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	Electron microscopy: EPU (ThermoFisher Scientific) nanoDSF: PR.ThermControl v2.3.1 (NanoTemper Technologies) DLS: ZS Explorer v3.0.0 (Malvern Panalytical)
Data analysis	CryoEM Data processing: CryoSPARC v3.3.1 Model building: Chimera-X v1.3, ISOLDE v1.1 (Croll et al., 2018), MolProbity (Chen et al., 2010), Coot v0.8.9 (Emsley and Cowtan., 2004), Phenix v1.3 (Liebschner et al., 2019) nanoDSF: PR.ThermControl v2.3.1 (NanoTemper Technologies) Processing of thermal denaturing experiments: Microsoft Excel DSF: BioRad CFX96 manager software (BioRad) Ancestral sequence reconstruction: MEGA-X v10.1.6, IQ-Tree v1.6.12, Cell counter: CELENA® S software 1.1.6 Concentration: CFR21 Software (Implen) DLS Data: ZS Explorer v3.0.0 (Malvern Panalytical) Serum binding assay: GraphPad Prism Biacore Insight Evaluation software (Cytiva) Figures: Affinity Designer

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

Additional information or request should be directed and will be fulfilled by Per-Olof Syrén (per-olof.syren@biotech.kth.se)

Materials availability:
Plasmids used in this study are available upon request.

Data availability:
PDB structures have been deposited to the wwPDB database under accession codes 8AJA and 8AJL for AnSA-5 and AnSA-6, respectively. The cryo-EM density maps have been deposited in the wwPDB database and Electron Microscopy database (EMBD) under accession code EMD-15475 and EMD-15482 for AnSA-5 and AnSA-6, respectively.

Human research participants

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

Reporting on sex and gender	Those data have been collected.
Population characteristics	The study includes 7 plasma samples from 7 healthy volunteers in Sweden and Italy recruited during 2021-2022.
Recruitment	Recruitment criteria for this study was above 18 years of age. Able to read, speak, and understand English. Able to provide informed consent. In current good general health.
Ethics oversight	The study was approved by the ethics committees in institutional review board (IRB) of Stockholm and the Institutional Review Board of Policlinico San Matteo.

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	For serum activity tests, 5 positive plasma samples and 2 controls were used.
Data exclusions	No data were excluded.
Replication	All experiments were replicated at least 2 times. If the number of replicates varies from two it can be found in the main text, figure legends and methods.
Randomization	We did not use or report on any randomized data.
Blinding	No data presented is subjected to blinding.

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: CR3022 IgG1 (InvivoGen, srbd-mab1)

Validation: CR3022 is a recombinant monoclonal antibody (mAb) that was raised specifically against the SARS-CoV and SARS-CoV-2 Spike receptor binding domain and a human IgG1 constant region. The antibody binding has been validated by ELISA using coated spike RBD. https://www.invivogen.com/sars2-spike-cr3022-mab-isotypes

Listed details above is based on the information given by the manufacturer.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): Expi293F (ThermoFisher Scientific)

Authentication: None of the cell lines were authenticated

Mycoplasma contamination: The cell lines were not tested for mycoplasma contamination prior to experiments but earlier the same year.

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