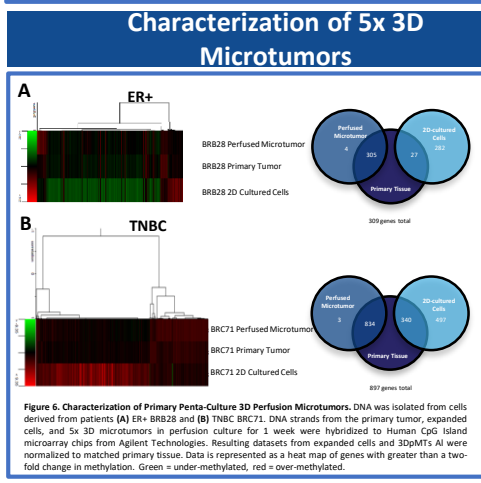
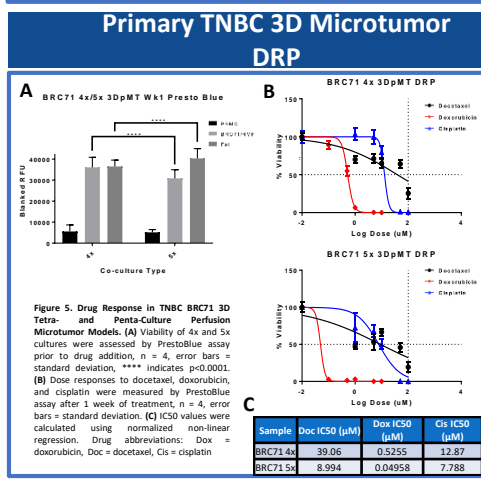
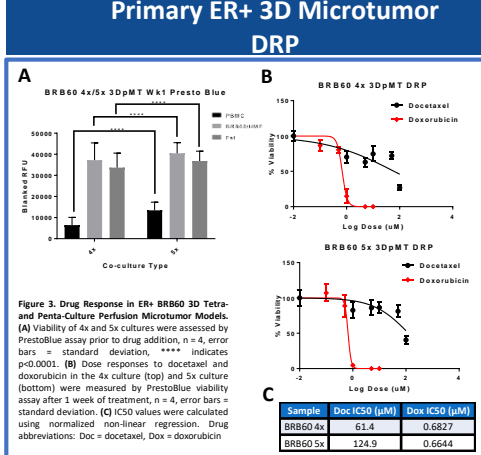
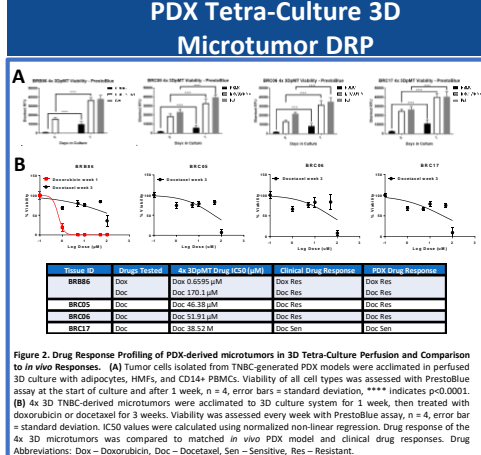
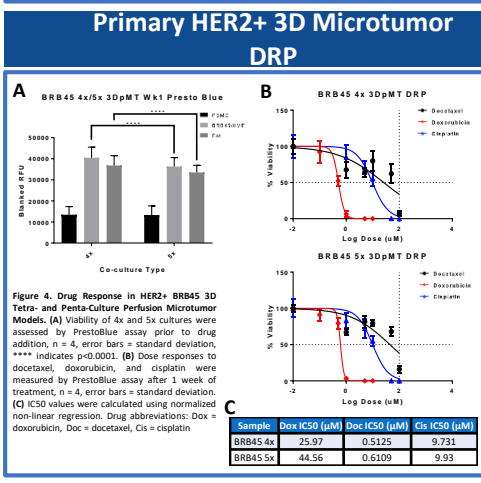
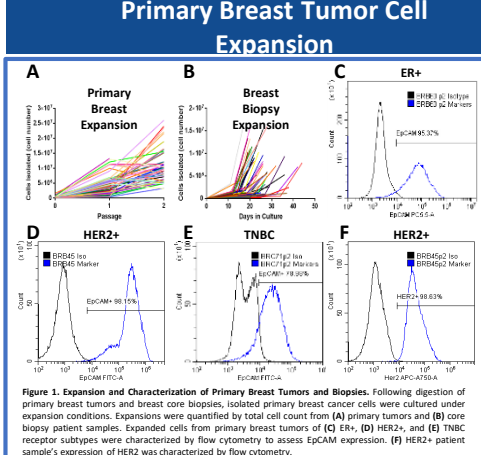
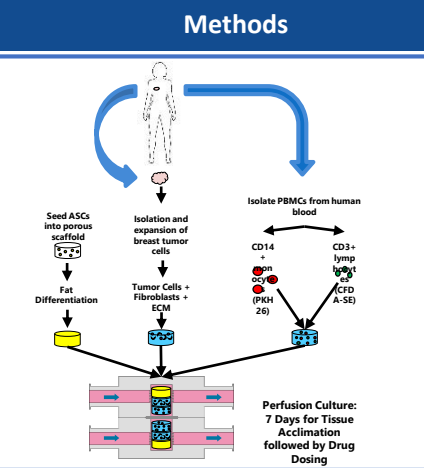


Complex, Patient-Derived, Multi-Cell Type, 3D Models of Breast Cancer for Personalized Prediction of Therapeutic Response

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Background

Breast cancer survival has drastically improved over the past decades; however, drug resistance and subsequent disease progression is responsible for the incurability of advanced disease. While the focus of many drug response studies is the transformed tumor cells, there is increasing evidence suggesting a role for stromal cells in tumorigenesis and drug resistance. Microenvironmental components, including extracellular matrix, fibroblasts, leukocytes, and adipocytes, all contribute to physiological mammary gland biogenesis. Accordingly, these stromal elements contribute to disease progression and resistance. However, many *in vitro* drug response studies still utilize 2D monolayer cultures with purified breast tumor cells. *In vivo* studies remain the gold standard for drug development, even though they are performed with immune-compromised mice that may not reflect the physiological tumor microenvironment and have been repeatedly shown to be a poor representation of clinical outcomes. Thus, there is a need for more complex *in vitro* models to test drug response effectively and accurately. We have previously demonstrated the benefits of using a patient-derived, tri-culture (3x), 3D perfusion microtumor (3DpMT) system. To further replicate the complex tumor microenvironment, we have expanded to a penta-culture (5x) model by incorporating macrophages and lymphocytes alongside the tumor cells, fibroblasts, and adipocytes of the 3x model. We have accrued over 207 primary tumor samples, including both resected tumor and core biopsies, from which we have generated 12 stable PDX models (~50% ER+) and >20 3x, 4x, and 5x 3DpMT with a focus on triple negative (TNBC). Our model has the potential to test a myriad of drugs, from conventional chemotherapies to novel immunotherapies over extended time periods with different dosing strategies in order to provide a more accurate prediction of patient-specific clinical response.



Conclusions

- Stable lines generated from patient-derived breast cancer samples can be successfully cultured in the 5x 3DpMT system
- Different patient lines show unique drug response profiles, indicating that 5x 3DpMT culture can identify patient variations in drug sensitivity
- Tumor cells cultured in the 5x 3DpMT system maintain gene expression patterns similar to the primary tumor and better than their 2D cultured counterparts

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