Methods

Viruses

Recombinant HCoV-229E[1], HCoV-229E-Rluc (expressing Renilla luciferase [Rluc] by replacing the majority of HCoV-229E ORF4)[2], HCoV-OC43[3], MHV strain A59[4], MHV-Gluc, strain A59 (expresses a Gaussia luciferase [Gluc] replacing accessory gene 4)[5], MHV-GFP strain A59[6], MERS-CoV strain EMC[7], and SARS-CoV strain Frankfurt-1[8] 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[9], and MHV stocks were propagated on 17Cl1 cells. Lentivirus particles using the SCRPSY and SCRBBL backbone were generated as described previously[9-12].
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[13].
The generation of viral stocks for the following viruses has been previously described: hPIV-3-GFP[14] (based on strain JS, generously provided by P.L. Collins), RSV-GFP[15] (based on strain A2, generously provided by P.L. Collins), YFV-Venus[16] (derived from YF17D-5′C25Venus2AUbi), DENV-GFP[17] (derived from IC30P-A, a full-length infectious clone of strain 16681), WNV-GFP[18] (derived from pBELO-WNV-GFP-RZ, generously provided by I. Frolov), HCV-Ypet[19] (based on the chimeric Jc1 virus of strains: J6 and JFH-1), SINV-GFP[20] (derived from pS300/pS300-GFP, generously provided by M.T. Heise), VEEV-GFP[21] (derived from pTC83-GFP infectious clone, generously provided by I. Frolov), CHIKV-GFP[22] (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[23].

Cell lines

Huh7 hepatocarcinoma cells (kind gift from V. Lohnmann), Huh7.5, STAT1$^{-/-}$ 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[24] were cultured in Glasgow's minimal essential medium with 5% FBS. 17Cl1 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 TMPRRS2 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[25]. 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$^{-/-}$_CEACAM1 cells, human STAT1$^{-/-}$ fibroblasts were transduced with lentiviruses encoding for the murine CoV receptor CEACAM1 (kind gift from David Wentworth, CDC, Atlanta, USA[24] 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*[26]. 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[26].

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[26]. 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[26]. 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[11,12]. Briefly, 5 x 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[27] 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[12]. 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 Transkriptase, 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[56] 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[57]. All viruses were propagated on BHK-G43 cells[58], 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)[28] (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[26]. 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 TaqManTM 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[29]). 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 x 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 x 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 x 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 × *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 x 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 x 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 x 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[30] . Briefly, following extraction of total RNA from uninfected and CoV-infected hAECs, the Bulk RNA Barcoding and sequencing (BRB-seq)[31] protocol was used to generate libraries, which were subsequently sequenced on the Illumina NextSeq500 platform. The STAR aligner[32] 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[33]. Counts were normalized and expression differences between samples were quantified using the DESeq2 package in R, with a fold change (FC) cut off ≥ 1.5 and False Discovery Rate (FDR) ≤ 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)[34]. 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)[35,36]. 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[34]. 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, Aarhaus).

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:

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

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 (11000, 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, cloneBA5b, BioLegend). The following antibodies were used to differentiate immune cell populations: anti-CD3ε-PE (1:200, 145-2C11, Tonbo Biosciences), anti-CD3ε-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	**DNAPTP6**	101.1	0.48	**PAD12**	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	**ABLIM3**	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	**LINCR**	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	CYP1B1	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	**Hercb**	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	**DNAPTP6**	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
ABLIM3	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	**TRAFD1**	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			
PAD12	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$^{fl/fl}$ mice	actcgagttgtcttaatggctacc
Ly6e tissue genotyping reverse	Generation of Ly6e$^{fl/fl}$ mice	cttcagactttggtactggagtgg
Ly6e gene expression forward	qPCR for *Ly6e* expression	atcttcggggcctcttcac
Ly6e gene expression reverse	qPCR for *Ly6e* expression	atgagaagcacatcagggaat
Rpl32 gene expression forward (housekeeping gene)	qPCR for *Rpl32* expression	aagcgaaactggcggaaac
Rpl32 gene expression reverse (housekeeping gene)	qPCR for *Rpl32* expression	taaccgatgttgggcatcag
HCoV-229E M forward	qPCR detection of HCoV-229E	ttccgacgtgctcgaacttt
HCoV-229E M reverse	qPCR detection of HCoV-229E	ccaacacggttgtgacagtga
FAM/BHQ1 probe	qPCR detection of HCoV-229E	FAM-tgggcatggaatcctgaggttaatgc-BHQ1
B2M gene expression forward (housekeeping gene)	qPCR detection of *B2M* expression	tgctcgcgctactctctctttc
B2M gene expression reverse (housekeeping gene)	qPCR detection of *B2M* expression	gtcaacttcaatgtcggatgga
YYE/BHQ1 probe	qPCR detection of B2M	YYE-aggctatccagcgtactccaaagattcaggtt-BHQ1

