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# **LY6E impairs coronavirus fusion and confers immune control of viral disease**

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## Methods

### Viruses

Recombinant HCoV-229E<sup>1</sup>, HCoV-229E-Rluc (expressing Renilla luciferase [Rluc] by replacing the majority of HCoV-229E ORF4)<sup>2</sup>, HCoV-OC43<sup>3</sup>, MHV strain A59<sup>4</sup>, MHV-Gluc, strain A59 (expresses a Gaussia luciferase [Gluc] replacing accessory gene 4)<sup>5</sup>, MHV-GFP strain A59<sup>6</sup>, MERS-CoV strain EMC<sup>7</sup>, and SARS-CoV strain Frankfurt-1<sup>8</sup> have been described previously. SARS-CoV-2 (SARS-CoV-2/München-1.1/2020/929) stocks used in VeroE6 infection were propagated on VeroE6 cells. SARS-CoV-2 (SARS-CoV-2 USA-WA1/2020) stocks used in Huh7.5 infection were propagated on VeroE6 cells. HCoV-229E viruses were propagated on Huh-7 cells, MERS-CoV and SARS-CoV were propagated on VeroB4 cells, HCoV-OC43 was propagated on HCT-8 cells<sup>9</sup>, and MHV stocks were propagated on 17C11 cells. Lentivirus particles using the SCRPSY and SCRBBL backbone were generated as described previously<sup>9-12</sup>.

VSV\*ΔG(Fluc) (G glycoprotein-deficient VSV encoding green fluorescent protein [GFP] and firefly luciferase [Fluc]) was generated as described previously and was propagated on BHK-G43 cells<sup>13</sup>.

The generation of viral stocks for the following viruses has been previously described: hPIV-3-GFP<sup>14</sup> (based on strain JS, generously provided by P.L. Collins), RSV-GFP<sup>15</sup> (based on strain A2, generously provided by P.L. Collins), YFV-Venus<sup>16</sup> (derived from YF17D-5'C25Venus2AUbi), DENV-GFP<sup>17</sup> (derived from IC30P-A, a full-length infectious clone of strain 16681), WNV-GFP<sup>18</sup> (derived from pBELO-WNV-GFP-RZ, generously provided by I. Frolov), HCV-Ypet<sup>19</sup> (based on the chimeric Jc1 virus of strains: J6 and JFH-1), SINV-GFP<sup>20</sup> (derived from pS300/pS300-GFP, generously provided by M.T. Heise), VEEV-GFP<sup>21</sup> (derived from pTC83-GFP infectious clone, generously provided by I. Frolov), CHIKV-GFP<sup>22</sup> (derived from pCHIKV-LR 5'GFP, generously provided by S. Higgs). ZIKV (PRVABC59, obtained from the CDC, Ft. Collins) was amplified and titrated as described previously<sup>23</sup>.

### Cell lines

Huh7 hepatocarcinoma cells (kind gift from V. Lohnmann), Huh7.5, STAT1<sup>-/-</sup> fibroblasts (kind gift from J.-L. Casanova), VeroE6 cells and VeroB4 cells (kindly provided by M.Müller/C.Drosten), 293LTV (Cell Biolabs), and A549 cells (ATCC cat# CCL-185) were maintained in Dulbecco's Modified Eagle Medium-GlutaMAX (Gibco) supplemented with, 1 mM sodium pyruvate (Gibco), 10% (v/v) heat-inactivated fetal bovine serum (FBS) (Gibco), 100 µg/ml streptomycin (Gibco), 100 IU/ml penicillin (Gibco) and 1% (w/v) non-essential amino acids (NEAA; Gibco) (cDMEM) BHK-21 (DSMZ collection # ACC61) were maintained in Glasgow's minimal essential medium (MEM) with 5% FBS and 1% tryptose. BHK-G43<sup>24</sup> were cultured in Glasgow's minimal essential medium with 5% FBS. 17C11 fibroblasts (gift from S.G. Sawicki) were cultured in MEM supplemented with 10% (v/v) heat inactivated FBS, 100 µg/ml streptomycin and 100 IU/ml penicillin. Cells were either newly purchased from a commercial source or cell line identities verified by a Multiplex human cell line authentication test, short tandem repeat (STR), or PCR-based analysis.

Huh7 cells expressing TMPRSS2 were generated as follows. In order to generate TMPRSS2-encoding retroviral vectors, the open reading frame of human TMPRSS2 was first PCR amplified with primers adding an N-terminal cMYC epitope to the TMPRSS2 coding sequence. The resulting sequence was inserted into a modified version of the pQCXIP plasmid that contains a blasticidin resistance cassette instead of the usual puromycin resistance cassette<sup>25</sup>. Huh7 cells stably expressing human TMPRSS2 were generated by retroviral transduction and selection with the antibiotic blasticidin (50 µg/ml). Following selection, cells were maintained in culture medium (cDMEM) supplemented with 10 µg/ml blasticidin. To generate STAT1<sup>-/-</sup>\_CEACAM1 cells, human STAT1<sup>-/-</sup> fibroblasts were transduced with lentiviruses encoding for the murine CoV receptor CEACAM1 (kind gift from David Wentworth, CDC, Atlanta, USA<sup>24</sup> and subsequently selected with 1 µg/mL puromycin. Stable LY6E expressing cell lines were generated upon lentiviral transduction with SCRPSY LY6E or SCRPSY empty as a control, in DMEM containing 4 µg/ml polybrene (Millipore) and 20 mM HEPES buffer solution (Gibco). Cells were selected using 2-4 µg/mL puromycin and were passaged until all cells in control wells without lentivirus were killed. The puromycin selected cells were further passaged and frozen down for subsequent experiments. For SARS-CoV-2 experiments in Huh7.5 cells, stable LY6E expressing cell lines were generated upon lentiviral transduction with SCRBBL LY6E or SCRBBL FLuc as a control in DMEM containing 4 µg/ml polybrene (Millipore) and 20 mM HEPES buffer solution (Gibco). Cells were selected using 15 µg/mL blasticidin and were passaged and frozen as described for SCRPSY cells. In order to generate ACE2-containing lentiviral vectors, the ORF of human ACE2 (NM\_21804.1) in a Gateway-compatible pENTR vector (kind gift from N. Alto, UTSW) was cloned into the pSCRPSY lentiviral backbone using Gateway technology per manufacturer's protocol. Stable SCRBBL cells were transduced with SCRPSY ACE2 or SCRPSY empty lentivirus as a control as described above and maintained in blasticidin-containing media. The stable cell lines harboring LY6E orthologues have been described before, with the exception of *C. dromedarius*<sup>26</sup>. For this, a gBlock was ordered (XM\_031439745.1) and Gateway cloning performed to generate pENTR and pSCRPSY plasmids. Constructs encoding for Ly6/uPAR family members and LY6E ASM mutants have been described before<sup>26</sup>.

To generate clonal LY6E KO cells and CRISPR-resistant LY6E, A549 cells were transduced with lentivirus containing a LY6E-specific sgRNA and Cas9 as described previously<sup>26</sup>. To generate a clonal cell line, the bulk transduced population was plated at single cell dilutions. Candidate clones were screened by Western blot for LY6E expression and Sanger sequencing. Silent mutations in the region targeted by the LY6E-specific sgRNA were introduced into HA-tagged LY6E to generate CRISPR-resistant LY6E (CR LY6E) as a Gateway-compatible gBlock and cloned to generate pENTR and pSCRPSY plasmids as previously described<sup>26</sup>. LY6E KO A549 cells were reconstituted with CR-LY6E by lentiviral transduction and expression confirmed by Western blot.

All cell lines were regularly tested to check they were free of mycoplasma contamination using a commercially available system (PCR Mycoplasma test kit I/RT Variant C, PromKine or Venor GeM Mycoplasma Detection Kit from Sigma).

### ISG screen

The ISG screen was performed as described previously with slight modifications<sup>11,12</sup>. Briefly,  $5 \times 10^3$  Huh7 cells were seeded, transduced with individual lentiviruses, and 48 hours post-transduction infected with HCoV-229E at 33°C. Infection was stopped 24 hours (MOI=0.1) or 48 hours (MOI=0.01) post-infection and plates were immuno-stained as described previously<sup>27</sup> with an anti-HCoV-229E N protein antibody and a AlexaFluor488-conjugated donkey anti-mouse secondary antibody (See ‘Antibodies for immunofluorescence and flow cytometry’). For high-content high-throughput imaging analysis ImageXpress Micro XLS (Molecular Devices, Sunnyvale, CA) was used as previously described<sup>12</sup>. Hits were normalized to cells expressing the empty vector. Depicted are genes that were expressed in two independent screens with a transduction efficiency of at least 1 % (cut off). ISGs which were cytotoxic for the cells were excluded from the analysis. Normalized data can be found in **Supplementary Table 1** and **Supplementary Table 2**.

