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	We used Microsoft Excel 2016 (16.05356.1000) for data storage.
Data analysis	Data was analyzed using Graphpad Prism 8.3 and RStudio 1.2.5033 (R4.0.3)

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

Source data file will be provided with this paper. Other data that support the findings of this study are available from the corresponding authors (K.S. and R.W.S.) upon reasonable request. Genbank accession codes can be found in the Methods section. PDB accession numbers can be found in the figure legends.

Human research participants

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

Reporting on sex and gender	N/A see below
Population characteristics	N/A see below
Recruitment	n/A see below
Ethics oversight	The mentioned dataset was originally published in Nature (DOI: 10.1038/s41586-019-0879-y). In this publication, the authors provide full details on acquiring the data (methods section) and on policy information regarding human research participants (see supplemental information). The data and code is publicly at: https://github.com/briney/grp_paper. Since public data has been used, approval for the analysis of these individuals data is not necessary.

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	NA
Data exclusions	No data were excluded.
Replication	All binding experiments were performed twice independently. Neutralization of HCV pseudoparticles were performed in triplo.
Randomization	NA
Blinding	NA

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	All antibodies were produced in the lab using transient transfection using plasmids expressing the antibody heavy and light chains. Goat-anti-human IgG Jackson Immunoresearch (cat# 109-035-170)
Validation	All antibody plasmids were validated by sequencing.

Eukaryotic cell lines

Cell line source(s)	HEK293 cell lines were obtained from Thermo Fisher or ATCC as described in the methods. Ramos B cells were obtained from dr. Li Wu and dr. Vineet N. KewalRamani via the NIH AIDS Reagent Program
Authentication	Authentication None of the cell lines were validated.
Mycoplasma contamination	Mycoplasma contamination All cell lines were tested negative for mycoplasma
Commonly misidentified lines (See ICLAC register)	No commonly misidentiefied cell lines were used

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	IgM-negative Ramos B cell lines were previously transduced with AR3C, HEPC74, gl-AR3C and gl-HEPC74 as described in the methods. Cells were then sorted for GFP+ IgG + IgM- using a FACS Aria-II SORP (BD Biosciences). B cells were expanded and cultured indefinitely. Cells were frozen for future use. For antigen specificity and Calcium flux assays, labelled probes and nonlabelled proteins were used as described in Methods and analysed using LSRFortessaTM(BD Biosciences).
Instrument	Aria-II SORP (BD Biosciences) and LSRFortessaTM (BD Biosciences).
Software	FlowJo v10.8.1. Data visualization with Graphpad Prism 8.3
Cell population abundance	Single cell line was used (so 100%).
Gating strategy	All cell lines were sorted as indicated in the gating strategy of supplementary figure 3

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