

## 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 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                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement                                                                                                                                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly                                                                                                                                               |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided<br><i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>                                                               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> A description of all covariates tested                                                                                                                                                                                                                                |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons                                                                                                                                        |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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) |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> For null hypothesis testing, the test statistic (e.g. $F$ , $t$ , $r$ ) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted<br><i>Give <math>P</math> values as exact values whenever suitable.</i>                            |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings                                                                                                                                                                      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes                                                                                                                                                |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> 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 | ThermoScientific FreeStyle 1.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Data analysis   | Mascot Daemon 2.6.0, Mascot Distiller v2.6.1.0, Mascot search engine (v2.6), Pescal (beta.01), R-4.0.0, RStudio (Version 1.2.5042), DRUMLR ( <a href="https://github.com/CutillasLab/DRUMLR">https://github.com/CutillasLab/DRUMLR</a> ), Term Enrichment Analysis ( <a href="https://github.com/CutillasLab/Term-Enrichment-Analysis">https://github.com/CutillasLab/Term-Enrichment-Analysis</a> ), foreach (v1.5.1), doParallel (v1.0.16), limma (v3.44.2), caret (v6.0-86), h2o (v3.32.0.1), Cubist (v0.2.3), pls (v2.7-3), glmnet (v4.0-2), kernlab (v0.9-29), ggdendro (v0.1.22) and randomForest (v4.6-14). |

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 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 raw mass spectrometry proteomics and phosphoproteomics data generated during this study have been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the dataset identifier PXD019591 (Project DOI: 10.6019/PXD019591).  
The processed omics datasets and EMDR data files are provided in <https://github.com/CutillasLab/DRUML-publication-datasets>.  
Drug sensitivity and RNA-seq data was sourced from PharmacoDB: <https://zenodo.org/record/1038045#.YCW3K2j7SHs>  
Colorectal phosphoproteomics validation data were obtained from PRIDE dataset identifier PXD001550 :<https://www.ebi.ac.uk/pride/archive/projects/PXD001550>

Proteomics validation data were drawn from PRIDE dataset identifier PXD013455: <https://www.ebi.ac.uk/pride/archive/projects/PXD013455>.  
 AML patient phosphoproteomics validation data was obtained from PRIDE project PXD005978: <https://www.ebi.ac.uk/pride/archive/projects/PXD005978>.  
 Drug information was sourced from DrugBank and ChEMBL: <https://go.drugbank.com/> and <https://www.ebi.ac.uk/chembl/>

## 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     | No sample size calculation was performed. Sample sizes were determined by cell line availability at the start of the project and these deemed sufficient as they produced learning models with reasonable low error.   |
| Data exclusions | No data were excluded from the analysis.                                                                                                                                                                               |
| Replication     | Samples were analyzed in triplicate (independent cell cultures per cell line). Reproducibility was assessed by hierarchical clustering showing that replicates grouped together.                                       |
| Randomization   | Samples were grouped into training and testing test using the createPartition function in the caret package. This function balances the class distributions within the splits. Partitions were specific for each drug. |
| Blinding        | Investigators were not blinded to the study design because model generation was carried out using supervised methods.                                                                                                  |

## 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                                     |
|-------------------------------------|-----------------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                       |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Human research participants      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern     |

### Methods

| n/a                                 | Involved in the study                           |
|-------------------------------------|-------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |

## Eukaryotic cell lines

Policy information about [cell lines](#)

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cell line source(s)                                               | <p>DSMZ-German Collection of Microorganisms and Cell Cultures GmbH and American Type Culture Collection (ATCC)</p> <p>The AML cell lines AML-193, CMK, K-052, Kasumi-1, KG-1, HEL, ME-1, ML-2, MOLM-13, MONO-MAC-6, MV4-11, OCI-AML2, OCI-AML3, OCI-AML5, P31/FUJ, PL-21, SIG-M5, SKM-1 and THP-1 were from GmbH.</p> <p>The hepatic cancer cell lines (HEP 3B2.1-7, HEP G2, JHH2, JHH4, SK-HEP-1, SNU182, SNU-398, SNU-423, SNU-449 and SNU-475) and the Esophagus cancer cell lines (KYSE-70, KYSE-140, KYSE-410, KYSE-450, OE-19, COLO-680N, KYSE-150, KYSE-510, KYSE-520 and EO-33) were from ATCC.</p> |
| Authentication                                                    | Cell lines were obtained from repositories with certificate of analysis, and used without further authentication.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Mycoplasma contamination                                          | Cells tested negative for mycoplasma contamination.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Commonly misidentified lines (See <a href="#">ICLAC</a> register) | No commonly misidentified cell lines were used in the study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |