nature portfolio

Corresponding author(s): Ashutosh Chilkoti

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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	No software was used to collect the data.
Data analysis	All data was entered and statistically analysed in GraphPad Prism v9.

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 main data supporting the results in this study are available within the paper and its Supplementary Information. Source data for the figures are provided with this paper. The raw and analysed datasets generated during the study are available for research purposes from the corresponding author on reasonable request.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	No human participants were involved in the study.
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

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	For each study, we determined the sample size so as to minimize the number of animals to be used in each experiment, on the basis of (1) the power needed to obtain significance in accordance with either the relevant parametric (ANOVA, Tukey HSD) or non-parametric (Mantel Cox log-rank) statistical test used to analyse the studies; (2) established literature precedence for preclinical oncology research; and (3) our past experience in designing similar experiments. The one exception to this was our dose-escalation experiments to evaluate synergy. Originally, a sample size of n=8–10 was anticipated, and was to be carried out over two experimental replications. However, drastic differences in effect observed between the monotherapy and combination groups allowed us to obtain high statistical significance ($p < 0.001$ for most cases). Thus, a smaller sample size was used for these experiments.
Data exclusions	No data were excluded.
Replication	We verified the replication of our findings by using several methods: first, we ensured the selected cell lines were well established in the pancreatic-cancer literature, having been treated with paclitaxel and radiation previously (as well as other common therapeutics). Second, we replicated our own previously published brachytherapy monotherapy studies to ensure replication of tumour responses in the BxPc3-luc2 cell line. Third, we maintained consistent control groups (untreated, CP-PTX, and 131I-ELP) across all dose-scaling experiments as well as a standard-of-care comparison. Fourth, we then ensured that our therapeutic synergy was replicated across different tumour cell lines and an orthotopic model. Fifth, we replicated our tumour permeability experiment using three different fluorescent drug compounds to ensure that the results were consistent regardless of the composition of the drug. Sixth, we verified that the tumour responses observed in the therapeutic studies for ELP brachytherapy and EBRT were consistently observed in the fluorescent-drug permeability studies. Moreover, each of these experiments were conducted with new, separate preparations of the therapeutic agents. This ensured that the effects were repeatable amongst batches and drug formulations.
Randomization	For all animal studies, mice were randomly assigned to therapeutic groups using a random-number-generator method. However, post-randomization analysis of tumour size was performed using a simple student t-test. If tumour size between each group were found to be statistically significant, mice were re-randomized until no disparity in tumour size between therapeutic groups was found. For histological studies, the animals within each group were censored according to a random number generated on the day of censorship. Tumours were then collected and sent for further histological processing. Specimens were blinded and randomized so as not to bias further downtream IHC preparation and pathological analysis.
Blinding	For histological studies, all specimens were blinded and randomized prior to being sent for histological preparation as well as for subsequent pathological analysis. Samples were only unblinded after the specimens had been both qualitative analysed and quantitatively H-scored. For the animal studies, all therapeutic mice were intermixed in between cages to as to prevent the biased housing of animals. All researchers were blinded to the animal groupings during measurements. However, the same researchers were unblinded to the animals during data entry and analysis. To account for this, a neutral researcher who remained permanently blinded to the experiment would assist and provide secondary animal measurements to ensure data accuracy over the course of the experiments.

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

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)	BxPc3-luc2: Perkin Elmer AsPc-1: ATCC MIA PaCa-2: ATCC
Authentication	Upon receipt of all cell lines, authentication was verified via STR profiling through IDEXX Laboratories, Inc.
Mycoplasma contamination	All cell lines were tested for mycoplasma contamination using the IDEXX IMPACT III PCR screen. Cells were verified to be negative prior to the commencement of any studies.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell 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	All studies utilized athymic nu/nu mice purchased from the Duke University Immunoincompetent Rodent and Biohazard Facility. Mice were all male, and obtained at ages of 6-to-8 weeks.
Wild animals	The study did not involve wild animals.
Reporting on sex	Sex stratification of our animal models was not done, as the clinical indication for pancreatic cancer is not specific to one sex. In our review of the literature regarding the tumour models used in these studies, we found no indication of bias or of differences in tumour xenografts when female or male mice were used. As such, we did not include studies to interrogate responses based on mouse sex.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All experimental protocols were reviewed and approved by Duke University's Institutional Animal Care and Use Committee. Methods involving animals were specifically checked to be in adherence to regulations provided by the NIH Guide for the Care and Use of Laboratory Animals.

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