### Generation of recombinant VSV vector driving CoV S protein expression (VSV\*ΔG(CoV))

Following extraction of total RNA from MERS-CoV (strain EMC) infected VeroE6 cells, the cDNA encoding the MERS-CoV S protein was generated by reverse transcription (RevertAid Premium Reverse Transcriptase, ThermoScientific). Three overlapping cDNA fragments were amplified by PCR (Phusion Hot Start II High Fidelity Polymerase, Thermo Scientific) and subsequently assembled by overlapping PCR. The cDNAs encoding the S proteins of either MERS-CoV (strain EMC) or HCoV-229E (truncated variant lacking the 10 amino acids at the C terminus, original plasmid pCAGGS-229E S) were amplified by PCR and inserted into the pVSV\* plasmid<sup>56</sup> between MluI and BstEII restriction sites. The resulting plasmids were used to generate the recombinant viruses VSV\*ΔG(MERS S) and VSV\*ΔG(229E S) according to a published procedure<sup>57</sup>. All viruses were propagated on BHK-G43 cells<sup>58</sup>, resulting in viruses predominantly containing the homotypic VSV glycoprotein G in the envelope.

### Western blotting

For SDS-PAGE and western blot analysis, lysates from cultured cells were prepared using the M-PER Mammalian Protein Extraction Reagent (Thermo) supplemented with protease inhibitors (cOmplete Mini, Roche). Proteins were separated on 10% (w/v) SDS-polyacrylamide gels (Bio-Rad), and electroblotted on nitrocellulose membranes (in a Mini Trans-Blot cell (eBlot L1 GenScript). Membranes were incubated in PBS 0.1% Tween (Merck Millipore) 5% milk (Dietisa, Biosuisse), probed with the respective primary antibodies, followed by incubation with horseradish peroxidase-conjugated secondary antibodies. LY6E in A549 was detected using anti-LY6E rabbit monoclonal antibody GEN-93-8-1 (Genentech) at a dilution of 1:5,000 and secondary Peroxidase-AffiniPure Donkey Anti-Rabbit IgG (Jackson ImmunoResearch, 711-035-152) at a dilution of 1:10,000. LY6E in MERS-CoV spike was detected using the monoclonal anti-human 1.6c7 ab (0.12 mg/ml)<sup>28</sup> (generated and kindly provided by B.J. Bosch) at a dilution of 1:1,000 and a secondary Peroxidase-AffiniPure Donkey Anti-Human IgG (Jackson ImmunoResearch, 709-035-098) at a dilution of 1:10,000. β-actin was detected using Monoclonal Anti-β-Actin-Peroxidase clone AC-15 (Sigma-Aldrich, A3854) at a dilution of 1:25,000. Proteins were visualized using WesternBright enhanced chemiluminescence horseradish peroxidase substrate (Advansta) and quantified in a Fusion FX7 Spectra (Vilber-Lourmat). Bands were quantified using the respective software (FusionCapt Software Version 18.05). For SDS-PAGE and western blotting of Huh7.5 lysates from cultured cells were prepared, run on tricine-based gels, and analyzed as described previously. LY6E was detected using anti-LY6E mouse monoclonal antibody 4D8.6.7 (1:300, Genentech) as described previously<sup>26</sup>. ACE2 was detected using anti-ACE2 goat polyclonal IgG AF933 (1:1000, R&D Systems). β-actin was detected using Monoclonal Anti-β-Actin-Peroxidase clone AC-15 (1:30,000, Sigma-Aldrich).

### RNA extraction and RT-qPCR from cultured cells

Viral RNA was extracted from cell lysates (NucleoMag-96RNA kit, Macherey Nagel) or supernatant (NucleoMag-Vet kit, Macherey Nagel) using the KingFisher Flex robot according to the manufacturer’s recommendations. The commercially

available TaqMan™ Fast Virus 1-Step Master Mix (Applied Biosystems) was used for RT-qPCR with 2 µl of RNA input added to 8 µl of prepared mastermix per sample. Viral RNA was detected using HCoV-229E specific primers normalized to a qRT-PCR standard for HCoV-229E (contains the M gene of HCoV-229E<sup>29</sup>). Intracellular viral RNA was normalized to total RNA (determined via the housekeeping gene Beta-2-Microglobulin (B2M)). Cellular RNA was extracted from cell lysates of Huh7 cells using the Nucleospin RNA kit (Machery Nagel) according to the manufacturer's recommendations, quantified via NanoDrop, and used to generate a standard curve. PCR conditions are available upon request.

### **Cellular CD13/DPP4 surface expression**

LY6E expressing or control cells were dissociated (TryPLE Express, Gibco) and enumerated.  $3 \times 10^5$  cells were stained in duplicate using Zombie Aqua™ Fixable Viability Kit (BioLegend) according to the manufacturer's recommendations. Cells were resuspended in 0.1% FBS/PBS and stained for CD13 or DPP4 expression (See 'Antibodies for immunofluorescence and flow cytometry'). Cells were washed with 0.1% FBS/PBS and resuspend in equal volumes. Cell suspensions were analyzed by flow cytometry using a FACS Canto (BD) and analyzed with FlowJo Software (Treestar).

### **Binding experiment**

Stable LY6E expressing or control Huh7 cells were seeded in a 24-well plate ( $4 \times 10^4$  cells) and mock infected or inoculated with HCoV-229E (MOI=5) in OptiMEM (Gibco) on ice for 1 hour. Cells were washed at least 3x with PBS and harvested immediately (t=0 h) or incubated at 33°C for 24 hours (t=24 h), before cell lysis and extraction of viral RNA as described above. Viral RNA was detected via RT-qPCR normalized to the housekeeping gene B2M as described above.

### **Time course experiment**

$8 \times 10^4$  cells stable LY6E expressing or control Huh7 cells were seeded in 12-well plates and mock infected or infected with 229E-CoV-Rluc (MOI=0.1) for 2 hours at 33°C in OptiMEM. Cells were washed 3x with PBS and samples harvested at the indicated time points. To determine intracellular replication, cell lysates were collected and viral RNA extracted (NucleoMag-96RNA kit, Macherey Nagel), followed by RT-qPCR as described before, or cells were lysed using the Renilla Luciferase Assay System kit (Promega) according to the manufacturer's recommendations and Rluc activity determined. To determine extracellular viral replication, viral supernatant was harvested, and viral RNA extracted (NucleoMag-Vet kit, Macherey Nagel), followed by RT-qPCR as described before. To determine intracellular infectivity, cells were subjected to 3 rounds of freeze/thaw cycles, centrifuged to remove debris ( $4,000 \times g$  for 10 min), and the supernatant titrated on naïve Huh7 cells. To determine extracellular infectivity, supernatant was harvested at the indicated time points and titrated on naïve Huh7 cells. For titration,  $1 \times 10^4$  Huh7 cells were seeded in a 96-well plate and infected with 22 µl of virus containing supernatant and incubated at 33°C. Cells were lysed 24 hours post-infection and infectivity determined using the Renilla Luciferase Assay System kit (Promega) according to the manufacturer's recommendations.

### **Protease inhibitor treatment**

To test various protease inhibitors,  $2 \times 10^4$  naïve or TMPRSS2-expressing, control or LY6E cells were seeded in a 96-well plate. One day post seeding, cells were pre-treated with the following compounds for 1 hour in OptiMEM, at 37°C: DMSO (1:500, Sigma-Aldrich), E64 D (10 µM, Sigma-Aldrich), and/or Camostat (100 µM, Sigma-Aldrich). Cells were mock infected or infected with HCoV-229E-Rluc (MOI 0.1) in the presence of the inhibitors for 2 hours at 33°C. Medium was changed to DMEM and cells incubated for 24 hours at 33°C. Cells were lysed and Rluc activity detected using the Renilla Luciferase Assay System kit (Promega) according to the manufacturer's recommendations.

### **Spike cleavage assays.**

LY6E expressing or control Huh7 ( $2 \times 10^5$  cells) were seeded in 6-well cell culture plates. Cells were transfected using Lipofectamine 2000 (Invitrogen) with an expression plasmid encoding for MERS-CoV S (pCAGGS-MERS S). Cell lysates were harvested 48 hours post-transfection and subjected to Western blot analysis as described.

### **RNA isolation and RT-qPCR from primary murine tissues**

Sections of liver and spleen were preserved in RNAlater Stabilization Solution (Thermo Fisher Scientific) and frozen. Thawed samples were transferred to PBS and homogenized. One-eighth of the homogenate was mixed with TRIzol Reagent (Thermo Fisher Scientific). BMDM were directly lysed in TRIzol Reagent and frozen. Total RNA was isolated according to the manufacturer's protocol. Liver and spleen RNA were subject to DNase treatment (TURBO DNA-Free kit, Thermo Fisher Scientific) per the manufacturer's protocol prior to RNA-seq analysis. BMDM RNA was analyzed by one-step qRT-PCR using QuantiFast SYBR Green RT-PCR Kit (Qiagen) using Applied Biosciences 7500 Fast Real-Time PCR System.

### RNA-seq of hAEC

For analysis of *LY6E* expression in the context of SARS-CoV and SARS-CoV-2 infection, data from an independent study that examined the host response at 24, 48, 72, and 96 hours post-infection in primary hAEC cultures were reanalyzed<sup>30</sup>. Briefly, following extraction of total RNA from uninfected and CoV-infected hAECs, the Bulk RNA Barcoding and sequencing (BRB-seq)<sup>31</sup> protocol was used to generate libraries, which were subsequently sequenced on the Illumina NextSeq500 platform. The STAR aligner<sup>32</sup> was used to align reads to a concatenation of the human and viral genomes (human hg38/SARS-CoV AY291315/SARS-CoV-2 NC\_045512) and then counted using HT-Seq<sup>33</sup>. Counts were normalized and expression differences between samples were quantified using the DESeq2 package in R, with a fold change (FC) cut off  $\geq 1.5$  and False Discovery Rate (FDR)  $\leq 0.05$ .

