

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 (<i>n</i>) 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> 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 <i>d</i> , Pearson's <i>r</i>), 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	Cryo-EM datasets were collected using EPU 3.0 (Thermo Fisher).
Data analysis	Data analysis was performed using R 4.4.1 and packages: edgeR_4.2.2, limma_3.60.6, SummarizedExperiment_1.34.0, dplyr_1.1.4, stringr_1.5.1, ggplot2_3.5.2, Biostrings_2.72.1, mutscan_0.3.2 and stringi_1.8.7. EM processing was done using CryoFlare v1.10 (www.cryoflare.org), RELION3.0, Motioncorr (Relion implementation), cryoSPARC v4, blob picker (in cryoSPARC). Model building was done using PHENIX v1.20.1-v1.21.2, ISOLDE v1.7 and COOT v0.9.8.1. Sharpening was done with DeepEMhancer v0.17. Validation for all models was carried out with MOLPROBITY v4.5.2. Structural figures were produced with UCSF ChimeraX v1.8-v1.9. Flow cytometry data was analysed with FlowJo (v10.4.0, BD Biosciences) The code for the sequencing analysis is accessible at https://github.com/LabThoma/Latent_CRBN-MGD_interactome. The surface mimicry code along with installation instructions are available on GitHub under MIT license at https://github.com/xiaosh9527/masif_mimicry.

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](#)

All DNA sequencing data have been deposited in the Gene Expression Omnibus (GEO) and is accessible with accession number GSE298800. The electron density reconstructions and final models have been deposited in the Electron Microscopy Data Bank (EMDB) and the PDB. They are accessible with the following IDs: SALL4: 9SQ4, EMD-55106; Ikaros: 9SQ5, EMD-55107; and Helios: 9SQ6, EMD-55108.

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	n/a
Reporting on race, ethnicity, or other socially relevant groupings	n/a
Population characteristics	n/a
Recruitment	n/a
Ethics oversight	n/a

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 cryo-EM: Sample sizes were not predetermined. Number of micrographs and particles used are described in the Extended figures for each cryo-EM map. Micrographs were collected until a sufficient resolution was reached, suggesting sufficient sample size. For GluePCA and the reporter degradation assay a sample size determination was not necessary. Our sample size of n = 3 per group are sufficient based on commonly used sample sizes in this field of research.
Data exclusions	For sequencing data we excluded data points with 10 or less reads in any DMSO or Input replicate. These low coverage variants have a high error due to sampling noise and are thus not informative. For cryo-EM we discarded all broken particles or particles that do not belong to a class during 2D and 3D classification. This is standard practice in cryo-EM studies to obtain homogeneous high resolution cryo-EM structures. For single-clone GluePCAs and NanoBiT all measurements are included in the analysis.
Replication	Cryo-EM datasets were collected with multiple samples in separate imaging sessions. For the sequencing datasets we have three independent biological replicates starting at the library transformation in yeast. For single-clone GluePCAs we have three biological replicates starting after transformation. NanoBiT also contain three biological replicates including transfection. For the western blot analysis 3 replicates were done, all of them are shown in Figure 5 and Extended Data Figure 8 accompanied by a uncropped version as source data. All attempts of replication were successful for the data included.
Randomization	There are no experimental groups, so randomization was not necessary.
Blinding	There are no study participant, so blinding is not required.

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-LgBiT monoclonal Antibody (Promega, Cat. Nr. N7100, Lot 0000672890) at 1 ug/mL. alpha-Tubuline monoclonal Antibody (DM1A, Cell Signaling Technology, 3873S, Lot 19) at 1 ug/mL. Anti-mouse IgG, HRP-linked Antibody (Cell signaling Technology, 7076S, Lot 38) at 0.1 ug/mL.
Validation	Validation was performed by Promega and CST (a-Tubuline: https://media.cellsignal.com/coa/3873/19/3873-lot-19-coa.pdf ; Anti-mouse: https://media.cellsignal.com/coa/7076/41/7076-lot-41-coa.pdf)

Eukaryotic cell lines

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

Cell line source(s)	Yeast strain BY4742, commercially available at Euroscarf (Y10000) HEK293T cells, commercially available at ATCC (CRL-3216) High five cells (Hi5) and SF9 cells, commercially available at Thermo Fisher Scientific (Hi5: B85502; SF9: 11496015)
Authentication	BY4742 was confirmed by growth in drop-out medium to confirm auxotrophies. HEK293T have been authenticated via STR profiling. Hi5 and SF9 cells were confirmed by Thermo Fisher Scientific.
Mycoplasma contamination	Hi5 and SF9 cells were tested negative using a mycoplasma detection kit (InvioGen). HEK293T cells also were regularly tested for Mycoplasma contamination via PCR following standard procedures.
Commonly misidentified lines (See ICLAC register)	None of commonly misidentified lines were used in this study.

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a

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

The media of ~50,000 cells per 96 well after treatment was aspirated, cells were washed with PBS and detached with 0.05% Trypsin. Cells were centrifuged resuspended in 100 µL PBS and measured directly.

Instrument

Becton Dickinson (BD) LSRII SORP Analyser running FACSDiva software.

Software

Data were analysed with FlowJo (v10.4.0, BD Biosciences)

Cell population abundance

Cell population abundance is indicated by percentage on the gating strategy in the Supplementary Information.

Gating strategy

Events were gated first in FSC/BSC and second in SSC height/width to obtain live and single cells. Cells were gated for mCherry (PE-TexasRed) and GFP positive signal and the median fluorescence ratio of GFP over mCherry was calculated in FlowJo.

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