nature research

Corresponding author(s): Matthias Nahrendorf and Daniel Anderson

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 Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	LSR II flow cytometer with BD FACSDiva software.
Data analysis	FlowJo V9, PRISM V6, OsiriX DICOM Viewer V10, ImageJ V1.52, Horos V4.0

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/reviewers upon request. 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 main data supporting the results in this study are available within the paper and its Supplementary Information. The raw and analysed datasets generated during the study are too large to be publicly shared, yet they are available for research purposes from the corresponding authors on reasonable request.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes were calculated on the basis of the predicted between-group difference and power needed to reach a p level of 0.05 (cutoff for statistical significance in this study).
Data exclusions	No data points were excluded.
Replication	Experiments were in general performed three times (two replications) to confirm the results. Experiments are only shown if replications were successful and all experimental results could be confirmed.
Randomization	Mice / cages were randomly allocated to the experimental groups.
Blinding	Given the need to properly formulate the nanoparticles, the researchers were not blinded to the components that were used to synthesize each formulation. Tie2 knockdown studies were conducted by an independent operator, who was unaware of the treatment conditions. ImageStream experiments were performed and analysed by a core facility unaware of the study rationale. MRI and biodistribution imaging were performed and analysed in a blinded fashion. Flow-cytometry experiments were performed and managed by only one researcher, which precluded blinding; but analysis, specifically FACS gating, was defined by negative controls and all FACS data were independently reviewed by M.N.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	All materials used are commercially available or made from commercially available materials (this applies to the nanoparticles). A detailed description of all the steps necessary to produce the nanoparticles is available in Methods.

Antibodies

Antibodies used	Information for the antibodies is listed as follows: fluorochrome; target; catalog #; supplier; clone; dilution FITC; CD34; 553733; BD; RAM34; 1:100 FITC; CD45.2; 553772; BD; 104; 1:100 FITC; Ly6c; 553104; BD; AL 21; 1:100 FITC; Ly6g; 127606; BioLegend; 1A8; 1:100 PE; B220; 103208; BioLegend; RA3-6B2; 1:100 PE; CD31; 102508; BioLegend; MEC13.3; 1:100 PE; CD90.2; 140308; BioLegend; 53-2,1; 1:100 PE; NK-1.1; 108708; BioLegend; PK136; 1:100

PE; Sca1; 12-5981-82; eBioscience; D7; 1:100
PE; Ter119; 553673; BD; TER-119; 1:100
PE; CD51; 104106; BioLegend; RMV-7; 1:50
PerCP5.5; CD41; 133918; BioLegend; MWReg30 ; 1:100
PerCP5.5; CX3CR1; 149010; BioLegend; SA011F11; 1:100
PE-Cy7; F4/80; 123114; BioLegend; BM8; 1:100
PE-Cy7; Sca1; 558162; BD; D7; 1:100
BV421; CD115; 135513; BioLegend; AFS98; 1:100
PacBlue; CD45.1; 110722; BioLegend; A20; 1:100
Aqua live cell; L34966; invitrogen; not applicable; 1:50
BV605; CD19; 115540; BioLegend; 6D5; 1:100
BV605; CD45.2; 563051; BD; 104; 1:100
BV605; CD140a; 135916; BioLegend; APA5; 1:100
BV605; ckit; 563146; BD; 2B8; 1:100
BV605; Ter119; 116239; BioLegend; TER-119; 1:100
Biotin; CD3epsilon; 100304; BioLegend; 145-2C11; 1:200
Biotin; CD4; 100404; BioLegend; GK1.5; 1:200
Biotin; CD8a; 100704; BioLegend; 53-6.7; 1:200
Biotin; CD90.2; 105304; BioLegend; 30-H12; 1:200
Biotin; CD19; 115504; BioLegend; 6D5; 1:200
Biotin; B220; 103204; BioLegend; RA3-6B2; 1:200
Biotin; CD11b; 101204; BioLegend; M1/70; 1:200
Biotin; CD11c; 117304; BioLegend; N418; 1:200
Biotin; GR1; 108404; BioLegend; RB6-8C5; 1:200
Biotin; Ter119; 116204; BioLegend; TER-119; 1:200
Biotin; NK-1.1; 108704; BioLegend; PK136; 1:200
Fc block; CD16/32; 553142; BD; 2.4G2; 1:100
BV711; CD16/32; 101337; BioLegend; 93; 1:100
BV711; CD45; 103147; BioLegend; 30-F11; 1:100
APC; Ly6g; 127614; BioLegend; 1A8; 1:100
AF647; CD11b; BioLegend; M1/70; 1:100
AF700; NK-1.1; 108730; BioLegend; PK136; 1:100
APC-Cy7; CD11b; 101218; BioLegend; M1/70; 1:100
APC-Cy7; Ter119; 560509; BD; TER-119; 1:100
APC-Cy7; CD45.2; 560694BD; 104; 1:100
APC/Fire; CD11b; 101262; BioLegend; M1/70; 10 mg/kg

