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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	FACSDIVA v8.0.1 was used for flow cytometry data collection and Incucyte ZOOM 2016B was used for Incucyte experiments. Both programs are commercially available.
Data analysis	In vitro cytotoxicity assays were analyzed for synergy utilizing Com benefit software (Lowe model). Di Veroli, G.Y., et al., Combenefit: an interactive platform for the analysis and visualization of drug combinations. Bioinformatics, 2016. 32(18): p. 2866-8. FACSDIVA v8.0.1 was used for flow cytometry analysis.

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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 sizes for in vitro and in vivo experiments were determined based on pilot and preliminary experiments, as well as, what has been previously reported in the literature. No statistical methods were used to predetermine sample sizes.
Data exclusions	No data was excluded from the analyses. Variability of sample sizes in xenografting experiments was due to animal deaths (<5%) or the xenograft not resulting in a measurable tumor prior to treatment
Replication	Flow cytometry experiments were performed in biological triplicate; cytotoxic synergy was performed in biological quadruplicate; Incucyte experiments were performed in biological triplicate; xenograft assays were performed as described. All attempts at replication were successful.
Randomization	Allocation of animals into the various treatment groups was random after xenografting.
Blinding	Blinding was not possible as it was clear what animals were being treated with (one could tell what drugs were in solution).

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	phospho-ERK 1:1000 T202/Y204 (CST clone D13.14.4E; cat# 4370; Lot 17), ERK 1:1000 (CST clone 137F5; cat# 4695; Lot 23), p62 1:500 (Progen clone p62-C; cat# GP62-C; Lot 7324-1), LC3A/B 1:500 (CST; cat# 4108; Lot 3), phospho-LKBl 1:500 (Abcam; cat# Ab63473; Lot GR91845-5), LKBl 1:500 (CST clone D60C5; cat# 3047; Lot 2), phospho-AMPK T172 1:500 (CST clone 40H9; cat# 5256; Lot 21), AMPK 1:500 (CST clone D5A2; cat# 5831; Lot 4), phospho-ULKl S555 1:500 (CST clone D1H4; cat# 5869; Lot 3), ULKl 1:500 (CST clone D8H5; cat# 8054; Lot 5), β-actin 1:10,000 (Sigma clone AC-74; cat# A2228) ,and ATG4B 1:500 (CST clone D1G2R; cat# 13507; Lot 1).
Validation	Antibody Registry: Cell Signaling Technology Cat# 4370, RRI D:AB_10694057; Cell Signaling Technology cat# 4695, RRID:AB_390779; Progen cat# GP62-C, RRID:AB_2687531; Cell Signaling Technology Cat# 4108, RRID:AB_2137703; Abcam cat# ab63473, RRID:AB_1523886; Cell Signaling Technology Cat# 3047, RRID:AB_2198327; Cell Signaling Technology Cat# 5256, RRID:AB_10705605; Cell Signaling Technology Cat# 5831, RRID:AB_10622186; Cell Signaling Technology Cat# 5869, RRID:AB_l0707365; Cell Signaling Technology Cat# 8054, RRID:AB_ll178668; Sigma-Aldrich Cat# A2228, RRID:AB_476697. The ATG4B Antibody was obtained from Cell Signaling Technology and has three prior referenced papers. The antibody was immunoblotted against an over-expression construct, which identified a protein band of the appropriate size. All other antibodies have been previously published with citations available from the vendor and were validated for use in western blot indicating a protein band at the expected size.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Mia-PaCa2 and BxPC3 -ATCC; PDX220-lab derived from PDX220 PDA PDX; SC196 and SC274-lab derived from tumors isolated from suitably manipulated KrasFSF-G12D/+; Trp53Frt/Frt; RosaFSF-CreERT2 mice.
Authentication	Cell lines were not intially authenticated, however, MiaPaCa2 cells have since been authenticated by STR profiling.
Mycoplasma contamination	Cell lines were tested for mycoplasma by PCR-based assay and tested negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Mice, Mus musculus, NOD/SCIO and NSG strain, Males and Females, 6-8 weeks old
Wild animals	No wild anmials were used in this study.
Field-collected samples	No field collected samples were used in this study
Ethics oversight	University of Utah Institutional Animal Care and Use Committee

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Single metastatic pancreatic cancer patient treated on a compassionate use basis and reported under University of Utah IRB guidelines. Please see attached IRB form.
Recruitment	No wild anmials were used in this study.
Ethics oversight	University of Utah Internal Review Board

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

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	pBabe Puro mCherry-GFP-LC3 was obtained from Addgene (plasmid# 22418) and the mCherry-GFP-LC3 cDNA was introduced into the lentiviral construct pUltra Hot resulting in pUltra Auto. pUltra Auto was lentivirally transduced into cell lines resulting in AFR cell lines. AFR cell lines were subjected to various treatments then resuspended via trypsinization for FACS.
Instrument	BD FACSCanto Analyzer
Software	Software Diva v8.0.1 was utilized to analyze raw data.
Cell population abundance	Cells were analyzed not sorted in experiments.
Gating strategy	Gating was based on a heuristic method for identifying an equal population of autophagic flux low, intermmediate, and high cell based on the control population. The gates remained constant throughout each experiment.

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