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# Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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 | High-throughput qPCR using Fluidigm Biomark - Fluidigm Biomark Collection Software Version 4.5.2<br>Histology and viral spread analysis - Aperio ImageScope software Version 12.3.3<br>Flow Cytometry - BD FACSDIVA Software Version 8.0.1<br>Immunofluorescence - Slidebook Software, Intelligent Imaging Innovations Version 6.0.19<br>Lung Resistance/Compliance - Buxco Finepointe Software Version 2.6<br>Multiplexed Cytokine Assays - Luminex xponent Version 3.1 |
| Data analysis | 10x Genomics Single Cell Gene Expression - Data processing: CellRanger v3.0.2 (10x Genomics), Data analysis: Seurat v3.0.0.900<br>Spatial Transcriptomics - Data processing: SpaceRanger v1.0.0 (10x Genomics), Data analysis: Seurat v3.1.4.9901<br>Cytokine Correlation Matrices - R psych package v1.9.11, R corrplot package v0.84<br>Severity Analyses - sjPlot package v2.8.2<br>Flow Cytometry - FlowJo 10.4.2<br>R packages were run using R statistical software, version 3.5.0 "Joy in Playing"<br>Statistical tests on data from mouse experiments was performed in Graphpad Prism 7.0d<br><br>All analyses were conducted using publicly available software as detailed in the methods. All code is available upon request. |

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

Cohort cytokine and ADAMTS4 data can be found in Supplemental Tables 6 and 7. Single-cell gene expression data and spatial gene expression data are available on the NCBI Short Read Archive under BioProjects PRJNA612345 and PRJNA613670. Hallmark gene sets from the Molecular Signatures Database were used for gene set enrichment analysis (https://www.gsea-msigdb.org/gsea/msigdb/index.jsp). The following publicly available datasets were used for meta-analysis: 20180822_PolypAll_cleaned_rawdata.txt.zip (http://shaleklab.com/wp-content/uploads/2018/08/20180822_PolypAll_cleaned_rawdata.txt.zip) and 20180822_PolypAll_cleaned_metadata.txt (http://shaleklab.com/wp-content/uploads/2018/06/20180822_PolypAll_cleaned_metadata.txt); celseq_matrix_ru1_molecules.tsv.725583.gz and celseq_meta_unfiltered.tsv.725587.gz (https://browser.immport.org/browser?path=SDY998%2FResultFiles%2FRNA_sequencing_result); GSE145926_RAW.tar (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE145926), GSE135893_barcodes.tsv.gz, GSE135893_genes.tsv.gz, and GSE135893_IPF_metadata.csv.gz (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE135893); GSE130148_raw_counts.csv.gz and GSE130148_barcodes_cell_types.txt.gz (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE130148); GSE122960_RAW.tar (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE122960); GSE128169_RAW.tar (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE128169); GSE132771_RAW.tar (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE132771).

# 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 | For experiments involving mice, sample sizes were determined empirically based on previous studies involving similar experiments. Sample sizes are indicated in the figure legends for each experiment. For studies involving human samples, sample sizes were not calculated due to the limited availability of samples. All available samples with excess sample and corresponding cytokine data were tested. |
| Data exclusions | No data were excluded from the analyses. |
| Replication | All experiments were replicated as indicated in the manuscript with at least two independent experiments. All attempts to replicate findings were successful. |
| Randomization | For experiments involving mice, animals were age and sex matched. For experiments involving human samples, samples were not randomized as there was no intervention based on group. Covariates, including age, gender, baseline health status, and corticosteroid administration, were controlled for as indicated in the methods section. |
| Blinding | For survival experiments in mice requiring euthanasia, investigators were blinded to identity of the animals. For histology, the pathologist was blinded to the genotype of the animals. For other non-survival experiments, mice were allocated to groups based on genotype and subsequently identified by ear tag number to reduce potential bias during collection of objective measurements. For experiments involving human samples, investigators collecting the data were blinded to patient group. |

# 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 |
| ☐ | ☒ Animals and other organisms |
| ☐ | ☒ Human research participants |
| ☒ | ☐ Clinical data |

