nature portfolio

Corresponding author(s): Jacob S. Yount

Last updated by author(s): Dec 30, 2025

# Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

## Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

| n/a | Confirmed |
|---|---|
| ☐ | ☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ The statistical test(s) used AND whether they are one- or two-sided<br>*Only common tests should be described solely by name; describe more complex techniques in the Methods section.* |
| ☒ | ☐ A description of all covariates tested |
| ☐ | ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted<br>*Give P values as exact values whenever suitable.* |
| ☒ | ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☐ | ☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated |

*Our web collection on statistics for biologists contains articles on many of the points above.*

## Software and code

Policy information about availability of computer code

| | |
|---|---|
| Data collection | SoftMax Pro Software v7, SpectroFlo v3.3.0 |
| Data analysis | Graphpad Prism (v10.4.1), R (v 4.4.2), FlowJo Software (version 10.8.1), DESeq2 (v 1.46.0). Network analysis was performed using 'WGCNA' (v 1.73) and functional analysis was done using 'enrichR' (v 3.2) in R. |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

## Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The RNA sequencing raw data have been deposited in the NCBI GEO database under accession code GSE291639. The virus sequencing data have been deposited in the NCBI GenBank database under accession numbers PV241309-PV241326. Source data are provided with this paper.

## Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

| | |
|---|---|
| Reporting on sex and gender | No human participants in this study |
| Reporting on race, ethnicity, or other socially relevant groupings | No human participants in this study |
| Population characteristics | No human participants in this study |
| Recruitment | No human participants in this study |
| Ethics oversight | No human participants in this study |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

# Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|---|---|
| Sample size | No statistical method was used to predetermine sample size. For in vivo experiments, we based the number of mice on preliminary studies that determined experimental variation in survival and weight loss following infection. For in vitro experiments, assays were performed using the indicated sample sizes to ensure reproducibility. |
| Data exclusions | No data were excluded from analysis. |
| Replication | The reported findings have been confirmed in large groups of mice/experimental group in multiple (>2) experiments. Mouse passaging studies utilized two SARS-CoV-2 strains to minimize strain-specific effects. All attempts at replication were successful. |
| Randomization | Prior to infection, we ensured that the mean weight and age were comparable among the various groups of mice. Each group was randomly assigned which virus they were challenged with. No randomization was used for the in vitro experiments, as it is not applicable to the study design. |
| Blinding | Blinding was not performed for this study, the investigators performing experiments were also the individuals most qualified for analyzing the results making blinding impractical. |

# Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a | Involved in the study |
|---|---|
| ☐ | ☒ Antibodies |
| ☐ | ☒ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology and archaeology |
| ☐ | ☒ Animals and other organisms |
| ☒ | ☐ Clinical data |
| ☒ | ☐ Dual use research of concern |
| ☒ | ☐ Plants |

### Methods

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ ChIP-seq |
| ☐ | ☒ Flow cytometry |
| ☒ | ☐ MRI-based neuroimaging |

## Antibodies

Antibodies used

Flow cytometry antibodies:
Lung flow cytometry myeloid panel:
(Target, clone, fluorophore, dilution, company/reference)
Viability, n/a, violet 510, 1:500, Tonbo/13-0870-T100
CD45, 30-F11, APC-R700, 1:300, BD/565478
CD11b, M1/70, APC eFluor 780, 1:200, eBioscience/47-0112-82
CD11c, N418, APC, 1:200, Invitrogen/17-0114-81
Ly6G, TC11-18H10.1, PE-Cy7, 1:100, 506922
MHCII, M5/114.15.2, eFluor 450, 1:400, eBioscience/48-5321-82
CD103, 2E7, BUV737, 1:200, BD/749393
CD64a, X54-5/7.1, BUV786, 1:200, BD/569507
SiglecF, E50-2440, BB515, 1:200, BD/564514

Lung flow cytometry lymphoid panel:
(Target, clone, fluorophore, dilution, company/reference)
Viability, n/a, Red 780, 1:1000, Tonbo/13-0865-T100
CD45, 30-F11, APC-R700, 1:300, BD/565478
CD3e, 145-2C11, BV711, 1:200, Biolegend/100349
TCRb, H57-597, BV605, 1:200, Biolegend/H57-597
TCRgd, GL3, PerCP-Cy5.5, 1:200, Biolegend/506922
CD4, RM4-5, BV650, 1:200, eBioscience/416-0042-82
CD8a, 53-6.7, BV480, 1:200, BD/566096
IL-17A, TC11-18H10.1, PE-Cy7, 1:100, Biolegend/506922
IFNg, XMG1.2, FITC, 1:100, Biolegend/505806

HEK293T flow cytometry antibodies
SARS-CoV/SARS-CoV-2 Nucleocapsid Antibiody, SinoBiological, Cat #40143-MM08. Conjugated to AF555 via Invitrogen AF555 Antibody Labeling Kit, Cat #A20187. Diltuion 1:1000 determined by optimization experiments.
c-Myc Monoclonal Antibody, Takara, Cat # 631206. Conjugated to AF647 via Invitrogen AF647 Antibody Labeling Kit, Cat #A20186. Dilution 1:1000 determined by optimization experiments.

