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Last updated by author(s): Sep 29, 2020

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	SerialEM automated image acquisition software version 3.7; BLU-ICE X-ray data collection software at SSRL; Tecan Infinite M1000 plate reader software; Biacore T200 instrument software
Data analysis	GraphPad Prism 8.4.3 was used for polyreactivity data analysis; XDS (Build 20200417), Xia2 v0.3.8, DIALS v2.2, and the CCP4 v7.0.6 suite of crystallographic programs (AIMLESS v0.7.4, PHASER v2.8.2), Sculptor v2.0, Phenix v1.18, Coot v0.8.9, cryoSPARC v2.15, CTFFIND4 v4.1.14, PyMOL v2.2, Chimera v1.13, ChimeraX-v1.0, and Molprobity v4.4 were used for structural analysis; Kinetic constants were calculated using Biacore T200 Evaluation Software v3.2; PDBePISA v1.48 for BSA calculations;

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 atomic models generated from X-ray crystallographic studies of the C102-RBD complex, C102 Fab, C002 Fab, C110 Fab, C121 Fab, and C135 Fab have been deposited at the Protein Data Bank (PDB, http://www.rcsb.org/) under accession codes PDB 7K8M, 7K8N, 7K8O, 7K8P, 7K8Q, and 7K8R, respectively. The atomic models and cryo-EM maps generated from cryo-EM studies of the C002-S 2P (state 1), C002-S 2P (state 2), C104-S 2P, C110-S 2P, C119-S 2P, C121-S 2P (state 1), C121-S 2P (state 2), C135-S 2P and C144-S 6P complexes have been deposited at the PDB (http://www.rcsb.org/) and the Electron Microscopy Databank (EMDB,

http://www.emdataresource.org/) under the following accession codes: PDB 7K8S, 7K8T, 7K8U, 7K8V, 7K8W, 7K8X, 7K8Y, 7K8Z, and 7K90; EMD 22729, 22730, 22731, 22372, 22733, 22734, 22735, 22736, and 22737.

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	Not applicable to this study, because no sample size calculation was performed to design the study.
Data exclusions	No data were excluded.
Replication	All experiments were replicated successfully, n values can be found in figure legends.
Randomization	Not applicable to this study, as we do not report experiments that use randomized data.
Blinding	Not applicable to this study, as we do not report any experiments that applied 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
☒	☐ 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	HRP-conjugated anti-human IgG secondary antibody (SouthernBiotech, Catalog 2040-04; Goat Anti-Human IgG-HRP; Lot B3919.NEB80B) used at a 1:5000 dilution. All other antibodies reported were expressed in this study.
Validation	Primary antibodies reported in this study were described previously in Robbiani et al. (doi:10.1038/s41586-020-2456-9). Target validation was done with multiple binding assays and structural studies using cryo-EM and X-ray crystallography. Control anti-HIV-1 antibodies reported in this study have been previously described and validated in a polyreactivity assay (Schoofs, et al. doi:10.1016/j.immuni.2019.04.014). Reactivity of the primary antibody listed above is based on the information on manufacturer's homepages.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Expi293F (ThermoFisher cat. A14527)
Authentication	Not authenticated after purchase.
Mycoplasma contamination	The cell lines were not contaminated by mycoplasma as determined by using the Lonza Mycoplasma Detection Kit.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.