Validation

All antibodies have been validated by the manufacturers for the applications used. The gating strategies used for identifying cell populations in this manuscript have been used and published by our group and others before.

CD34: Validated for use in mice and as a stem cell marker https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/mouse/fitc-rat-anti-mouse-cd34-ram34/p/553733 and is widely used for this application https://dx.doi.org/10.1016%2Fj.stem.2015.04.008
CD45: Validated for use in mice and as a leukocyte marker https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/mouse/fitc-mouse-anti-mouse-cd452-104/p/553772 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
Ly6c: Validated for use in mice and as a leukocyte marker https://www.bdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-mouse-antibodies/cell-surface-antigens/fitc-rat-anti-mouse-ly-6c-al-21/p/553104 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
B220: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/pe-anti-mouse-human-cd45r-b220-antibody-447 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
CD31: Validated for use in mice and as a endothelial cell marker https://www.biolegend.com/en-us/products/pe-anti-mouse-cd31-antibody-379 and is widely used for this application https://dx.doi.org/10.1084%2Fjem.20070885
CD90.2: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/fr-ch/products/pe-anti-mouse-cd90-2-thy-1-2-antibody-6867 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
NK-1.1: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/pe-anti-mouse-nk-1-1-antibody-431 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
Sca1: Validated for use in mice and as a leukocyte and endothelial cell marker https://www.thermofisher.com/antibody/product/Ly-6A-E-Sca-1-Antibody-clone-D7-Monoclonal/12-5981-82 and is widely used for these applications https://dx.doi.org/10.1084%2Fjem.20070885 and https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
Ter119: Validated for use in mice and as a red blood cell marker https://www.bdbiosciences.com/eu/applications/research/stem-cell-research/mesoderm-markers/mouse/pe-rat-anti-mouse-ter-119erythroid-cells-ter-119/p/553673 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
CD41: Validated for use in mice and as a stem cell marker https://www.biolegend.com/en-us/products/percp-cyanine5-5-anti-mouse-cd41-antibody-9696 and is widely used for this application https://dx.doi.org/10.1016%2Fj.stem.2015.04.008
CD51: Validated for use in mice https://www.biolegend.com/en-us/products/pe-anti-mouse-cd51-antibody-488 and used as an osteblast marker https://dx.doi.org/10.1038/nm.3589.
CX3CR1: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/percp-cyanine5-5-anti-mouse-cx3cr1-antibody-10461 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
F4/80: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/pe-cyanine7-anti-mouse-f4-80-antibody-4070 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
CD115: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/brilliant-violet-421-anti-mouse-cd115-csf-1r-antibody-8971 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567

CD19: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/search-results/brilliant-violet-605-anti-mouse-cd19-antibody-7645 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
ckit: Validated for use in mice and as a stem cell marker https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/mouse/bv605-rat-anti-mouse-cd117-2b8/p/563146 and is widely used for this application https://dx.doi.org/10.1016%2Fj.stem.2015.04.008
CD3epsilon: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/biotin-anti-mouse-cd3epsilon-antibody-22 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
CD4: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/biotin-anti-mouse-cd4-antibody-247 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
CD8a: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/biotin-anti-mouse-cd8a-antibody-152 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
CD11b: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/biotin-anti-mouse-human-cd11b-antibody-346 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
CD11c: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/biotin-anti-mouse-cd11c-antibody-1814 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
GR1: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/biotin-anti-mouse-ly-6g-ly-6c-gr-1-antibody-457 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567
CD16/32: Validated for use in mice and as a stem cell marker https://www.bdbiosciences.com/us/applications/research/b-cell-research/surface-markers/mouse/purified-rat-anti-mouse-cd16cd32-mouse-bd-fc-block-24g2/p/553142 and is widely used for this application https://dx.doi.org/10.1016%2Fj.stem.2015.04.008
Ly6g: Validated for use in mice and as a leukocyte marker https://www.biolegend.com/en-us/products/apc-anti-mouse-ly-6g-antibody-6115 and is widely used for this application https://dx.doi.org/10.1161%2FCIRCRESAHA.115.303567

