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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	Donor data was collected using RedCAP data capture software. ELISpot data was collected using the Cellular Technology Limited system (CTL; Shaker Heights, OH, USA), which run ImmunoSpot 5.0.9.21 software. Multiplex bead binding assay data (including antigen specific data) was analyzed using a Luminex FLEXMAP 3D®instrument (Luminex; Austin, TX, USA), which run xPonent 4.3 software. Flow cytometry data was collected on a Cytek Aurora Spectral Flow Cytometer using Cytek SpectroFlo software.
Data analysis	Statistical analyses were assessed using Student's t-test (two-tailed unpaired t-test) or one-way ANOVA performed with GraphPad Prism (v8.4.2; GraphPad Software; Boston, MA, USA).

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

There are no restrictions on experimental data availability from this study. All the datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. There was no data with mandated deposition presented in this study. Also, there was no bulk sequencing data nor single cell VDJ sequencing data presented in this study.

Human research participants

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

Reporting on sex and gender	Sex & gender information was collected for subject characteristics purpose only but was not relevant to this study. Sex- & gender-based analyses were not performed in this study.
Population characteristics	Population characteristics are fully described in Table 1 of the manuscript.
Recruitment	Written informed consent was obtained from all participants or, if they were unable to provide informed consent, obtained from designated healthcare surrogates. Healthy subjects were recruited using promotional materials approved by the Emory University Institutional Review Board. There were no potential self-selection bias or other biases that may be present or likely to impact results.
Ethics oversight	Written informed consent was obtained from all subjects. All research was approved by the Emory University Institutional Review Board (Emory IRB numbers IRB00066294 and IRB00057983) and was performed in accordance with all relevant guidelines and regulations.

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 was pre-selected. Samples from subjects receiving SARS-CoV-2 mRNA vaccines were collected on an ongoing basis until: i) clear patterns emerged in ELISpot data capable of statistically distinguishing different antibody-secreting cell subsets (i.e. long-lived plasma cells & short-lived plasma cells) with the antigen specificities of interest; & ii) the longest possible time for bone marrow samples after SARS-CoV-2 mRNA vaccination were obtained.
Data exclusions	To make sure the quantity of antibody secreting cells (ASC) was sufficient for antigen specificity assays, all subjects with <3,000 sorted ASC in each of the three bone marrow ASC populations was excluded from the study. No other criteria were used to exclude any subjects from the analysis.
Replication	Donor samples were collected, processed, and analyzed on different days and by a small group of certain different personnel. The nature of this study does not lend itself to simple replication; however, all analysis presented maintained consistency over time and within technical replicates.
Randomization	No randomization was performed.
Blinding	Blinding was not relevant to this study.

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

For the antibody-secreting cell sorting panels, cellular enriched fractions from blood or bone marrow aspirates were stained with the following anti-human antibodies: IgD–FITC (Cat. #555778; BD Biosciences) or IgD-Brilliant Violet 480 (Cat. #566138; BD Biosciences), CD3-BV711 (Cat. #317328; BioLegend) or CD3-BUV737 (Cat. #612750; BD Biosciences), CD14-BV711 (Cat. #301838; BioLegend) or CD14-BUV737 (Cat. #612763; BD Biosciences), CD19-PE-Cy7 (Cat. #560911; BD Biosciences) or CD19-Spark NIR 685 (Cat. #302270; BioLegend), CD38-V450 (Cat. #561378; BD Bioscience) or CD38-Brilliant Violet 785 (Cat. #303530; BioLegend), CD138-APC (Cat. #130-117-395; Miltenyi Biotech) or CD138-APC-R700 (Cat. #566050; BD Biosciences), CD27-APC-e780 (Cat. #5016160; eBiosciences) or CD27-Brilliant Violet 711 (Cat. #356430; BioLegend), and LiveDead (Cat. #L34966; Invitrogen) or Zombie NIR Fixable Viability Kit (Cat. #423106; BioLegend).

