nature portfolio

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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 *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	The cancer genome atlas data (TCGA), ENCODE, Molecular Signatures Database (MSigDB), Drug Signatures Database (DSigDB), Genomics of Drug Sensitivity in Cancer (GDSC) , Cancer Cell Line Encyclopedia (CCLE), and LINC1000 data have been used here. The unique identifiers of all data used from these large collections are provided in the supplemental tables S1a and S2a. Several datasets were used for independent validations that are also listed in supplemental tables S2g.
Data analysis	Graphpad Prism Version 10.2.3 (347) DataGraph v4.6 RSEM v1.3.1 EdgeR v3.28.1 DESeq2 v1.26.0 HOMER v4.11.1 GSEA v4.1.0 Morpheus https://software.broadinstitute.org/morpheus Python v>=3.7 SankeyMATIC https://sankeymatic.com/ venny v2.1.0 Biorender N/A R v4.2.3 EGSEA v1.14.0 PIANO v3.18 EnrichmentBrowser v2.2

decoupleR v1.5.0
Benchmark: https://github.com/hedgehug/Benchmark
PET: https://github.com/hedgehug/PET
All data files for PET and Benchmark: https://doi.org/10.6084/m9.figshare.c.7252324

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 RNA-seq datasets generated from three independent biological replicates of DMSO or CCT068127-treated T24 bladder cancer cells are available in the GEO repository with accession number GSE222567 [https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE222567]. All data generated or analyzed during this study are included in this published article and its supplementary information files. Benchmark data is available at https://doi.org/10.6084/m9.figshare.c.7252324.

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	The TCGA reported sex designations were used. There was no exclusion criteria based on the reported sex. Sex was specifically tested as a confounder in the analysis and was found not to be a confounder.
Reporting on race, ethnicity, or other socially relevant groupings	NA
Population characteristics	The TCGA reported vital status, age, pathological tumor stage, and days to death was utilized and also provided in Table S2a-b for convenience. The analysis were adjusted to remove age as a confounder of prognosis.
Recruitment	NA
Ethics oversight	All procedures involving mice were conducted in accordance with the guidelines established in the Guide and Use of Laboratory Animals of the National Institutes of Health, USA. The protocol was approved by the Institutional Animal Care and Use Committee at the Purdue University (PACUC Protocol #1908001941). Animals were housed in Hansen mouse facility at Purdue University. All mice are fed and watered ad libitum, with consistent access to food and water, and housed in a facility maintained at ambient temperature and humidity with 12-hour light/12-hour dark cycles. All mice were sacrificed prior to the tumors reaching a mean diameter of 2.0 cm or in the event of ulceration with necrosis/infection as outlined in the PACUC policy on “Human endpoint criteria for rodent tumor studies.

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	Sample size was chosen according to standard practices in the field, RNA-seq samples were prepared in triplicates. All biochemical experiments were preformed >3 times. All samples from indicated early cancer stage from TCGA collection for 12 analyzed cancer type were used.
Data exclusions	None
Replication	All in vivo, in vitro experiments were performed >3 times and all attempts for replication were included in the manuscript
Randomization	The randomization was performed for identifying false positive pathways and adjusting an imbalance in certain datasets.

Blinding	There was no blinding.

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

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	three cell lines were used for experimental validations, T-24(HTB-4), UMUC3(CRL-1749) and Hela(CCL-2). These are originally derived from male, female and female, respectively. All cells were purchased from ATCC.
Authentication	The cell lines were purchased from ATCC and were not independently authenticated
Mycoplasma contamination	Cells were routinely confirmed to be mycoplasma negative according to PCR Mycoplasma Detection Kit (ABM Inc.) and were used at low passage (<10) number.
Commonly misidentified lines (See ICLAC register)	None

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	The original strain of all mice used in this study were purchased from Jackson Laboratory, Strain# 025216, NOD.Cg-Prkdcscid H2-K1b-tm1Bpe H2-Ab1g7-em1Mvw H2-D1b-tm1Bpe Il2rgtm1Wjl/SzJ and were acclimatized and maintained in Hansen mice facility at Purdue University.
Wild animals	None
Reporting on sex	10-11 weeks old female mice were used in this study due to the availability.
Field-collected samples	NA
Ethics oversight	All procedures involving mice were conducted in accordance with the guidelines established in the Guide and Use of Laboratory Animals of the National Institutes of Health, USA. The protocol was approved by the Institutional Animal Care and Use Committee at the Purdue University (PACUC Protocol #1908001941). Animals were housed in Hansen mouse facility at Purdue University. All mice are fed and watered ad libitum, with consistent access to food and water, and housed in a facility maintained at ambient temperature and humidity with 12-hour light/12-hour dark cycles. All mice were sacrificed prior to the tumors reaching a mean diameter of 2.0 cm or in the event of ulceration with necrosis/infection as outlined in the PACUC policy on "Human endpoint criteria for rodent tumor studies.

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Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA