Breast cancer patient-derived whole-tumor cell culture model for efficient drug profiling and treatment response prediction

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Highlights
We established a new ex vivo model named Whole-Tumor cell Culture (WTC) with a high success rate (≥90%) for all types of breast tumors. It represents the original tumor characteristics to a large extent and allows us to accomplish personalized drug testing within 10 days, highlighting its potential for individualized breast cancer therapy. Good predictive value and strong clinical relevance of WTC-based testing were also confirmed in a neoadjuvant validation study. Coupled with genomic and transcriptomic analyses, the WTC model can also help stratify specific patient groups for assignment into appropriate clinical trials and validate potential biomarkers.

Introduction
Breast cancer (BC) is a complex disease comprising multiple distinct subtypes with specific genomic and pathological characteristics. Although some 30 anti-neoplastic compounds have been approved for clinical use, patient-to-patient variability in drug response is frequently observed. Several patient-derived tumor models have been proposed to serve as therapeutic prediction tools. However, the lack of tumor microenvironment considerations and time-consuming procedures make their clinical utility limited.

Method
Cells were recovered from newly resected breast tumors as whole-tumor cell cultures (WTCs). Immunohistochemistry, flow cytometry, DNA- and RNA-sequencing were performed to ensure the WTCs recapitulate the biology of original tumors. A broad range of clinically relevant drugs was tested on the WTCs. Cell viability assay, real-time imaging tool, transcriptomic analysis, and panel gene-expression analysis were carried out to investigate the models’ predictive value and clinical relevance. A separate validation study was also carried out to compare WTC-based test results and patients’ clinical responses in neoadjuvant treatment settings.

Multi-drug profiling and gene expression analysis indicates the WTC as a promising platform to predict the responses of individual BC patients

By evaluation with different criteria, WTC-based drug profiling data were largely in line with the patient clinical responses, particularly for epirubicin and anti-HER2 dual inhibitors. We were able to identify epirubicin as the decisive regimen for patient outcomes in this study and provided distinct DSS reference ranges. Example mammography images are shown for both patients who achieved complete response (CR) and stable disease (SD) after EC treatment.

Significance
There is an urgent demand for discovering more accurate and predictive tools to facilitate precision oncology. Here we report the WTC model could provide us with a platform to efficiently identify drug sensitivity and resistance for individual BC patients. We consider it also a technical breakthrough by considering the stromal components to represent a more unbiased snapshot of the original patient’s disease.