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	MiSeq(Illumina) iSeq 100 System (Illumina) 7500 Fast Dx Real-Time PCR Instrument (ABI) FinePointe software (SATRR) CosmoScan Database software (Rigaku Corporation) Bio-Plex Manager Software (Bio-Rad Laboratories) ImmunoSpot S6 Analyzer (Cellular Technology) ImmunoCapture software (Cellular Technology) BioSpot software (Cellular Technology)
Data analysis	Prism 8.0 was used for the statistical analysis.

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 paper in the Source Data. There are no restrictions to obtaining access to the primary data. All databases/datasets used in this study are available from GISAID database (https://www.gisaid.org), Genbank database (https://www.ncbi.nlm.nih.gov/genbank/), or UniprotKB database (https://www.uniprot.org/).

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 calculations were performed. No statistical method was used to determine sample size. Hamster and mouse experiments were performed with at least n = 4 and n = 5, respectively, per group. For serology tests, at least 10 blood samples were obtained from each group. All sample sizes were chosen based on standard practices in the field.
Data exclusions	No data exclusions.
Replication	All experiments with multiple biological replicates are indicated in the figure legends.
Randomization	No method of randomization was used to determine how the animals were allocated to the experimental groups and processed in this study. However, covariates including sex and age were identical in groups.
Blinding	No blinding was carried out due to the limited number of staff available to conduct these studies.

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
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	Amino acid sequences for the variable region of the heavy and light chains of the following human monoclonal antibodies against the S protein were used for gene synthesis: clones tixagevimab (COV2-2196/AZD8895; GenBank accession numbers QLI33947 and QLI33948), casirivimab (REGN10933; PDB accession numbers 6XDG_B and 6XDG_D), cilgavimab (COV2-2130/AZD1061; GenBank accession numbers QKY76296 and QKY75909), imdevimab (REGN10987; PDB accession numbers 6XDG_A and 6XDG_A), and S309 (PDB accession numbers 6WS6_A and 6WS6_F). An artificial signal sequence and the constant gamma heavy (IgG1, UniProtKB/Swiss-Prot accession number P01857) and kappa (UniProtKB/Swiss-Prot accession number P01834) or lambda (UniProtKB/Swiss-Prot accession number P0DOY2) light chain coding sequences were added before and after each variable region. Codon usage was optimized for expression in CHO cells. The synthesized genes were cloned into a plasmid for protein expression and transfected into

CHO cells. Cell culture media were harvested after incubation for 10–14 days at 37 °C. A human monoclonal antibody (1430E3/9) against the hemagglutinin of influenza B virus was previously identified in our group (ref.53) and cloned into the expression vector Mammalian Power Express System (TOYOBO) and was transiently expressed by Expi293 cells. Monoclonal antibodies were purified by using MabSelect SuRe LX (Cytiva) or a protein A column. Purity was confirmed by SDS-PAGE and/or HPLC before use.
Peroxidase-conjugated goat anti-human IgG, Fcγ Fragment specific antibody (Cat# 109-035-098, Jackson Immuno-Research) was used as the secondary antibody in the Enzyme-linked immunosorbent assay (ELISA).
A mouse monoclonal antibody against SARS-CoV-1/2 nucleoprotein [clone 1C7C7 (Sigma-Aldrich)] and a horseradish peroxidase-labeled goat anti-mouse immunoglobulin (SeraCare Life Sciences) were used for the focus reduction neutralization test.
A rabbit polyclonal antibody for SARS-CoV nucleocapsid protein (ProSpec) was used for immunohistochemical staining.
A peroxidase-conjugated goat anti-human IgG, Fcγ Fragment specific antibody (Jackson Immuno-Research) was used for ELISAs.

Validation

The therapeutic monoclonal antibodies were validated in previous publications:
Takashita, E. et al. Efficacy of Antibodies and Antiviral Drugs against Covid-19 Omicron Variant. N Engl J Med, doi:10.1056/NEJMc2119407 (2022); Uraki, R. et al. Therapeutic efficacy of antibodies and antivirals against a SARS-CoV-2 Omicron variant. Research Square, doi:10.21203/rs.3.rs-1240227/v1 (2022).

The human monoclonal antibody (1430E3/9) against the hemagglutinin of influenza B virus was validated in a previous publication:
Yasuhara, A. et al. Antigenic drift originating from changes to the lateral surface of the neuraminidase head of influenza A virus. Nat Microbiol 4, 1024-1034, doi:10.1038/s41564-019-0401-1 (2019).

