nature portfolio

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Last updated by author(s): Apr 27, 2023

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	No software was used for data collection.
Data analysis	Open source R (> 4.1) and R packages were used for analysis or visualization. All R codes used in this study are available at GitHub (https://github.com/aifimmunology/MOCHA_Manuscript). An open-source R implementation of MOCHA is freely available (https://cran.r-project.org/web/packages).

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 HealthyDonor (GSE190992) and COVID19 (GSE173590) scATAC-seq datasets have been deposited in the Gene Expression Omnibus (GEO) database under accession numbers GSE190992 and GSE173590, respectively. The corresponding raw data are available via authorized access at dbGaP under accession number phs003203.v1.p1 and phs002576.v1.p1, respectively. This mouse dataset used in this study is available in the GEO database under accession code GSE111586, and

was obtained by downloading from https://atlas.gs.washington.edu/mouse-atac/. The Hematopoiesis dataset was downloaded from the ArchR Manuscript Repository. Source data files are provided with this paper.

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Human research participants

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

Reporting on sex and gender	Self-reported sex is provided for all participants in the COVID19 datasets. Sex-specific modeling was performed in the COVID19 longitudinal modeling by including sex as a covariate. The sex information is described in Methods.
Population characteristics	Our COVID19+ cohort is composed of 18 participants (10 females and 8 males, aged 22-79 years) who were tested positive (COVID+) for SARS-CoV-2 virus (Wuhan strain) and n=23 uninfected (COVID-) participants (10 females and 13 males, aged 29-77 years). All COVID+ participants had mild to moderate symptoms. Peripheral blood mononuclear cell (PBMC) and serum samples were collected from the COVID- participants at a single time point and from the COVID+ participants at 3-5 time points over a period of 1-121 days post-symptom-onset (PSO, total samples n=70).
Recruitment	We recruited in the greater Seattle area n=18 participants (10 females and 8 males, aged 22-79 years) who were tested positive (COVID+) for SARS-CoV-2 virus (Wuhan strain) and n=23 uninfected (COVID-) participants (10 females and 13 males, aged 29-77 years) in our longitudinal COVID-19 study, "Seattle COVID-19 Cohort Study to Evaluate Immune Responses in Persons at Risk and with SARS-CoV-2 Infection". Study data were collected and managed using REDCap electronic data capture tools hosted at Fred Hutchinson Cancer Research Center (FHCRC). The FHCRC Institutional Review Board (IRB) approved the studies and procedures. Informed consent was obtained from all participants at the Seattle Vaccine Trials Unit to participate in the study and to publish their corresponding research data.
Ethics oversight	Fred Hutchinson Cancer Research Center Institutional Review Board (IRB) approved the studies and procedures.

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 determination was performed. Sample size was based on availability of samples.
Data exclusions	No data exclusion
Replication	Longitudinal samples were collected from individual donors but no replicate samples were collected at the same time point.
Randomization	Not applicable.
Blinding	Not applicable.

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	BioLegend, 422302, BioLegend, 304038, BD, 562371
Validation	All antibodies are commercially available from major vendors.