

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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☒	☐ 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 <i>Give P values as exact values whenever suitable.</i>
☒	☐ 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	During collection of flow cytometry data on the AttuneNxT, the Attune software was used. FACSDiva was used during flow cytometry collection on the LSRFortessa. IVIS Imaging was performed on the IVIS Lumina, which used Living Image software for image acquisition and analysis. Confocal imaging used the Olympus FV3000RS and Cellsens software for image acquisition. Western blot imaging was performed using Biorad Chemidoc and analyzed using ImageJ.
Data analysis	FlowJo, Prism, R (used to make bubble plots), Living Image (ROI analysis for IVIS imaging), Excel, ImageJ (used for confocal and western blot analysis), BioRender (for schematic illustrations).

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](#)

As stated in the manuscript: "All data are available in the main text or the supplementary materials. Any other data is available upon reasonable request and should be addressed to Kristy Ainslie."

The mass spectrometry proteomics data have been deposited in ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD077329.

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	The only human study data presented in this work were human peripheral blood mononucleated cells PBMCs which were de-identified.
Reporting on race, ethnicity, or other socially relevant groupings	The only human study data presented in this work were human peripheral blood mononucleated cells PBMCs which were de-identified.
Population characteristics	The only human study data presented in this work were human peripheral blood mononucleated cells PBMCs which were de-identified.
Recruitment	The only human study data presented in this work were human peripheral blood mononucleated cells PBMCs which were de-identified.
Ethics oversight	The only human study data presented in this work were human peripheral blood mononucleated cells PBMCs which were de-identified.

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](https://www.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	Sample sizes were determined based on preliminary data and prior trafficking and EAE results to ensure statistical analyses could be performed.
Data exclusions	Fig 4I-L, Fig S26, Fig S27, Fig S28A: One spinal cord sample from the MOG-AMP-B treatment group was excluded from analysis due to an error while processing into single-cell suspension Fig S32E-F: 2 samples did not have enough cells for this panel, so the PBS group and the PBS+PC61 group have n=4 per group (rest of groups have n=5) Fig S5J: One cLN excluded from B Cell group in MFI analysis for having less than 20 events via flow cytometry.
Replication	All in vitro experiments were replicated on 3 independent occasions. In vivo trafficking has been replicated on 3 separate occasions testing both the fluorophore encapsulated in particles and conjugated. In vivo therapeutic EAE was replicated first in a pilot study, then the full day 60 study discussed in Fig 4, the PC61 Treg depletion study in Fig 4, and finally EAE was replicated to test trafficking of the particles in Fig 5. The viral challenge study had 2 preliminary studies to determine viral dose, followed by the full study discussed in Fig 6.
Randomization	For trafficking studies and the viral challenge study, animals were randomly assigned treatment groups. For EAE studies, groups were assigned at peak disease based on clinical score, % weight of day 0, and weight (grams); so that each cage had an average clinical score of 3, an average of 90% day 0 weight, and average nominal weight of 19grams. After this, each cage was randomly assigned a treatment group. This enrollment data for the 60 day therapeutic study is reported in Figure S23.

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

Each panel, dilution, and corresponding gating strategy is detailed per experiment in the supplement in figures (Figures S4-5, S12, S16, S18, S20, S25, S30, S31, S34, S37, S38).

Order for all flow antibodies is written as: antibody/stain name and fluorophore, vendor, clone, catalog number,