For the panel for CD45 BM ASC flow cytometry, bone marrow mononuclear cells were stained with the following anti-human antibodies: IgD-Brilliant Violet 480 (Cat. #566138; BD Biosciences), CD3-BUV737 (Cat. #612750; BD Biosciences), CD14-BUV737 (Cat. #612763; BD Biosciences), CD19-Spark NIR 685 (Cat. #302270; BioLegend), CD38-Brilliant Violet 785 (Cat. #303530; BioLegend), CD138-APC-R700 (Cat. #566050; BD Biosciences), CD27-Brilliant Violet 711 (Cat. #356430; BioLegend), CD134 (OX40)-Brilliant Violet 510 (Cat. #350025; BioLegend), CD246 (ALK)-Alexa Fluor 488 (Cat. #NBP3-08771AF488; Novus), CD357 (GITR)-Brilliant Violet 605 (Cat. #747664; BD Biosciences), and CD45-PE-Cy5 (Cat. #304009; BioLegend).

Validation

All antibodies have been validated by the manufacturer for use in targeting human proteins as indicated above. Furthermore, all antibodies were also validated experimentally by our own research groups who used them for over a decade.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration

Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.

Study protocol

Note where the full trial protocol can be accessed OR if not available, explain why.

Data collection

Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.

Outcomes

Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.

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

Peripheral blood samples & bone marrow aspirates were collected in heparin sodium tubes & processed within 1-2 hours of collection. Peripheral blood and bone marrow mononuclear cells (MNC) were isolated by density gradient centrifugation at 1000 x g for 10 minutes. MNC were subsequently enriched by either a commercial human Pan-B cell enrichment kit (that removes cells expressing CD2, CD3, CD14, CD16, CD36, CD42b, CD56, CD66b, CD123, and glycophorin A) (StemCell Technologies) or a custom-designed negative selection cell isolation kit (that removes cells expressing CD3, CD14, CD66b, and glycophorin A) (StemCell Technologies) in prior to being stained with the following above-mentioned antibody panels. Post-

	sort ASC off-sorter were cultured in MSC secretome (ASC survival medium) at 37°C overnight. Cultured cells were then collected for ELISpot assaying for IgG & IgA secreting ASC & the culture supernatants were collected for multiplex bead binding assays for detection/quantification of secreted IgG.
Instrument	For CD45 flow cytometric analysis, stained bone marrow mononuclear cells were analyzed on a Cytek's Aurora Spectral Flow Cytometer using Cytek SpectroFlo software.
Software	Cells were analyzed on a Cytek Aurora flow cytometer using Cytek SpectroFlo software. Up to 3 x 106 cells were analyzed using FlowJo vl0 (Treestar) software.
Cell population abundance	The yields for bone marrow ASC subsets post-sort vary greatly among different subsets & from sample to sample. Sorted ASC populations were generally 93-99% pure except for PopA (whose purity was usually ~60-75%) when checked upon the sorts being finished.
Gating strategy	Gating strategy is provided in Figure 1b (bone marrow samples) & Supplemental Figure S1 (blood samples). Briefly, bone marrow MNC were first gated for lymphocytes, singlets, and viable cells (based on their FSC/SSC and Live/Death properties). CD3 and CD14 were then used as dump markers to capture CD19+ and CD19- B cell populations. Subsequent sub-gating from CD19+ population on the IgD- fraction (versus CD27) and using CD138 versus CD38 allow for breaking down bone marrow ASC populations into 3 subsets of interest: PopA (CD19+CD38hiCD138-), PopB (CD19+CD38hiCD138+), and PopD (LLPC; CD19-CD38hiCD138-). For blood samples, peripheral blood mononuclear cells were also first gated for lymphocytes, singlets, and viable cells (based on their FSC/SSC and Live/Death properties). CD3 and CD14 were then used as dump markers to capture CD19+ and CD19- B cell populations. Subsequent sub-gating using CD38 versus CD27 on the IgD- fraction (of CD19+ population) allows for sorting for blood ASC (CD27hiCD38hi).

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