### Single cell RNA-seq of hAEC

To determine the basal expression levels of *LY6E*, *ACE2*, *CD13*, and *DPP4* in the distinct cell types found in hAEC cultures, data from a previous study that performed single cell RNA sequencing (scRNA-seq) on primary hAEC cultures was reanalyzed (uninfected samples only)<sup>34</sup>. Cell Ranger software (10x Genomics) was used to align and count reads in ~8,000 single cells and the resulting count matrices were pre-processed, filtered, and merged in Seurat (v3.1)<sup>35,36</sup>. The SCTransform option in Seurat was used for data scaling, normalization, and regression and dimensional reduction was performed using Uniform Manifold Approximation and Projection (UMAP) embedding. For cell type annotation, both cluster-specific marker genes and canonical marker genes were used to annotate individual cells as ciliated, secretory, goblet, preciliated, or basal cells, as previously described<sup>34</sup>. Finally, the relative expression and distribution of specific genes was visualized using the FeaturePlot command in Seurat and UMAP plots.

### RNA library construction and sequencing for MHV studies

The quantity and quality of the extracted RNA was assessed using a Thermo Fisher Scientific qubit 2.0 fluorometer with the Qubit RNA BR Assay Kit (Thermo Fisher Scientific, Q10211) and an Advanced Analytical Fragment Analyzer System using a Fragment Analyzer RNA Kit (Agilent, DNF-471), respectively. Sequencing libraries were prepared using an Illumina TruSeq Stranded Total RNA Library Prep Gold kit (Illumina, 20020599) in combination with TruSeq RNA UD Indexes (Illumina, 20022371) according to the Illumina guidelines. Sequencing libraries were sequenced paired-end (2 x 50 bp) using an Illumina NovaSeq 6000 S1 Reagent Kit (100 cycles; Illumina, 20012865) on an Illumina NovaSeq 6000 sequencer. The quality control assessments, generation of libraries and sequencing run were all performed at the Next Generation Sequencing Platform, University of Bern, Switzerland.

Data generated from individual samples (>30 million read per sample, single read 50-mers) were mapped separately against the GRCm38 murine reference genome. Gene expression was calculated for individual transcripts as reads per kilobase per million bases mapped (RPKM). All transcriptomic analyses were performed using CLC Genomics Workbench 20 (Qiagen, Aarhus).

Differentially expressed genes (DEGs) were identified by calculating fold changes in expression, p-values were corrected by taking false discovery rate (FDR) for multiple comparison into account.

Mus Musculus EBI Gene Ontology Annotation Database was used to execute Gene ontology (GO) Enrichment Analyses for biological processes. Gene identifiers for DEGs (absolute FC > 5, RPKM > 2) were used as input and identification of significantly enriched GO categories. P-values for specific GO categories were generated after Bonferroni correction for multiple testing. Z-scores, used as indicator for activation of biological processes (positive value) or inactivation (negative value), were calculated based on the expression fold change as follows:

$$z\text{-score} = \frac{(\text{up-regulated} - \text{down-regulated})}{\sqrt{\text{total count}}}$$

### Antibodies for immunofluorescence and flow cytometry

HCoV-229E infection was detected by staining permeabilized cells for N protein (1:1000, Anticuerpo Monoclonal, 1E7, Ingenasa) and a secondary donkey anti-mouse AlexaFluor488-conjugated antibody (1:400, Jackson Immuno Research). HCoV-OC43 infection was detected by staining permeabilized cells for nucleoprotein (1:500, MAB9013, Millipore) and a secondary goat anti-mouse AlexaFluor488-conjugated antibody (1:2000, Thermo Fisher Scientific). SARS-CoV-2 infection was detected by staining permeabilized cells for dsRNA (1:500 for immunofluorescence and 1:10,000 for flow cytometry, J2, Scicons) and a secondary goat anti-mouse AlexaFluor488-conjugated antibody. ZIKV infected cells were stained for viral antigen using a monoclonal antibody anti-flavivirus group antigen 4G2 (1:500, MAB10216; RRID: AB\_827205, EMD Millipore) as primary antibody and AlexaFluor488 (1:1000, A-11001, RRID: AB\_2534069, Thermo Fisher Scientific) as

secondary antibody. CD13 was stained anti-human CD13 Antibody, APC conjugated (1:20, clone WM15, BioLegend). DPP4 was stained using anti-human DPP4, FITC conjugated (1:20, clone BA5b, BioLegend). The following antibodies were used to differentiate immune cell populations: anti-CD3 $\epsilon$ -PE (1:200, 145-2C11, Tonbo Biosciences), anti-CD3 $\epsilon$ -FITC (1:200, 145-2C11, Tonbo Biosciences), anti-CD11c-PECy7 (1:800, N418, Tonbo Biosciences), anti-Ly6G-PE (1:400, 1A8, Tonbo Biosciences), anti-Ly6G-FITC (1:400, 1A8, Tonbo Biosciences), anti-Ly6g-PerCPCy5.5 (1:400, 1A8, Tonbo Biosciences), anti-CD11b-PECy7 (1:800, M1/70, Tonbo Biosciences), anti-CD19-PE (1:800, 6D5, BioLegend), anti-CD19-FITC (1:400, 1D3, Tonbo Biosciences), anti-CD19-PECy5 (1:800, 6D5, BioLegend), anti-F4/80-PECy5 (1:200, BM8, BioLegend), anti-Nkp46-PECy7 (1:100, 29A1.4, BioLegend), anti-CD4-PECy5 (1:800, GK1.5, Tonbo Biosciences), and anti-CD8-PECy7 (1:800, 53-6.7, Tonbo Biosciences).

### **Software**

For sequence analysis, Geneious Prime (Geneious), SeqMan Pro (DNASTAR), and ApE were used. Biorender was used to generate cartoons. Adobe Illustrator was used to assemble figure panels.

## Tables

Supplementary Table 1. Large scale ISG screen: HCoV-229E in Huh7 at 24 h (page 1 of 2)

