nature research

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Last updated by author(s): Jul 17, 2021

Reporting Summary

Nature Research 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 Research 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	The X-ray crystallographic data were collected at Southeast Regional Collaborative Access Team (SER-CAT) 22-ID and Lilly Research Laboratories Collaborative Access Team (LRL-CAT) 31-ID beamlines at the Advanced Photon Source (APS), Argonne National Laboratory, using software developed for those beamlines at APS. The ITC data was collected on a MicroCal ITC-200 isothermal calorimeter, using commercial software (Malvern Panalytical, UK)
Data analysis	The X-ray crystallographic data were analyzed using publicly available software: CCP4 (www.ccp4.ac.uk) and Phenix (http://www.phenix-online.org). The ITC thermograms were integrated by NITPIC (Keller, et al., Anal. Chem. 2012) and fitted using SEDPHAT (Zhao, et al., Methods, 2015)

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 Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

The coordinates and structure factors for eE2/2A12, tCD81-LEL, and tCD81-LEL/DeltaHVR1-eE2/2A12 have been deposited into the Protein Data Bank under accession numbers 7MWW, 7MWS, and 7MWX, respectively.

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	The eE2/2A12, tCD81-LEL, and tCD81-LEL/DHVR1-eE2/2A12 crystallographic data sets are 99, 100, and 99.5% complete with 2, 40, and 13 fold redundancy, respectively.
Data exclusions	No data was excluded
Replication	The structures were determined multiple times from different crystals. The manuscript reports the highest resolution example for each. The isothermal calorimetry data was collected multiple times, yielding similar thermodynamic values. The membrane flotation experiments were done multiple times and the results from two independent experiments are provided in Extended Data Figure 8.
Randomization	The experiments were not randomized as this is not relevant to structural biology studies
Blinding	Blinding is not relevant to this study as knowledge of the protein sequence is needed in order to accurately determine its structure

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used	2A12 and 2C1 are anti HCV E2 from genotype J6 and were generated in Dr. Arash Grakoui's lab Emory University School of Medicine against purified, recombinant protein. Secondary antibody IRDye 800CW Goat anti-Mouse IgG was purchased from a commercial source (cat. no. 926-32210 from Li-Cor)
Validation	2C1 neutralizes HCV infection and binds to the HVR1 region of E2. 2A12 was shown to bind E2 by ELISA, isothermal calorimetry, size exclusion chromatography, and X-ray crystallography (Khan et al. Nature, 2014).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	HEK293T GNTI- and 293expi GNTI- cells were purchased from ATCC (cat. no. CRL-3022) and ThermoFisher (Cat. No. A39240), respectively
Authentication	The cells line were not authenticated
Mycoplasma contamination	The cells were not tested for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	no commonly misidentified cell lines were used