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	Zetasizer software (Malvern); IVIS software (PerkinElmer); Infinite M200 Pro plate reader (TECAN).
Data analysis	GraphPad Prism 10 was used for statistical analysis and generating data plots. In vivo luminescence was quantified using Livingimage software. Flow cytometry data was analyzed using FlowJo_V10. Bayesian optimization described in this work is implemented within AutODEx framework available at https://autodex.ai. Additional implementation details can be found at https://autodex.csail.mit.edu. The source code can be found at https://github.com/yunshengtian/AutoOED.

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

The RBD sequence used for this study is available at GenBank (OP839194). Datasets generated and analyzed during these studies are available at a public Zenodo repository (https://zenodo.org/records/21726997). Additional datasets are available from the corresponding author upon reasonable request.

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	n/a
Reporting on race, ethnicity, or other socially relevant groupings	n/a
Population characteristics	n/a
Recruitment	n/a
Ethics oversight	n/a

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	No power analysis was performed. Exploratory screening studies were carried out using at least n=3. Sample sizes are stated in each figure legend. The sample size employed in this study were consistent with previously published works (Nature materials, 2018, 17(6): 528-534; Nature materials, 2017, 16(489-496).
Data exclusions	No data were excluded from the analysis.
Replication	Each in vivo experiment was replicated in at least 3 animals. Given the resource-intensive nature of in vivo experiments, studies involving non-human primates was performed once.
Randomization	Mice were randomly allocated to each group. Non-human primates were stratified by age and sex and allocated to experimental groups to ensure balanced representation across groups.
Blinding	Data collection for in vitro experiments was blinded by distributing samples across 96-well plates in a non-intuitive layout, such that sample identities were not readily apparent during measurement. Blinding was not implemented for in vivo studies due to the nature of the experimental design, which involved distinct administration routes (intramuscular injection versus microneedle delivery).

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
☒	☐ Plants

Methods

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

Antibodies

Antibodies used

Enzyme-Linked Immunosorbent Assay (ELISA)
Goat Anti-Mouse IgG HRP (SouthernBiotech; Cat #1030-05; Lot D1922-QA54)
Goat Anti-Monkey IgG H&L HRP (abcam; Cat # AB112767; Lot 1045749-17)
Flow cytometry:
Anti-mouse CD16/32 Antibody (BioLegend; Cat # 156603; Clone S17011E; Lot B433751)
APC anti-mouse/human GL7 Antigen Antibody (BioLegend; Cat # 144606; Clone GL7; Lot B435511)
Brilliant Violet 711 anti-mouse CD4 Antibody (BioLegend; Cat # 100550; Clone RM4-5; LotB416421)
Alexa Fluor 488 anti-mouse CD38 Antibody (BioLegend; Cat # 102714; Clone 90; Lot B394658)
PE/Cyanine7 anti-mouse/human CD45R/B220 Antibody (BioLegend; Cat # 103222; Clone R3-6B2; LotB395209)
PE anti-mouse CD185 (CXCR5) Antibody (BioLegend; Cat # 145504; Clone L138D7; Lot B428601)
BV605 Rat Anti-Mouse CD279 (PD-1) (BD; Cat # 568868; Clone 29F.1A12; Lot 5078293)

Validation

All antibodies used are from commercial sources and have been validated by the vendors. Validation data are available on the manufacturer's website.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	We acquired A549 cells from the cell bank at the Koch Institute for Integrative Cancer Reacher at MIT (ATCC, CCL-185).
Authentication	The cell line has been authenticated.
Mycoplasma contamination	Cell line tested negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

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	Six-week-old female BALB/c mice were purchased from Charles River Laboratory and housed in an MIT animal facility. For nonhuman primate experiments, fifteen (five females, ten males) genetically unselected cynomolgus macaques ranging in age from 1 year 2 months to 6 years 4 months were purchased from and housed at Alpha Genesis, Inc (Yemassee, SC).
Wild animals	No wild animals were used in this study.
Reporting on sex	Sex of the animals is indicated above and in the Methods section.
Field-collected samples	Study does not involve field-collected samples.
Ethics oversight	All animal experiments were authorized by the Division of Comparative Medicine at the Massachusetts Institute of Technology (IACUC protocol No. 2208000412 and No. 2408000722R001) and Alpha Genesis, Incorporated (IACUC No. 24-01).

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

Plants

Seed stocks	No plants were used in this study.
Novel plant genotypes	No plants were used in this study.
Authentication	No plants were used in this study.

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	All staining steps were carried out at 4°C in FACS buffer (1x PBS with 2% heat inactivated FBS and 2 mM EDTA). Single cell suspensions were Fc blocked with anti-CD16/CD32 monoclonal antibody (mAb) and stained with Fixable Viability dye eFluor780. Cells were washed and incubated for 30 minutes with a cocktail of fluorescently labeled anti-mouse mAbs containing CD38-BB515, GL7-APC, PD1-BV605, CD4-BV711, CXCR5-PE, B220-PE-Cy7 and biotinylated BUV 396-conjugated and BV421-conjugated Spike RBD-His recombinant protein. Next, cells were washed and fixed with 0.5% paraformaldehyde (PFA) for 30 minutes. To obtain accurate cell counts, precision count beads (BioLegend) were added to each sample. All samples were acquired on a 5 laser FACSymphony A3 (Becton Dickinson) and data analyzed in FlowJo v10 (Treestar).
Instrument	FACSymphony A3 (Becton Dickinson)
Software	Data collection was performed using FACSDiva and data was analyzed using FlowJo_V10.
Cell population abundance	No sorting was performed.
Gating strategy	The gating strategy has been provided in Supplementary Information.

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