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	Packmol 20.3.1; Gromacs 2021.5; SoftMax Pro; NanoDrop 1000 and 2000; FACSDiva v6.1.3;
Data analysis	Gromacs 2021.5; VMD 1.9.4a51; ProteinSurfacePrinter; GraphPad Prism 9.5; FlowJo v10; ImageJ; Adobe Illustrator; Inkscape;

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 data supporting the findings of this study are available within the paper and its Supplementary Information.

Human research participants

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

Reporting on sex and gender	All human tissue samples utilized for mast cell isolation were de-identified and thus there is no reporting on sex/gender, population, recruitment, or ethics oversight. We have added a statement to our methods further reiterating this.
Population characteristics	N/A
Recruitment	N/A
Ethics oversight	N/A

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	The selection of a minimum of 5 mice per group and 3 biological replicates of cells per group was calculated from a two tailed power analysis with a confidence level of 95% using standard freely available software G Power 3.1.9.2, as recommended by the literature (Charan et al.,"How to calculate sample size in animal studies", J Pharmacol Pharmacother. 2013 OctDec; 4(4): 303–306). Additionally, we have previously found that this sample size allows statistically significant differences to be found for biodistribution and immunological studies using PEG-b-PPS nanomaterials (Velluto et al., Biomaterials, Volume 32, Issue 36, December 2011, Pages 98399847; Stano et al. Volume 34, Issue 17, June 2013, Pages 4339–4346).
Data exclusions	One data point was excluded from the TNFalpha ELISA in Supp. Fig. 18. It was excluded due to questions that arose around sample contamination during pipetting. A note has been added to the caption of that figure. The statistical analysis/results remain the same, as this exclusion was included when we first submitted the manuscript, but mention of it was an oversight on our part.
Replication	All attempts of replication were successful. Mouse experiments were repeated 3 additional times independent of the data shared in this manuscript (which is the product of two indepedent experiments), as intermediate steps in additional ongoing studies. Flow cytometry experiments were repeated 3 independent times to produce the data in this manuscript, and specific groups have been repeated in subsequent experiments 3 times. ELISA data was obtained from two independent experiments and combined into a single assay shown in Supp Fig 18 and has been replicated once.
Randomization	Mice were allocated randomly into treatment groups. In vitro samples were randomized across homogeneous cell cultures under uniform ambient conditions with positive and negative control groups.
Blinding	For mouse studies, nanoparticle treatment group blinding was employed at the time of data collection and analysis. In vitro samples were blinded with numeric IDs prior to data collection and analysis. Flow cytometry samples also had accompanying blends of cells obtained from each test and control sample that were used to create fluorescence-minus-one controls to further eliminate any potential bias by subjective interpretation of marker positivity.

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

Anti-CD3 (Clone OKT3 from BioXcell; Cat BE0001-2) and anti-CD4 (Clone OKT4 from Biolegand; Cat 317402) antibodies from Thermo Fisher Scientific; Goat anti-Mouse IgG H&L (10nm Gold) from Abcam (ab39619). BV421 labeled anti-CD117 (KIT) (clone 104D2 from BioLegend, Lot: B369859). PE labeled anti-Siglec-6 (clone 767329 from R&D Systems, Lot: ADZQ0221091), BV650 labeled anti-CD63 (clone H5C6, from BioLegend, Lot: B356296), APC labeled anti-CD107a (lamp1) (clone H4A3, from BD Biosciences, Lot: 1264705) and FITC labeled anti-FcεRIα (clone AER-37, from BioLegend, Lot: B323076). Unlabeled antibodies used are anti-Siglec-6 (clone 767329 from R&D Systems, Lot: CIIM0221111) and anti-FcεRIα (clone AER-37 from Invitrogen, Lot: 2011282), and mouse IgG2a isotype control (from Invitrogen, Lot: UF285470)

Validation

Antibodies were validated by manufacturers via a combination of SDS-PAGE, staining of multiple endogenous cell types to confirm specificity, testing of comparable MFI between lots, and titration assays.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

Primary mast cells were derived from de-identified human skin samples procured by the Midwestern Division of the Cooperative Human Tissue Network. Human CD34+ stem cells were obtained from Lonza. (Cat. # 2C-101). Jurkat T cells were obtained from ACTT (Clone E6–1).

Authentication

Human derived mast cell purity was confirmed using flow cytometry to quantify KIT+, Siglec-6+, FcERI+ cells. CLonza cord blood CD34+ cells are isolated from cord blood mononuclear cells (MNCs) via positive immunomagnetic separation and are guaranteed to have a purity of ≥90% as indicated by CD34+ expressing cells via flow cytometry.

Mycoplasma contamination

All cell lines were confirmed to not contain mycoplasma contamination.

Commonly misidentified lines
(See ICLAC register)

To our knowledge, none of the lines used in this study are commonly misidentified.

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 mice 3-4 weeks of age (strain #013062) were obtained from Jackson Laboratory and engrafted with CD34+ stem cells from Lonza, or pre-engrafted NSG-SGM3 mice were obtained aged 13-18 weeks from Jackson Laboratory.

Wild animals

This study did not involve wild animals.

Reporting on sex

Only the female mice of this strain possess a complete set of homozygous genetic modifications, thus for consistency of engraftment and development of mast cell populations, we utilized females. In humans, dependence on sex in the context of allergies is variable as far as prevalence, sensitivity, and type. However, the mechanism of degranulation and anaphylaxis is the same across both sexes, therefore use of male versus female is of little consequence in the context of these experiments.

Field-collected samples

This study did not involve field-collected samples.

Ethics oversight

All experiments conducted in vivo were performed in accordance with animal protocols approved by the Institutional Animal Care and Use Committee (IACUC) at Northwestern University. Approved IACUC study #IS00017606

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	Details regarding all sample preparation procedures are listed in the manuscript.
Instrument	BD FACSymphony A5
Software	FACSDiva v6.1.3; FlowJo v10
Cell population abundance	This manuscript used flow cytometry, however, we did not perform physical cell sorting (i.e. FACS) in any of the experiments.
Gating strategy	The gating strategy is described in detail in both the methods section and in the supplementary materials of the manuscript.

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