

Corresponding author(s): Kevin Moreau

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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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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 Diamond Light Source synchrotron; Protein Data Bank

Data analysis DIA-NN; Spectronaut V 17.3; UniProt human database (February 2021); Genedata Screener; Chemstation Version B.03.01 (Agilent); autoproc; Graphpad Prism 9; OMIQ™ (Dotmatics)

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 data generated in this study is available in Supplementary Information, as well as from the corresponding authors. Proteomics data have been deposited to the Center for Computational Mass Spectrometry under the accession number MSV000099766 (<https://massive.ucsd.edu/ProteoSAFe/dataset.jsp?task=d69d9281eae24de7be6404357af02697>). Crystal structure of humanised cereblon from Magnetospirillum gryphiswaldense bound by compound 2 is available in PDB (Protein Data Bank) under the PDB ID 9GJQ (<https://doi.org/10.2210/pdb9GJQ/pdb>). Source data are provided with this paper.

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	NA
Reporting on race, ethnicity, or other socially relevant groupings	NA
Population characteristics	NA
Recruitment	NA
Ethics oversight	NA

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](https://www.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	For proteomics studies, we compare the statistical power of 3 concentrations in 4 replicates vs 6 concentrations in 2 replicates and found that both studies were equally powered. The 6 concentrations in 2 replicates were chosen to account for a better capture of the dose range for protein regulation. For WB analysis, no sample size calculation was performed and positive and negative controls were added to ensure data quality. For luciferase based assays, the same power calculation was used as for the proteomics. The dose response analysis ensures better representation of degradation potency. For animal work, the number of animals was distributed based on genetics (CRBN wildtype or I391V transgenic) and sex to distribute equally across compound treatment. Lenalidomide was used as positive control for Ikaros degradation in the I391V transgenic.
Data exclusions	No data were excluded from the analysis
Replication	All attempts at replication were successful except of the animal experiment measuring the degradation of IKZF1 and IKZF3 with the new CRBN binder due to ethical reason. The method reproducibility was evaluated with two to four biological replicates.
Randomization	Not relevant to our study.
Blinding	High throughput degradation and mass spectrometry experiments were blinded by the scientist running the assay.

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	CRBN (71810S, CST), GAPDH (60004, Proteintech), IKZF1 (14859S, CST), IKZF3 (15103S, CST), Vinculin (V9131, Sigma), CD34:APC-Cy7 (343614, Biolegend), CD38:PE (303506, Biolegend), CD36:BV421 (336230, Biolegend), CD235a:BV786 (740984, BD), CD41:APC (303710, Biolegend), CD71:BUV395 (743308, BD), CD16:BV480 (566108, BD), CD13:BUV737 (741828, BD), CD42b:BV711 (740779, BD)
Validation	CRBN (validated using CRISPR KO); IKZF1 (validated using CRISPR KO); IKZF3 (validated using drug target); GAPDH (validated extensively in the literature); Vinculin (validated extensively in the literature); CD34:APC-Cy7 (343614, Biolegend), CD38:PE (303506, Biolegend), CD36:BV421 (336230, Biolegend), CD235a:BV786 (740984, BD), CD41:APC (303710, Biolegend), CD71:BUV395 (743308, BD), CD16:BV480 (566108, BD), CD13:BUV737 (741828, BD), CD42b:BV711 (740779, BD) were validated previously in literature for flow cytometry analysis of bone-marrow cells.

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	NB-4 from DSMZ (ACC 207), HiBiT-IKZF3 MM.1S from Promega (CS3023229), HiBiT-SALL4 SK-N-DZ from Promega (CS3023238), HEK-293 cells from DSMZ (ACC-305); CD34+ human hematopoietic stem/progenitor cells from Lonza (2M-101; male donor)
Authentication	All immortalised cell lines used in this study were tested by STR (short tandem repeat) Fingerprint
Mycoplasma contamination	All cells have been tested for Mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	N/A

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	C57Bl6/N mouse
Wild animals	Not applicable
Reporting on sex	Both sexes were used
Field-collected samples	Not applicable
Ethics oversight	All animal work has been approved by the Animal Welfare Ethical Review Body at the Babraham Institute under the project license PPL PP7736793.

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

Plants

Seed stocks	Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.
Novel plant genotypes	Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.
Authentication	Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.

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	For the animal study, peripheral blood samples were collected at Day 21 after cardiac bleed under terminal isoflurane/oxygen anaesthesia and mixed with EDTA anticoagulant. For the in vitro studies, samples were analysed using the Cytex Aurora™ 5L (Cytex Biosciences) spectral flow cytometer, spectral unmixing was performed on the SpectroFlo software (Cytex Biosciences) and analysis was carried out using OMIQ™ (Dotmatics).
Instrument	In vivo samples: Sysmex XN-V haematology analyzer; in vitro samples: Cytex Aurora™ 5L
Software	In vivo: Sysmex and GraphPad Prism 9; in vitro: SpectroFlo software (Cytex Biosciences) and OMIQ™ (Dotmatics)
Cell population abundance	No cell sorting were used to analyse sub-populations.
Gating strategy	In vivo: Automated gating from Sysmex analyzer; In vitro: gating strategy based on 10 validated antibodies/dye

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