

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 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

Western Blot: Fusion FX Imager (Vilber), Image Lab software version 6.0
Flow cytometry data: BD Biosciences, BD FACSDiva V9.1 or 8.0.1
Immunofluorescence: Leica SP8 confocal microscope, Application Suite LAS-X Version 3.1.5.16308
Biolayer interferometry: Octet Data Acquisition software version 10.0.0.87, ForteBio Data Analysis software version 10.0
Cryo-EM: Titan Krios (Thermo Fisher Scientific), SerialEM software version 3.8.0 beta
S1- and RBD-binding IgG assay data; Cytokine profiling: Gen5 V3.0.9 or Bioplex200 system (Bio-Rad),
Surface plasmon resonance spectroscopy: Biacore T200 device (Cytiva), Biacore T200 Evaluation Software Version 3.1
pVNT: IncuCyte Live Cell Analysis system (Sartorius), IncuCyte 2019B Rev2 software
ELISPOT spot count data: ImmunoSpot® S6 Core Analyzer or Universal Analyzer [CTL], Image Acquisition V7.0 or the ImmunoSpot 7.0.17.0 Professional
VNT: Cell Imaging Multi-Mode Reader (BioTek), Gen5 Image Prime version 3.09
RT-qPCR: QuantStudio 3 instrument (Applied Biosystems)

Data analysis

Flow cytometry: FlowJo V10.6 or 10.4.1 (FlowJo LLC, BD Biosciences)
Biolayer interferometry: Octet Data Analysis v10.0 (FortéBio)
Cryo-EM: RELION 3.1-beta
Cytokine profiling: ProcartaPlex Analyst 1.0 software (Thermo Fisher Scientific)
Data visualisation and statistical analysis: GraphPad Prism V8

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 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

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The vaccine sequence is based on GenBank: MN908947.3

For P2 S, the atomic model from PDB ID 6XR8 was rigid-body fitted into the map density (<https://www.rcsb.org/structure/6XR8>).

The cryo-EM maps and atomic coordinates have been deposited to the Electron Microscopy Data Bank (EMDB) and Protein Data Bank (PDB) with accession numbers EMD-23211 and PDB 7L7F for the ACE2/B0AT1/RBD-foldon complex and EMD-23215 and PDB 7L7K for P2 S.

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](https://www.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. For mouse studies, a two-sided test with the hypothesis that the mean is a given value, with the shift to be detected a multiple of the standard deviation was taken into account. For $\alpha=0.05$ and a desired power of 80%, a group size of $n = 8$ is required to find significant differences between groups. For non-human primate studies, sample size was limited by availability of suitable animals.
Data exclusions	No data was excluded.
Replication	Replication was not attempted. Independent studies and analysis methods to analyse immune responses were performed.
Randomization	Mice or NHP were randomly allocated to groups. No formal randomization was done.
Blinding	Studies were performed unblinded as analysis results could not be manipulated by interpretation. Thoracic radiographs and computed tomography scan images were interpreted by a board-certified veterinary radiologist blinded to treatment groups. Histopathology slides were read by veterinary pathologists blinded to treatment groups.

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

Used reagents (specificity/ fluorochrome/ clone/ manufacturer/ catalogue number/lot number/dilution):

Anti-mouse:

