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.

- 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

Provide a description of all commercial, open source and custom code used to collect the data in this study, specifying the version used OR state that no software was used.

Data analysis

Provide a description of all commercial, open source and custom code used to analyse the data in this study, specifying the version used OR state that no 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

The data that support the findings of this study are available from the corresponding author upon reasonable request.
Human research participants

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

**Reporting on sex and gender**

Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design whether sex and/or gender was determined based on self-reporting or assigned and methods used. Provide in the source data disaggregated sex and gender data where this information has been collected, and consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.

**Population characteristics**

Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write “See above.”

**Recruitment**

Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.

**Ethics oversight**

Identify the organization(s) that approved the study protocol.

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-flap.pdf](http://nature.com/documents/nr-reporting-summary-flap.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

**Sample size**

Three to 10 animals were used per group to permit for assessment of mean and standard deviation. Since 100% of control mice succumb to infection, using 5 mice per experimental group provides 80% power to detect a difference between the groups with an alpha of 0.05 if 60% or more of the mice survive in the experimental groups.

**Data exclusions**

No data were excluded from the analysis.

**Replication**

Data were consistent amongst replicates.

**Randomization**

No randomization.

**Blinding**

No blinding.

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

**Study description**

Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study).

**Research sample**

State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.

**Sampling strategy**

Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.

**Data collection**

Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper,
Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

| Study description | Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates. |
| Research sample | Describe the research sample (e.g. a group of tagged Passer domesticus, all Stenocercus thurberi within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source. |
| Sampling strategy | Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. |
| Data collection | Describe the data collection procedure, including who recorded the data and how. |
| Timing and spatial scale | Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken. |
| Data exclusions | If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established. |
| Reproducibility | Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful. |
| Randomization | Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why. |
| Blinding | Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study. |

Did the study involve field work? Yes ☐ No ☒

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: FITC CD45.1 (A20, Beckton Dickenson [BD]), APC CD45.2 (104, BD), PE CD19 (BD5, BioLegend), FITC CD11b (M1/70, BD), APC CD4 (806, BD), BV421 CD40 (3/23, BD), BVV395 CD4 (RM4-5, BD), PECy7 CD8 (53-6.7, BD), BV510 CD3 (17A2, BD), AF488 CD3 (17A2, BD), APC CD45 (50-F11, BD), APC CD8 (53-6.7, BD), PCP-Cy5.5 CD4 (RM4-4, BD).

Validation: All flow antibodies were purchased commercially and validated by the manufacturer. FMO controls on these clones demonstrated specificity.

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: C57Bl/6 mice CD45.1 and CD45.2

Wild animals: None.

Reporting on sex: All mice were female. We’ve previously demonstrated that sex has no role in RVFV lethality in C57Bl/6 mice.

Field-collected samples: N/A

Ethics oversight: This study complied with institutional guidelines, the US Department of Agriculture Animal Welfare Act, and the National Institutes of Health Guidelines for humane use of laboratory animals. All procedures were approved by the University of Pittsburgh Institutional Animal Care and Use Committee (Protocols 17080998 and 19044158).

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: Cells from tissues were processed as described (Harmon et al. J Virology, 2018) were washed in PBS, then incubated in live/dead near IR (Thermo Fisher) at 1:500 for 10 min. Following a wash in flow buffer (PBS with 2% FBS) cells were stained for 30 minutes using various combinations of antibodies. After staining, cells were washed in flow buffer then fixed in BD/Fix Perm then washed again prior to acquisition.

Instrument: BD LSRII

Software: Flowjo

Cell population abundance: Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.

Gating strategy: FSC/SSC lymphocyte gate, FSCA/FSCCH single cell gate, Live gate, CD3 by CD19, then CD3 further gated on CD4 and CD8 when appropriate.

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