### Methods

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

## Antibodies

Antibodies used

Trustain FcX anti-mouse CD16/32 antibody - 93, Biolegend, Cat: 101320, Lot: P0161031218704
Human Trustain FcX - Biolegend, Cat: 422302
Ghost Dye Violet 510 - TONBO, Cat: 13-0870,Lot: D0870082117133
APC anti-mouse CD45.2 antibody - Mouse IgG2a, 104, Biolegend, Cat: 109814
PE anti-mouse H-2 antibody - Rat IgG2a, M1/42, Biolegend, Cat: 125506, Lot: B236343
PE anti-human CD45 - Mouse IgG1, HI30, iCyt, Lot: 41152
PE anti-human beta2-microglobulin - Mouse IgM, TU99, BD Pharmigen, Cat: 551337, Lot: 43471
FITC anti-influenza A antibody - Mouse IgG2a, A1, Millipore, Cat: MAB8257F, Lot:2730954
PE/Cy7 anti-mouse CD45.2 - Mouse IgG2a, 104, Biolegend, Cat: 109830, Lot: B228756
PE anti-mouse CD90.2 - Rat IgG2a, 53-2.1, Biolegend, Cat: 140308, Lot: B204073
PerCP Cy5.5 anti-mouse CD31 - Rat IgG2a, 390, Biolegend, Cat: 102420, B247172
PacBlue anti-mouse CD11c - Armenian Hamster IgG, N418, Biolegend, Cat: 117322, Lot: B213515
APC/Cy7 anti-mouse CD11b - Rat IgG2b, M1/70, TONBO, Cat: 25-0112, Lot: C0112112916253
BV650 anti-mouse Gr-1 - Rat IgG2b, RB6-8C5, Biolegend, Cat: 108442, Lot: B234643
APC anti-mouse CD326 (EpCAM) - Rat IgG2a, G8.8, Biolegend, Cat:118214, Lot: B217174
PE/Cy7 anti-mouse IFNg - Rat IgG1, XMG1.2, BD Pharmigen, Cat: 561040, Lot: 7202642
FITC anti-mouse CD3 - Rat IgG2b, 17A2, Biolegend, Cat: 100204, Lot:E16592-103
BV650 anti-mouse CD8a - Rat IgG2a, 53-6.7, Biolegend, Cat: 100742, Lot: B212054
APC/Cy7 anti-mouse CD4 - Rat IgG2b, GK1.5, Biolegend, Cat: 100414, Lot: B180930
Anti-mouse CD3 - Rat IgG2b, 17A2, Biolegend, Cat: 100202, Lot: B248471
Anti-mouse versican GAG beta domain - Rabbit, Polyclonal, Millipore Sigma, Cat: AB1033, Lot: 2960529
Anti-influenza A, USSR (H1N1) - Donkey, Polyclonal, US Biological, Cat: I7650-80B
BV605 anti-mouse CD45 - Rat IgG2b, 30-F11, Biolegend, Cat: 103155, Lot: B278000
BV421 anti-mouse CD326 (EpCAM) - Rat IgG2b, G8.8, Biolegend, Cat: 118225, Lot: B265073
FITC anti-mouse CD317 (BST2) - Rat IgG2b, 927, Biolegend, Cat: 127008, Lot: B292371
PE anti-mouse CD9 - Rat IgG2a, MZ3, Biolegend, Cat: 124806, Lot: B253483
APC anti-mouse CD49e (ITGA5) - Rat IgG2a, 5H10-27(MFR5), Biolegend, Cat: 103814, Lot: B264927
APC anti-human CD45 - Mouse IgG1, 2D1, Biolegend, Cat: 368512, Lot: B237418
Secondary biotinylated anti-goat IgG, Donkey polyclonal, Santa Cruz, Cat: sc-2042
CF488 anti-rat IgG, Donkey polyclonal, Biotium, Cat: 20027, Lot: 16C0301
CF568 anti-rabbit IgG, Donkey polyclonal, Biotium, Cat: 20098, Lot: 19C0110
Biotin anti-mouse B220 - Rat IgG2a, RA3-6B2, Biolegend, Cat: 103204, Lot: B268525
Biotin anti-mouse MHC II (I-A/I-E) - Rat IgG2b, M5/114.15.2, Biolegend, Cat: 107604, Lot: B235112
Biotin anti-mouse CD4, Rat IgG2b, GK1.5, Biolegend, Cat: 100404, Lot: B191781
Biotin anti-mouse CD49b - Rat IgM, DX5, Biolegend, Cat: 108904, Lot: B215293
Biotin anti-mouse CD11b - Rat IgG2b, M1/70, Biolegend, Cat: 101204, Lot: B241116
Anti-mouse CD3e - Armenian Hamster IgG, 145-2C11, Biolegend, Cat: 100302, Lot: B211546
Anti-mouse CD28 - Syrian Hamster IgG, 37.51, eBioscience, Cat: 14-0281-86, Lot: E03644-1632
BV605 anti-human CD45 - Mouse IgG1, HI30, Biolegend, Cat: 304042, Lot: B242281
BV785 anti-human CD326 (EpCAM) - Mouse IgG2b, 9C4, Biolegend, Cat: 324237, Lot: B262589
APC Fire 750 anti-human CD31 - Mouse IgG1, WM59, Biolegend, Cat: 303142, Lot: B292519
PE/Cy7 anti-human CD140a (PDGFRA) - Mouse IgG1, 16A1, Biolegend, Cat: 323508, Lot: B250541
APC anti-human CD49e (ITGA5) - Mouse IgG2b, NKI-SAM-1, Biolegend, Cat: 328012, Lot: B243442
PE anti-human CD9 - Mouse IgG1, HI9a, Biolegend, Cat: 312106, Lot: B297661

