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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	Real-time qPCR: CFX384 Touch Real-Time PCR Detection System Cell Counting: Z2 Coulter Particle Count and Size Analyzer Plate Reader for luminescence assays: TECAN infinite M1000Pro Blot image scanning: Epson Perfection V600 Photo DNA/RNA concentration measurement: Thermo Fisher NanoDrop Lite
Data analysis	GraphPad Prism v7, 8.0.2, 9.0.1 Microsoft Excel 2016-2021 Microsoft Word 2016-2021 RStudio Version 1.1.463, 1.3.1073 R version 3.5.1, 4.0.2 Packages: stats 4.1.1, tidyverse 1.3.1, gplots 3.1.1, dplyr 1.0.7, ggrepel 0.9.1, FactoMineR 2.4 ‘StatMod’ package (http://bioinf.wehi.edu.au/software/elda/index.html) Adobe Illustrator CC 2017, 2020 EPSON Scan 3.9.4 Enrichr (https://amp.pharm.mssm.edu/Enrichr/); accessed January 2020 FACS Analysis: Becton Dickinson FACSCanto II and Beckman Coulter Astrious Cell Sorter Complete script for analyzing CRISPR screens available at https://github.com/linkvein/selinexor_p2ry2_akt

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 data associated with this study are available in the main text or the supplementary materials. Raw counts table for both the CRISPR/Cas9 sensitizer and p-AKT T308 FACS based screen are included as Table S9 and Table S10, and on GitHub as below. RNA-seq data from OCI-AML2 and MOLM-13 cells treated with selinexor is available at GSE181003. Script and associated raw data for reanalyzing sensitizer and FACS-based CRISPR–Cas9 screens are available on Github (https://github.com/linkvein/selinexor_p2ry2_akt).

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 mouse study, sample size was chosen based on historical demonstration that the in vivo models were highly penetrant and consistent. No statistical methods were used to pre-determine sample sizes but our sample sizes are similar to those reported in previous publications (ref 71, 82, 83). As described, sample sizes ranged from n=3 to n=6 biological replicates per condition for cell-based studies. No statistical methods were used to pre-determine sample size. Sample sizes were sufficient to identify significant changes as indicated in each figure.
Data exclusions	Mice were only excluded from study when leukemic engraftment failed; this exclusion occurred prior to randomization/cohorting and treatment. Otherwise, no animals or data points were excluded unless noted.
Replication	CRISPR screens were performed in biological replicate; all attempts at replication were successful. Experimental findings were reproduced by multiple individuals and/or multiple independent experiments at least three times (specified in figure legend).
Randomization	Where noted, mice were randomized according to their disease burden in blood or bone marrow prior to treatment. Mice were randomized twelve days after injection
Blinding	The investigators were not blinded to allocation during experiments. To establish humane endpoint for mouse study, blinded observers visually inspected mice for obvious signs of distress, such as loss of appetite, hunched posture. For cell-based studies, investigators were not blinded to allocation during experiments or analysis. Blinding was not possible due to experimental design and is not necessary due to objective nature of analysis approaches (ie sequencing, luminescence, etc.).

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
☐	☒	Human research participants
☒	☐	Clinical data
☒	☐	Dual use research of concern