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	bEnd.3 (spelled BEND3 as well); manufacturer ATCC; catalog # CRL-2299
Authentication	The authentication was provided by the manufacturer.
Mycoplasma contamination	Mycoplasma free cells were purchased. No further testing for mycoplasma was done.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	C57BL/6J(Jackson Laboratory, stock # 000664), B6.129P-Cx3cr1tm1Litt/J (Jackson Laboratory, stock # 005582), B6.SJLPtprcaPepcb/BoyJ (Jackson Laboratory, stock # 002014) mice were used at 11 to 13 weeks of age. To receive hemizygous B6.129P-Cx3cr1tm1Litt/J (Jackson Laboratory, stock # 002052) mice, homozygous mice were crossed with C57BL/6J mice. B6.129P2-Apoetm1Unc/J were started on high fat diet at 8 weeks of age. Mice of both sexes were used.
Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.

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	Single-cell suspensions were obtained from peripheral blood, bone marrow, aorta and lung. Briefly, blood was collected by eye bleeding using heparinised capillaries or, if larger volumes were needed, by cardiac puncture and the addition of 50 mmol/L EDTA. Red-blood-cell lysis was achieved by adding 1x red-blood-cell lysis buffer (Biolegend) for 2 minutes. After blood collection, mice were perfused through the left ventricle with 30 mL ice-cold PBS. Bone marrow was harvested by flushing femurs in PBS with 0.5% bovine serum albumin (BSA) for leukocyte and HSPC staining or with HBSS containing 2% FBS, 2 mg/ml disease 2 and 1 mg/ml collagenase IV and incubated with gentle agitation for 30 minutes at 37°C for endothelial cells. Lungs were excised and minced with a fine scissor before digestion in DMEM w/o phenol red containing 2% FBS, 2 mg/ml dispase 2, 5 mg/ml collagenase I (Worthington) and 1 mg/ml DNase I (Sigma) at 37°C and 125 revolutions for 20 minutes. Tissues were then plunged thorough

	40-µm nylon mesh (BD Falcon), washed and centrifuged (8 minutes; 300g; 4°C). The obtained single-cell suspensions were stained at 4°C for 30 minutes and afterwards washed, centrifuged and resuspended.
Instrument	LSR II flow cytometer with BD FACSDiva software. For cell sorting the populations were defined as described and sorted using a FACSAria II cell sorter.
Software	FlowJo V9
Cell population abundance	For qPCR experiments at least 10.000 cells were sorted. Purity for endothelial cells was confirmed by a second sorting step, PCR and microscopy.
Gating strategy	Monocytes were identified as CD90- CD19- NK1.1- Ly-6G- D45.2+ CD11bhighCD115+ F4/80low and separated into Ly-6Clow and a Ly-6Chigh populations. Neutrophils were identified as CD90- CD19- NK1.1- D45.2+ CD11bhigh Ly-6G+. Blood and bone marrow LSK were identified as (B220 CD3e CD4 CD8a CD11b CD11c CD19 CD90.2 GR1 IL7Ra NK1.1 Ter119)- c-kit+ Sca-1+, LKs as (B220 CD3e CD4 CD8a CD11b CD11c CD19 CD90.2 GR1 NK1.1 Ter119)- c-kit+ Sca-1- and subdivided into CMP, MEP and GMP by their CD16/32 and CD34 expression. Bone-marrow and lung endothelial cells were gated as CD45.2- CD41- Ter119- CD31+ Sca-1+ and Ter119- CD45+ CD31+, respectively.

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