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**
- 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 software was used. |
| Data analysis   | 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 datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.
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**: Groups sizes were determined by power analysis.
- **Data exclusions**: No data was excluded.
- **Replication**: All in vitro experiments were performed in duplicate or triplicate. Most (but not all) experiments were repeated multiple times. In vivo challenge experiments were performed once, but all of the control groups (and the VLP-CIS43 vaccine group) had been reported in a previous manuscript and the data in this study was consistent with our previous results.
- **Randomization**: Mice were randomly selected for group assignment.
- **Blinding**: Challenge studies were performed using blinded groups.

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 | Methods |
|----------------------------------|---------|
| n/a | Involved in the study | Involved in the study |
| ☐ | Antibodies | ☒ | ChIP-seq |
| ☒ | Eukaryotic cell lines | ☒ | Flow cytometry |
| ☒ | Palaeontology and archaeology | ☒ | MRI-based neuroimaging |
| ☐ | Animals and other organisms | ☐ | |
| ☒ | Human research participants | ☐ | |
| ☒ | Clinical data | ☐ | |
| ☒ | Dual use research of concern | ☐ | |

**Antibodies**

- Antibodies used: L9 and CIS43, obtained from Robert Seder at the NIH.
- Validation: Antibody binding to CSP was validated by ELISA.

**Animals and other organisms**

Policy information about studies involving animals: ARRIVE guidelines recommended for reporting animal research

- **Laboratory animals**: Mice, Balb/c and C57Bl/6 strains, 4–8 weeks old females.
- **Wild animals**: not applicable
- **Field-collected samples**: not applicable
- **Ethics oversight**: All animal research complied with the Institutional Animal Care and Use Committee of the University of New Mexico School of Medicine (Approved protocol #: 19-200870-HSC), Johns Hopkins University (Approved protocol permit #: MO18H419).

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