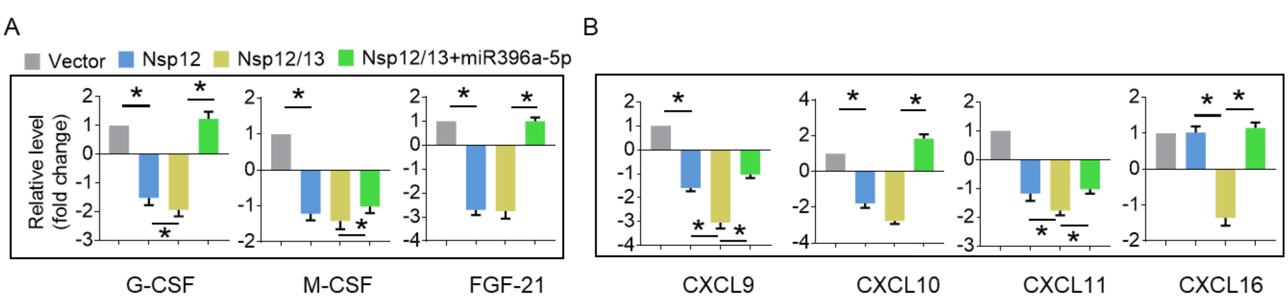


Table S1: **Plasmid of SARS-CoV-2 used in the study**

Plasmids of SARS-CoV-2	Cat. #	Source
pcDNA3-SARS-CoV-2-S-sfGFP	141184	Addgene
pLVX-EF1alpha-SARS-CoV-2-nsp12-2xStrep-IRES-Puro	141378	Addgene
pLXV-EF1alpha-2xStrep-SARS-CoV-2-orf3b-IRES-Puro	141384	Addgene
pLVX-EF1alpha-SARS-CoV-2-orf8-2xStrep-IRES-Puro	141390	Addgene
pLVX-EF1alpha-SARS-CoV-2-orf10-2xStrep-IRES-Puro	141394	Addgene
pTwist-EF1alpha-SARS-CoV-2-E-2xStrep	141385	Addgene
pLVX-EF1alpha-SARS-CoV-2-nsp7-2xStrep-IRES-Puro	141373	Addgene
pLVX-EF1alpha-SARS-CoV-2-nsp10-2xStrep-IRES-Puro	141376	Addgene
pLVX-EF1alpha-SARS-CoV-2-nsp13-2xStrep-IRES-Puro	141379	Addgene
Bacterial Expression plasmid for SARS-CoV-2 M	145746	Addgene
Bacterial Expression plasmid for SARS-CoV-2 Spike	145730	Addgene
Bacterial Expression plasmid for SARS-CoV-2 Nsp12	145616	Addgene
pAcGFP1-C1	632470	Addgene

Table S2 GELN miRNAs predicted target genes of SARS-CoV2

Name	Seed sequence	SARS-CoV2 (NC_045512)			Mapping to miRNAs in	
		Start	End	Gene	Human	Mouse
bta-miR-2284b	AAAGTTCGTTT	68	78	5'UTR		
sko-miR-4825-3p	CCTGTCAAC	152	160	5'UTR		
aly-miR157d-5p	CAGAAGATAGA	175	185	5'UTR		
esi-miR8629	TCACCACTA	562	570	Nsp1		
aly-miR396a-5p	TTTCTTGAA	735	743	Nsp1		
pma-miR-22b-5p	AGGTCTTTA	868	876	Nsp2		
osa-miR5792	GTTCGGACA	909	917	Nsp2		
gma-miR1516a-5p	AGCTCTTTT	1002	1010	Nsp2		
ppc-miR-8335-5p	AGGCACATT	1207	1215	Nsp2		
bbe-miR-252b-3p	GTCCTACTT	1395	1403	Nsp2		
sly-miR164b-3p	CCTTCTCCAAC	1580	1590	Nsp2		
mtr-miR396c	TTCAAGAAGGT	1611	1621	Nsp2		
gga-miR-1775-5p	TGAATGCTT	1755	1763	Nsp2		
cel-miR-791-5p	GTAGCCAAA	2032	2040	Nsp2		
dps-miR-2537-5p	CAACCGTCT	2194	2202	Nsp2		
lva-miR-182-5p	ATTCACACT	2777	2785	Nsp3		
ppc-miR-240	TCAATCCTT	2806	2814	Nsp3		
bmo-miR-3308-5p	TACTTTATC	2813	2821	Nsp3		
bmo-miR-3329	TTTATGACAG	2898	2907	Nsp3		
gma-miR393h	TTCCAAAGG	3140	3148	Nsp3		
cca-miR6117	GGTTGAAGA	3169	3177	Nsp3		
esi-miR3455-5p	AAGTTCCATC	3304	3313	Nsp3		
