nature portfolio

Corresponding author(s): Shaomeng Wang

Last updated by author(s): Mar 5, 2025

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	not applicable
Data analysis	not applicable

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

not applicable

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	Frozen Human PBMCs from healthy donors was purchased from Miaoshun Biotechnology Co (Shanghai). Sex and gender was not a factor in selecting the donors for commercially available Human PBMCs.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethinicity was not a factor in selecting the donors for commercially available Human PBMCs.
Population characteristics	Human PBMCs purchased for the study were obtained from healthy volunteers.
Recruitment	Not applicable since commercially available Human PBMCs were purchased for the study
Ethics oversight	As per the vendor website, samples from healthy volunteers were collected in accordance with their IRB. Informed consent was obtained from all participants and all ethical regulations were respected.

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	Our established animal models consistently yield low variance. Power calculation estimates determined that 8 animals per group was sufficient to determine statistical significance at p value of 0.05 and power level of 80% if the difference in the mean between groups is greater than 25%.
Data exclusions	No data were excluded from the analysis
Replication	Single agent efficacy studies in vivo were replicated 2 times with similar results. All combination in vivo efficacy studies were performed once with 8-10 animals per group. In vitro experiments were typically run with triplicate technical replicates and were reproduced at least 2 times in independent experiments with similar results.
Randomization	For in vivo tumor models, mice were randomized to ensure equal mean tumor burden before treatment initiation
Blinding	For in vitro studies, experiments were not performed in a blinded way. All data were analyzed by software with objective standard. For all animal studies, investigators were not blinded to the group allocation and data collections.

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	From Cell Signaling Technology: Helios (D8W4X) XP (#42427, 1:1000 for WB), Helios (D8W4X) XP Alexa Fluor 488 Conjugate (#56424, 1:100 for FACS), beta-Actin (13E5) (#4970, 1:1000) From Millipore Sigma: CRBN (#HPA045910, 1:1000) From Biolegend: PE anti-human CD8 (#344706, Clone SK1, 2 ul/assay) From Santa Cruz Biotechnology: anti-GAPDH (# sc-47724, 1:1000 for WB), anti-β-Actin mouse monoclonal antibody [C4] (# sc-47778, 1:1000 for WB) From Bioxcell: anti-PD1 antibody (BioXcell, Cat. #BE0146), isotype control antibody for anti-PD1 (BioXcell, Cat. #BE0089), anti-LAG3 antibody (BioXcell, Cat. #BE0174), isotype control antibody for anti-LAG3 (BioXcell, Cat. #BE0088). All BioXcell antibodies were used in in vivo efficacy studies only.
Validation	All antibodies were validated by the respective manufacturer for reactivity to human and/or mouse antigens. All antibodies were either validated or recommended for flow cytometry and/or western blotting.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	Jurkat (CLone E6-1) (#TIB-152) was purchased from ATCC and used for FACS experiment and to generate Jurkat CRBN KO cell line. HEK293 Flp-IN (#R75007) were purchased from ThermoFisher Scientific and used for generating IKZF1-HiBit, IKZF2-HiBit, IKZF3-HiBit, IKZF4-HiBit, CK1a-HiBit, SALL4-HiBit, and GSPT-HiBit stable expression cell lines. MC38 (#SCC172) was purchased from Millipore Sigma and used for all in vivo studies.
Authentication	All cell lines were authenticated by Vendor but were not authenticated in our laboratory.
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination in our laboratory
Commonly misidentified lines (See ICLAC register)	not applicable

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	CRBNI391V (C57BL/6-Crbntm1.1Ble/J) mice breeding pairs were purchased from the Jackson Laboratory (Strain # 032487) under the Leap License Agreement. CRBNI391V mice for all the studies described below were obtained from the University of Michigan breeding colony. CrbnI391V mice were housed in a controlled environment with a 12 h light/dark cycle, with ambient temperature maintained between approximately 20–22°C and relative humidity between 30–70%.
Wild animals	The study did not involve wild animals.
Reporting on sex	Sex of animals was not considered in study design. All animals were sex and age matched in each experiment. The authors conclude that the findings are applicable, relevant, and reproducible for both males and females based on observed findings.
Field-collected samples	No field collected samples were used in this study.
Ethics oversight	All animal studies performed under protocols (PRO00011174 and PRO00009463) approved by the Institutional Animal Care & Use Committee (IACUC) of the University of Michigan, in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

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

Plants

Seed stocks	not applicable
Novel plant genotypes	not applicable
Authentication	not applicable

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	After desired treatment cells were washed, fixed (3.7% PFA), and permeabilized with perm buffer (0.3% Triton X-100 in 1% BSA Solution). Subsequently, cells were stained in staining buffer (1% BSA in PBS) and assessed using iQue Flowcytometer.
Instrument	iQue Flow cytometer (Sartorius)
Software	iQue Forcyte Software
Cell population abundance	For IKZF2 FACS Assay: Jurkat cells were cultured in RPMI + 10% FBS and used for FACS assay as pure population. For Treg Suppression Assay: CD4+CD127lowCD25+ regulatory T-Cells were enriched from PBMCs using Human Treg isolation kit (Stemcell, #18063) CD3+ T cells and were enriched from PBMCs using Human T cell isolation kit (Stemcell, #17951) prior to experimentation and analysis.
Gating strategy	For IKZF2 FACS Assay in Jurkat Cells: Samples are gated on FSC/SSC Jurkat cell population. For Treg Suppression Assay: All samples are gated on FSC/SSC lymphocyte populations, live populations, then CD3+ & CD8+. Frequency of positive gates is determined using an isotype or FMO control. Proliferating CD8+ cells were evaluated based on CFSE dye dilution.

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