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	No software used
Data analysis	Raw NGS sequencing data analyzed with Absolve, available from https://github.com/Genentech/Absolve. X-ray diffraction data was processed with XDS/Aimless, and phases were obtained using Phaser for molecular replacement. Model building and refinement was conducted using Coot and Phenix, respectively. Molecular dynamics (MD) simulations were carried out using Amber19 (https://ambermd.org/), with structure preparation using PyMOL v2.5.4, PROPKA v3.0, PDB2PQR (v2.1.1), and tleap (part of Amber). For MD analyses, built-in algorithms were used for alignment, RMSD measurements, and rendering within Visual Molecular Dynamics (VMD) v1.9.3, a freely available MD visualization software (https://www.ks.uiuc.edu/Research/vmd/). The PyRosetta (version 2022.41+release.28dc2a1) software package was used for energetic analyses, which employed standard built-in algorithms such as FastRelax, InteractionEnergyMetric, and MutateResidue. The flags used to control the behavior of FastRelax in the initial structure preparation step are already provided in the Methods. PyRosetta is available on the internet via both academic and commercial licenses (https://www.pyrosetta.org/, https://github.com/RosettaCommons/rosetta).

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

Variable region sequences of all antibodies tested are provided in Supplementary File 1. Atomic coordinates for the structures of the hu3.10C2 and huPara.09 Fab fragments in complex with TREM2 have been deposited in the Protein Data Bank with accession numbers 8T51 and 8T59

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Not applicable
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable
Population characteristics	Not applicable
Recruitment	Not applicable
Ethics oversight	Not applicable

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	1 sample for antigen-positive dataset, 3 samples for repertoire datasets
Data exclusions	No data were excluded from the analyses
Replication	Biacore SPR experiments for 3.10C2 and Para.09 antibodies perfored 4 independent times. Jurkat-NFAT repeorter assays performed in triplicate. Soluble TREM2 binding performed 2 to 4 indpendent times. Soluble TREM2 binding performed in triplicate. Molecular simulations ran three times for each antibody/antigen pair and free antigen. SPR binding for 3.10C2 CDR H3 mutants performed once.
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
[ ]	[x] Antibodies
[ ]	[x] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[ ]	[x] Animals and other organisms
[x]	[ ] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[x]	[ ] Flow cytometry
[x]	[ ] MRI-based neuroimaging

Antibodies

Antibodies used: Anti-TREM2 antibodies described generated in study; variable region sequences for all antibodies tested provided in Supplementary File 1. Anti-TREM2 antibodies 1.16B8 and 3.17A9 derived in this study as described in Methods. The following commercially-obtained antibodies were used: anti-rat CD4 (BD Biosciences, clone OX-35, Cat. 554836), anti-rat CD8a (BD Biosciences, clone OX-8, Cat. 554855), anti-rat CD161a (BD Biosciences, clone 10/78, Cat. 550978), anti-rat granulocyte (eBioscience, clone HIS48, Cat. 13-0570-82), anti-rat CD11b/c (Biolegend, clone OX-42, Cat. 201803), anti-rat erythrocytes (ThermoFisher, clone OX-83, Cat. MA5-17580), anti-IgM antibody at 5 µg/ml (BD Biosciences, clone G53-238, Cat. 553886), anti-rat IgG1-fluorescein isothiocyanate (FITC) (Bethyl Laboratories, Cat. A110-106F), anti-rat IgG2a-FITC (Bethyl Laboratories, Cat. A110-109F) and anti-rat IgG2b-FITC (Bethyl Laboratories, Cat. A110-111F).

Validation: Validation of antibodies derived in this study descibed in results. Validation of commercial antibodies by vendors.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): CHO cells, Genentech-maintained sub-line; HEK293, Genentech-maintained sub-line; Expi293, ThermoFisher Scientific

Authentication: CHO and HEK293, no authentication; Expi293, authentication by vendor

Mycoplasma contamination: Negative

Commonly misidentified lines (See ICLAC register): Not applicable

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals: Sprague Dawley rats

Wild animals: None

Reporting on sex: N/A

Field-collected samples: N/A

Ethics oversight: All animals used in this study were housed and maintained at Genentech in accordance with American Association of Laboratory Animal Care guidelines. All experimental studies were conducted under protocols approved by the Institutional Animal Care and Use Committee of Genentech Lab Animal Research in an Association for Assessment and Accreditation of Laboratory Animal Care International-accredited facility in accordance with the Guide for the Care and Use of Laboratory Animals and applicable laws and regulations.

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