bmo-miR-2797d	TAAGTAGACATT	3779	3790	Nsp3		
ppt-miR1069-5p	TCTTATCAT	3948	3956	Nsp3		
bmo-miR-3400	ATTTTCTTA	3952	3960	Nsp3		
ppe-miR6261	TATATGGAG	4113	4121	Nsp3		
esi-miR8629	CCACAGCAGT	4154	4163	Nsp3		
aly-miR858-5p	TTGTCTGTT	4228	4236	Nsp3		
sma-miR-8437-5p	GTAGAATGT	4326	4334	Nsp3		
bta-miR-2463	CTGCATGTG	4404	4412	Nsp3		
mdo-miR-7283-5p	CTATGGCTT	4452	4460	Nsp3		
gma-miR4391	AAGAAGAAG	4737	4745	Nsp3		
dsi-miR-961-5p	AAGTGAGAT	4778	4786	Nsp3		
zma-miR395l-5p	ACTTCACCA	4906	4914	Nsp3		
sko-miR-4825-3p	ACACCTTAA	4968	4976	Nsp3		
aly-miR166a-5p	AATGTTGTCT	4987	4996	Nsp3		
mdo-miR-7319-3p	AAGTTGGAC	5049	5057	Nsp3		
vvi-miR3631a-5p	TGACATCAT	5681	5689	Nsp3		
dps-miR-2537-5p	ACCGTCTAT	5807	5815	Nsp3		
ppc-miR-8274-5p	GAGGACTTT	5827	5835	Nsp3		
bmo-miR-3308-5p	AATTGGTTG	5993	6001	Nsp3		
prd-miR-7579-3p	AGAATTTGT	6821	6829	Nsp3		
sly-miR5302b-5p	TGCTATAGT	6854	6862	Nsp3		
zma-miR395l-5p	CAAACACTT	6973	6981	Nsp3		
dps-miR-2537-5p	ACAACCGTCTA	7467	7477	Nsp3		
bmo-miR-3208	GAGAGAGAGA	7814	7823	Nsp3		
bma-miR-5847	ATTTTGCAG	7923	7931	Nsp3		
cbr-miR-791	CGCTGATTT	7928	7936	Nsp3		
bmo-miR-2797d	AGACATTGTC	8144	8153	Nsp3		
mtr-miR5215	GCTACCTGC	8368	8376	Nsp3		
cbr-miR-7583a-5p	AATATCGTG	8878	8886	Nsp4		
nve-miR-9468	GTACATTGGT	9071	9080	Nsp4		
mdo-miR-7269-5p	TGTCAGGGCGT	9109	9119	Nsp4		
mdo-miR-7267-3p	AGCCATCCA	9135	9143	Nsp4		

bdi-miR171f	GAACCAATA	9725	9733	Nsp4
pxy-miR-8526	TACAACCCT	10095	10103	Nsp5
sma-miR-8437-5p	TAGAATGTC	10290	10298	Nsp5
gma-miR167c	TGCCAGCATGA	10567	10577	Nsp5
eca-miR-9064	AAGGTCCAT	10599	10607	Nsp5
cca-miR6114-3p	ACGTCCATT	10883	10891	Nsp5
bma-miR-5847	ACCCAACTA	11236	11244	Nsp6
str-miR-7880x-3p	ATCCAACCATG	11259	11269	Nsp6
sme-miR-2160-1-3p	TAAGAGCCCA	11465	11474	Nsp6
oan-miR-7422a-3p	TCTGAGGCT	12097	12105	Nsp8
gga-miR-1775-5p	GTGCAACAGGA	12700	12710	Nsp9
gma-miR6300	GTTGTAGTA	12776	12784	Nsp9
esi-miR8629	CCACTAGCT	13117	13125	Nsp10
bmo-miR-3308-5p	ATTGGTTGTC	13128	13137	Nsp10
