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	For flow cytometry data collection we used a BD FACSymphony A5 SE (BD Biosciences) For sulfatase activity assays, all data was acquired using a microplate reader (SpectraMaxi3x, Molecular Devices) All histology slides were digitalized using a Nanozoomer S210 (Hamamatsu).
Data analysis	All FACS data was analyzed using FlowJo (version 10.8.0). For image analysis, we used CellProfiler (version 4.2.4). All data graphs and statistical analysis were performed with GraphPad Prism version 9.2.0 for Windows (GraphPad Software, San Diego, CA)

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 data supporting the findings in this study is available from the corresponding author upon reasonable request.

Human research participants

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

Reporting on sex and gender	There is not human participants
Population characteristics	not relevant.
Recruitment	Not relevant
Ethics oversight	Not relevant.

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 animal experiments a "n" of at least 20 animals (10-12 per sex) were used per group. The samples size is indicated in the figure and/or figure legend. No statistical methods were used to pre-determine sample sizes, but our sample sizes are similar to those reported in previous publications. For all molecular, biochemistry and histology data a "n" of at least 8 animals was used. Sample size is indicated in the figure and/or figure legend.
Data exclusions	Data sets were tested for outliers using the ROUT method and Q=5%. Excluded points are highlighted in blue in the "supplementary data" file.
Replication	BMT were performed in 2 cohorts of 10 animals each, for each experimental arm. The data from both cohorts is reported as pooled data.
Randomization	Animals from multiple litters were randomly assigned to each experimental arm.
Blinding	The in vivo data collection as well as the Image analysis and quantification was performed in a blind fashion to the conditions of the experiment and genotype of the animals.

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

The following primary antibodies were utilized:
anti-CD68 (Abcam, 378 ab125212),
anti-GFAP (Abcam , ab16997),
anti-Iba1 (Abcam, ab178846),
anti-Neun (Abcam, ab104225).
For flow cytometry:
Fluorochrome Marker Catalog# Company Clone
FITC-CD11c, cat# 35-0114-U100, Tonbo, clone N418
BB700-CD19, cat# 566411, BD Biosciences, clone 1D3
PE-CD45.1, cat# 110708, BioLegend, clone A201.7
PE-CF594-CD3e, cat# 562286, BD Biosciences, clone 145-2C11
PC7-CD11b, cat# 552850, BD Biosciences, clone M1/70
APC-CD45.2, cat# 20-0454-u100, Tonbo, clone 1042.1
APC-R700-CD8, cat# 564983, BD Biosciences, clone 53-6.72
BV421-Ly6G, cat# 562737, BD Biosciences, clone 1A8
BV570-Ly6C, cat# 128029, BioLegend, clone HK1.4
BV711-NK1.1, cat# 108745, BioLegend, clone PK136
BUV496-B220, cat# 612950, BD Biosciences, clone RA3-6B2
BUV805-CD4, cat# 564922, BD Biosciences, clone GK1.5

Validation

All antibodies were validated internally for each application and have been either validated in literature or commonly used by our colleagues in the field for similar approaches.

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

All animals used corresponds to the species Mus musculs, and the strains listed below:
Jax stock number 31558, C57BL/6J-Sumf1<em8>Lutzy/Mmjax
Jax stock number 664, C57BL/6J
Jax stock number 33076, C57BL/6J-Ptprc<em6>Lutzy/J
Jax stock number 31423, C57BL/6J-Sumf1<em3>Lutzy/Mmjax

Wild animals

This study did not involve wild animals

Reporting on sex

Sex was considered in this study. Animal cohorts were designed in sex-balanced fashion. Data were pooled when sex was not relevant in the outcomes. Animal cohorts were separated by sex when results were sex dependent.

Field-collected samples

This study did not involve samples collected from the field

Ethics oversight

All experiments were performed in accordance with the NIH Guidelines and approved by The Jackson Laboratory

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

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	PBL's were obtained from whole blood collected in the presence of 5mM EDTA, red blood cells removed by lysis with Gey's Buffer. For bone marrow analysis, long bones were crushed in a mortar and flushed with FACS Buffer, then strained through a 35µm filter, in 1ml of FACS Buffer. For spleen cell staining, spleens were mashed with forceps and filtered through nylon mesh in 2ml of FACS Buffer. RBC were lysed using Gey's buffer, and splenocytes washed using FACS Buffer.
Instrument	All samples were run on a BD FACSymphony A5 SE (BD Biosciences).
Software	All data was analyzed using FlowJo (version 10.8.0).
Cell population abundance	For engraftment efficiency, the percentage of donor (CD45.1) and recipient (CD45.2) cells over the total of CD45+ cells is reported. For leukocyte profile, common leukocytes populations are represented as percentage over the total of live cells (DAPI negative)
Gating strategy	Gating strategy is shown in the supplemental figures 1a,b.

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