Validation

Trustain FcX anti-mouse CD16/32 - validated for flow cytometry by staining mouse lung cells according to vendor's website.
Human Trustain FcX - validated for flow cytometry by staining human lung cells according to vendor's website.
Ghost Dye Violet 510 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
APC anti-mouse CD45.2 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
PE anti-mouse H-2 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
PE anti-human CD45 - validated for flow cytometry by staining human PBMCs. Flow plot shown on vendor's website.
PE anti-human beta2-microglobulin - validated for flow cytometry by staining human PBMCs. Flow plot shown on vendor's website.
FITC anti-influenza A antibody - validated for flow cytometry by staining mouse lung cells according to vendor's website.
PE/Cy7 anti-mouse CD45.2 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
PE anti-mouse CD90.2 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
PerCP Cy5.5 anti-mouse CD31 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
PacBlue anti-mouse CD11c - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
APC/Cy7 anti-mouse CD11b - validated for flow cytometry by staining mouse bone marrow cells. Flow plot shown on vendor's website.
BV650 anti-mouse Gr-1 - validated for flow cytometry by staining mouse bone marrow cells. Flow plot shown on vendor's website.
APC anti-mouse CD326 (EpCAM) - validated for flow cytometry by staining TE-71 cells (mouse thymic epithelial stromal cell line). Flow plot shown on vendor's website.
PE/Cy7 anti-mouse IFNg - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
FITC anti-mouse CD3 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
BV650 anti-mouse CD8a - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
APC/Cy7 anti-mouse CD4 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
Anti-mouse CD3 - validated for immunohistochemistry by staining mouse spleen sections. Sections shown on vendor's website.

Anti-mouse versican GAG beta domain - validated for immunohistochemistry by staining mouse neural tube and limb bud. Sections shown on vendor's website.
Anti-influenza A, USSR (H1N1) - validated for immunohistochemistry by staining uninfected and infected mouse lung sections according to vendor's website.
BV605 anti-mouse CD45 - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website
BV421 anti-mouse CD326/EpCAM - validated for flow cytometry by staining TE-71 cells (mouse thymic epithelial stromal cell line). Flow plot shown on vendor's website.
FITC anti-mouse CD317 (BST2) - validated for flow cytometry by staining mouse splenocytes. Flow plot shown on vendor's website.
PE anti-mouse CD9 - validated for flow cytometry by staining mouse bone marrow cells. Flow plot shown on vendor's website.
APC anti-mouse CD49e (ITGA5) - validated for flow cytometry by staining mouse bone marrow cells. Flow plot shown on vendor's website.
APC anti-human CD45 - validated for flow cytometry by staining human PBMCs. Flow plot shown on vendor's website.
Biotin anti-mouse B220 - validated by flow cytometric staining of mouse splenocytes. Flow plot shown on vendor's website.
Biotin anti-mouse MHC II (I-A/I-E) - validated by flow cytometric staining of mouse splenocytes. Flow plot shown on vendor's website.
Biotin anti-mouse CD4 - validated by flow cytometric staining of mouse splenocytes. Flow plot shown on vendor's website.
Biotin anti-mouse CD49b - validated by flow cytometric staining of mouse splenocytes. Flow plot shown on vendor's website.
Biotin anti-mouse CD11b - validated by flow cytometric staining of mouse bone marrow cells. Flow plot shown on vendor's website.
Anti-mouse CD3e - validated by flow cytometric staining of mouse splenocytes. Flow plot shown on vendor's website.
Anti-mouse CD28 - validated by flow cytometric staining of mouse thymocytes. Flow plot shown on vendor's website.
BV605 anti-human CD45 - validated for flow cytometry by staining mouse bone marrow cells. Flow plot shown on vendor's website.
BV785 anti-human CD326 (EpCAM) - validated for flow cytometry by staining human colon carcinoma cell line HT29.Flow plot shown on vendor's website
APC Fire 750 anti-human CD31 - validated for flow cytometry by staining human PBMCs. Flow plot shown on vendor's website.
PE/Cy7 anti-human CD140a (PDGFRA) - validated for flow cytometry by staining human PDGFRA transfected NIH/3T3 cells. Flow plot shown on vendor's website.
APC anti-human CD49e (ITGA5) - validated for flow cytometry by staining human PBMCs. Flow plot shown on vendor's website.
PE anti-human CD9 - validated for flow cytometry by staining human PBMCs. Flow plot shown on vendor's website.