gBlock Gene Fragment	**Usage**	**Sequence**
Gateway Cloning-compatible LY6E sgRNA #4-resistant human LY6E with N-terminal HA epitope tag CRISPR-resistant LY6E (CR-LY6E)	Reconstitution of LY6E expression in A549 LY6E$^{-/-}$ clonal cell lines	Ggggacaagtttgtacaaaaaagcaggcttcaccatgaag atcttcttgccagtgctgctggctgcccttctgggtgtggagc gagccagctcgctgatgtgcttctcctgcttgaaccagaaga gcaatctgtactgcctgaagccaacaatatgttcagatcagg acaactactgcgtgactgtgtctgctagtgccggcattggga atctcgtgacatttggccacagcctgagcaagacctgttccc cggcctgccccatcccagaaggcgtcaatgttggtgtggctt ccatgggcatcagctgctgccagagctttctgtgcaatttcT ACCCATACGATGTTCCAGATTACGCT agtgcggccgatggcgggctgcgggcaagcgtcaccctg ctgggtgccgggctgctgctgagcctgctgccggccctgct gcggtttggcccctgaacccagctttcttgtacaaagtggtccc cc
Gateway Cloning-compatible *Camelus dromedarius* LY6E (based on XM_031439745.1)	Expression of camel (*C. dromedarius*) LY6E	ggggacaagtttgtacaaaaaagcaggcttcaccatgaagg tcttcctgccggtgctgctggctgccctcctgggtgtggagc gagcccgctccctggtgtgcttctcctgcacgaataagaaca gcaactggtactgcctgaagcccaccgtctgctccgactcc gacaactactgcgtgaccatatctgcatccgctggcatcggg aacgtggtggactttggctacaccctgaacaagggctgctcc ccgatctgtcccggcccgagcgtcaatcttggagtggcgtc cgtgggcacccactgctgccagagcttcctgtgcaacatca gtgcagccgacggcgggctgcgggccagcacccacgtgc tgggcctcgggctcctgctcagcctgctgtccgccctgctgc ggcttggcccctgaacccagctttcttgtacaaagtggtcccc

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=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 (GPFHBPI) 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.

References

1 Thiel, V. & Siddell, S. G. Reverse genetics of coronaviruses using vaccinia virus vectors. *Curr Top Microbiol Immunol* **287**, 199-227, doi:10.1007/3-540-26765-4_7 (2005).

2 van den Worm, S. H. *et al.* Reverse genetics of SARS-related coronavirus using vaccinia virus-based recombination. *PLoS One* **7**, e32857, doi:10.1371/journal.pone.0032857 (2012).

3 Bruckova, M., McIntosh, K., Kapikian, A. Z. & Chanock, R. M. The adaptation of two human coronavirus strains (OC38 and OC43) to growth in cell monolayers. *Proc Soc Exp Biol Med* **135**, 431-435, doi:10.3181/00379727-135-35068 (1970).

4 Coley, S. E. *et al.* Recombinant mouse hepatitis virus strain A59 from cloned, full-length cDNA replicates to high titers in vitro and is fully pathogenic in vivo. *J Virol* **79**, 3097-3106, doi:10.1128/JVI.79.5.3097-3106.2005 (2005).