B220/CD45R / AF647 / RA3-6B2 / BioLegend / 103226 / B243962 / 1:1500

CD138 / BV605 / 281-2 / BioLegend / 142531 / B299222 / 1:200
 CD19 / BV786 / 1D3 / BD Bioscience / 563333 / 0023948 / 1:1000
 CD19 / AF700 / 6D5 / BioLegend / 115528 / B261756 / 1:100
 CD278/ICOS / PerCPeF710 / 7E.17G9 / Invitrogen / 46-9942-82 / 2029789 / 1:50
 CD38 / PE / 90 / eBioscience / 12-0381-82 / 2150667 / 1:400
 CD38 / AF488 / 90 / BioLegend / 102714 / B298187 / 1:100
 CD3e / BUV395 / 145-2C11 / BD Bioscience / 563565 / 9204644 / 1:100
 CD4 / PerCP-Cy5.5 / RM4-5 / BioLegend / 100540 / B261856 / 1:800
 CD4 / BV480 / RM4-5 / BD Bioscience / 565634 / 9016508, 0107454 / 1:250
 CD44 / BUV563 / IM7 / BD Bioscience / 741227 / 0119427 / 1:5000, 1:2500
 CD62L / BV785 / MEL-14 / BioLegend / 104440 / B258213 / 1:200
 CD8a / PerCP-Cy5.5 / 53-6.7 / BD Bioscience / 551162 / 9098816 / 1:800
 CD8a / BUV737 / 53-6.7 / BD Bioscience / 564297 / 9030634 / 1:200
 CD8a / FITC / 53-6.7 / BD Bioscience / 553031 / 9143776 / 1:200
 CD95/Fas / FITC / Jo2 / BD Bioscience / 561979 / 8296755 / 1:100
 CXCR5 / Purified / 2G8 / BD Bioscience / 551961 / 9143926 / 1:100
 CXCR5 / BV421 / L138D7 / BioLegend / 145512 / B281252 / 1:100
 F4/80 / PerCP-Cy5.5 / BM8 / BioLegend / 123128 / B276793 / 1:800
 FC block CD16/CD32 / Purified / 2.4G2 / BD Bioscience / 553142 / 9060742 / 1:100
 GATA3 / PE-Cy7 / TWAJ / Invitrogen / 25-9966-42 / 2142972 / 1:25
 GR-1 / PerCP-Cy5.5 / RB6-8C5 / BioLegend / 108428 / B278340 / 1:800
 IFN γ / PE-Cy7 / XMG1.2 / BD Bioscience / 564336 / 9337390 / 1:1000
 IgD / BV421 / 11-26c.2a / BioLegend / 405725 / B280598 / 1:2500
 IgG1 / BV480 / A85-1 / BD Bioscience / 746811 / 0115095 / 1:200
 IgG2a / BV711 / R19-15 / BD Bioscience / 744533 / 0115092 / 1:200
 IgG2a / Biotin / RG7/1.30 / BD Bioscience / 553894 / 9288614 / 1:100
 IgM (Igh-Ca/Cb) / PE-Cy7 / R6-60.2 / BD Bioscience / 552867 / 9269114 / 1:200
 IL-2 / APC-R700 / JES6-5H4 / BD Bioscience / 565186 / 9303906 / 1:5000
 PD-1/CD279 / BV605 / 29F.1A12 / BioLegend / 135219 / B303691 / 1:50
 T-bet / AF647 / 4B10 / bioLegend / 644804 / B248741 / 1:200
 TNF / BB700 / MP6-XT22 / BD Bioscience / 566510 / 0021825 / 1:5000

Anti-rhesus, anti-human:

CD154 / BV605 / 24-31 / BioLegend / 310826 / B250362 / 1:60
 CD20 / PE-Cy5.5 / 2H7 / Invitrogen / 35-0209-41 / 2005219 / 1:600
 CD3 / AF700 / SP34-2 / BD Bioscience / 557917 / 9277122 / 1:15
 CD4 / BF480 / SK3 / BD Bioscience / 566104 / 58964 / 1:60, 1:30
 CD8 / BB700 / RPA-T8 / BD Bioscience / 566452 / 16984 / 1:1200
 IFN γ / FITC / B27 / BD Bioscience / 552887 / 9329760 / 1:15
 IL-2 / PE-Cy7 / MQ1-17H12 / Invitrogen / 25-7029-42 / 2136515 / 1:60
 IL-4 / BV421 / MP4-25D2 / BD Bioscience / 564110 / 15834 / 1:30
 TNF / BUV395 / Mab11 / BD Bioscience / 563996 / 10280 / 1:30
 TruStain FcX / Purified / - / BioLegend / 422302 / B298875 / 1:60

