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	All code used to generate data was implemented in R v 4.0.2. We used the MIPSAlign wrapper with the matchAlign aligner in the MIPSAlign (v.0.0.9.0) package to map all sequencing reads. Next, we used the edgeR (v.3.32.0) package with the MIPSAlign function enrichProt to determine which protein reactivities were enriched. All code is available on request. The MIPSAlign package for alignment and UCI-ORF matching is available on github (repository: jgunn123/MIPSAlign).
Data analysis	MIPSAlign (v.0.0.9.0) package for alignment and UCI-ORF matching, available on github (repository: jgunn123/MIPSAlign). Heatmaps were constructed using the heatmaply (v.1.2.1) package, and all other plots were generated utilizing the ggplot2 (v.3.3.3) package. The Student's t-test was utilized to determine statistical significance for comparing distributions unless noted otherwise.

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 data supporting the results in this study are available within the paper and its Supplementary Information. Source data are provided with this paper. The raw and analysed datasets are available from the corresponding author on request.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Because of the small samples size, subgroup analyses based on sex and gender were not performed.
Population characteristics	Population characteristics are provided in Supplementary Table 1.
Recruitment	The study cohort was defined as in patients who had: 1) a confirmed RNA diagnosis of COVID-19 from a nasopharyngeal swab sample; 2) survival to death or discharge; and 3) remnant specimens in the Johns Hopkins COVID-19 Remnant Specimen Biorepository, an opportunity sample that includes 59% of Johns Hopkins Hospital COVID-19 patients and 66% of patients with length of stay ≥3 days. Patient outcomes were defined by the World Health Organization (WHO) COVID-19 disease severity scale.
Ethics oversight	The study was approved by the JHU Institutional Review Board (IRB00248332, IRB00273516), with a waiver of consent because all specimens and clinical data were de-identified by the Core for Clinical Research Data Acquisition of the Johns Hopkins Institute for Clinical and Translational Research. The study team had no access to identifiable patient data.

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	In the severe COVID-19 cohort, we analysed plasma from all severe cases that were available at the time. The remainder of wells on a 96-well plate were back-filled with an equal mix of pre-pandemic controls and mild COVID-19 convalescent plasma.
Data exclusions	One IBM sample was excluded from analysis in Fig. 4c because it was highly discordant between replicates.
Replication	To determine IFNL3 neutralizing activity, all plasma were evaluated in triplicate. Owing to limited sample availability, we have not yet replicated the IFNL3 finding in an independent cohort.
Randomization	Randomization was not relevant because the exact same testing and analytical conditions were applied to all samples.
Blinding	Blinding was not relevant because the exact same testing and analytical conditions were applied to all samples.

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

Methods

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

Antibodies

Antibodies used: Anti-FLAG (Sigma), anti-HaloTag (Promega), anti-IFNa2 (InvivoGen), anti-IFNL3 (InvivoGen)

Validation:
https://www.sigmaaldrich.com/catalog/product/sigma/f3165?lang=en&region=US
https://www.promega.com/products/protein-detection/primary-and-secondary-antibodies/anti-halotag-monoclonal-antibody/?catNum=G9211
https://www.invivogen.com/sites/default/files/invivogen/products/files/anti_hifna_igg_tds.pdf
https://www.invivogen.com/sites/default/files/invivogen/products/files/anti_hifn_lambda_vds.pdf

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): A549 cells isolated from the lung tissue of a 58-year-old Caucasian male with lung cancer.

Authentication: The cells were not authenticated.

Mycoplasma contamination: The cells were not tested for mycoplasma contamination.

Commonly misidentified lines (See ICLAC register): No misidentified cell lines were used.