5 Lundin, A. *et al.* Targeting membrane-bound viral RNA synthesis reveals potent inhibition of diverse coronaviruses including the middle East respiratory syndrome virus. *PLoS Pathog* **10**, e1004166, doi:10.1371/journal.ppat.1004166 (2014).

6 Eriksson, K. K., Cervantes-Barragan, L., Ludewig, B. & Thiel, V. Mouse hepatitis virus liver pathology is dependent on ADP-ribose-1"-phosphatase, a viral function conserved in the alpha-like supergroup. *J Virol* **82**, 12325-12334, doi:10.1128/JVI.02082-08 (2008).

7 Kindler, E. *et al.* Efficient replication of the novel human betacoronavirus EMC on primary human epithelium highlights its zoonotic potential. *mBio* **4**, e00611-00612, doi:10.1128/mBio.00611-12 (2013).

8 Thiel, V. *et al.* Mechanisms and enzymes involved in SARS coronavirus genome expression. *J Gen Virol* **84**, 2305-2315, doi:10.1099/vir.0.19424-0 (2003).

9 Richardson, R. B. *et al.* A CRISPR screen identifies IFI6 as an ER-resident interferon effector that blocks flavivirus replication. *Nat Microbiol* **3**, 1214-1223, doi:10.1038/s41564-018-0244-1 (2018).

10 Kane, M. *et al.* Identification of Interferon-Stimulated Genes with Antiretroviral Activity. *Cell Host Microbe* **20**, 392-405, doi:10.1016/j.chom.2016.08.005 (2016).

11 Schoggins, J. W. *et al.* A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature* **472**, 481-485, doi:10.1038/nature09907 (2011).

12 Dittmann, M. *et al.* A serpin shapes the extracellular environment to prevent influenza A virus maturation. *Cell* **160**, 631-643, doi:10.1016/j.cell.2015.01.040 (2015).

13 Berger Rentsch, M. & Zimmer, G. A vesicular stomatitis virus replicon-based bioassay for the rapid and sensitive determination of multi-species type I interferon. *PLoS One* **6**, e25858, doi:10.1371/journal.pone.0025858 (2011).

14 Zhang, L. *et al.* Infection of ciliated cells by human parainfluenza virus type 3 in an in vitro model of human airway epithelium. *J Virol* **79**, 1113-1124, doi:10.1128/JVI.79.2.1113-1124.2005 (2005).

15 Biacchesi, S. *et al.* Recovery of human metapneumovirus from cDNA: optimization of growth in vitro and expression of additional genes. *Virology* **321**, 247-259, doi:10.1016/j.virol.2003.12.020 (2004).

16 Jones, C. T. *et al.* Real-time imaging of hepatitis C virus infection using a fluorescent cell-based reporter system. *Nat Biotechnol* **28**, 167-171, doi:10.1038/nbt.1604 (2010).

17 Schoggins, J. W. *et al.* Dengue reporter viruses reveal viral dynamics in interferon receptor-deficient mice and sensitivity to interferon effectors in vitro. *Proc Natl Acad Sci U S A* **109**, 14610-14615, doi:10.1073/pnas.1212379109 (2012).

18 McGee, C. E. *et al.* Infection, dissemination, and transmission of a West Nile virus green fluorescent protein infectious clone by Culex pipiens quinquefasciatus mosquitoes. *Vector Borne Zoonotic Dis* **10**, 267-274, doi:10.1089/vbz.2009.0067 (2010).

19 Liu, D. *et al.* Fast hepatitis C virus RNA elimination and NS5A redistribution by NS5A inhibitors studied by a multiplex assay approach. *Antimicrob Agents Chemother* **59**, 3482-3492, doi:10.1128/AAC.00223-15 (2015).

20 Suthar, M. S., Shabman, R., Madric, K., Lambeth, C. & Heise, M. T. Identification of adult mouse neurovirulence determinants of the Sindbis virus strain AR86. *J Virol* **79**, 4219-4228, doi:10.1128/JVI.79.7.4219-4228.2005 (2005).