Methods

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

Antibodies

Antibodies used	β-actin (13E5) (CST #4970 diluted 1:5000 in 5% BSA), p-AKT T308 (244F9) (CST #4056 diluted 1:1000 in 5% BSA), p-AKT S473 (D9E) (CST #4060 diluted 1:1000 in 5% BSA), T-AKT (C67E7) (CST #4691 diluted 1:3000 in 5% BSA), p-GSK3β S9 (D85E12) (CST #5558 diluted 1:1000 in 5% BSA), p-BAD S136 (D25H8) (CST #4366 diluted 1:1000 in 5% BSA), XPO1 (C-1) (sc # 74454 diluted 1:100 in 5% BSA), cleaved-PARP (D64E10) (CST #5625 diluted 1:1000 in 5% BSA), cleaved-Caspase3 D175 (CST #9661 diluted 1:500 in 5% BSA), p110-g (D55D5) (CST #5405 diluted 1:1000 in 5% BSA), p110α (C73F8) (CST #4249 diluted 1:1000 in 5% BSA), p110β (C33D4) (CST #3011 diluted 1:1000 in 5% BSA), p110δ (D1Q7R) (CST #34050 diluted 1:1000 in 5% BSA) or p101 (D32A5) (CST #5569 diluted 1:1000 in 5% BSA), Phospho-PKC Substrate Motif [(R/K)XpSX(R/K)] MultiMab™ Rabbit mAb mix (CST #6967 diluted 1:1000 in 5% BSA), Phospho-PKA Substrate (RRXS*/T*) (100G7E) Rabbit (CST #5569 diluted 1:1000 in 5% BS, T-S6K1 (CST#9202 1:1000 in 5% BSA) or p-S6K1 (CST#9205 1:500 in 5% BSA).
Validation	All antibodies have been validated by supplier to detect the human protein of interest by western immunoblotting. Validation is in adherence with the CST (https://www.cellsignal.com/about-us/cst-antibody-validation-principles).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	MV4;11 (CRL-9591), HL-60 (CCL-240), Kasumi-1 (CRL-2724), U937 (CRL-1593.2), and THP-1 (TIB-202) cell lines were purchased from American Duke University Cell Culture Facility (CCF). OCI-AML2, MOLM13, and OCI-AML3 cell lines were received as a gift from the lab of Dr. Anthony Letai.
Authentication	All cell lines were authenticated by STR profiling prior to use. All experiments were performed using aliquots of positively identified cell lines
Mycoplasma contamination	All cell lines were confirmed as mycoplasma-free upon receipt.
Commonly misidentified lines (See ICLAC register)	No cell lines were misclassified. No commonly 'misidentified' cell lines were used in the study.

Animals and other organisms

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

Laboratory animals	Cell line xenograft: Mus Musculus, 5-6 week old NOD-scid IL2Rgammanull males PDX:Mus Musculus, 6–8-week-old huNOG-EXL males MLL-AF9: Mus Musculus, 6-8 week-old C57BL/6 males
Wild animals	No wild animals were used in this study.
Field-collected samples	No samples collected from the field were used in this study.
Ethics oversight	The Duke University Institutional Animal Care & Use Committee (IACUC) reviewed and approved the cell line xenograft transplantation and treatment protocol described in this study. The French National Ethics Committee on Animal Care reviewed and approved the PDX and MLL-AF9 experiments described in this study.

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	For human study, we have provided a table (table S5) listing sex (M = 15, F = 17), disease state and diagnosis for all samples.
Recruitment	Primary patient samples were collected as part of an ongoing clinical registry at St Louis Hospital (THEMA, IRB approval: IDRCB 2021-A00940-41) and stored at the St Louis Hospital tumor biobank. Informed consent was obtained prior to collection; no compensation was provided.
Ethics oversight	IRB approval: IDRCB 2021-A00940-41. Samples retrieved from the St Louis Hospital tumor biobank were anonymized and their storage in our laboratory was declared to the Ministry of Higher Education, Research and Innovation. Secondary use of primary patient cells derived from clinical practice (bone marrow biopsies or blood samples) was approved by the INSERM IRB. No identifying information and no personal data were made available to the research teams, and only anonymized clinical data were accessible, in compliance with French protection of personal data law and in accordance with the Declaration of Helsinki

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	p-AKT T308 FACS screen: Cells were fixed with IC Fixation Kit and stained with p-AKT T308 followed by Alexa Fluor 488 Conjugate staining. Cells were strained with a 0.3μM filter. PDX model: Samples were washed once in PBS and resuspended in 0.5% BSA, 2 mM EDTA–PBS before staining with either APC- conjugated anti-human CD45 (BioLegend, catalog no. 368512, 3:100) antibody and flow cytometry analysis. MLL-AF9 model: Bone marrow biopsies were performed on anesthetized animals 24 hours after the end of the treatment, and biopsies were washed once in PBS and resuspended in 0.5% BSA, 2 mM EDTA–PBS before flow cytometry analysis.
Instrument	p-AKT T308 FACS screen: Beckman Coulter Astrious Cell Sorter PDX/MLL-AF9 mouse model: Becton Dickinson FACSCanto II
Software	FlowJo 2019
Cell population abundance	For the MLL-AF9 model, leukemic blasts were defined by dsRed+ staining. For the PDX model, leukemic blasts were defined by CD45+ stating.
Gating strategy	Cells were gated for live cells based on FSC/SSC and singlets based on FSC. For the MLL-AF9 model, leukemic blasts were defined by dsRED+ staining and positive cells are superior to 10^3 of mean of dsRED fluorescence. For PDX model, leukemic blasts were defined by CD45+ staining and positive cells are superior to 10^2.5 of mean of PE-Cy7 fluorescence. Individual cell populations were defined based on expression of established differentiation markers.

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