| Gene     | Percent Infected | Z score | Gene     | Percent Infected | Z score | Gene      | Percent Infected | Z score | Gene     | Percent Infected | Z score |
|----------|------------------|---------|----------|------------------|---------|-----------|------------------|---------|----------|------------------|---------|
| CDKN1A   | 135.7            | 3.52    | CXCL10   | 107.1            | 1.01    | ANKRD22   | 101.8            | 0.55    | MTHFD2L  | 98.0             | 0.22    |
| SSBP3    | 129.8            | 3.00    | ALDH1A1  | 106.9            | 1.00    | THBD      | 101.8            | 0.55    | NAPA     | 98.0             | 0.21    |
| ZNF295   | 128.2            | 2.86    | TMEM51   | 106.5            | 0.96    | GLRX      | 101.7            | 0.54    | TNFAIP6  | 97.8             | 0.20    |
| MAFB     | 127.2            | 2.78    | HES4     | 106.3            | 0.94    | FAM134B   | 101.2            | 0.50    | ADM      | 97.7             | 0.19    |
| PAK3     | 126.1            | 2.68    | MX1      | 106.3            | 0.94    | MSR1      | 101.1            | 0.49    | CCL8     | 97.7             | 0.19    |
| CASP7    | 121.1            | 2.24    | IL28RA   | 106.2            | 0.93    | BCL2L14   | 101.1            | 0.49    | MCL1     | 97.6             | 0.18    |
| IFIT2    | 121.0            | 2.23    | SOCS1    | 105.9            | 0.91    | DNAPT6    | 101.1            | 0.48    | PADI2    | 97.6             | 0.18    |
| HK2      | 120.7            | 2.20    | NMI      | 105.8            | 0.90    | PRAME     | 101.0            | 0.48    | CCL19    | 97.6             | 0.18    |
| SLC25A28 | 119.7            | 2.11    | CPT1A    | 105.7            | 0.89    | CNP       | 100.9            | 0.47    | BATF2    | 97.5             | 0.17    |
| STAT3    | 118.3            | 1.99    | PARP12   | 105.7            | 0.89    | USP18     | 100.9            | 0.47    | CXCL9    | 97.4             | 0.17    |
| GCH1     | 118.1            | 1.98    | HCP5     | 105.5            | 0.87    | IFI16     | 100.8            | 0.46    | CREB3L3  | 97.4             | 0.16    |
| CTCFL    | 118.1            | 1.98    | SLC15A3  | 105.5            | 0.87    | PNRC1     | 100.7            | 0.45    | GMPR     | 97.3             | 0.16    |
| SOCS2    | 118.0            | 1.97    | ATF3     | 105.4            | 0.86    | NCF1      | 100.7            | 0.45    | B4GALT5  | 97.3             | 0.15    |
| AHNAK2   | 117.8            | 1.95    | PPM1K    | 105.3            | 0.85    | PSMB8     | 100.6            | 0.45    | TRAFD1   | 97.2             | 0.15    |
| CD80     | 117.1            | 1.89    | CD74     | 104.9            | 0.82    | LOC400759 | 100.6            | 0.45    | MAFF     | 97.2             | 0.14    |
| EPAS1    | 117.0            | 1.88    | DTX3L    | 104.7            | 0.80    | IRF7      | 100.6            | 0.44    | PDGFRL   | 97.1             | 0.14    |
| ARHGAP17 | 116.4            | 1.83    | DEFB1    | 104.6            | 0.80    | HSPA6     | 100.5            | 0.44    | CEACAM1  | 97.0             | 0.13    |
| BCL3     | 116.2            | 1.81    | IGFBP2   | 104.6            | 0.79    | FLJ39739  | 100.5            | 0.44    | CHMP5    | 97.0             | 0.12    |
| SMAD3    | 115.3            | 1.73    | MKX      | 104.2            | 0.76    | MCOLN2    | 100.4            | 0.43    | C4orf32  | 96.9             | 0.12    |
| XAF1     | 114.9            | 1.70    | FLJ23556 | 104.2            | 0.76    | CRY1      | 100.4            | 0.43    | CLEC4A   | 96.8             | 0.11    |
| DDX3X    | 113.3            | 1.55    | UBA7     | 104.0            | 0.74    | N4BP1     | 100.3            | 0.42    | PFKFB4   | 96.7             | 0.11    |
| IFI44L   | 112.6            | 1.49    | MICB     | 104.0            | 0.74    | TRIM5     | 100.2            | 0.41    | CCL2     | 96.7             | 0.11    |
| TREX1    | 111.9            | 1.43    | RBM43    | 104.0            | 0.74    | ERLIN1    | 99.9             | 0.39    | MDA5     | 96.7             | 0.10    |
| HESX1    | 111.8            | 1.42    | TBX3     | 103.9            | 0.73    | PSCD1     | 99.9             | 0.38    | TRIM25   | 96.6             | 0.10    |
| STAP1    | 111.4            | 1.39    | TNK2     | 103.7            | 0.72    | IL6ST     | 99.7             | 0.37    | RBM25    | 96.6             | 0.10    |
| HPSE     | 111.1            | 1.36    | LGMN     | 103.7            | 0.72    | EHD4      | 99.7             | 0.36    | PCTK2    | 96.5             | 0.09    |
| FNDC4    | 110.9            | 1.34    | ARHGEF3  | 103.6            | 0.70    | EXT1      | 99.6             | 0.35    | INDO     | 96.5             | 0.09    |
| PUS1     | 110.8            | 1.33    | VEGFC    | 103.5            | 0.70    | BLZF1     | 99.5             | 0.35    | RIPK2    | 96.5             | 0.08    |
| RSAD2    | 110.7            | 1.33    | RPL22    | 103.4            | 0.69    | AQP9      | 99.5             | 0.34    | LRG1     | 96.4             | 0.08    |
| TRIM34   | 110.7            | 1.33    | ZNF385B  | 103.4            | 0.69    | ANGPTL1   | 99.4             | 0.34    | ABLM3    | 96.4             | 0.07    |
| TMEM49   | 110.6            | 1.32    | SP110    | 103.4            | 0.69    | IFITM1    | 99.4             | 0.34    | GZMB     | 96.2             | 0.06    |
| MT1G     | 110.5            | 1.31    | DHX58    | 103.2            | 0.67    | FCGR1A    | 99.3             | 0.33    | MAFF     | 96.2             | 0.06    |
| TFEC     | 110.4            | 1.30    | PRKD2    | 103.1            | 0.67    | DUSP5     | 99.3             | 0.33    | C9orf19  | 96.1             | 0.05    |
| ARNTL    | 110.2            | 1.29    | SIRPA    | 103.0            | 0.66    | Empty 1   | 99.1             | 0.32    | RGS1     | 96.1             | 0.05    |
| C15orf48 | 109.9            | 1.26    | IRF2     | 103.0            | 0.65    | SIGLEC1   | 98.9             | 0.30    | PBEF1    | 96.0             | 0.04    |
| BAG1     | 109.8            | 1.25    | SAA1     | 102.9            | 0.65    | TRIM14    | 98.9             | 0.29    | GEM      | 95.9             | 0.03    |
| NT5C3    | 109.5            | 1.23    | ADFP     | 102.9            | 0.65    | P2RY6     | 98.9             | 0.29    | DCP1A    | 95.9             | 0.03    |
| SERPINB9 | 109.4            | 1.21    | TNFSF10  | 102.9            | 0.64    | GALNT2    | 98.8             | 0.29    | S100A8   | 95.8             | 0.02    |
| SERPINE1 | 109.3            | 1.20    | FUT4     | 102.9            | 0.64    | BUB1      | 98.8             | 0.29    | TNFAIP3  | 95.8             | 0.02    |
| KIAA0040 | 108.3            | 1.12    | FKBP5    | 102.5            | 0.61    | VAMP5     | 98.7             | 0.28    | GBP2     | 95.7             | 0.02    |
| HLA-E    | 108.0            | 1.09    | CCDC92   | 102.3            | 0.60    | ETV7      | 98.6             | 0.27    | SAMHD1   | 95.7             | 0.02    |
| C10orf10 | 108.0            | 1.09    | ZNF313   | 102.3            | 0.60    | MT1L      | 98.5             | 0.26    | TRIM38   | 95.7             | 0.02    |
| SCARB2   | 107.9            | 1.09    | OPTN     | 102.3            | 0.59    | CCL5      | 98.5             | 0.26    | IFI30    | 95.7             | 0.02    |
| C9orf91  | 107.9            | 1.08    | ETV6     | 102.3            | 0.59    | IDO1      | 98.4             | 0.25    | C19orf66 | 95.6             | 0.01    |
| MS4A4A   | 107.8            | 1.08    | LINCRC   | 102.3            | 0.59    | Hercb     | 98.3             | 0.24    | PADI2    | 95.6             | 0.00    |
| JUNB     | 107.8            | 1.07    | CD69     | 102.0            | 0.56    | LAMP3     | 98.2             | 0.24    | IFI6     | 95.3             | -0.02   |
| STEAP4   | 107.6            | 1.06    | CXCL11   | 102.0            | 0.56    | MTHFD2L   | 98.2             | 0.23    | NFIL3    | 95.2             | -0.03   |
| COMMD3   | 107.6            | 1.05    | MT1M     | 102.0            | 0.56    | TXNIP     | 98.1             | 0.22    | GBP5     | 95.2             | -0.03   |
| PHF15    | 107.5            | 1.05    | NOS2A    | 102.0            | 0.56    | SAMD4A    | 98.0             | 0.22    | RTP4     | 95.1             | -0.03   |
| LEPR     | 107.4            | 1.04    | DDIT4    | 102.0            | 0.56    | ANKFY1    | 98.0             | 0.22    | PDK1     | 95.1             | -0.04   |