## Eukaryotic cell lines

Policy information about cell lines

| | |
|---|---|
| Cell line source(s) | MDCK cells were obtained from ATCC. |
| Authentication | MDCK cells were authenticated by ATCC |
| Mycoplasma contamination | Cells were not tested for mycoplasma contamination. |
| Commonly misidentified lines (See ICLAC register) | Commonly misidentified cell lines were not used in this study. |

## Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

| | |
|---|---|
| Laboratory animals | Mice used in this study were age- and sex-matched (8 - 12 weeks old). C57BL6/J and B6.129P2-Adamts4tm1Dgen/J , which were back-crossed for at least 10 generations with in-house bred C57BL6/J mice, were used in this study. Cages, water bottles, and food for animals were sterilized by autoclave before use. ABSL2 rooms were kept under negative pressure with a ventilation system providing HEPA-filtered outside air. Average temperature in the housing rooms was 68 degrees F, and humidity was approximately 45%. Light cycle was 12 hours light/12 hours dark. |
| Wild animals | This study did not involve wild animals. |
| Field-collected samples | This study did not involve samples collected from the field. |
| Ethics oversight | Studies involving mice were approved by the St. Jude Children's Research Hospital Committee on Care and Use of Animals. |

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

## Human research participants

Policy information about studies involving human research participants

| | |
|---|---|
| Population characteristics | Co-variate relevant population characteristics are presented in Figure 4 and Supplemental Tables 3, 4, 5, and 6. |
| Recruitment | This study involved samples from three distinct human cohorts. Samples were collected as a part of the care of the patients. For the PICFLU cohort, children were excluded if they had an underlying condition predisposing them to severe influenza virus infection as the focus of the study was on otherwise healthy individuals. Patients were approached for participation in the study |

following admission to the hospital, and we do not anticipate self-selection biases for recruitment into the study.

Ethics oversight

For the PICFLU cohort, the study was approved by the lead site Boston Children's Hospital (IRB X08-11-0534) and then at each enrolling site's IRB (enrolling sites are listed in acknowledgments) and written informed consent was obtained from at least one parent or guardian.

For the Guangzhou cohort, the study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (No: 2016-78), and informed consent was obtained from all patients or their guardians.

For the Taiwan cohort, the human subjects' protocol was reviewed and approved by the Johns Hopkins School of Medicine and the Chang Gung Memorial Hospital Institutional Review Boards (IRB00091667). Informed consent was obtained from all patients or their guardians.

For lung samples from de-identified, deceased donors, the tissues utilized were procured by the National Disease Research Interchange (NDRI) with support from NIH grant U42OD11158. All NDRI consent forms and protocols are reviewed and approved by the Institutional Review Board at the University of Pennsylvania. Research involving these tissues was determined to not involve human subjects by the Institutional Review Board at St. Jude Children's Research Hospital.

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

For mouse lung samples, lungs were perfused with 10 mL of cold 1x PBS injecting into the right ventricle of the heart and then minced and digested in lung digestion buffer containing 400 U/mL of Collagenase I (Worthington Biochemical Corporation) and 50 U/ml of DNaseI (ThermoFisher) in Hanks Balanced Salt Solution (HBSS) for 75 minutes at 37 degrees C. Digested lungs were filtered through a 100 µm cell strainer and washed with HBSS. Red blood cell lysis was performed

Instrument

BD LSRFortessa

Software

Data Collection: BD FACSDIVA software Version 8.0.1
Data Analysis: FlowJo 10.4.2

Cell population abundance

Frequency and total cell numbers of cell populations are indicated in the figures. Cells were counted using a Vi-CELL XR cell counter (Beckman Coulter). Viability of cell samples was determined using Ghost Dye Violet 510 (TONBO).

Gating strategy

Preliminary gates based on FSC and SSC were drawn to identify all cells. FSC-H vs. FSC-A or SSC-H vs. SSC-A were then used to identify single cells. For all experiments, Ghost Dye Violet 510 was used to identify live cells. For downstream gating of CD45- and CD45+ populations, gates were drawn according to the strategy presented in the supplementary figures and figure legends.

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