CD19 FITC, Biolegend, 6D5, 115506

CD49b BV421, BD Biosciences, DX5, 563063

Live/Dead eFluor 506, Invitrogen, NA, 65-0866-18

CD45 BV785, Biolegend, 30-F11, 103149

CD3 PE, Biolegend, 145-2C11, 100308

Ly6G FITC, Biolegend, S19018G, 164508

CD8 PerCp-Cy5.5, Biolegend, 53-6.7, 100734

CD11c BV421, Biolegend, N418, 117330

Ly6C BV605, Biolegend, HK1.4, 128036

CD11b PE/Cy7, Biolegend, M1/70, 101216

B220 PerCp-Cy5.5, Biolegend, RA3-6B2, 103236

CD19 PE-Dazzle594, Biolegend, 6D5, 115554

CD44 APC-Cy7, Biolegend, IM7, 103028

Cell Trace Violet, Invitrogen, NA, C34571

CD4 BV605, Biolegend, RM4-5, 116027

CD62L BV785, Biolegend, MEL-14, 104440

B220 FITC, Biolegend, RA3-6B2, 103206

Foxp3 PE, Biolegend, MF-14,126403

PD-1 PE-Cy7, Biolegend, 29.F.1A12, 135216

CD25 APC, Biolegend, 3C7, 101910

MHCII BV711, Biolegend, M5/114.15.2, 107643

MHCII FITC, Biolegend, M5/114.15.2, 107606

CD11c PE, Biolegend, N418, 117308

CD4 AF647, Biolegend, RM4-5, 100530

IFNγ BV605, Biolegend, XMG1.2, 505840

IL-17A BV650, Biolegend, TC11-18H10.1, 506930

IL-10 PE, Biolegend, JES5-16E3, 501404

CD44 PE/Cy7, Biolegend, QA19A43, 163608

CD21/35 FITC, Biolegend, 7E9, 123408

CD43 PerCP-Cy5.5, Biolegend, S11, 143220

CD40 AF647, Biolegend, HM40-3, 102912

IgM APC-Fire750, Biolegend, RMM-1, 406538

IgD BV711, Biolegend, 11-26c.2a, 405731

CD27 BV785, Biolegend, LG.3A10, 124241

CD11c FITC, Biolegend, N418, 117306

TCRb BVU395, BD Biosciences, H57-597, 742485

CD11b BV711, Biolegend, M1/70, 101242

Ly6G PE, Biolegend, 1A8, 127676

MHCII PE/Cy7, Biolegend, M5/114.15.2, 107630

MHCII PerCp/Cy5.5, Biolegend, M5/114.15.2,107626

CD4, APC-Fire750, Biolegend, RM4-5, 100568

CTLA4, BV605, Biolegend, UC10-4B9
 Lag3, BV785, Biolegend, C9B7W, 12519
 CD5, PE/Cy7, Biolegend, 53-7.3, 100622
 CD86, BV421, Biolegend, GL-1, 105032
 CD80, PE/Cy7, Biolegend, 16-10A, 104734
 CD11b, FITC, Biolegend, M1/70, 101206
 Ly6C, BV785, Biolegend, HK1.4, 128041
 Ly6G, APC-Fire750, Biolegend, 1A8, 127652
 CD11c, APC, Biolegend, N418, 117310
 CD44, BV421, Biolegend, IM7, 100039
 MHCII, PE-Cy7, Invitrogen, M5/114.15.2, 25-5321-82
 CD86, PE, Biolegend, GL-1, 105008
 CD80, BV605, Biolegend, 16-10A1, 104729
 CD206 PerCp/Cy5.5, Biolegend, C068C2, 141716
 Foxp3 AF647, Biolegend, MF-14, 126407
 CD19 BUV395, BD Biosciences, 1D3, 56557
 CD11b BUV737, BD Biosciences, M1/70, 612800
 CD25 PE, Biolegend, A18246A, 113704
 iNOS PE/Cy7, Biolegend, W160330C, 696814
 CD19 FITC (human), Biolegend, H1B19, 982420
 CD19 APC/Cy7, Biolegend, 6D5, 115530
 CD27 PE/Cy7, Biolegend, LG.3A10, 124216

Western Blots:

Cell Signaling Technology phospho-p44/42-MAPK (Erk1/2) (Thr202/Tyr204) (D13.14.4E) Rabbit Monoclonal antibody, CAT# 4370
 Millipore Sigma Anti-Vinculin Antibody, mouse monoclonal, hVIN-1, CAT #V9131
 Cell Signaling Technology Anti-mouse IgG, HRP-linked Antibody, CAT #7076
 Bio-rad Clarity Western ECL Substrate, CAT# 1705060S

Treg Depletion:

InVivoMAB anti-mouse CD25 (IL-2R α), PC-61.5.3, BioXCell, #BE0012
 InVivoMAB rat IgG1 isotype control, anti-horseradish peroxidase, BioXCell, #BE0088

ELISAs:

ELISA MAX[™] Standard Set Mouse IL-2, Biolegend, 431001
 ELISA MAX[™] Standard Set Mouse IL-10, Biolegend, 431411
 ELISA MAX[™] Deluxe Set Mouse IL-17A/F, Biolegend, 426204
 ELISA MAX[™] Standard Set Mouse IFN- γ , Biolegend, 430801
 ELISA MAX[™] Standard Set Mouse IL-6, Biolegend, 431301
 ELISA MAX[™] Standard Set Mouse TNF- α , Biolegend, 430901
 ELISA MAX[™] Standard Set Mouse IL-1 β , Biolegend, 432601
 ELISA MAX[™] Deluxe Set Mouse IL-12 (p70), Biolegend, 433604
 ELISA MAX[™] Deluxe Set Mouse IL-12/IL-23 (p40), Biolegend, 431604
 ELISA MAX[™] Standard Set Mouse IL-4, Biolegend, 431101