Anti-viral:

SARS-CoV-2 (2019-nCoV) Spike Antibody, Rabbit Mab / AF647 (labelled) / #007 / Sino Biological / 40150-R007 / MA14FE2702 / 1:400 [flow cytometry]
 SARS-CoV-2 (2019-nCoV) Spike Antibody, Rabbit Mab / Purified / #007 / Sino Biological / 40150-R007 / MA14FE2702 / 1:1000 [Western blot]
 SARS-CoV-2 (2019-nCoV) Spike Antibody, Rabbit Mab / AF647 (labelled) / #007 / Sino Biological / 40150-R007 / MA14FE2702 / 1:100 [Immunofluorescence]
 B38 monoclonal antibody, SARS-CoV-2 receptor binding domain; produced at Pfizer for internal research (no catalogue number); 10 μ g/mL (biolayer interferometry)
 VSV-G Antibody (clone 8G5F11) / purified / monoclonal / Kerafast Inc. / EB0010 / - / 1:2000

Secondary antibodies and others:

Peroxidase AffiniPure Goat Anti-Mouse IgG, Fcy fragment specific / HRP / polyclonal / Jackson ImmunoResearch / 115-035-071 / 144460 / 1:15000 [S1- and RBD-specific serum Ab, mouse]
 Anti-Rabbit IgG (whole molecule)-Peroxidase antibody produced in goat / HRP / polyclonal / Sigma Aldrich / A0545 / 028M4755V / 1:10000 [Western blot]
 AffiniPure Goat Anti-Rabbit IgG (H+L) / AF488 / polyclonal / Jackson ImmunoResearch / 111-545-003 / 122290 / 1:300 [Immunofluorescence]
 AffiniPure Goat Anti-Mouse IgG, Fcy fragment specific (min X Hu, Bov, Hrs Sr Prot) / HRP / polyclonal / Jackson ImmunoResearch / 115-005-071 / 107421 / 1:56.7 [SPR spectroscopy of polyclonal mouse immune sera]
 goat anti-human polyclonal secondary antibody / R-PE / polyclonal / Jackson ImmunoResearch / 109-115-098 / 147186 / 1:500
 Mouse IgG-UNLB / Purified / polyclonal / Southern Biotech / 0107-01 / D2519-N640 / 1:300 - 1:656100 [S1- and RBD-specific serum Ab, mouse]
 Fixable Viability Dye / eF780 / - / eBioscience / 65-0865-14 / 2178170 / 1:1000 and 1:1600 (mouse flow cytometry)
 Fixable Viability Dye / eF450 / - / eBioscience / 65-0863-14 / 2143488 / 1:500 (HEK293T/17 flow cytometry)
 Fixable Viability Dye / eF780 / - / eBioscience / 65-0865-14 / 2186489 / 1:5000 (rhesus flow cytometry)
 Streptavidin / BV421 / - / BD Bioscience / 563259 / 9197684 / 1:200 [mouse flow cytometry]
 Concanavalin A / AF594 / - / ThermoFisher Scientific / C11253 / 2160047 / 1:100 [Immunofluorescence]
 Lectin GS-II From Griffonia simplicifolia / AF594 / - / ThermoFisher Scientific / L21416 / 2047156 / 1:100 [Immunofluorescence]
 Hoechst 33342 / - / - / ThermoFisher Scientific / H3570 / 1733139 / 1:5000 [Immunofluorescence]

Validation

Commercial available Western blot, flow cytometry and immunofluorescence antibodies were selected based on their antigen

Validation

specificity and suggested application as described on the manufacturer's website and data sheets. Secondary antibodies and others were validated by the manufacturers for the different detection methods. All antibody concentrations for staining were optimized by titrating down each reagent starting at the manufacturer's recommendation. The optimal amounts of the reagents were defined by (i) minimal unspecific shift of the negative population (flow cytometry) and (ii) a maximal separation of the negative and positive population (flow cytometry) or (iii) no minimal to no background signal (ELISA, western Blot, immunofluorescence, SPR). The specificity of the B38 monoclonal antibody was originally described in Wu et al., Science 368:1274-8. The specificity was confirmed in these experiments by the absence of a background signal by biolayer interferometry and presence of signal when reacted with SARS-CoV-2 spike antigens with identities confirmed by structure determination.

