Patient-derived organoids (PDO) as functional models to capture interindividual heterogeneity in breast cancer chemotherapy response.

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Submitted Abstract Summary

Breast cancer (BC) remains a leading cause of mortality in women, and resistance to chemotherapy limits durable outcomes. Using patient-derived organoids (PDOs) from 29 BC patients treated with AC-T, we quantified drug responses via Growth Rate (GR) metrics and integrated them into a Sequential Efficacy of Chemotherapy (SEC) score. PDOs recapitulated tumor phenotypes and revealed marked heterogeneity: 43% were resistant to doxorubicin, 25% to 4-hydroxy-cyclophosphamide, and 71% to paclitaxel. Only 32% showed true synergy between doxorubicin and cyclophosphamide, consistent with the Independent Drug Action (IDA) model. PDO profiling identified alternative sensitivities and supports individualized monotherapy selection to maximize efficacy and reduce toxicity in BC treatment.

Introduction

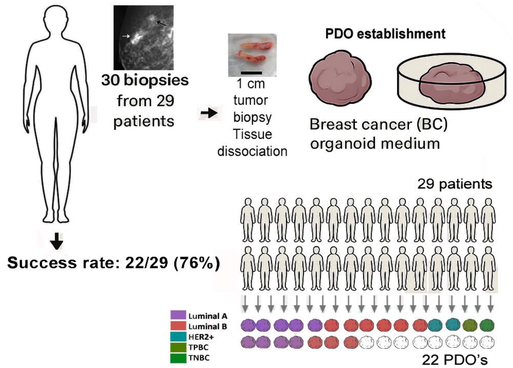
BC remains the leading cause of cancer-related mortality among women worldwide. Despite significant advances in systemic therapies, chemoresistance continues to limit durable clinical benefit for many patients. Standard polychemotherapy regimens, such as AC-T (doxorubicin/cyclophosphamide → paclitaxel), are still applied empirically, often exposing patients to unnecessary toxicity in the absence of robust predictive biomarkers.

Recent evidence suggests that the apparent efficacy of many combination regimens arises from Independent Drug Action (IDA), whereby distinct patients benefit from different agents rather than from true pharmacologic synergy. This paradigm emphasizes the need for functional precision oncology approaches capable of prospectively identifying the most effective single agent for each individual tumor.

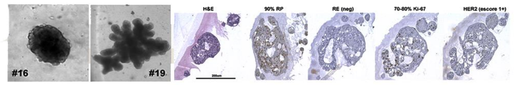
To address this, we developed a translational platform based on PDOs and introduced the Sequential Efficacy of Chemotherapy (SEC) score, a quantitative metric integrating Growth Rate (GR)–based drug response[1] with clinically relevant free plasma concentrations (C_{Max}). This framework enables direct comparison of chemotherapeutic efficacy under physiologically meaningful conditions, bridging in vitro pharmacodynamics with patient-level therapeutic relevance.

Methods

We developed a PDO platform to functionally assess drug sensitivity in BC.

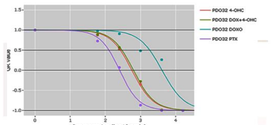


Characterization: PDOs retained key histopatological and immunohistochemical features of the parental tumors (ER/PR/HER2 and Ki-67)



Drug testing (AC-T regimen)

Doxorubicin, 4-hydroxy-cyclophosphamide and paclitaxel



GRmetrics $GR(c) = 2^{\frac{\log_2(x(c)/x_0)}{\log_2(x_{ctrl}/x_0)}} - 1$

ng/ml	GR50	GRmax	GR_AOC	hGR
Ciclofosfamida (C)	inf	0.59	0.1	1.24
Docetaxel (T)	18159	0.47	0.09	0.68
T+C	23377	0.52	0.12	0.45

Integration:

Drug sensitivity data were summarized using a Sequential Efficacy of Chemoterapy (SEC) score aligned with Cmax:

if GRmax < 0:

$$SEQ = -GR_{\max} \times \left(\frac{C_{\max\,free}/GR_{50}}{10}\right)$$

Otherwise:

$$SEQ = -\left(\frac{C_{\max\,free}/GR_{50}}{\exp(GR_{\max}) \times 10}\right)$$

Results

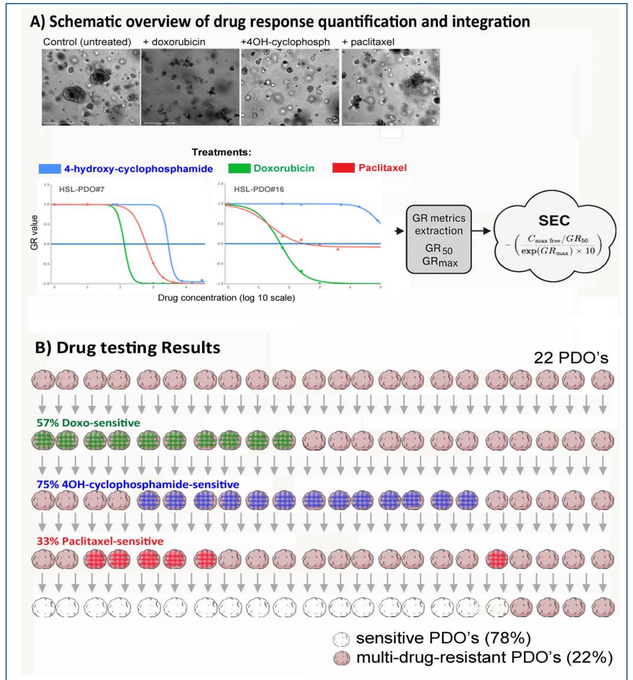
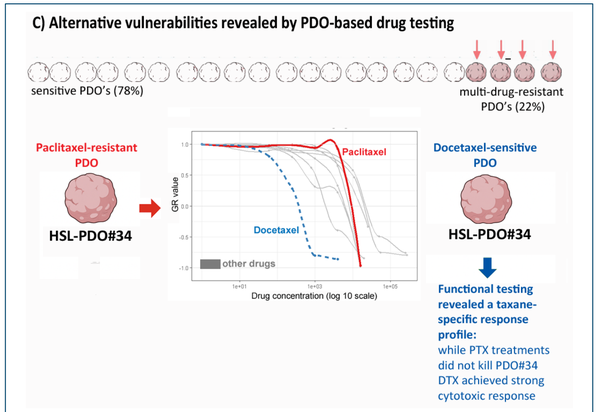


Figure 2. Functional drug testing and integration of PDO-based chemotherapy response. (A) Schematic overview of drug response quantification, including representative bright-field images of PDOs treated with doxorubicin, 4-OH-cyclophosphamide, and paclitaxel (PTX). Representative dose–response curves showing interindividual variability in growth rate (GR)inhibition profiles for each agent. GR_{50} and GR_{max} values were extracted[1] and applied to the SEC formula to align drug efficacy with pharmacokinetics. **(B)**Summary of functional results across 22 PDOs. Sensitivity was observed with22% of PDOs showing multidrug resistsance. Each outline represents an PDO for an individual patient.



(C) HSL-PDO#34 exhibited taxane-specific response: paclitaxel-resistant (red) but docetaxel-sensitive (blue). Gray curves represent other tested agents (doxorubicin, 4-hydroxy-cyclophosphamide, cisplatin, carboplatin, 5-FU, DBR46).

Conclusions

PDO-based assays provide a functional snapshot of patient-specific chemosensitivity, revealing variability consistent with Independent Drug Action. This approach enables prospective identification of the optimal single agent for each patient, supporting a shift from empiric polychemotherapy toward personalized monotherapy strategies that can maximize efficacy and minimize toxicity. Finally, we believe that functional testing of PDOs represents a translational bridge between laboratory precision models and individualized clinical decision-making, with the potential to redefine how chemotherapy is prescribed in breast cancer.

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