Enabling therapeutic decisions for a breast cancer patient cohort using matched diseased and normal tissue in tumor organoids.

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ABSTRACT

Pre-clinical cancer studies have been limited by the availability of patient cell models that accurately represent the diversity of patient populations. The utility of these studies is further impacted by the lack of normal tissue from the same patient. Furthermore, clinical evaluation of targeted therapeutics, like tarceva (erlotinib), would benefit from patient models expressing the target for robust characterization of drug response.

Moreover, individual patient responses to the same anti-cancer compound cannot be assessed with high precision unless healthy controls are used from the same tumor donor.

Here, we present two breast cancer patient-derived tumor models, accompanied by cancer (tumor)-associated fibroblasts (CAFs). These paired and matched sample cohorts were studied in the context of spheroid models of the metastatic breast cancer niche. We show that these models allow an increased understanding of chemotherapy modulation by non-cancerous cells, which are present within the tumor but not targeted by the current chemotherapies or other anti-tumor approaches. We used a three-drug set to create a viability profile for each patient-associated tumor sample, which in turn can be used to aid clinical decision-making and increase the personalization of each treatment for an individual.

METHODS

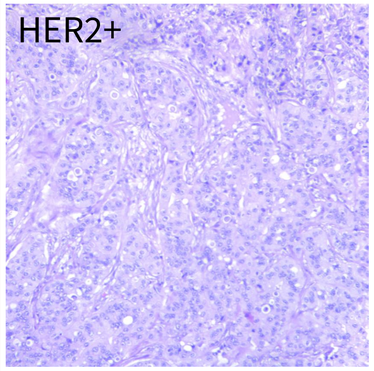
1. All cancer cell models were derived and grown in **Renaissance Essential tumor medium (RETM**) with 5% FBS.
2. Cancer associated fibroblasts were derived from cancer adjacent healthy tissue and expanded in **Fibroblast media.**
3. Culture conditions of all cells were normoxic (21% O2) at 37° C.
4. 3D Spheroids, composed of cancer and fibroblasts were established in **U-Bottom ultra-low-attachment plates.**
5. 3D scaffolds were formed using **Canvas.**
6. Drug response assays were performed utilizing **CellTiterGlo**.
7. Logarithmic curves were visualized using the drug response database's visualization toolkit.

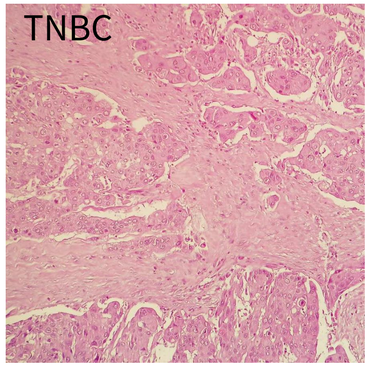
Cell Model Characterization

A. Clinical Profiles

Cell Line	Diagnosis	Cancer Subtype	Clinical Profile
HER2+	Invasive Ductal Carcinoma	Her2 Positive	Caucasian Female, 55-60
TNBC	Parenchyma of the left breast	Triple Negative	Caucasian Female, 80-85

B. Hematoxylin & Eosin

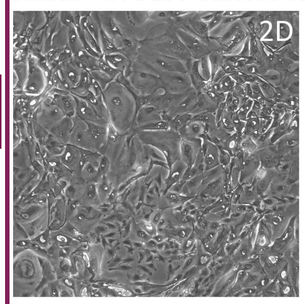


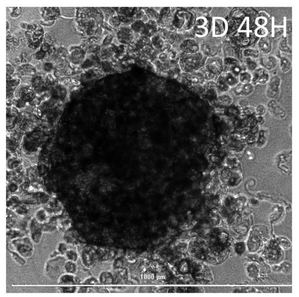


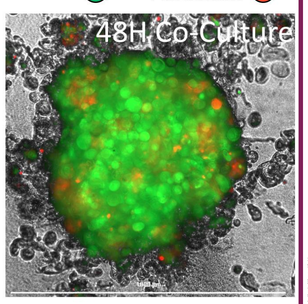
C. Cell Model Characterization: 2D/3D/Co-Culture Morphology