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)

Human embryonic kidney (HEK)293T/17, Cercopithecus aethiops kidney Vero 76 and CCL81 cells (all ATCC); human embryonic kidney Expi293F™ (Thermo Fisher Scientific)

Authentication

Reauthentication of cell lines was performed by short tandem repeat (STR) profiling at supplier

Mycoplasma contamination

All used cell lines tested negative for mycoplasma contamination

Commonly misidentified lines
(See [ICLAC](#) register)

No commonly misidentified cell lines were used

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals

Male rhesus macaques (Macaca mulatta) (2–4 years)
Female BALB/c mice (Janvier; 8-12 weeks)

Wild animals

The study did not involve wild animals.

Field-collected samples

The study did not involve animals collected from the field.

Ethics oversight

All mouse studies were performed at BioNTech SE, and protocols were approved by the local authorities (local welfare committee), conducted according to Federation of European Laboratory Animal Science Associations recommendations and in compliance with the German Animal Welfare Act and Directive 2010/63/EU. Only animals with an unobjectionable health status were selected for testing procedures.

Immunisations for the non-human primate (NHP) study were performed at the University of Louisiana at Lafayette-New Iberia Research Centre (NIRC), which is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC, Animal Assurance #: 000452). The work was in accordance with USDA Animal Welfare Act and Regulations and the NIH Guidelines for Research Involving Recombinant DNA Molecules, and Biosafety in Microbiological and Biomedical Laboratories. All procedures performed on these animals were in accordance with regulations and established guidelines and were reviewed and approved by an Institutional Animal Care and Use Committee or through an ethical review process. Infectious SARS-CoV-2 challenge of NHPs following immunisation was performed at the Southwest National Primate Research Centre (SNPRC), Texas Biomedical Research Institute, which is also accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC, Animal Assurance #: 000246). Animal husbandry followed standards recommended by AAALAC International and the NIH Guide for the Care of Use of Laboratory Animals. This study was approved by the Texas Biomedical Research Institute Animal Care and Use Committee.

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

This manuscript describes preclinical studies. As a benchmark for the non-human primate serology, SARS-CoV-2 neutralising titers and RBD-binding IgG levels of a panel of human SARS-CoV-2/COVID-19 convalescent sera are reproduced, verbatim, from three clinical publications (Sahin et al., Nature 10.1038/s41586-020-2814-7, 2020; Mulligan et al., Nature 10.1038/s41586-020-2639-4, 2020; Walsh et al., The New England Journal of Medicine; 10.1056/NEJMoa2027906, 2020). Please refer to the clinical reports for background to the referenced clinical data.

Recruitment

This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.

Ethics oversight

This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.

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

Clinical data

Policy information about [clinical studies](#)

All manuscripts must comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.
Study protocol	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.
Data collection	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.
Outcomes	This manuscript describes preclinical studies. See the clinical reports for background to the referenced clinical data.

