nature portfolio

Corresponding author(s): Jens Hansen, Ravi Iyengar, Nicole Dubois

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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	https://iyengarlab.org/dtoxs/datasets.php - 'Datasets used for prediction of transcriptomic and genomic signatures for TKI-induced cardiotoxicity'
Data analysis	https://github.com/DToxS/SVD-curated_transcriptomic_signatures_cardiotoxic_drugs

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

Transcriptomic and genomic data generated in this and our previous study 16 have been deposited in the NCBI GEO and dbGAP databases under the accession codes GSE174773, GSE217421, GSE253490 and phs002088.v1.p1, respectively. The processed lists of DEGs and genomic variants that are used by our code deposited on github are available at https://iyengarlab.org/dtoxs/datasets.php ('Datasets used for prediction of transcriptomic and genomic signatures for TKI-

induced cardiotoxicity'). All original findings obtained for the cardiomyocytes treated in isolation are available at Predictox.org. DEGs and genomic variants that are used by our code. Cardiomyocyte cell lines are available upon request.

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	Suppl Table 01 - Cell line metadata
Reporting on race, ethnicity, or other socially relevant groupings	Suppl Table 01 - Cell line metadata
Population characteristics	NA
Recruitment	Details are previously published please see Schaniel C et al Stem Cell Reports. 2021 Dec 14;16(12):3036-3049. doi: 10.1016/j.stemcr.2021.10.005. Epub 2021 Nov 4. PMID: 34739849
Ethics oversight	The Mount Sinai IRB approved the study protocol (nubmer: GCO-13-1945/HSM14-00530).

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	6 cell lines treated in isolation with each of 54 drugs, 2 cell lines treated with or without endothelial cocultures with each of two drugs
Data exclusions	Biological replicates with outlier characteristics were excluded as described in Xiong, Y. et al. A Comparison of mRNA Sequencing with Random Primed and 3'-Directed Libraries. Sci Rep 7, 14626 (2017). https://doi.org:10.1038/s41598-017-14892-x. See Suppl. Tables 2A and B for detailed information.
Replication	With a few exceptions of 2 or 3 replicates, we generally treated 4 biological replicates of each cell line with each drug. Control biological replicates ranged from 4 to 12. See Suppl. Table 2 for detailed information.
Randomization	NA
Blinding	samples were blinded for RNA, extraction, library prep and sequencing and identification of expressed genes.

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)	Skin fibroblasts of healthy human donors; Human Coronary Artery Endothelial Cells (HCAEC) obtained from a single donor were purchased from PromoCell (Catalog# C-12221), sex of the donor is unknown
Authentication	fibroblasts: STR analysis/DNA fingerprinting; HCAEC: purchased from PromoCell
Mycoplasma contamination	fibroblasts: Mycoplasma testing was performed early during the banking but not routinely during culture.; HCAEC: purchased from PromoCell, cell testing for mycoplasma is part of the PromoCell quality control, no additional testing for mycoplasma contamination by us
Commonly misidentified lines (See ICLAC register)	NA

Plants

Seed stocks	NA
Novel plant genotypes	NA
Authentication	NA