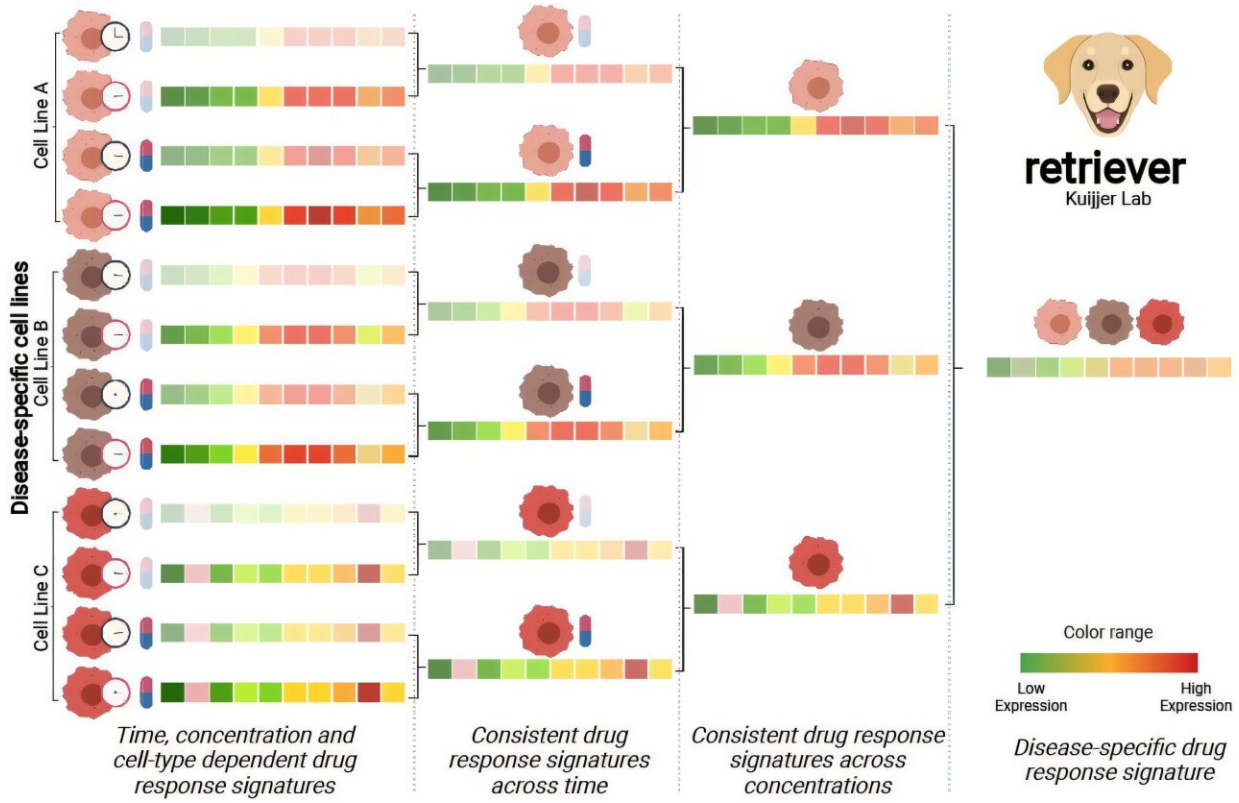
Computational tool extracting disease-specific drug response signatures could improve cancer treatment discoveries

February 4 2025, by Emily Packer



Overview of the retriever algorithm. Credit: *eLife* (2025). DOI: 10.7554/eLife.102442.1

A new computational tool could help researchers identify promising drug

combinations for treating cancer, according to a new study.

The research, published as a Reviewed Preprint in *eLife*, is described by the editors as an important and timely study, with the potential to revolutionize personalized cancer treatment strategies by providing a method to predict effective drug combinations to treat the disease. They say the strength of evidence for the effectiveness of the tool, named "retriever," is solid.

Developing new cancer treatments is an expensive and time-consuming process. Drug discovery is often aided by computational methods to quantify the transcriptional signatures—the changes in gene activity—associated with the disease and match them to the response profiles of cell lines that act as surrogates for the disease's response to different drugs. These data can then be combined to identify drugs that may reverse the disease's transcriptional changes, returning it to a more healthy-like state.

Recently, the LINCS-L1000 project published transcriptional profiles of several cell lines treated with hundreds of drugs at different concentrations and time points of administration. It is also able to rank drugs based on their predicted ability to reverse disease-associated changes in gene expression.

"A current limitation of the LINCS-L1000 project is that its predictions are not disease-specific. They include drug-treated transcriptional profiles from multiple cell lines, but without a clear link to specific cancer subtypes, meaning it may over or underestimate a drug's effect," says lead author Daniel Osorio, former postdoctoral fellow at the Centre for Molecular Medicine Norway, University of Oslo, Norway.

"Being able to extract robust, disease-specific transcriptional drug response signatures that are consistent at different time points, drug

concentrations or cell lines from the data provided in the project would significantly improve drug prioritization and accelerate the identification of new personalized treatments for cancer patients."

The team developed retriever to remedy this issue. The tool integrates single-cell RNA sequencing signatures to capture how individual cells within a tumor express genes to create disease-specific transcriptional signatures. Retriever refines drug response predictions using three key steps.

The first step summarizes the cellular responses at different time points after the application of the drug. The second step summarizes the responses at different drug concentrations. And lastly, it summarizes the responses to the drug across different cell lines. This can then be combined with drug response data from LINCS-L1000 to extract more reliable, disease-specific profiles.

"By applying these filters, retriever generates transcriptional drug response profiles that are more tailored to a given form of cancer than those from the LINCS-L1000 project alone," says Osorio.

To demonstrate retriever's potential, Osorio and colleagues used it to predict effective drug combinations against triple-negative breast cancer (TNBC)—an aggressive breast cancer with limited treatment options.

First, they compiled single-cell RNA sequencing data for healthy breast tissue and breast cancer cells from multiple, publicly available datasets. They then used retriever to analyze 4,899 drug response profiles from TNBC cell lines in the LINCS-L1000 database, while removing the variability caused by different time points of drug administration, drug concentrations, and different cell lines.

This testing suggested that a combination of two kinase inhibitors—QL-

XII-47 and GSK-690693—was the most effective at reversing the transcriptional profile of TNBC back to a healthy-like state. By using a Gene Set Enrichment Analysis, the team discerned that this combination may act by targeting key biological pathways associated with the inhibition of TNBC growth and preventing the growth of secondary tumors. They confirmed the validity of this prediction by treating lab-grown TNBC cells with QL-XII-47 and GSK-690693, either alone or in combination.

Both drugs individually reduced cancer cell viability, but the combination of both had the most significant effect, supporting retriever's potential to identify effective drug combinations based on transcriptional responses.

The researchers acknowledge some current limitations of retriever. For example, the tool ranks drugs and drug combinations based on how well they counteract disease transcriptional signatures, but experimental validation is still required to determine optimal dosing, assess synergy between drugs, and evaluate potential side effects.

"Retriever allows us to identify drugs and drug combinations that target specific tumor cell types and subpopulations. Furthermore, the approach can be applied to disease profiles derived from a single patient, making it highly suitable for informing the development of personalized cancer treatments," concludes senior author Marieke Kuijjer, Group Leader at the Center for Molecular Medicine Norway, University of Oslo, Norway, and Associate Professor at the iCAN Digital Precision Cancer Medicine Flagship and Department of Biochemistry and Developmental Biology, University of Helsinki, Finland.

"Thanks to the multiple cell lines available in the LINCS-L1000 project, our approach can be extended to at least 13 other cancer types, including prostate carcinoma and adult acute monocytic leukemia. As more single-

cell RNA sequencing and drug targeting data become available, we expect retriever to be applicable to most cancer types in the near future."

More information: Daniel Osorio et al, Drug combination prediction for cancer treatment using disease-specific drug response profiles and single-cell transcriptional signatures, *eLife* (2025). DOI: 10.7554/eLife.102442.1

Provided by eLife

Citation: Computational tool extracting disease-specific drug response signatures could improve cancer treatment discoveries (2025, February 4) retrieved 7 February 2025 from https://medicalxpress.com/news/2025-02-tool-disease-specific-drug-response.html

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