prd-miR-7911c-5p	GATGCACCA	13231	13240	Nsp10
prd-miR-7930-3p	TGTTGGTAG	13677	13686	Nsp12b
ppc-miR-240	CAATCCTTA	13710	13718	Nsp12b
eca-miR-1911	GCCATTGTG	13806	13814	Nsp12b
gga-miR-1775-5p	CAACAGGAA	14132	14140	Nsp12b
odi-miR-1479	AATTACCGG	14675	14684	Nsp12b
prd-miR-7930-3p	GTTGGTAGA	14817	14825	Nsp12b
cbr-miR-791	GCTGATTTG	14937	14945	Nsp12b
aly-miR157a-5p	AGATAGAGA	15119	15127	Nsp12b
bmo-miR-3329	CAATAATTT	15160	15168	Nsp12b
ath-miR4228-3p	GAAACGGTG	15388	15396	Nsp12b
crm-miR-7582	GGCAATTTT	15580	15589	Nsp12b
hma-miR-3013	CTATAGAGA	15630	15638	Nsp12b
aly-miR396a-5p	AGCTTTCTT	16104	16112	Nsp12b
gma-miR4391	GCAAAGAAC	16252	16260	Nsp13
bmo-miR-3329	TAATTTATG	16351	16359	Nsp13
dsi-miR-2583-5p	AAAGTTGAGTC	16416	16426	Nsp13
bmo-miR-3329	TACAATAAT	16445	16453	Nsp13
eca-miR-9004	GTGTTAGCT	16602	16610	Nsp13
dme-miR-4980-3p	CCAACTTCC	16737	16745	Nsp13
bmo-miR-281-5p	AGAGAGCTA	17120	17128	Nsp13
prd-miR-7579-3p	AATTTGTGG	17372	17380	Nsp13
aly-miR168a-5p	TGGTGCAGGT	17451	17460	Nsp13
ath-miR5653	TTGAGTTGG	17821	17829	Nsp13
stu-miR156f-5p	AGAGTGAGC	17893	17901	Nsp13
dme-miR-4969-5p	GGTAAATTG	18348	18356	Nsp14
osa-miR5792	GCGGTGGTT	18455	18463	Nsp14
bdi-miR7738-3p	ACGACTCTG	18576	18584	Nsp14
cbr-miR-35g	AAACTGGTA	19685	19693	Nsp15
eca-miR-9004	ACAGTGTTA	19704	19712	Nsp15
ptc-miR6478	TCAGTTGGT	19950	19958	Nsp15
eca-miR-9064	TTGAAGGTC	20734	20742	Nsp16
smo-miR1112-3p	ACAAAGTCA	20961	20969	Nsp16
bmo-miR-3400	AGTCATTTTCTT	21080	21091	Nsp16
aly-miR848-5p	CATGTCAAA	21391	21399	Nsp16
mdo-miR-7319-3p	GACTAGAGA	21594	21602	S
sme-miR-2169-5p	TTGAAATTC	21956	21964	S
ppc-miR-8274-5p	ACTTTCCAT	22019	22027	S
odi-miR-1479	TTGAAATTACC	22112	22122	S
sme-miR-2169-5p	TTTGAAATT	22115	22123	S
cbn-miR-7629	GTGATGTTA	22261	22269	S
rlcv-miR-rL1-28-3p	AGGAAAGTA	23027	23035	S
mtr-miR2678	AAATTGTTG	23249	23257	S

prd-miR-7579-3p	ATTTGTGGG	23705	23713	S		
nve-miR-9468	TGTACATTG	23778	23786	S		
bdi-miR171f	AATATCACC	24086	24095	S		