HER2+ Breast Cancer Model

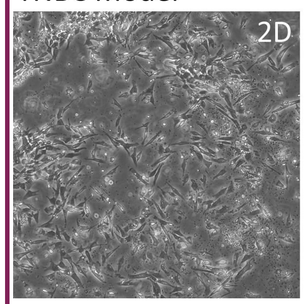
Cancer Fibroblasts

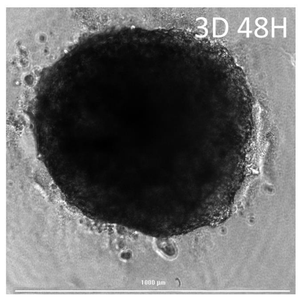


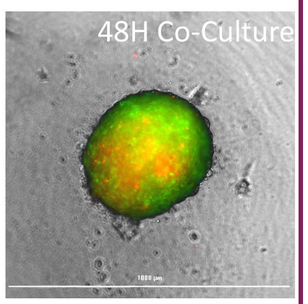




TNBC Model

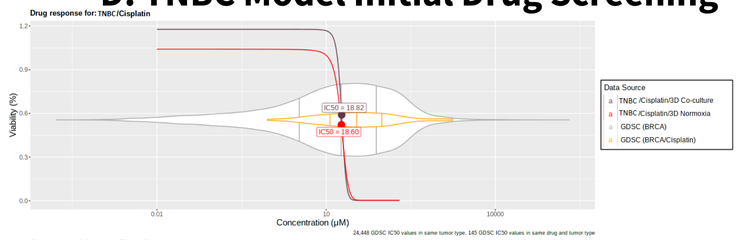




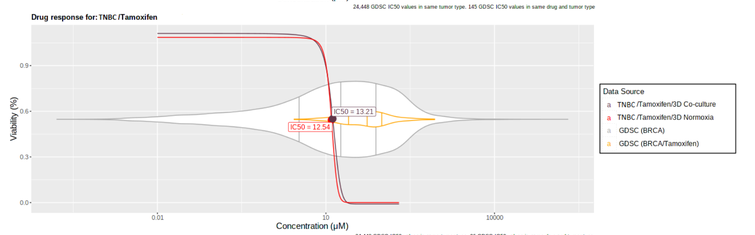


RESULTS

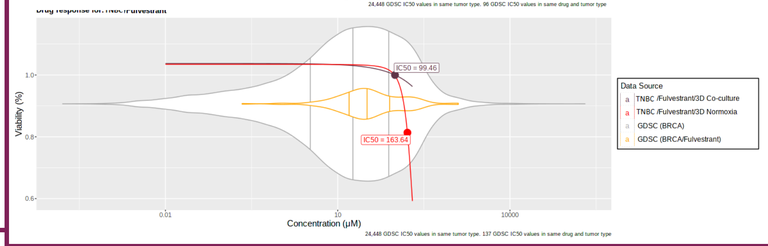
D. TNBC Model Initial Drug Screening



24,448 GDSC IC50 values in same tumor type. 145 GDSC IC50 values in same drug and tumor type

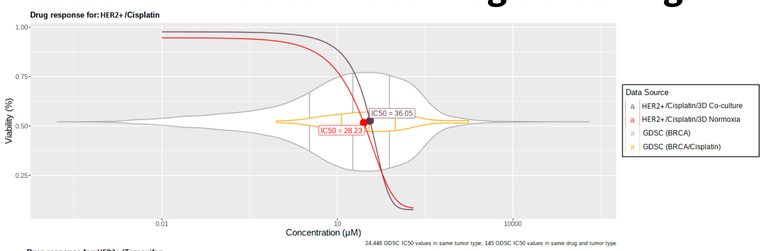


24,448 GDSC IC50 values in same tumor type. 96 GDSC IC50 values in same drug and tumor type



24,448 GDSC IC50 values in same tumor type. 137 GDSC IC50 values in same drug and tumor type

E. HER2+ Model Initial Drug Screening



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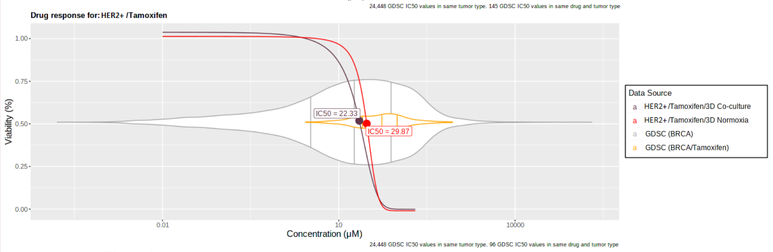

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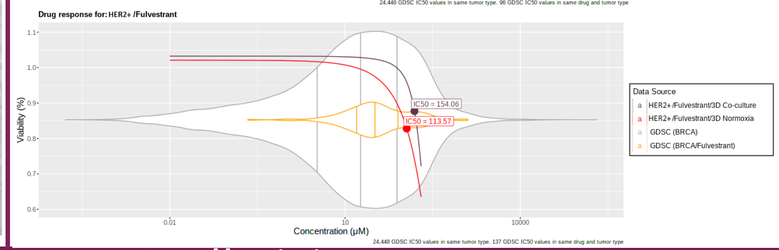

24,448 GDSC IC50 values in same tumor type. 137 GDSC IC50 values in same drug and tumor type

KEY FINDINGS

1. Renaissance media allows for rapid and reproducible derivation of cancer cell models from original patient specimen.
2. The fibroblast media used allows for rapid and reproducible derivation of cancer associated fibroblasts from healthy cancer adjacent tissue.
3. The breast cancer cell lines form consistent but patient-unique spheroids in 3D culture, including when seeded in combination with fibroblasts derived from healthy tissue.
4. When integrated with cancer associated fibroblasts, a small increase in the resistance to the three chemotherapeutic agents was noted in the triple negative breast cancer line.
5. The above resistance was observed in both Cisplatin and Fulvestrant, but not Tamoxifen in the Her2 positive breast cancer line.

FUTURE WORK

1. Using this media platform, the breast cancer model can be utilized for drug screening with increased complexities through the support of mesenchymal stem cells.
2. Expansion of the drug screen will provide further insight into the effectiveness of certain chemotherapeutic agents on specific subtypes of breast cancer.
3. The introduction of T-cells derived from the same patient may allow for immunotherapy modeling in-vitro, utilizing this model platform.

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