The rabbit polyclonal antibody for SARS-CoV nucleocapsid protein (ProSpec) was validated in previous publications:
Imai, M. et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Proc Natl Acad Sci U S A 117, 16587-16595, doi:10.1073/pnas.2009799117 (2020); Imai, M. et al. Characterization of a new SARS-CoV-2 variant that emerged in Brazil. Proc Natl Acad Sci U S A 118, doi:10.1073/pnas.2106535118 (2021); Halfmann, P. J. et al. SARS-CoV-2 Omicron virus causes attenuated disease in mice and hamsters. Nature, doi:10.1038/s41586-022-04441-6 (2022).

The mouse monoclonal antibody against SARS-CoV-1/2 nucleoprotein [clone 1C7C7 (Sigma-Aldrich)], the horseradish peroxidase-labeled goat anti-mouse immunoglobulin (SeraCare Life Sciences), and the peroxidase-conjugated goat anti-human IgG, Fcγ Fragment specific antibody (Jackson Immuno-Research) were validated in a previous publication:
Takashita, E. et al. Efficacy of Antibodies and Antiviral Drugs against Covid-19 Omicron Variant. N Engl J Med, doi:10.1056/NEJMc2119407 (2022).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

VeroE6/TMPRSS2 cells (available at the Japanese Collection of Research Bioresources Cell Bank, JCRB 1819); Expi293F cells (available at Thermo Fisher Scientific); CHO cells (available at GenScript); and Vero-hACE2-TMPRSS2 cells (Graham laboratory, VRC/ NIH).

Authentication

Vero-hACE2-TMPRSS2 cells were validated by using monoclonal antibodies and flow cytometry. VeroE6/TMPRSS2, Expi293F, and CHO cells were assumed to have been authenticated by the cell bank or manufacturers. No further authentication was performed by the authors.

Mycoplasma contamination

All cell lines are routinely tested each month and were negative for mycoplasma.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified lines were used in this study.

Animals and other organisms

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

Laboratory animals

Heterozygous female K18-hACE2 C57BL/6J mice (strain 2B6.Cg-Tg(K18-ACE2)2Prlmn/J, 12-week-old) were obtained from the Jackson Laboratory. Female BALB/c mice (5-week-old) were purchased from Japan SLC Inc., Shizuoka, Japan.
Male Syrian hamsters (5- to 6-week-old) were obtained from Japan SLC Inc. The K18-hACE2 transgenic hamster lines [lines M51 (male, 16-month-old) and M41 (female, 8- to 9-week-old)] are described in Gilliland T. et al. bioRxiv, doi:10.1101/2021.07.26.453840.

Wild animals

No wild animals were used in this study.

Field-collected samples

This study did not involve samples collected from the field.

Ethics oversight

Animal studies were carried out in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocols were approved by the Institutional Animal Care and Use Committee at the Washington University School of Medicine (assurance number A3381–01), University of Wisconsin, Madison (V006426) and the Animal Experiment Committee of the Institute of Medical Science, the University of Tokyo (approval numbers PA19-72 and PA19-75).

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	A total of 83 individuals [male/female = 29/54; mean age = 42 years (range: 23–75 years)] were enrolled in this study. Detailed information about the kind of mRNA vaccines, age, sex, gender, and sampling days after vaccination/infection are shown in the Source Data.
Recruitment	Individuals from Japan with SARS-CoV-2 infection, COVID-19 convalescent individuals, and COVID-19 vaccinees volunteered and were enrolled in the cohort study at three medical facilities (IMSUT Hospital of the Institute of Medical Science, Eiju General Hospital, and National Center for Global Health and Medicine Hospital), and those from the US volunteered and were enrolled in the Immunity-Associated with SARS-CoV-2 (IASO) cohort study at the University of Michigan Medical School, regardless of age, sex , gender, race, ethnicity, or other characteristics. Self-selection biases may have affected the demographics of the enrolled population, but are not expected to affect the results. Written informed consent was obtained from all participants before study enrollment.
Ethics oversight	The research protocol was approved by the Research Ethics Review Committee of the Institute of Medical Science of the University of Tokyo (approval numbers: 2019–71–0201 and 2020-74-0226) and by the institutional review board at the University of Michigan Medical School (protocol number HUM00184533).

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