zma-miR396g-3p	GCTGTGGAAGA	24377	24387	S		
odi-miR-1479	CTTGAAATT	24478	24486	S		
sme-miR-2169-5p	AACTTTGAA	24564	24572	S		
prd-miR-7884-5p	AGGTGCTGA	24725	24733	S		
tgu-miR-7644-3p	AAATGGCAG	24798	24806	S		
rlcv-miR-rL1-28-3p	GAGGAAAGT	24825	24834	S		
cbr-miR-7583a-5p	AGTTGCAAA	25631	25639	Orf3a		
aly-miR157a-5p	AAGATAGAG	25708	25716	Orf3a		
dme-miR-2535b-3p	ACGGCATTTC	25785	25794	Orf3a		
ath-miR5653	TGAGTTGAGT	26036	26045	Orf3a		
zma-miR395l-5p	TTCCAAACA	26500	26508			
gma-miR1516a-5p	TAAGCTCTT	26554	26562	M		
ppc-miR-8274-5p	TTCCATTGTTCA	26573	26584	M		
ssa-miR-375-2-5p	GCTGAGCCAC	26795	26804	M		
dme-miR-4969-5p	ATTGAATGA	26853	26861	M		
mdo-miR-7319-3p	AGATGGTGT	26981	26989	M		
mdo-miR-7345-5p	GTAGCGACTGT	27109	27119	M		
sme-miR-2160-1-3p	TTTTCATGT	27392	27400	Orf7a		
ptc-miR396g-5p	TTCTTGAACTT	27668	27678	Orf7a		
ppt-miR319a	CTTGGACTGA	28584	28593	N (Orf9)		
gma-miR396e	CTTGAACTG	28849	28857	N (Orf9)		
eca-miR-1911	CCAGCCATT	28900	28908	N (Orf9)		
mdo-miR-7269-5p	AATCTGTCA	28945	28953	N (Orf9)		
eca-miR-9004	AGTGACAGT	29006	29014	N (Orf9)		
vvi-miR3631a-5p	TCATCCAAT	29287	29295	N (Orf9)		
sme-miR-2169-5p	CTTTGAAAT	29307	29315	N (Orf9)		
vvi-miR3631a-5p	ATCATCCAA	29471	29479	N (Orf9)		
oan-miR-7422a-3p	GGCTCTTTC	29711	29719	3'UTR		
bta-miR-2463	ATGTGGTGG	29718	29726	3'UTR		
ssc-miR-9819-5p	CTCGATCGT	29749	29757	3'UTR		
eca-miR-9021	TTGTTCACTGT	29761	29771	3'UTR		
bmo-miR-3315	GGGCTGTTC	458	466	Nsp1		mmu-miR-298-5p
mml-miR-7181-3p	AGGACTCAG	1853	1861	Nsp2	hsa-miR-3919, hsa-miR-4418	mmu-miR-6955-5p
gma-miR4391	CTAAGAAGA	2484	2492	Nsp2	hsa-miR-4659a-5p, hsa-miR-	
hsa-miR-6867-3p	TCTCCCTCT	2491	2499	Nsp2	hsa-miR-615-3p, hsa-miR-6867-3p	mmu-miR-615-3p, mmu-miR-6916-3p, mmu-miR-12203-3p
ath-miR5653	TTGAGTTGA	3095	3103	Nsp3		mmu-miR-7230-3p
bmo-miR-3308-5p	CTTGGTAAT	3126	3134	Nsp3	hsa-miR-4705	
dsi-miR-961-5p	TCAGTAAGT	3364	3372	Nsp3	hsa-miR-4797-3p	mmu-miR-325-5p
eca-miR-9021	AGAGTTGTT	3985	3993	Nsp3	hsa-miR-4680-3p	
