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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	no previously unreported software was used
Data analysis	no previously unreported software was used

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

All flow cytometry datasets presented in this study are available in Flowrepository, experiment number - TBD. The authors declare that all the remaining data that supporting the findings of our study are described within the paper, its Supplementary Information files, or are available from the corresponding author upon reasonable request. The source data underlying figures 1b-d, 1j, 2a, 2c-e, 3b-d, 4d-h, 4k, 5b-e, Supplementary Figures 1b-e, 3a-b, 4a-b,5 table 1 are provided as source data file.

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	male patient derived fibroblasts used to generate iPSC line used in our study
Reporting on race, ethnicity, or other socially relevant groupings	caucasian
Population characteristics	not relevant
Recruitment	not relevant
Ethics oversight	RNIPH 23-5116 CRISPAVI

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 sample size calculation was performed.
Data exclusions	no data were excluded
Replication	all experiments were replicated at least 3 times. Engraftment studies were carried out with two different donor-derived stem cells in multiple mice.
Randomization	not relevant
Blinding	not relevant

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	AB_1732008, AB_399969, AB_2889063, AB_395969, AB_2563814, AB_2738974, AB_314185, AB_1727434, AB_2732051, AB_2737745, AB_2563645, AB_1575008, AB_314185, AB_1134170, AB_2563645, AB_2732051, AB_10709590, AB_1603223, AB_2716864, AB_2563050, AB_2561668, AB_2282499, AB_2744293 and CD10-PE Texas Red (clone:Hi10a, BD Biosciences)

Validation	Most of the antibodies used have been validated in previously published articles by the team. For the others, they were validated both by the expected expression based on the cell type and through the use of appropriate controls.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	iPSC line derived from SAVI patient-derived fibroblast
Authentication	Sanger sequencing was used to confirm the presence of V155M pathogenic SAVI mutation
Mycoplasma contamination	Not tested
Commonly misidentified lines (See ICLAC register)	N/A

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	NSG-SGM3 [(NOD.Cg-Prkdcscid IL2rgtmlWjl/Sz)] mice expressing human stem cell factor (SCF), human granulocyte-macrophage colony-stimulating factor (GM-CSF), and human interleukin-3 (IL3) were obtained from Jackson Laboratory. The mice were housed in 12-h dark/light cycle, temperature and humidity-controlled environment with pressurized individually ventilated caging, sterile bedding and unlimited access to sterile food and water in the animal barrier facility at Stanford University.
Wild animals	No wild animals were used in the study.
Reporting on sex	Transplantation experiments were carried out in newly born mice, irrespective of their gender. All surviving animals were subjected to end-point analyses. Cord-blood-derived and mobilized peripheral blood-derived CD34+ HSPC were obtained from male and females healthy donors.
Field-collected samples	No field-collected samples were used in the study
Ethics oversight	All experiments involving mice were performed in accordance with National Institute of Health institutional guidelines and were approved by the University Administrative Panel on Laboratory Animal Care (IACUC 20565).

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

Plants

Seed stocks	not relevant
Novel plant genotypes	not relevant
Authentication	not relevant

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	The following biological samples were used in our studies: Fresh human umbilical cord blood-derived CD34+ HSPCs were

Sample preparation	obtained through The Binns Program for Cord Blood Research Program and not by investigators themselves. The Program was approved by Stanford's IRB. Eligible donors were expected mothers scheduled to deliver at Lucile Packard Children's Hospital who provided informed consent prior to collections. Human mobilized peripheral blood CD34+ HSPCS were purchased frozen from All Cells (Alameda, CA, USA). iPS cells derived from SAVI-derived fibroblasts were obtained through informed consent and regulatory authorization provided by Hospices Civils de Lyon (RNIPH 23-5116 CRISPAVI). Mice-derived bone marrow and spleen were obtained post-euthenazia described and approved in IACUC protocol 20565.
Instrument	BD FACS Aria II flow cytometry
Software	FACSDIVA v8.0.1 software. Analysis of all flow cytometry data was done using FlowJo v10.10
Cell population abundance	not relevant
Gating strategy	Gating strategies are detailed in the supplementary figure 5

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