**Supplementary Table 1. Large scale ISG screen: HCoV-229E in Huh7 at 24 h (page 2 of 2)**

| Gene     | Percent Infected | Z score | Gene     | Percent Infected | Z score | Gene     | Percent Infected | Z score | Gene         | Percent Infected | Z score |
|----------|------------------|---------|----------|------------------|---------|----------|------------------|---------|--------------|------------------|---------|
| MT1F     | 95.1             | -0.04   | PTMA     | 91.5             | -0.36   | NOD2     | 88.3             | -0.63   | SAT1         | 79.8             | -1.38   |
| ATP10D   | 94.8             | -0.06   | ISG15    | 91.3             | -0.37   | C22orf28 | 88.3             | -0.63   | BST2         | 79.6             | -1.39   |
| CD38     | 94.8             | -0.06   | OAS1     | 91.3             | -0.37   | IFI35    | 88.2             | -0.65   | UPP2         | 79.2             | -1.43   |
| C5orf27  | 94.8             | -0.07   | IL1R     | 91.2             | -0.38   | ABTB2    | 87.9             | -0.67   | CYP11B1      | 79.1             | -1.44   |
| APOL2    | 94.8             | -0.07   | THOC4    | 91.2             | -0.38   | ZNF107   | 87.7             | -0.69   | ELF1         | 78.9             | -1.45   |
| LGALS9   | 94.7             | -0.07   | AIM2     | 91.2             | -0.38   | RASGEF1B | 87.6             | -0.69   | NCOA3        | 78.1             | -1.53   |
| CRP      | 94.7             | -0.07   | CMAH     | 91.1             | -0.39   | IRF9     | 87.4             | -0.71   | APOL3        | 77.9             | -1.55   |
| IL17RB   | 94.7             | -0.08   | IL15     | 91.0             | -0.40   | MAFF     | 87.3             | -0.72   | ENPP1        | 77.8             | -1.56   |
| FNDC3B   | 94.5             | -0.09   | MOV10    | 90.9             | -0.40   | EIF3EIP  | 87.3             | -0.72   | GBP3         | 77.7             | -1.56   |
| CX3CL1   | 94.5             | -0.09   | IFI44    | 90.9             | -0.41   | HEG1     | 87.2             | -0.73   | PI4K2B       | 77.5             | -1.58   |
| PABPC4   | 94.3             | -0.10   | IFIT1    | 90.9             | -0.41   | WARS     | 87.2             | -0.73   | MAP3K5       | 77.0             | -1.62   |
| TRIM56   | 94.3             | -0.11   | MT1H     | 90.8             | -0.41   | PIM3     | 86.9             | -0.76   | APOL1        | 76.9             | -1.63   |
| LGALS3   | 94.1             | -0.12   | UNC93B1  | 90.7             | -0.42   | PMM2     | 86.8             | -0.76   | RAB27A       | 76.4             | -1.68   |
| Empty 2  | 94.0             | -0.13   | MASTL    | 90.7             | -0.43   | MX2      | 86.8             | -0.77   | CD274        | 75.5             | -1.76   |
| GBP1     | 93.9             | -0.14   | ARG2     | 90.6             | -0.43   | FBXO6    | 86.5             | -0.80   | IFI27        | 74.8             | -1.82   |
| PMAIP1   | 93.9             | -0.14   | PCTK3    | 90.5             | -0.44   | ISG20    | 86.2             | -0.81   | RNF24        | 73.4             | -1.94   |
| TGFB1    | 93.8             | -0.15   | RGL-1    | 90.4             | -0.45   | STAT2    | 86.2             | -0.82   | UNC84B       | 73.3             | -1.95   |
| TAP1     | 93.8             | -0.15   | MARCK    | 90.4             | -0.45   | BLVRA    | 86.1             | -0.82   | G6PC         | 73.3             | -1.95   |
| FAM70A   | 93.8             | -0.15   | CD163    | 90.3             | -0.45   | CLEC4D   | 86.1             | -0.83   | FAM46A       | 73.1             | -1.96   |
| TNFSF13B | 93.8             | -0.15   | FER1L3   | 90.3             | -0.46   | NUP50    | 85.6             | -0.87   | supernatantN | 73.0             | -1.98   |
| TIMP1    | 93.6             | -0.17   | GK       | 90.3             | -0.46   | MYD88    | 85.6             | -0.87   | SPSB1        | 72.9             | -1.98   |
| FAM348   | 93.4             | -0.18   | CCL4     | 90.3             | -0.46   | GJA4     | 85.3             | -0.90   | SLFN12       | 70.7             | -2.17   |
| RBCK1    | 93.4             | -0.19   | SLFN5    | 90.1             | -0.47   | HLA-C    | 85.3             | -0.90   | HERC5        | 69.0             | -2.33   |
| ZBP1     | 93.3             | -0.19   | CCNA1    | 90.1             | -0.47   | SPTLC2   | 85.2             | -0.91   | OAS2         | 68.5             | -2.37   |
| B2M      | 93.3             | -0.20   | IRF2     | 90.1             | -0.48   | IRF1     | 85.0             | -0.92   | NRN1         | 66.2             | -2.57   |
| PML      | 93.2             | -0.20   | NDC80    | 90.1             | -0.48   | UBE2L6   | 85.0             | -0.93   | IFIH2        | 64.8             | -2.69   |
| GTPBP2   | 93.2             | -0.21   | CASP1    | 90.0             | -0.48   | LMO2     | 84.9             | -0.93   | IFITM2       | 61.2             | -3.01   |
| BTN3A3   | 93.1             | -0.22   | HERC6    | 89.8             | -0.50   | CFB      | 84.8             | -0.94   | FAM46C       | 59.4             | -3.17   |
| KIAA0082 | 93.1             | -0.22   | CCDC75   | 89.8             | -0.50   | STAT1    | 84.7             | -0.95   | STARD5       | 58.7             | -3.23   |
| CSDA     | 92.9             | -0.23   | C4orf33  | 89.7             | -0.51   | SECTM1   | 84.3             | -0.98   | SLC1A1       | 53.5             | -3.68   |
| IFNGR1   | 92.8             | -0.24   | AMPH     | 89.7             | -0.51   | IFITM3   | 83.6             | -1.05   | TLR3         | 44.5             | -4.47   |
| RNF19B   | 92.8             | -0.24   | ADAMDEC1 | 89.6             | -0.52   | RARRES3  | 83.5             | -1.05   | SQLE         | 43.6             | -4.55   |
| TAGAP    | 92.7             | -0.25   | EPSTI1   | 89.6             | -0.52   | IMPA2    | 83.3             | -1.07   | LY6E         | 6.7              | -7.78   |
| SLC25A30 | 92.7             | -0.25   | CCR1     | 89.4             | -0.53   | MAB21L2  | 83.1             | -1.09   |              |                  |         |
| ZC3HAV1  | 92.7             | -0.25   | PLSCR1   | 89.4             | -0.53   | MAX      | 83.1             | -1.09   |              |                  |         |
| CCND3    | 92.5             | -0.26   | GPX2     | 89.2             | -0.55   | PFKFB3   | 83.1             | -1.09   |              |                  |         |
| CES1     | 92.5             | -0.26   | SLC16A1  | 89.2             | -0.55   | KIAA1618 | 82.9             | -1.11   |              |                  |         |
| WHDC1    | 92.4             | -0.27   | ODC1     | 89.2             | -0.55   | SCO2     | 82.8             | -1.12   |              |                  |         |
| CEBPD    | 92.4             | -0.28   | NPAS2    | 89.2             | -0.56   | GBP4     | 82.7             | -1.12   |              |                  |         |
| HSH2D    | 92.3             | -0.28   | TDRD7    | 89.1             | -0.56   | FFAR2    | 82.7             | -1.12   |              |                  |         |
| HLA-F    | 92.2             | -0.29   | FAM125B  | 89.1             | -0.57   | C6orf150 | 82.5             | -1.14   |              |                  |         |
| ADAR     | 92.2             | -0.29   | GCA      | 89.0             | -0.57   | FLT1     | 82.1             | -1.18   |              |                  |         |
| AKT3     | 92.1             | -0.30   | SERPING1 | 88.7             | -0.59   | BIRC3    | 82.1             | -1.18   |              |                  |         |
| CCDC109B | 92.1             | -0.30   | PSMB9    | 88.7             | -0.60   | TLR7     | 82.1             | -1.18   |              |                  |         |
| APOL6    | 92.0             | -0.31   | AXUD1    | 88.7             | -0.60   | TAP2     | 81.7             | -1.21   |              |                  |         |
| RNASE4   | 91.9             | -0.32   | LAP3     | 88.6             | -0.60   | CLEC2B   | 81.4             | -1.23   |              |                  |         |
| PXK      | 91.8             | -0.32   | ULK4     | 88.6             | -0.61   | CD9      | 81.3             | -1.25   |              |                  |         |
| Empty 3  | 91.8             | -0.33   | OASL     | 88.6             | -0.61   | C1S      | 81.2             | -1.26   |              |                  |         |
| HLA-G    | 91.7             | -0.33   | RASSF4   | 88.4             | -0.63   | IL15RA   | 81.1             | -1.26   |              |                  |         |
| GAK      | 91.5             | -0.35   | LIPA     | 88.3             | -0.63   | C2orf31  | 81.1             | -1.27   |              |                  |         |

**Supplementary Table 2. Large scale ISG screen: HCoV-229E in Huh7 at 48 h (page 1 of 2)**

| Gene      | Percent Infected | Z score | Gene     | Percent Infected | Z score | Gene     | Percent Infected | Z score | Gene     | Percent Infected | Z score |
|-----------|------------------|---------|----------|------------------|---------|----------|------------------|---------|----------|------------------|---------|
| ZNF107    | 131.1            | 3.00    | GAK      | 103.7            | 0.73    | WARS     | 101.2            | 0.53    | TLR7     | 98.8             | 0.33    |
| PAK3      | 119.7            | 2.05    | C5orf27  | 103.7            | 0.73    | MT1H     | 101.2            | 0.53    | IGFBP2   | 98.7             | 0.32    |
| PNRC1     | 118.4            | 1.95    | CLEC4D   | 103.6            | 0.72    | C15orf48 | 101.1            | 0.52    | IFIT1    | 98.7             | 0.32    |
| LEPR      | 116.9            | 1.83    | B4GALT5  | 103.6            | 0.72    | SECTM1   | 101.1            | 0.52    | COMMD3   | 98.7             | 0.32    |
| HSPA6     | 116.6            | 1.80    | SIGLEC1  | 103.5            | 0.72    | SSBP3    | 101.0            | 0.52    | GALNT2   | 98.7             | 0.32    |
| CDKN1A    | 116.4            | 1.78    | SMAD3    | 103.4            | 0.71    | RPL22    | 101.0            | 0.51    | TDRD7    | 98.6             | 0.31    |
| IL28RA    | 113.2            | 1.52    | GEM      | 103.3            | 0.70    | TRIM34   | 101.0            | 0.51    | NCF1     | 98.6             | 0.31    |
| ZBP1      | 112.6            | 1.47    | OASL     | 103.3            | 0.70    | LMO2     | 101.0            | 0.51    | CXCL11   | 98.6             | 0.31    |
| KIAA0040  | 111.5            | 1.38    | MAFF     | 103.2            | 0.70    | CD69     | 100.8            | 0.50    | CD274    | 98.6             | 0.31    |
| EPAS1     | 111.3            | 1.36    | SLC16A1  | 103.1            | 0.69    | MCL1     | 100.7            | 0.49    | SERPINB9 | 98.4             | 0.30    |
| MAFB      | 109.8            | 1.24    | NAPA     | 103.1            | 0.69    | FAM125B  | 100.7            | 0.48    | UBA7     | 98.3             | 0.29    |
| RIPK2     | 109.5            | 1.21    | SP110    | 103.1            | 0.69    | Empty 1  | 100.6            | 0.48    | BAG1     | 98.2             | 0.28    |
| HES4      | 109.4            | 1.20    | HCP5     | 103.0            | 0.68    | PFKFB4   | 100.5            | 0.47    | AQP9     | 98.0             | 0.27    |
| AHNAK2    | 109.0            | 1.17    | Herclb   | 103.0            | 0.67    | PRKD2    | 100.5            | 0.47    | LAP3     | 98.0             | 0.27    |
| BATF2     | 108.8            | 1.16    | RTP4     | 103.0            | 0.67    | NMI      | 100.4            | 0.46    | MT1G     | 97.8             | 0.25    |
| PLEKHA4   | 108.7            | 1.15    | AXUD1    | 102.9            | 0.67    | PML      | 100.4            | 0.46    | GPX2     | 97.7             | 0.24    |
| ALDH1A1   | 108.4            | 1.12    | ADFP     | 102.7            | 0.65    | HLA-G    | 100.4            | 0.46    | DEFB1    | 97.7             | 0.24    |
| DDX60     | 108.2            | 1.11    | SPTLC2   | 102.7            | 0.65    | ADM      | 100.3            | 0.46    | PDK1     | 97.7             | 0.24    |
| APOL6     | 108.1            | 1.10    | MICB     | 102.6            | 0.65    | FUT4     | 100.2            | 0.45    | IFIT2    | 97.7             | 0.24    |
| SLC25A28  | 108.1            | 1.10    | P2RY6    | 102.6            | 0.64    | TMEM51   | 100.1            | 0.44    | C10orf10 | 97.7             | 0.24    |
| CTCFL     | 107.9            | 1.08    | CMAH     | 102.6            | 0.64    | TLR3     | 100.1            | 0.44    | LAMP3    | 97.6             | 0.23    |
| SCARB2    | 107.4            | 1.04    | SAA1     | 102.6            | 0.64    | DCP1A    | 100.0            | 0.43    | FER1L3   | 97.6             | 0.23    |
| TNK2      | 107.4            | 1.04    | JUNB     | 102.5            | 0.64    | C6orf150 | 100.0            | 0.43    | C1S      | 97.5             | 0.23    |
| MSR1      | 107.4            | 1.04    | IL17RB   | 102.5            | 0.64    | PHF15    | 99.9             | 0.42    | NDC80    | 97.5             | 0.22    |
| TAGAP     | 107.0            | 1.01    | PMM2     | 102.4            | 0.63    | PCTK2    | 99.9             | 0.42    | UNC84B   | 97.4             | 0.21    |
| PCTK3     | 106.6            | 0.98    | SIRPA    | 102.4            | 0.63    | TBX3     | 99.8             | 0.41    | APOL3    | 97.2             | 0.20    |
| DDX3X     | 106.3            | 0.95    | BCL3     | 102.4            | 0.63    | OAS1     | 99.8             | 0.41    | C4orf32  | 97.0             | 0.18    |
| IL6ST     | 106.2            | 0.94    | TNFSF10  | 102.4            | 0.63    | CCNA1    | 99.7             | 0.41    | TNFSF13B | 97.0             | 0.18    |
| PUS1      | 105.8            | 0.91    | PSMB8    | 102.3            | 0.62    | PRAME    | 99.6             | 0.40    | STAT3    | 96.9             | 0.18    |
| ZC3HAV1   | 105.7            | 0.90    | IFI44    | 102.3            | 0.62    | USP18    | 99.6             | 0.40    | CCR1     | 96.9             | 0.17    |
| HPSE      | 105.5            | 0.89    | MT1M     | 102.3            | 0.62    | SAMHD1   | 99.6             | 0.40    | NOS2A    | 96.9             | 0.17    |
| DDIT4     | 105.5            | 0.88    | ARNTL    | 102.1            | 0.61    | FLJ39739 | 99.6             | 0.40    | TFEC     | 96.9             | 0.17    |
| LOC400759 | 105.3            | 0.87    | TAP2     | 102.0            | 0.60    | GBP2     | 99.6             | 0.40    | GCA      | 96.8             | 0.17    |
| RSAD2     | 105.2            | 0.86    | SLC15A3  | 102.0            | 0.59    | CASP7    | 99.6             | 0.39    | RAB27A   | 96.8             | 0.16    |
| NT5C3     | 105.0            | 0.84    | FAM134B  | 102.0            | 0.59    | FNDC3B   | 99.6             | 0.39    | DDX58    | 96.7             | 0.16    |
| CX3CL1    | 104.9            | 0.83    | HK2      | 102.0            | 0.59    | HLA-C    | 99.5             | 0.39    | TRIM56   | 96.7             | 0.16    |
| VAMP5     | 104.8            | 0.83    | HLA-F    | 102.0            | 0.59    | RBM43    | 99.5             | 0.39    | FAM348   | 96.6             | 0.15    |
| IFNGR1    | 104.8            | 0.82    | CYP1B1   | 101.9            | 0.58    | HEG1     | 99.4             | 0.38    | MAX      | 96.5             | 0.14    |
| STAT1     | 104.6            | 0.81    | KIAA1618 | 101.9            | 0.58    | CCDC109B | 99.4             | 0.38    | ADAMDEC1 | 96.5             | 0.14    |
| LINCR     | 104.6            | 0.81    | IFITM1   | 101.7            | 0.57    | CLEC4A   | 99.4             | 0.38    | TRIM38   | 96.5             | 0.14    |
| MAFF      | 104.5            | 0.80    | NFIL3    | 101.7            | 0.57    | CD80     | 99.3             | 0.37    | EHD4     | 96.4             | 0.14    |
| N4BP1     | 104.5            | 0.80    | CD163    | 101.6            | 0.56    | TIMP1    | 99.2             | 0.36    | PBEF1    | 96.4             | 0.13    |
| S100A8    | 104.4            | 0.80    | CRP      | 101.5            | 0.56    | MS4A4A   | 99.2             | 0.36    | CXCL10   | 96.4             | 0.13    |
| TGFB1     | 104.3            | 0.78    | IFI44L   | 101.5            | 0.55    | GBP1     | 99.1             | 0.36    | MTHFD2L  | 96.3             | 0.13    |
| TXNIP     | 104.2            | 0.78    | MAFF     | 101.4            | 0.54    | ETV6     | 99.1             | 0.35    | BIRC3    | 96.3             | 0.13    |
| MKX       | 104.2            | 0.78    | ARHGEF3  | 101.3            | 0.54    | LRG1     | 99.0             | 0.35    | PXK      | 96.2             | 0.12    |
| ATF3      | 104.0            | 0.76    | C4orf33  | 101.3            | 0.54    | HLA-E    | 98.9             | 0.34    | IL15     | 96.1             | 0.11    |
| FKBP5     | 103.8            | 0.75    | BUB1     | 101.3            | 0.54    | PSCD1    | 98.9             | 0.34    | GBP3     | 96.1             | 0.10    |
| SERPINE1  | 103.8            | 0.75    | STAP1    | 101.3            | 0.53    | EPSTI1   | 98.9             | 0.34    | ULK4     | 96.0             | 0.10    |
| ZNF295    | 103.8            | 0.74    |          |                  |         | RBCK1    | 98.8             | 0.33    | KIAA0082 | 96.0             | 0.10    |