sma-miR-8439-5p	AGATAACCA	4726	4734	Nsp3		mmu-miR-9b-3p
ppc-miR-8274-5p	ATTGTTCAT	5592	5600	Nsp3	hsa-miR-384	
hma-miR-3013	TCTGACTTC	6349	6357	Nsp3	hsa-miR-5683	mmu-miR-7235-3p
dme-miR-4980-3p	CAACTTCCG	8016	8024	Nsp3		mmu-miR-8120
ppc-miR-8274-5p	TTTCCATTG	8079	8087	Nsp3		mmu-miR-6920-3p
eca-miR-9021	AGTTGTTCA	8431	8439	Nsp3	hsa-miR-582-5p	mmu-miR-582-5p, mmu-miR-3088-5p
mdo-miR-7269-5p	GTCAGGGCG	9110	9118	Nsp4	hsa-miR-4734	
dme-miR-4969-5p	AAATTGAAT	9149	9157	Nsp4	hsa-miR-1252-5p	
cte-miR-2685-5p	TGATCTTTC	9233	9241	Nsp4	hsa-miR-6856-3p	

mmu-miR-5106	TCTGTAGCT	9938	9946	Nsp4	hsa-miR-4320, hsa-miR-4420	mmu-miR-5106
bmo-miR-3308-5p	TTGGTAATT	10551	10559	Nsp5	hsa-miR-4705	
bma-miR-5847	TTTTGCAGT	10867	10875	Nsp5		mmu-miR-450b-5p
sly-miR5302b-5p	TTGGAAAGT	10964	10972	Nsp5	hsa-miR-412-5p	
mml-miR-1323-5p	GGCATTTTC	11087	11095	Nsp6	hsa-miR-1323	
cfa-miR-8837	TTCTTGCTG	11352	11360	Nsp6		mmu-miR-6400
mml-miR-1323-5p	CAAAACTGAG	11884	11893	Nsp7	hsa-miR-1323	
sme-miR-2f-3p	GCCATGCTA	12630	12638	Nsp8	hsa-miR-1269b	
eca-miR-9125	AGGTGTGTC	12917	12925	Nsp9	hsa-miR-3650	
ppt-miR1069-5p	TTATCATTG	13554	13562	Nsp12		mmu-miR-374b-3p
bfl-miR-4875d-3p	TACAAAGTA	13645	13653	Nsp12	hsa-miR-876-3p	mmu-miR-876-3p
dre-miR-181c-3p	ACAATGAAT	14153	14161	Nsp12	hsa-miR-181b-3p	mmu-miR-181b-1-3p
cbn-miR-7629	TGTGATGTT	16344	16352	Nsp13	hsa-miR-153-5p, hsa-miR-499b-5p	
mmu-miR-664-5p	AAAATGACT	17101	17109	Nsp13		mmu-miR-664-5p
mmu-miR-7091-3p	TGTCGTCTC	17329	17338	Nsp13		mmu-miR-7091-3p
gma-miR1516a-5p	TTATAAGCT	19116	19124	Nsp14		mmu-miR-6374
bmo-miR-3308-5p	TGGTAATTG	19360	19368	Nsp14	hsa-miR-4705	
gma-miR1516a-5p	GTTATAAGC	19528	19536	Nsp14		mmu-miR-6374
gma-miR396e	TTGAACTGT	20142	20150	Nsp15	hsa-miR-203b-3p	mmu-miR-203b-3p
hsa-miR-6867-3p	CCCTCTTTA	21093	21101	Nsp16	hsa-miR-6867-3p	
gma-miR4391	ACTAAGAAG	21478	21486	Nsp16		mmu-miR-5124b
mml-miR-1323-5p	AAACTGAGG	21696	21704	S	hsa-miR-1323, hsa-miR-3934-5p	