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	Mice: For flow cytometry or ELISpot, blood or cell suspensions from lymph node and spleen were used directly or after peptide stimulation. Peripheral blood was collected from the retro-orbital venous plexus or vena facialis under isoflurane anaesthesia. Spleen single-cell suspensions were prepared in PBS by mashing tissue against the surface of a 70 µm cell strainer (BD Falcon) using the plunger of a 3-mL syringe (BD Biosciences). Erythrocytes were removed by hypotonic lysis. Popliteal, inguinal and iliac lymph nodes were pooled, cut into pieces, digested with collagenase D (1 mg/mL; Roche) and passed through cell strainers. For intracellular stains, cells were fixed and permeabilized using the eBioscience™ Foxp3/Transcription Factor Staining Buffer Set. NHP: Blood for serum and PBMCs was collected in compliance with animal protocol 2017-8725-023 approved by the NIRC Institutional Animal Care and Use Committee. Animals were anesthetised with ketamine HCl (10 mg/kg; IM) during blood collection and immunisation, and monitored for adequate sedation.
Instrument	Cell culture cells were acquired on a FACSCanto II flow cytometer (BD Biosciences). Mouse cells were acquired on a BD Symphony A3 or BD Celesta (B-cell subtyping) flow cytometer (BD Bioscience). NHP cells were analyzed on a LSR Fortessa X-20
Software	Cell culture cells were analyzed using BD FACSDiva software version 8.0.1 and analysed by FlowJo software version 10.6.2 (FlowJo LLC, BD Biosciences). Mouse cells were analyzed using BD FACSDiva software version 9.1 or 8.0.1.1, respectively, and analysed with FlowJo 10.6 (FlowJo LLC, BD Biosciences). NHP cells were analyzed using FlowJo (10.4.1).
Cell population abundance	Sorted CD4 CD8 T cells from mouse were confirmed following magnetic bead separation.
Gating strategy	The gating strategies are detailed in the supplementary information. Mouse: Flow cytometry gating strategy for the identification of IFNγ, IL-2, and TNF secreting CD8+ T cells in the mouse spleen. was performed after CD8+ T cells were gated within single, viable lymphocytes, excluding CD4+ T cells. Flow cytometry gating strategy for identification of TFH cells, activated T cells and B cells in lymph nodes and the spleen was performed by CD3+CD19- T cells gating within single, viable lymphocytes. CD4+ and CD8+ T cells were gated from CD3+ cells; TFH cells were gated from CD4+ T cells and defined as CD4+ T-bet- GATA3- CD44+ CD62L- PD-1+ CXCR5+ cells. Flow cytometry gating strategy for the identification of B cells in lymph nodes and the spleen was done by gating activated B cells within single, viable lymphocytes defined as IgD-Dump (CD4, CD8, F4/80, GR-1)- cells. Plasma cells (PC) were gated from activated B cells and defined as CD138+ B220low/- cells. Switched B cells were gated from non-PC and defined as CD19+ CD138- IgM-. Germinal centre (GC) and IgG1+ and IgG2a+ B cells were gated from switched B cells and defined as CD19+ IgM- CD38- CD95+ and CD19+ IgM- IgG1+/IgG2a+, respectively. Flow cytometry gating strategy for the identification of T cells, B cells and TFH cells in peripheral blood was performed by gating CD3+ CD19- T cells within single, viable lymphocytes. CD4+ and CD8+ T cells were gated from CD3+ CD19- cells. TFH cells were gated from CD4+ T cells and defined as CD4+ T-bet- GATA3- CD44+ CD62L- PD-1+ CXCR5+ cells. Rhesus macaque: Flow cytometry gating strategy for identification of spike-specific SARS-CoV-2 modRNA vaccine BNT162b2-induced T cells started with events acquired with a constant flow stream and fluorescence intensity, viable cells, lymphocytes and single events were identified and gated. Within singlet lymphocytes, CD20- CD3+ T cells were identified and gated into CD4+ T cells and CD8+ T cells. Antigen-specific CD4+ T cells were identified by gating on CD154 and cytokine-positive cells, and CD8+ T cells were identified by gating on CD69 and cytokine-positive cells. The antigen-specific cells were used for further analysis. in vitro:

Flow cytometry gating strategy for the identification of HEK293T cells transfected with BNT162b1 or BNT162b2, or BNT162b1-RNA or BNT162b2-RNA using a transfection reagent or no RNA (control) was performed by gating S1+ HEK293T cells within single, viable HEK293T cells.

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