**Supplementary Table 2. Large scale ISG screen: HCoV-229E in Huh7 at 48 h (page 2 of 2)**

| ./.      | Percent Infected | Z score | Gene         | Percent Infected | Z score | Gene    | Percent Infected | Z score | Gene     | Percent Infected | Z score |
|----------|------------------|---------|--------------|------------------|---------|---------|------------------|---------|----------|------------------|---------|
| RGS1     | 96.0             | 0.10    | APOL2        | 93.6             | -0.10   | DNATP6  | 90.9             | -0.32   | RBM25    | 83.8             | -0.91   |
| MARCK    | 96.0             | 0.10    | MT1F         | 93.5             | -0.11   | IRF1    | 90.9             | -0.32   | EIF2AK2  | 83.1             | -0.97   |
| IFI16    | 96.0             | 0.10    | ABTB2        | 93.5             | -0.11   | SAMD4A  | 90.8             | -0.33   | SOCS2    | 82.3             | -1.04   |
| CCL19    | 95.9             | 0.09    | PMAIP1       | 93.5             | -0.11   | TNFAIP3 | 90.7             | -0.34   | FNDC4    | 81.9             | -1.07   |
| FLJ11286 | 95.8             | 0.08    | CD38         | 93.5             | -0.11   | TRIM21  | 90.6             | -0.35   | ANGPTL1  | 81.8             | -1.08   |
| CEBPD    | 95.8             | 0.08    | RNASE4       | 93.5             | -0.11   | FCGR1A  | 90.0             | -0.40   | GBP4     | 81.7             | -1.08   |
| MX2      | 95.8             | 0.08    | AKT3         | 93.4             | -0.12   | RASSF4  | 89.9             | -0.41   | B2M      | 81.7             | -1.08   |
| TAP1     | 95.8             | 0.08    | SERPING1     | 93.3             | -0.12   | ETV7    | 89.8             | -0.41   | CNP      | 81.5             | -1.10   |
| PARP12   | 95.7             | 0.08    | SAT1         | 93.3             | -0.13   | CSDA    | 89.8             | -0.41   | HERC6    | 81.4             | -1.11   |
| UBE2L6   | 95.7             | 0.07    | supernatantN | 93.3             | -0.13   | FBXO6   | 89.8             | -0.41   | LGALS3   | 81.2             | -1.12   |
| DTX3L    | 95.7             | 0.07    | MX1          | 93.3             | -0.13   | VEGFC   | 89.8             | -0.41   | IFI27    | 81.0             | -1.14   |
| IFI30    | 95.7             | 0.07    | ENPP1        | 93.1             | -0.14   | G6PC    | 89.7             | -0.42   | MAB21L2  | 80.0             | -1.22   |
| EXT1     | 95.4             | 0.05    | XAF1         | 93.1             | -0.14   | BLZF1   | 89.7             | -0.42   | PSMB9    | 78.6             | -1.34   |
| CHMP5    | 95.4             | 0.05    | CEACAM1      | 93.0             | -0.15   | CFB     | 89.4             | -0.45   | PLSCR1   | 78.5             | -1.34   |
| CXCL9    | 95.4             | 0.05    | CCDC75       | 92.9             | -0.16   | IRF7    | 89.4             | -0.45   | LIPA     | 78.3             | -1.37   |
| ABLM3    | 95.2             | 0.03    | PABPC4       | 92.9             | -0.16   | CCND3   | 89.1             | -0.47   | TMEM49   | 78.1             | -1.38   |
| FAM70A   | 95.2             | 0.03    | C5orf27      | 92.8             | -0.17   | RGL-1   | 89.0             | -0.48   | IRF2     | 77.8             | -1.40   |
| TRIM25   | 95.2             | 0.03    | ZNF313       | 92.8             | -0.17   | ANKRD22 | 89.0             | -0.48   | IL1R     | 77.5             | -1.43   |
| ERLIN1   | 95.2             | 0.03    | FLJ23556     | 92.8             | -0.17   | FFAR2   | 88.9             | -0.48   | NPAS2    | 75.8             | -1.57   |
| WHDC1    | 95.2             | 0.03    | IFITM3       | 92.6             | -0.18   | DHX58   | 88.7             | -0.50   | IFI6     | 73.9             | -1.72   |
| RARRES3  | 95.2             | 0.03    | IRF9         | 92.6             | -0.18   | IL15RA  | 88.6             | -0.51   | RASGEF1B | 73.4             | -1.76   |
| IRF2     | 95.1             | 0.03    | NUP50        | 92.6             | -0.18   | EIF3EIP | 88.5             | -0.52   | OAS3     | 73.4             | -1.77   |
| ZNF385B  | 95.1             | 0.03    | CD9          | 92.5             | -0.19   | APOL1   | 88.3             | -0.53   | HERC5    | 71.5             | -1.93   |
| CCL2     | 95.1             | 0.03    | CES1         | 92.5             | -0.19   | TNFAIP6 | 88.3             | -0.53   | SPSB1    | 71.3             | -1.94   |
| MCOLN2   | 95.0             | 0.02    | STAT2        | 92.3             | -0.20   | IDO1    | 88.2             | -0.55   | ELF1     | 71.0             | -1.97   |
| CCDC92   | 95.0             | 0.02    | SLFN12       | 92.3             | -0.21   | PADI2   | 88.1             | -0.55   | IFITM2   | 70.7             | -1.99   |
| GLRX     | 94.9             | 0.01    | ARG2         | 92.3             | -0.21   | NOD2    | 88.0             | -0.56   | NRN1     | 65.1             | -2.45   |
| INDO     | 94.9             | 0.01    | TRAFFD1      | 92.2             | -0.22   | LGMN    | 88.0             | -0.56   | FAM46A   | 64.4             | -2.52   |
| RNF19B   | 94.9             | 0.01    | RNF24        | 92.2             | -0.22   | ADAR    | 87.7             | -0.59   | BST2     | 62.7             | -2.65   |
| CPT1A    | 94.9             | 0.01    | NCOA3        | 92.1             | -0.22   | GK      | 87.6             | -0.60   | STARD5   | 56.9             | -3.13   |
| TRIM14   | 94.9             | 0.01    | PDGFRL       | 92.0             | -0.23   | LGALS9  | 87.4             | -0.61   | MDA5     | 56.0             | -3.21   |
| GCH1     | 94.8             | 0.00    | ISG20        | 92.0             | -0.23   | STEAP4  | 87.3             | -0.62   | IFIH2    | 51.8             | -3.55   |
| C9orf91  | 94.7             | 0.00    | SOCS1        | 91.9             | -0.24   | C9orf19 | 87.3             | -0.62   | BCL2L14  | 48.7             | -3.81   |
| GMPR     | 94.7             | -0.01   | PIM3         | 91.8             | -0.24   | IFI35   | 87.1             | -0.64   | OAS2     | 37.8             | -4.71   |
| THOC4    | 94.7             | -0.01   | UNC93B1      | 91.8             | -0.25   | PI4K2B  | 86.9             | -0.65   | SLC1A1   | 34.1             | -5.01   |
| ATP10D   | 94.6             | -0.01   | CCL4         | 91.8             | -0.25   | GTPBP2  | 86.7             | -0.67   | SQLE     | 17.5             | -6.39   |
| BLVRA    | 94.6             | -0.02   | MT1L         | 91.6             | -0.26   | ANKFY1  | 86.0             | -0.72   | LY6E     | 4.7              | -7.45   |
| ISG15    | 94.4             | -0.03   | CREB3L3      | 91.6             | -0.26   | DYNLT1  | 85.9             | -0.73   |          |                  |         |
| CCL5     | 94.4             | -0.04   | C22orf28     | 91.4             | -0.28   | CCL8    | 85.9             | -0.73   |          |                  |         |
| TREX1    | 94.3             | -0.04   | THBD         | 91.3             | -0.29   | TRIM5   | 85.9             | -0.73   |          |                  |         |
| CD74     | 94.1             | -0.06   | MASTL        | 91.3             | -0.29   | SLFN5   | 85.4             | -0.77   |          |                  |         |
| UPP2     | 94.1             | -0.06   | C2orf31      | 91.3             | -0.29   | PFKFB3  | 85.4             | -0.78   |          |                  |         |
| AIM2     | 94.1             | -0.06   | MYD88        | 91.3             | -0.29   | HSH2D   | 85.2             | -0.80   |          |                  |         |
| GJA4     | 94.0             | -0.07   | ODC1         | 91.2             | -0.30   | GBP5    | 85.1             | -0.80   |          |                  |         |
| DUSP5    | 94.0             | -0.07   | CRY1         | 91.2             | -0.30   | PTMA    | 85.0             | -0.81   |          |                  |         |
| AMPH     | 93.9             | -0.08   | CASP1        | 91.1             | -0.31   | GZMB    | 85.0             | -0.81   |          |                  |         |
| PADI2    | 93.8             | -0.08   | CLEC2B       | 91.0             | -0.32   | FAM46C  | 84.9             | -0.81   |          |                  |         |
| Empty 2  | 93.8             | -0.09   | ZNF107       | 91.0             | -0.32   | MOV10   | 84.2             | -0.87   |          |                  |         |
| HESX1    | 93.6             | -0.10   | OPTN         | 90.9             | -0.32   | BTN3A3  | 84.2             | -0.88   |          |                  |         |
| IMPA2    | 93.6             | -0.10   | SLC25A30     | 90.9             | -0.32   | MAP3K5  | 83.9             | -0.90   |          |                  |         |

### **Common ISG Aliases**

DDX3X - DDX3, VIPERIN - RSAD2, SERPINE1 - PAI 1, IL28RA - CRF2, VEGFC – VRP, SP110 - IFI41, IRF2 - PRIC285, ZNF313 - RNF114, DNAPTP6 - LOC26010, LOC400759 – PSEUDOGENE, PSCD1 - CYTH1, IFITM1 - IFI17, SIGLEC1 – FRAG, CCL5 - SYCA5, CXCL9 – MIG, IFIH1 - MDA5, INDO – IDO, C9orf19 - GLIPR2, PBEF1 – NAMPT, FLJ11286 - C19orf66, TAP1 - ABCB2, IFIT1 - IFI56/ISG56, FER1L3 – MYOF, CCR1 - CMKBR1, TDRD7 - PCTAIRE2BP, SERPING1 - C1NH, ENPP1 - PDNP1, BST2 – THN

**Supplementary Table 3. Primers and gBlocks**

| Primer name                                       | Usage                                    | Sequence                                 |
|---------------------------------------------------|------------------------------------------|------------------------------------------|
| Ly6e tissue genotyping forward                    | Generation of Ly6e <sup>fl/fl</sup> mice | actcgagttgtcttaaatggctacc                |
| Ly6e tissue genotyping reverse                    | Generation of Ly6e <sup>fl/fl</sup> mice | cttcagactttgggtactggagtg                 |
| Ly6e gene expression forward                      | qPCR for <i>Ly6e</i> expression          | atcttcggggcctcttcac                      |
| Ly6e gene expression reverse                      | qPCR for <i>Ly6e</i> expression          | atgagaagcacatcagggaat                    |
| Rpl32 gene expression forward (housekeeping gene) | qPCR for <i>Rpl32</i> expression         | aagcgaaactggcggaac                       |
| Rpl32 gene expression reverse (housekeeping gene) | qPCR for <i>Rpl32</i> expression         | taaccgatgttggtcatcag                     |
| HCoV-229E M forward                               | qPCR detection of HCoV-229E              | ttccgacgtgctcgaacttt                     |
| HCoV-229E M reverse                               | qPCR detection of HCoV-229E              | ccaacacggtgtgacagtga                     |
| FAM/BHQ1 probe                                    | qPCR detection of HCoV-229E              | FAM-tgggcatggaatcctgaggttaatgc-BHQ1      |
| B2M gene expression forward (housekeeping gene)   | qPCR detection of <i>B2M</i> expression  | tgctcgcgtactctctcttc                     |
| B2M gene expression reverse (housekeeping gene)   | qPCR detection of <i>B2M</i> expression  | gtcaacttcaatgtcgatgga                    |
| YYE/BHQ1 probe                                    | qPCR detection of B2M                    | YYE-aggtatccagcgtactccaaagattcaggtt-BHQ1 |

| gBlock Gene Fragment                                                                                                                | Usage                                                                           | Sequence                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gateway Cloning-compatible LY6E sgRNA #4-resistant human LY6E with N-terminal HA epitope tag<br><br>CRISPR-resistant LY6E (CR-LY6E) | Reconstitution of LY6E expression in A549 LY6E <sup>-/-</sup> clonal cell lines | Ggggacaagttgtacaaaaagcaggcttcaccatgaag<br>atcttctgccagtgctgctggctgccctctgggtgtggagc<br>gagccagctcgtgatgtgcttctctgctgaaccagaaga<br>gcaatctgtactgctgaagccaacaatatgttcagatcagg<br>acaactactgctgactgtgtctgtagtccggcattggga<br>atctcgtgacatttggccacagcctgagcaagacctgttccc<br>cggcctgccccatcccagaaggcgtcaatgttggtgtggctt<br>ccatgggcatcagctgctgccagagcttctgtgcaatttcT<br>ACCCATACGATGTTCCAGATTACGCT<br>agtgcggccgatggcgggctgcgggcaagcgtcacctg<br>ctgggtgccgggctgctgctgagcctgctgccggcctgct<br>gcggttggccccgaaccagcttctgtacaaagtgggtcc<br>cc |
| Gateway Cloning-compatible <i>Camelus dromedarius</i> LY6E (based on XM_031439745.1)                                                | Expression of camel ( <i>C. dromedarius</i> ) LY6E                              | ggggacaagttgtacaaaaagcaggcttcaccatgaagg<br>tcttctgccggtgctgctggctgccctcctgggtgtggagc<br>gagcccgtccctgggtgtgcttctctgacgaataagaaca<br>gcaactggtactgctgaagcccaccgtgctgccgactcc<br>gacaactactgctgaccatatctgcatccgctggcatcggg<br>aacgtggtggacttggctacacctgaacaagggtgctcc<br>ccgatctgtcccggcccgagcgtcaatcttgagtggtgcgc<br>cgtgggcaccactgctgccagagcttctgtgcaacatca<br>gtgcagccgacggcgggctgcccggcagcaccacgtgc<br>tgggcctcgggctcctgctcagcctgctgtccgcctgctgc<br>ggcttggcccctgaaccagcttctgtacaaagtgggtcccc                                      |

**Supplementary Table 4. *P* values > 0.05.**

| Figure                 | Panel | P-value (top-bottom, then left-right)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Figure 1               | l     | ns=0.9812, ns=0.9756, ns=0.8617                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                        | p     | ns p=0.0740                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Figure 2               | a     | ns p=0.4384                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | b     | ns p=0.1638                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | f     | ns p=>0.9999, ns p=0.1761, ns p=0.0827                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                        | h     | ns p=0.9932, ns p=0.9937, ns p=0.9734                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Figure 3               | d     | ns p=0.2136                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | f     | ns p=0.3698                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | j     | ns p=0.1321                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Figure 4               | d     | B cells: ns p=0.1850, ns p=0.2957, ns p=0.9941; CD8+ T cells: ns p=0.1692, ns p=0.2998, ns p=0.9898, ns p=0.2598, ns p=0.9284, ns p=0.9940; CD4+ T cells: ns p=0.6216, ns p=0.9475, ns p=0.9348, ns p=0.1838, ns p=0.511; NK cells: ns p=0.9999, ns p=0.9994, ns p=0.9979; dendritic cells: ns p=0.0538, ns p=0.9862, ns p=0.0604, ns p=0.7810, p=0.9443; macrophages: ns p=0.371, ns p=0.3430, ns p=0.9999, ns p=0.1344, ns p=0.9965, ns p=0.9986; neutrophils: ns p=0.1846, ns p=0.7337, ns p=0.9980, ns p=0.7425, ns p=0.9980.                                                          |
|                        | e     | B cells: ns p=0.2534, ns p=0.3030, ns p=0.9996, ns p=0.0716, ns p=0.9959, ns p=0.9860; CD8+ T cells: ns p=0.9860, ns p=0.9999, ns p=0.9841, ns p=0.5289, ns p=0.8617, ns p=0.6381; CD4+ T cells: ns p=0.9518, ns p=0.9986, ns p=0.9341, ns p=0.9145, ns p=0.9999, ns p=0.9016; NK cells: ns p=0.8057, ns p=0.7910, ns p=0.9999; dendritic cells: ns p=0.5038, ns p=0.5202, ns p=0.9999, ns p=0.6550, ns p=0.6383; macrophages: ns p=0.7676, ns p=0.5821, ns p=0.9926, ns p=0.2498, ns p=0.9306, ns p=0.9916; neutrophils: ns p=0.4330, ns p=0.5729, ns p=0.9967, ns p=0.7779, ns p=0.6391. |
|                        | h     | ns p=0.9957                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | i     | ns p=0.8357                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Extended Data Figure 1 | j     | ns p=0.5188                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | k     | ns p=0.7421                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | l     | ns= >0.9999 (CHIKV) >0.9999 (PIV) >0.9999 (RSV) >0.9999 (SINV) >0.9999 (VEEV) 0.9679 (WNV) 0.8794 (ZIKV) 0.3172 (YFV) 0.7667 (DENV) (For CHIKV one outlier was removed in the control cells)                                                                                                                                                                                                                                                                                                                                                                                               |
|                        | m     | ns p=0.9993 (GPIHBP1) 0.9998 (LY6H) 0.9991 (PSCA) 0.9990 (LY6G6D) 0.9997 (CD59) >0.9999 (LYPD1) 0.9994 (LYPD2) 0.9997 (GML) 0.9997 (LY6D) 0.9992 (LY6K)                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                        | n     | ns p=0.8472                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Extended Data Figure 2 | a     | ns p=0.9448, ns p=0.0752                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Extended Data Figure 3 | c     | ns p=0.1909                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | f     | ns p=0.4968                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | g     | ns p=0.9999 (WT) >0.9999 (NYT) >0.9999 (ASAA) >0.9999 (ASVA) >0.9999 (ASAA+ASVA) >0.9999 (SSVR) 0.9867 (VSV)                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Extended Data Figure 6 | c     | ns p=0.1144                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | d     | ns p=0.1407                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | f     | ns p=0.1708                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | g     | ns p=0.0779                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | i     | ns p=0.6191                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | j     | ns p=0.6842                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | l     | ns p>0.9999                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                        | m     | ns p=0.0779                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Extended Data Figure 7 | f     | ns p=0.1544                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

|                         |   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         | g | ns p=0.5322                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                         | h | ns p=0.0662                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                         | i | ns p=0.0592                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                         | j | ns p=0.9064                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Extended Data Figure 10 | a | B cells: ns p=0.3027, ns p=0.4974, ns p=0.9879, ns p=0.1824, ns p=0.0947; CD8+ T cells: ns p=0.8596, ns p=0.1912; CD4+ T cells: ns p=0.9601, ns p=0.9953, ns p=0.9970, ns p=0.2741, ns p=0.7155, ns p=0.5656; NK cells: ns p=0.8600; dendritic cells: ns p=0.08537, ns p=0.0899; macrophages: ns p=0.9948, ns p=0.9997, ns p=0.9980; neutrophils: ns p=0.4834, ns p=0.3525, ns p=0.9999                                                                                                                                   |
|                         | b | B cells: ns p=0.7552, ns p=0.2045, ns p=0.7958, ns p=0.3575, ns p=0.9137; CD8+ T cells: ns p=0.7492, ns p=0.9845, ns p=0.9416, ns p=0.8347, ns p=0.3638, ns p=0.7297; CD4+ T cells: ns p=0.4906, ns p=0.6142, ns p=0.9998, ns p=0.0586, ns p=0.5491; NK cells: ns p=0.6030, ns p=0.9732, ns p=0.8901; dendritic cells: ns p=0.9533, ns p=0.9969, ns p=0.9925, ns p=0.0563; macrophages: ns p=0.05993, ns p=0.6229, ns p=0.9999, ns p=0.0898; neutrophils: ns p=0.1365, ns p=0.2739, ns p=0.9833, ns p=0.3470, ns p=0.1838 |
|                         | c | CD8+ T cells: ns p=0.7905, ns p=0.9611, ns p=0.9175; CD4+ T cells: ns p=0.3199, ns p=0.9663, ns p=0.4452; NK cells: ns p=0.9594, ns p=0.7113, ns p=0.8747; dendritic cells: ns p=0.7224, ns p=0.5624, ns p=0.9711; macrophages: ns p=0.5716, ns p=0.4972, ns p=0.9956; neutrophils: ns p=0.2169, ns p=0.5441                                                                                                                                                                                                              |
|                         | d | CD8+ T cells: ns p=0.0678, ns p=0.9901, ns p=0.1255; CD4+ T cells: ns p=0.1307, ns p=0.39906, ns p=0.8010; NK cells: ns p=0.8957, p=0.8892, ns p=0.9999; dendritic cells: ns p=0.6221, ns p=0.1058; macrophages: ns p=0.5074, ns p=0.2607; neutrophils: ns p=0.6518, ns p=0.2681, ns p=0.0843.                                                                                                                                                                                                                            |

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