Immunofluorescence:

CellTracker green CMFDA, Invitrogen, NA, C2925

Validation

All flow cytometry antibodies were titrated in house prior to performing any experiments. Concentrations of 1:50 followed by 2-fold dilutions to 1:1600 were assessed. Staining index (SI) was calculated by (MFI(positive population) - MFI (negative population))/ 2* (standard deviation of negative population)). The optimal SI was used in subsequent experiments, selected by having the largest SI (if multiple concentrations had the same SI within 0.3; the lowest concentration was selected to preserve antibody).

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

In vivo trafficking studies used 10-12-week-old BALB/c mice (Jackson, stock #000651).
 In vitro association assays used cells from 8-12-week-old C57BL/6 mice (Jackson, stock #000664).
 In vitro studies involving OVA peptide used cells from 8-12-week-old C57BL6/OTII mice (bred in house)
 In vitro studies involving p31 peptide used cells from 8-12-week-old BDC2.5 mice (bred in house - Tisch Lab)
 In vitro BCR studies used 8-12 week old C57BL/6-Tg(IghelMD4)4Ccg/J (MD4 mice; Jackson stock# 002595) in addition to C57BL/6 controls.
 EAE studies used 12–13-week-old pathogen-free C57BL6 /nTac mice (Taconic Farms, stock # B6-F) . Hooke Laboratory kits were used to induce EAE for MOG35-55 (Cat. # EK-2110)
 The viral challenge H1N1 CA/09 study used 12-13-week-old C57BL6 mice (Jackson Farms, stock #000664)

Wild animals

The study did not involve wild animals.

Reporting on sex	All animals studied were females as females have a significantly higher rate of autoimmunity (>80%) in humans. Similar, in mice, the incidence of autoimmunity is also higher and more reliable in females than males.
Field-collected samples	The study did not involve field-collected samples.
Ethics oversight	All procedures involving animals were approved by UNC-Chapel Hill's Institutional Animal Care and Use Committee (IACUC). Care of the mice was in accordance the standards dictated by the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Additionally, EAE studies also followed Hooke Laboratory's recommended protocols for care of EAE mice, as we used their kit for disease induction.

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

Plants

Seed stocks	Seed stocks were not used in this study.
Novel plant genotypes	Novel plant genotypes were not used in this study.
Authentication	Not needed for 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	Detailed sample preparation and appropriate references are described in the Methods Section heading of "Flow Cytometry". In brief, spleens and lymph nodes were processed by mechanical dissociation through a 70um filter. Spleens used ACK lysis buffer to remove red blood cells and were filtered twice. Brains and spinal cords were processed by a 15mL Dounce homogenizer for tissue grinding. After the homogenizer, a 30% percoll gradient was used on brains and spinal cords to remove fat and debris (the pellet was retained). Finally, the brains and spinal cords were filtered through a 70um filter. Subcutaneous depots were processed via removing a 2cm x 2cm skin section. The skin section was mechanically minced with surgical scissors into approximately 2mm x 2mm sections. These sections were placed in a collagenase D digest (2mg/mL collagenase D and 10ug/mL DNase in RPMI media with no FBS) for 20min at 37C. After 20min, these cells were placed on ice to halt the enzymatic digestion and then mechanically dissociated through a 70um filter. These cells were placed in a 30% percoll and the pellet was filtered a final time through a 70um filter.
Instrument	Attune NxT (Thermofisher) or the LSRFortessa (BD Biosciences)
Software	FlowJo was used to analyze all flow data (BD Biosciences)
Cell population abundance	FACs sorting was not used in this study.
Gating strategy	The general gating strategy used was FSC/SSC gate for debris exclusion (low SSC), then double removal via SSC-A v SSC-H, then live cell gating. Live cell gating was sometimes combined with primary marker gating such as live cells v CD45. All primary markers were gated first (such as cell lineage markers like CD3, CD19, etc.), followed by secondary antigens (such as surface markers to subset a primary cell type like CD21, CD23, etc.), followed by tertiary (such as activation markers and cytokines like PD-1, IL-10, IFNs, etc.). Gating strategies for each experiment are detailed in the supplement (Supplementary Figures S4-5, S12, S15-17, S23, S28).

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