

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	1. Flow cytometry was conducted using FACSAria (BD Biosciences) or Invitrogen Attune with accompanying softwares 2. Live cell imaging of cell depletion experiments was performed using Incucyte S3 (Sartorius) and Incucyte 2024B Software 3. qPCR was performed using QuantStudio 3 (ThermoFisher) and accompanying software 4. IVIS Spectrum Bioluminescent and Fluorescent Imager and Living Image 4.8.2 Software were used for bioluminescence imaging of small animals
Data analysis	python 3.13; Living Image, version: 4.8.2.20231220104933; Aura analysis 1.0; Flowjo 10; Ilastik 1.4.1; https://github.com/zeng-j-k/TP53-mutation-compatible-SuCas12a2-PFS

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](#)

p53 mutation data from TCGA Pan-Cancer Atlas Studies and MSK-CHORD studies are publicly available on <https://www.cbioportal.org/>
All other data are available upon reasonable request.

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

Reporting on race, ethnicity, or other socially relevant groupings

Population characteristics

Recruitment

Ethics oversight

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 FISH measurement of RNA copies, sample sizes were chosen according to existing publications with similar analyses (PMID: 31501331; PMID: 9554849). For in vivo experiments, sample sizes were chosen according to existing publications with similar tumor models (PMID: 28370287; PMID: 24480331; PMID: 38935790). For cell-based assays, sample sizes follow standard practice in the field and were sufficient to demonstrate reproducibility and statistical significance where applicable.
Data exclusions	No data was excluded, unless for significant outliers.
Replication	All experiments involving statistical comparisons were performed with at least three biological replicates to ensure reproducibility. For qualitative experiments, the number of independent repeats and/or fields imaged is indicated in the corresponding figure legends.
Randomization	Animals were randomized into treatment groups after tumor implantation, with group sizes matched for baseline tumor burden where applicable. For experiments involving cultured cells, samples were randomly drawn from common parental cultures and maintained under identical conditions to control for covariates. Randomization was not applied to in vitro biochemical assays, as these involve defined molecular components without biological variables that would require randomization.
Blinding	Investigators were not blinded to group allocation during data collection or analysis. Blinding was not applied because outcome measurements were objective and quantitative (e.g., flow cytometry gating, automated image analysis, sequencing reads, qPCR Ct values, tumor volume measurements), and identical analysis pipelines and gating strategies were applied to all samples within each experiment, minimizing the risk of investigator bias.

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	p-KAP1 (1:1000, Bethyl Laboratories, A300-767A), p-H2A.X S139 (1:1000, Millipore, 05-636), GAPDH (1:1000, Santa Cruz, sc-365062), anti-Mouse HRP(1:5000, Invitrogen, 31430), anti-Rabbit HRP (1:5000, Invitrogen, 65-6120), anti-Rabbit IRDye800 (1:5000, Licor, 926-32211) and anti-Mouse IRDye680 (1:5000, Licor, 926-68070)
Validation	p-KAP1: https://www.thermofisher.com/antibody/product/Phospho-KAP-1-Ser824-Antibody-Polyclonal/A300-767A p-H2A.X S139: https://www.sigmaaldrich.com/US/en/product/mm/05636?srltid=AfmBOop1-W1Dhnb6paFel7CfHJ__lRqxf98Q44LjTiAtZoK-214B24u GAPDH: https://www.scbt.com/p/gapdh-antibody-g-9?srltid=AfmBOoo8Pb4rlHagD0PCysY3KysrOwYe3W3KDdwZt1YuNw34uI32J01h

Eukaryotic cell lines

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

Cell line source(s)	Parental cell lines (PC9, RPE1, U2OS) were obtained from ATCC or indicated commercial vendors. Engineered cell lines were created based on these parental cell lines and are described in Supplementary Table 4.
Authentication	None of the cell lines were authenticated by us. We bought the parental lines commercially.
Mycoplasma contamination	Cell lines were not tested for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used.

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	6-8 weeks old FVB/NJ mice and 8-12 weeks old NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ (NSG) mice
Wild animals	No wild animals were used.
Reporting on sex	FVB/NJ mice used in liver tumor studies are all female, according to previous studies that established these liver tumor models (PMID: 24480331) NSG mice used in lung tumor studies are all male because PC9 cells used to generate lung tumor xenografts are of male origin.
Field-collected samples	No field-collected samples were used.
Ethics oversight	The work and all procedures conducted in living mice were approved by UCSF Institutional Animal Care and Use Committee (IACUC)

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

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	Cultured cells were trypsinized and stained as indicated in methods, and resuspended in FBS/PBS for flow. Lung tissues were harvested, dissociated into single cells by digestion with collagenase and passing through 40 µm filters, before flow.
Instrument	Attune NxT Flow Cytometer - ThermoFisher FACSAria - BD
Software	Flowjo 10
Cell population abundance	N/A. We were using flow cytometers for analysis not sorting.
Gating strategy	Negative populations were determined using non-stained or non-treated samples. Gating strategies are indicated in extended figures.

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