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	No original code or software was developed.
Data analysis	Statistical analysis: Prism GraphPad (San Diego, California, USA) was used to analyze the data. A mixed effect model with repeated measures, multiple comparisons done by Tukeys multiple comparison test was used to evaluate weight data. ELISA and neutralizing antibody data was Log transformed and evaluated using One-way ANOVA with multiple comparisons. Two-way ANOVA with repeated measures and Tukeys multiple comparisons test was used for evaluating viral load quantifications. A Kruskal Wallis test was used with Dunn's multiple comparisons for comparing histopathology. A p value of ≤ 0.05 was considered statistically significant with p<0.05:*; p<0.01:**; p<0.001:***; p<0.0001:****. Survival was calculated according to the experimental design considering predetermined necropsy days for randomized hamster removals. Phylogenetic Analysis: Spike gene sequences were translated and aligned using the MUSCLE algorithm implemented in the SEAVIEW phylogenetic package. Phylogenetic trees were constructed with IQ-TREE252, using a amino acid substitution model selected by ModelFinder (Q.yeast). Protein analysis: CD data was analyzed using the Beta Structure Selection (BeStSel) online tool (https://bestsel.elte.hu/ssfrompdb.php). The data was normalized using the following equation: Θnorm= □((Θ (λ) x ε205)/(10 xA205 x (N-1))), where Θnorm is normalized molar ellipticity, Θ(λ) is raw ellipticity in millidegrees, ε205 protein extinction coefficient at 205nm, A205 absorbance at 205 nm, and N is the number of amino acid residues. Changes in the secondary structure were analyzed with CHIRASCAN software Pro-Data viewer to determine the melting temperature of each construct. The experimentally determined secondary structure content was compared to the predicted using PSI-BLAST - based prediction tool (PSIPRED) https://bio.tools/psipred. Protein structural and epitope prediction and MD simulations: GROMACS version 2020.1 with CHARMM36 all-atom force field was employed to conduct the Molecular dynamics (MD) simulations. The 3-dimensional modeling of the candidate vaccine protein antigens were constructed using AlphaFold2 (AlphaFold2 (Colab-Fold) (ChimeraX plugin for AlphaFold2/Colab-Fold with default criteria). The structural

predictions were then validated using SWISS-MODEL. Protein structures were visualized in PyMol (The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC) and ChimeraX. The conformation of our vaccine constructs was predicted through using TAMARIND BIO – Boltz-2, which is based on AlphaFold3 reproduction. The conformations were used for B-cell epitope prediction through DiscoTope 3.0, with the threshold being set to 0.9, and HADDOCK2.4, and default criteria for molecular docking. Molecular docking was predicted to the neutralizing antibody CT-P59 (PDB: 7CM4).

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

Data or data sources are available in the main text or the supplementary materials. Sequences of candidates have been submitted to an open source data and will be available at time of publication.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	This study did not involve humans.
Reporting on race, ethnicity, or other socially relevant groupings	This study did not involved humans and therefore reporting of race, ethnicity, or other socially relevant groups are not applicable.
Population characteristics	No human research participants were used in the study.
Recruitment	No human research subjects were used in the study.
Ethics oversight	No human studies or human ethics were used in the study.

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	Group sample sizes were determined by standards in the field for vaccinology and high containment virology research.
Data exclusions	No data points were excluded from the analysis. Samples that were not included in the analysis were samples that did not exist if an animal had met humane endpoint in the experiment prior to the sample being taken. All animals that met humane endpoints and were removed from the study ahead of their intended end day were reported in the manuscript.
Replication	Animal challenge studies were completed once with 10 animals per group or 5 animals per time point to serve for statistical testing. Assays were performed once with 1-3 replicates per sample depending on the assay: ELISA (1 replicate), TCID50 (three replicates), microneutralizations (2 replicates), and pseudoneutralizations (1 replicate).
Randomization	Animals were randomized to groups.
Blinding	The pathology was assessed by a board certified pathologist who was blinded to the sample experimental specifics. All authors involved in the study were not blinded.

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
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Anti-IL-5 (Cat: 554397, BD Bioscience); anti-IFN-γ (Cat: 554410, BD Bioscience); streptavidin conjugated alkaline phosphatase (Cat: 016-050-084, Cedarlane Labs; alkaline phosphatase labelled anti-mouse IgG (Cat: 5220-0355 (KPL), MilliporeSigma); goat anti-Hamster IgG HRP at 1:7000 dilution (ThermoFisher Scientific); in-house generated rabbit polyclonal primary antibody S1-CoV19; donkey anti-rabbit IRDye 800CW (Li-COR®)
Validation	All antibodies except in-house rabbit polyclonal antibody to S1-CoV19 were purchased from reputable biotechnology industries and validated through company specific methods. In-house generated rabbit polyclonal primary antibody S1-CoV19 was generated by VIDO prior to commercial antibody availability. Once commercial antibodies were available, the in-house antibody was compared to the in-house antibody in western blot analyses.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	VERO 76 Cells (ATCC CRL-1587); ExpiCHO™ cells (ThermoFisher Scientific); HEK 293T/17 cells (ATCC CRL-11268); 293T-hsACE2 cells (Integral Molecular); ACE2/TMPRSS2 expressing 293T cells (Temperton lab)
Authentication	Cell lines were purchased directly from cell line distributors where possible. Cell culture is conducted through SOP drive processes and morphology is evaluated on a weekly basis. Record are kept for expansions, storage, and passage of cell lines. Where possible, cells line are authenticated.
Mycoplasma contamination	Cell lines are monitored for mycoplasma and at intervals tested for mycoplasma using InvivoGen's MycoStrip Mycoplasma Detection Kit (Product Code: rep-mys) or similar kits.
Commonly misidentified lines (See ICLAC register)	No cell lines used are found as registered commonly misidentified cell lines.

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	8-week old male LVG Golden Syrian hamsters (Charles River Laboratories). 5-6 week old female BALB/c mice (Charles River Laboratories)
Wild animals	No wild animals were used in th study.
Reporting on sex	Male hamsters were used in this study. Female mice were used in this study. The vaccine responses were similar across species and sexes. Therefore we can suggest that similar responses would be seen regardless of sex; however, a thorough sex analysis of protection and greater depth of immune responses is need to make concrete conclusions.
Field-collected samples	This study did not involve samples collected in the field.
Ethics oversight	All work was done in accordance with CCAC (Canadian Council of Animal Care) and AUPS approved by the University Animal Care Committee (UACC) Animal Research Ethics Board at the University of Saskatchewan.

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

Plants

Seed stocks	No plants or seeds were used in this study.
Novel plant genotypes	No plants or seeds were used in this study.
Authentication	No plants or seeds were used in this study.