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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 Authors & Referees 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	N/A
Data analysis	FlowJo v.10.1 for FACS data. Graphpad Prism 5 for curve fitting. RosettaScripts included in manuscript, and Rosetta used as cited in Methods. Original Enrich for Illumina sequencing analysis. PyMOL Molecular Graphics System, Version 2.0 . Original PatchDock for docking. Original OpenBabel for small molecule parameter generation. Crystallography: HKL2000, Phaser, COOT, Refmac5. Library design scripts used as cited in Methods. Scripts written in Python v. 2.7 used for imaging analysis and data fitting.

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/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 atomic coordinates and experimental data of the DNCR2/danoprevir/NS3a crystal structure have been deposited in the Protein Data Bank (ID 6N4N). Illumina data is deposited in the Sequence Read Archive under accession number SRP126450. Key DNA constructs are deposited in Addgene. All plasmid sequences are available in this Benchling project: https://benchling.com/s/seq-OJeDzb2IUfv5dpTIXfro.

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	n>= 3 reported for most experiments. n=1 or 2 for Western blot in Supplementary Fig. 4. n=2 for Fig. 3e,f,g.
Data exclusions	NA
Replication	All attempts at replication were successful.
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
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	FITC-conjugated chicken anti-c-myc (Immunology Consultants Laboratory) pSER473 AKT (rabbit mAb, Cell Signaling Technologies #4060) pan-AKT (mouse mAb, Cell Signaling Technologies #2920) APC anti-human CD184 (CXCR4) [12G5] (BioLegend 306510) PE anti-human CD95 (Fas) [DX2] (BioLegend 305607) GAPDH (Cell Signaling Technologies #2118)
Validation	Validated in the corresponding assay in which they were used. CD95 and CXCR4 antibodies were compared to isotype control antibodies and found to give specific signals.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	NIH3T3 cells (Flp-In-3T3, ThermoFisher Scientific) COS-7 cells (ATCC) HEK293T cells (293T/17, ATCC) HEK293T cell line with GFP stably integrated in a tetracycline-inducible landing pad (7xTRE3G operator) created in a similar manner as a previously published TetBxb1BFP HEK293T cell line (gift from Doug Fowler). TREx-HeLa (ThermoFisher Scientific)
Authentication	None authenticated

Mycoplasma contamination	Confirmed mycoplasma free at least once every 6 months.
Commonly misidentified lines (See ICLAC register)	None

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	Saccharomyces cerevisiae EBY100 HEK293T cells
Instrument	Analysis: FACSCanto cytometer (BD Biosciences) or C6 flow cytometer (Accuri) (yeast), and FACSLSRII (BD Biosciences) (mammalian). Yeast sorting: SH800 (Sony Biotechnology) cell sorter or a FACSAria III (BD Biosciences) cell sorter
Software	FlowJo v.10.1
Cell population abundance	NA
Gating strategy	Yeast: Gated on FSC-A/SSC-A. Sorts were performed on FITC-positive cells. Analysis results were reported as median PE signal from FITC-positive cells. HEK293T: Cells were gated on FSC-A/SSC-A, then on FSC-H/FSC-W ("single cells"). 10,000 single cell events were analyzed per sample. Of these events, a gate was set to include the top 1% and above of the BFP signal of an untransfected sample. Median GFP or immunofluorescence values were reported for this BFP-positive subset.

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