Virus titering:
Primary - SARS-CoV/SARS-CoV-2 Nucleocapsid Antibiody, SinoBiological, Cat #40143-MM08, 1:1000.
Secondary - Alexa Fluor 488 goat anti-mouse IgG (H+L), Invitrogen Cat #A11029, 1:1000.

Validation

All antibodies used are commercially available and validation has been performed by the manufacturer. Corresponding certificates of analysis are available at the manufacturer's website. For cytometric experiments, each antibody was validated using appropriate FMO/isotype controls where applicable.

## Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

Vero E6 cells were obtained from ATCC (CRL-1586). Vero-TMPRSS2 (NR-54970), HEK293T-ACE2 (NR-52511), and A549-ACE2 (NR-53821) were obtained from BEI Resources. All cell lines were obtained and authenticated directly by the supplier.

Authentication

Original cell stocks maintained in liquid N2 storage and each thawed aliquot discarded after 20 cell passages.

Mycoplasma contamination

No contamination present, confirmed negative of mycoplasma using the Lonza Mycoalert detection kit. All cell lines were maintained for <20 passages to minimize mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

None used

## Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals

Male and female mice between 6 and 10 weeks of age were used in our experiments. All mice used in this study were of the C57BL/6N background. Ifitm3-/- mice with a 53 base pair deletion in exon 1 of the Ifitm3 gene were described previously (Kenney, PNAS, 2019). WT mice for comparison to Ifitm3-/- mice were obtained from Charles River Laboratories (strain #027). Mice were housed in the Ohio State University's Biomedical Research Tower (ABSL3) vivarium, which is maintained at 68–76 degrees F, with a 12:12 light dark cycle, and humidity between 30–70%. Autoclaved individually ventilated cages (Allentown) were used for housing. Mice were fed irradiated natural ingredient chow ad libitum (Evnigo Teklad Diet 7912). Reverse osmosis purified water was provided through water bottles that were replaced weekly. Cages included 1⁄4 inch of corn cob bedding (Bed-o-Cobs, The Andersons) with cotton square nesting material.

Wild animals

None used

| | |
|---|---|
| Reporting on sex | Both male and female mice were used in our experiments and we did not collect any sex-specific data. |
| Field-collected samples | N/A |
| Ethics oversight | All experiments with SARS-CoV-2 were performed in the Ohio State University (OSU) Biosafety Level 3 (BSL3) facility. Experimental procedures were approved by the OSU Institutional Biosafety Committee and OSU BSL3 Advisory Group under protocol number 2020R00000025. Research samples analyzed outside BSL3 containment were decontaminated according to experimentally validated and institutionally approved protocols. Additional oversight for SARS-CoV-2 mouse adaptation experiments was provided by an ad hoc dual use research of concern evaluation committee assembled by the OSU Office of Research at the request of the principal investigator. |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

# Flow Cytometry

## Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

## Methodology

| | |
|---|---|
| Sample preparation | Lung flow cytometry: Lungs were harvested and single cell suspensions were created by enzymatic digestion using DNase, Liberase, and GentleMacs processing. For intracellular staining, cells were stimulated with a stimulation cocktail for four hours.<br><br>HEK293T flow cytometry: Cells were grown in 24 well dishes, transfected for 24hr, and infected immediately after transfection period for 18hr. After infection incubation, cells were harvested using trypsin and immediately fixed for staining. |
| Instrument | Lung flow cytometry: CYTEK Aurora Flow Cytometer 5L.<br>HEK293T cell flow cytometry: BD FACSCanto II |
| Software | Flowjo (v10.8.0) was used for flow all flow cytometric data analysis. |
| Cell population abundance | Gating strategies are provided and no unusual or rare cell populations are studied in this manuscript. |
| Gating strategy | Lung flow cytometry: Both myeloid and lymphoid gating strategies for all cells of interest are shown in Supplemental Data Figure 13.<br>HEK293T flow cytometry: The entire gating strategy for all cells of interest are shown in Supplemental Data Figure 2c. |

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.