

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 (<i>n</i>) 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give <i>P</i> 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 <i>d</i> , Pearson's <i>r</i>), 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	1. Cytation imaging reader (BioTek), 2. 400 MHz NMR (Bruker), 3. IVIS Lumina III In Vivo Imaging System (PerkinElmer), 4. AXIO Observer 7 (Zeiss), 5. Flow cytometer (cytoFLEX S). 6. Small-angle X-ray scattering (Anton Paar SAXSpace). 7. Cryo-TEM (FEI Tecnai F20 electron microscope).
Data analysis	1. Graphpad Prism v9 software was used for statistical analyses; 2. FlowJo v10 was used for data plotting; 3. Chemdraw v22.0.0 was used for chemical data; 4. Mestrenova v14.2.3 was used for NMR data; 5. ZEN 2012, Living Image v .5.5, was used for Luminance data from animals; 6. JMP v16, was used for formulation optimization. 7. GMS 3 and iTEM was used for Cryo-TEM data. 8. SAXSanalysis™ was used for SAXS data.

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 main data supporting the findings of this study are included in this paper and supplementary information files. The raw and analyzed datasets are too numerous to readily share publicly. Source data for the figures are available for research purposes from the corresponding author on 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

Reporting on race, ethnicity, or other socially relevant groupings

Population characteristics

Recruitment

Ethics oversight

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

Data exclusions

Replication

Randomization

Blinding

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

Methods

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

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

Antibodies

Antibodies used

1. anti-mouse CD45-FITC (BioLegend, Cat#147709, Clone13/2.3),
2. anti-mouse CD31-Alexa Fluor 594 (BioLegend, Cat#102520, CloneMEC13.3),
3. anti-mouse EpCAM-BrilliantViolet 421 (BioLegend, Cat#118225, CloneG8.8),
4. anti-mouse NeuN-Alexa Fluor 647 (BioLegend, Cat#608453, CloneW18230A),
5. anti-mouse GFAP-BrilliantViolet 421 (BioLegend, Cat#644710, Clone2E1.E9),
6. anti-firefly Luciferase-PE (Abcam, Cat#ab237253),
7. anti-PCSK9-FITC (Bioss, Cat#bsm-43105m-fitc-100ul),
8. anti-mouse APC/Cyanine7 (BioLegend, Cat#117323, CloneN418),
9. anti-mouse CD86 PerCP/Cyanine5.5 (BioLegend, Cat#105027, CloneGL-1),
10. anti-mouse CD11b Brilliant Violet 510 (BioLegend, Cat#101245, CloneM1/70),
11. anti-mouse CD11b PE (BioLegend, Cat#101207, CloneM1/70)

Validation

All antibodies have been validated for target specificity and applications by the manufacturers and published literature:

1. anti-mouse CD45-FITC (<https://www.biolegend.com/de-de/products/fitc-anti-mouse-cd45-antibody-9796>),
2. anti-mouse CD31-Alexa Fluor 594 (<https://www.biolegend.com/en-us/products/alexa-fluor-594-anti-mouse-cd31-antibody-9633>)
3. anti-mouse EpCAM-BrilliantViolet 421 (<https://www.biolegend.com/en-us/products/brilliant-violet-421-anti-mouse-cd326-ep-cam-antibody-9964>)
4. anti-mouse NeuN-Alexa Fluor 647 (<https://www.biolegend.com/en-us/products/alexa-fluor-647-anti-rbfox3-neun-antibody-25084>)
5. anti-mouse GFAP-BrilliantViolet 421 (<https://www.biolegend.com/en-us/products/brilliant-violet-421-anti-gfap-antibody-12793>)
6. anti-firefly Luciferase-PE (<https://www.abcam.com/en-us/products/primary-antibodies/pe-firefly-luciferase-antibody-epr17789-ab237253>)
7. anti-PCSK9-FITC (https://www.biossusa.com/products/bsm-43105m-fitc?srsltid=AfmBOopo_c9ikCF43YBDz6oLd_wHi0T8iQGTbjqKqpgVV3XLZ4bp0CQl)
8. anti-mouse-APC/Cyanine 7 (<https://www.biolegend.com/en-us/products/apc-cyanine7-anti-mouse-cd11c-antibody-3931>)
9. anti-mouse CD86 PerCP/Cyanine5.5 (<https://www.biolegend.com/en-us/products/percp-cyanine5-5-anti-mouse-cd86-antibody-4276>)
10. anti-mouse CD11b Brilliant Violet 510 (<https://www.biolegend.com/en-us/products/brilliant-violet-510-anti-mouse-human-cd11b-antibody-7993>)
11. anti-mouse CD11b PE (<https://www.biolegend.com/en-us/products/pe-anti-mouse-human-cd11b-antibody-349>)

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

HepG2, C2C12, and HEK293T cells were cultured in DMEM (Sigma-Aldrich) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. BEAS-2B cells was maintained in MEM medium (Sigma-Aldrich) with the same supplements. RAW264.7 was maintained in RPMI-1640 medium (Sigma-Aldrich) with the same supplements. N2A cells was maintained in EMEM medium (Sigma-Aldrich) with the same supplements. Cells were passaged at approximately 80% confluency. Briefly, cells were washed with DPBS, detached with 0.25% trypsin-EDTA, neutralized with complete medium, and centrifuged at 300xg for 3 min. Pellets were resuspended in fresh medium and replated at appropriate densities. Gal-9 cells were maintained in DMEM medium (Sigma-Aldrich) with BSA (Sigma-Aldrich) and 1% penicillinstreptomycin (Life Technologies).

Authentication

Cell lines were authenticated by morphology, growth characteristics according to instructions provided on the suppliers' website during the study.

Mycoplasma contamination

All the cells were tested and no mycoplasma contamination were observed.

Commonly misidentified lines
(See [ICLAC](#) register)

Nocommonlymisidentified 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	All mouse-related animal experiments were approved by the University Health Network Animal Resources Centre and performed under AUP#6842. Mice were housed under a 12-h light-dark cycle at 24-26 °C and 40-60% relative humidity. C57BL/6, B6.Cg-Gt(ROSA)26Sortm9(CAG-589 TdTomato)Hze/J (Ai9), and C57BL/6J-Gt(ROSA)26SoremlCrx/J (LumA) mice were sourced from the Jackson Laboratory. R553X exon 12 replacement (CFTR R553X) mice were kindly provided by Dr. Craig A. Hodges from Cystic Fibrosis Mouse Models Core. All liver-humanized mouse were kindly provided by Dr. Brandon K. Wilder from Oregon Health and Science University.
Wild animals	This study did not involve wild animals.
Reporting on sex	Male and female mice were used in this study.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal studies were approved and conducted in compliance with the University Health Network Animal Resources Centre and Oregon Health and Science University guidelines.

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

Plants

Seed stocks	No research involving plants was done in this study.
Novel plant genotypes	No research involving plants was done in this study.
Authentication	No research involving plants was done 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	As described in the Methods section in detail, briefly, The cell suspensions were filtered through a 70 um cell strainer and centrifuged. The cells were resuspended at 4 °C in staining buffer for 30 min at 4 °C
Instrument	CytoFLEX S flow cytometer (Beckman Coulter, Inc, USA).
Software	Collection: FACS DIVA; Analysis: FlowJo v10
Cell population abundance	Cell populations were generally distinct and as many events were collected as possible from the starting sample.
Gating strategy	Gating was first based on FSC/SSC and single cells were gated for further analysis. The cell populations were then analyzed based on expression of markers. Gating was then based on positive level.

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