21 Petrakova, O. *et al.* Noncytopathic replication of Venezuelan equine encephalitis virus and eastern equine encephalitis virus replicons in Mammalian cells. *J Virol* **79**, 7597-7608, doi:10.1128/JVI.79.12.7597-7608.2005 (2005).

22 Tsetsarkin, K. *et al.* Infectious clones of Chikungunya virus (La Reunion isolate) for vector competence studies. *Vector Borne Zoonotic Dis* **6**, 325-337, doi:10.1089/vbz.2006.6.325 (2006).

23 Hoffmann, H. H. *et al.* Diverse Viruses Require the Calcium Transporter SPCA1 for Maturation and Spread. *Cell Host Microbe* **22**, 460-470 e465, doi:10.1016/j.chom.2017.09.002 (2017).

24 Schickli, J. H., Thackray, L. B., Sawicki, S. G. & Holmes, K. V. The N-terminal region of the murine coronavirus spike glycoprotein is associated with the extended host range of viruses from persistently infected murine cells. *J Virol* **78**, 9073-9083, doi:10.1128/JVI.78.17.9073-9083.2004 (2004).

25 Kleine-Weber, H., Elzayat, M. T., Hoffmann, M. & Pohlmann, S. Functional analysis of potential cleavage sites in the MERS-coronavirus spike protein. *Sci Rep* **8**, 16597, doi:10.1038/s41598-018-34859-w (2018).

26 Mar, K. B. *et al.* LY6E mediates an evolutionarily conserved enhancement of virus infection by targeting a late entry step. *Nature Communications* **9**, 3603, doi:10.1038/s41467-018-06000-y (2018).

27 Michailidis, E. *et al.* A robust cell culture system supporting the complete life cycle of hepatitis B virus. *Sci Rep* **7**, 16616, doi:10.1038/s41598-017-16882-5 (2017).

28 Widjaja, I. *et al.* Towards a solution to MERS: protective human monoclonal antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein. *Emerg Microbes Infect* **8**, 516-530, doi:10.1080/22221751.2019.1597644 (2019).

29 Vijgen, L. *et al.* Development of one-step, real-time, quantitative reverse transcriptase PCR assays for absolute quantitation of human coronaviruses OC43 and 229E. *J Clin Microbiol* **43**, 5452-5456, doi:10.1128/JCM.43.11.5452-5456.2005 (2005).

30 V'kovski, P. *et al.* Disparate temperature-dependent virus – host dynamics for SARS-CoV-2 and SARS-CoV in the human respiratory epithelium. *bioRxiv* (2020).

31 Alpern, D. *et al.* BRB-seq: ultra-affordable high-throughput transcriptomics enabled by bulk RNA barcoding and sequencing. *Genome Biol* **20**, 71, doi:10.1186/s13059-019-1671-x (2019).

32 Dobin, A. *et al.* STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* **29**, 15-21, doi:10.1093/bioinformatics/bts635 (2013).

33 Anders, S., Pyl, P. T. & Huber, W. HTSeq--a Python framework to work with high-throughput sequencing data. *Bioinformatics* **31**, 166-169, doi:10.1093/bioinformatics/btu638 (2015).

34 Kelly, J. N. *et al.* Comprehensive single cell analysis of pandemic influenza A virus infection in the human airways uncovers cell-type specific host transcriptional signatures relevant for disease progression and pathogenesis. *bioRxiv* (2020).

35 Hafemeister, C. & Satija, R. Normalization and variance stabilization of single-cell RNA-seq data using regularized negative binomial regression. *Genome Biol* **20**, 296, doi:10.1186/s13059-019-1874-1 (2019).

36 Butler, A., Hoffman, P., Smibert, P., Papalexi, E. & Satija, R. Integrating single-cell transcriptomic data across different conditions, technologies, and species. *Nat Biotechnol* **36**, 411-420, doi:10.1038/nbt.4096 (2018).