mmu-miR-664-5p	GGAAAATGA	22679	22687	S	hsa-miR-664a-5p	mmu-miR-664-5p
hma-miR-3013	GTCTGACTT	22779	22787	S		mmu-miR-1843b-5p, mmu-miR-7090-3p
sly-miR5302b-5p	GTTGGAAAG	23244	23252	S	hsa-miR-412-5p	
vvi-miR3631a-5p	TGTTGACAT	23526	23534	S		mmu-miR-669g
bta-miR-200c	AATGATGGA	23633	23641	S	hsa-miR-200c-3p	mmu-miR-200c-3p
cbr-miR-35g	ACTGGTAGA	23740	23748	S	hsa-miR-183-5p, hsa-miR-6720-3p	mmu-miR-183-5p
aly-miR858-5p	GTTGTCTGT	24911	24919	S	hsa-miR-410-5p, hsa-miR-6868-3p	mmu-miR-410-5p
aly-miR166a-5p	TGTTGTCTG	24912	24920	S	hsa-miR-6868-3p	
mmu-miR-7028-5p	TGAGGCTTG	25504	25512	Orf3a		mmu-miR-7028-5p
aly-miR159a-3p	TGGATTGAA	26856	26864	M	hsa-miR-6839-5p	
gma-miR1516a-5p	TCTTTTGAG	27739	27747	Orf7a	hsa-miR-371a-3p	
bmo-miR-3315	CCTTGGGGC	28396	28404	N(Orf9)	hsa-miR-5008-5p	
cte-miR-2685-5p	GTGATCTTT	28700	28709	N(Orf9)	hsa-miR-6856-3p, hsa-miR-8066	
lva-miR-182-5p	TTTGGCAAT	28771	28779	N(Orf9)	hsa-miR-182-5p	mmu-miR-182-5p

Table S3 Primer sequences used for gene expression analysis by qPCR

Primers	Forward (5'-3')	Reverse (5'-3')
aly-miR396a-5p	TTCCACAGCTTTCTTGAACTG	Universal primer (Qiagen)
rlcv-miR-rL1-28-3p	GAGGAAAGTATCGCCTTCTAG	Universal primer (Qiagen)
hTNFalpha	CTCTTCTGCCTGCTGCACTTTG	ATGGGCTACAGGCTTGTCACTC
hIL-1beta	CCACAGACCTTCCAGGAGAATG	GTGCAGTTCAGTGATCGTACAGG
hIL-1alpha	TGTATGTGACTGCCCAAGATGAAG	AGAGGAGGTTGGTCTCACTACC
hIL-6	AGACAGCCACTCACCTCTTCAG	TTCTGCCAGTGCCTCTTTGCTG
mTNFalpha	TCTATGGCCCAGACCCTCAC	GACGGCAGAGAGGAGGTTGA
mIL-1beta	GTGTGCCGTCTTTCATTACACAG	CAGACCCTCACACTCAGATCATCT
mIL-1alpha	ATCAGTACCTCACGGCTGCT	TGGGTATCTCAGGCATCTCC
mIL-6	GAGAGGAGACTTCACAGAGGATAC	GTACTCCAGAAGACCAGAGG
mGAPDH	GGTCGGTGTGAACGGATTTG	GGAGTCATACTGGAACATGTAG
hGAPDH	GTATGACAACAGCCTCAAGAT	GTCCTTCCACGATACCAAAG
CoV2-Nsp12	ACCGTAGCTGGTGTCTCTAT	GTGCCAACCACCATAGAATTTG
CoV2-Nsp12-cloning	CAGAGAAGGAGCTCGGTACCATGGCTGATGCACAATCGTT	TATCTAGATCCGGTGGATCCTTATAAGACTGTATGCGGTGTGTAC
pAcGFP1-C1	TGCTGGAGCAGGACGGAATC	TCTACAAATGTGGTATGGCTG