nature portfolio

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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 *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 *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	Flow cytometry data was acquired by BD FACSDiva™ Software (BD Biosciences), ELISA data was acquired by BioTek Gen5 Software (Agilent Technologies) RT-qPCR data was acquired by Applied Biosystems ViiA 7 (Thermo Fisher Scientific) Fluorescence images were taken by using ZEN 3.3 software (Blue edition) (Zeiss) Pathology images were taken by using cellSens Version 1.5 Software (Olympus)
Data analysis	Statistical analysis was performed by GraphPad Prism version 10.2.0 Flow cytometry data was analyzed by FlowJo_v10

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

All data supporting the findings of this study are available within the article and its supplementary information. Source data are provided.

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	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design; whether sex and/or gender was determined based on self-reporting or assigned and methods used. Provide in the source data disaggregated sex and gender data, where this information has been collected, and if consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Reporting on race, ethnicity, or other socially relevant groupings	*Please specify the socially constructed or socially relevant categorization variable(s) used in your manuscript and explain why they were used. Please note that such variables should not be used as proxies for other socially constructed/relevant variables (for example, race or ethnicity should not be used as a proxy for socioeconomic status). Provide clear definitions of the relevant terms used, how they were provided (by the participants/respondents, the researchers, or third parties), and the method(s) used to classify people into the different categories (e.g. self-report, census or administrative data, social media data, etc.) Please provide details about how you controlled for confounding variables in your analyses.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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 sample size calculation was performed and no statistical methods were used to predetermine sample size; Cell based experiments were repeated at least three times; For mice experiments, 4 or 5 mice per group were used, as noted in figure legends.
Data exclusions	No data was excluded from analysis.
Replication	Most experiments were replicated at least two times, with similar results obtained.
Randomization	Mice were randomly allocated into control or experimental groups.
Blinding	Lung pathological lesions scores were assessed in a blinded fashion by two independent people.

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

Rabbit anti-Influenza NP antibody (Invitrogen, cat#: PA5-32242, clone: polyclonal), 1:1000 used for IF staining.
AF488-conjugated goat anti-rabbit IgG (Invitrogen, cat#: Cat # A-11034, clone: polyclonal), 1:1000 used for IF staining.
Mouse anti-Influenza NP antibody (Invitrogen, cat#: MA5-29926, clone: 7B4G10G8), 1:1000 used for anti-NP ELISA.
HRP-conjugated anti-human IgG (Sigma Aldrich, cat#: AP112P, clone: polyclonal), 1:4000 used for ELISA.
HRP-anti-His antibody (Abcam, cat#: ab1187, clone: polyclonal), 1:2000 used for ELISA.
APC-conjugated anti-human IgG (Invitrogen, cat#: A21445, clone: polyclonal), 1:1000 used for flow cytometry.
APC-conjugated anti-His antibody (BioLegend, cat#: 362605, clone: J095G46), 1:1000 used for flow cytometry.
HRP-conjugated anti-mouse IgG (Invitrogen, cat#: 31430, clone: polyclonal), 1:20000 used for anti-NP ELISA.
Monoclonal antibody MEDI8852 (developed in a previous study - doi: 10.1016/j.cell.2016.05.073) were used for binding assay, in vitro antiviral activity determination and in vivo experiments of this study.

Validation

All commercial antibodies were validated by the manufacturers. Validation data about the monoclonal antibody MEDI8852 in this study are provided in the manuscript.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

MDCK cells (ATCC, CCL34) and HEK293T cells (ATCC, CRL-3216) were obtained from ATCC. Expi293F™ cells (A14527) were obtained from Thermo Fisher Scientific.

Authentication

All cells used in this study were authenticated by ATCC and Thermo Fisher Scientific.

Mycoplasma contamination

All cell lines were tested negative by PCR for mycoplasma.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified lines were used in this study.

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

Eight-week-old female BALB/c mice were used in this study.

Wild animals

No wild animals used in this study.

Reporting on sex

Female mice were used in this study, mice experiments in this study were sex independent.

Field-collected samples

No field-collected samples were used in this study.

Ethics oversight

All animal experimental protocols were approved by the Committee on the Use of Live Animals in Teaching and Research of HKU.

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

Plants

Seed stocks — *Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*

Novel plant genotypes — *Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*

Authentication — *Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

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 the sialic acid receptors binding experiment, MDCK cells were digested and incubated with various concentrations of MEDI8851, M-SiaB and Fc-SiaB in PBS with 2% FBS for 1 hour. After two washes with PBS, cells were incubated with APC-conjugated anti-human IgG antibody (BioLegend) for 30 minutes.
For Fc-SiaB blocking experiment, MDCK cells were digested and washed with PBS. The cells were either pre-incubated with 1 µM Fc-SiaB in PBS containing 2% FBS for 2 hours, or left untreated. Following two washes with PBS, 10 µg/mL of HA proteins were added to the cells and incubated for 1 hour. After two washes with PBS, APC-conjugated anti-His antibody were incubated for 30 minutes.
For viral release experiment, Cells were detached and incubated with 1 µg/mL MEDI8852 mAb in PBS with 2% FBS for 40 minutes, after two washes with PBS, cells were incubated with APC-conjugated anti-human IgG antibody (BioLegend) for 30 minutes.

Instrument — BD LSRFortessa X-20 Cell Analyzer

Software — Flow cytometry data was collected by BD FACSDiva Software and analyzed by FlowJo_v10.

Cell population abundance — Sorting was not performed in this study.

Gating strategy — Gated for live cells with FSC-A and SSC-A, gated for single cells with FSC-H and FSC-A, then gated the fluorescent cells.

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