Abstract# 192

A novel and rapid patient-derived organoid breast cancer platform for precision medicine

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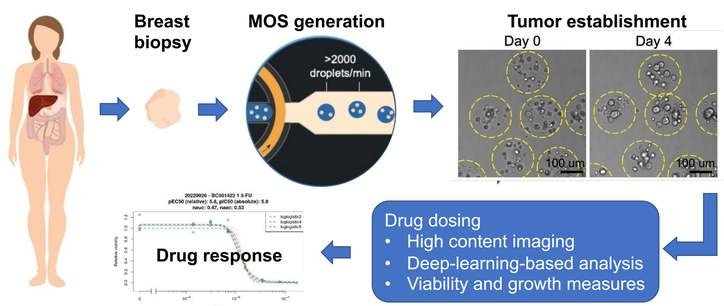
Background

An increasing number of studies performing correlative drug screens on patient-derived organoids (PDO) are revealing enormous potential for these models in predicting patient response to therapy[1,2]. Despite this, their future use in a clinical setting is hindered by intrinsic limitations of traditional PDO models, namely low success rates in establishing growing cell cultures from tumor tissue samples and long return times for drug response data that fall outside timescales of clinical actionability.

We developed a novel emulsion-based microfluidic technology that generates PDOs from tissue samples within days to weeks as opposed to months. The core technology, known as MicroOrganoSpheres (MOS), relies on creating a microscale tumor environment containing a patient's cells. MOS retain structural, cellular, and genetic properties of an individual patient's diseased tissue and are amenable to liquid dispense.

Here, we tested the feasibility of generating MOS from breast cancer tissue biopsies across different subtypes of breast cancer. We performed dose response studies across standard-of-care chemotherapies, providing response data within 2-3 weeks from receiving a sample.

Method

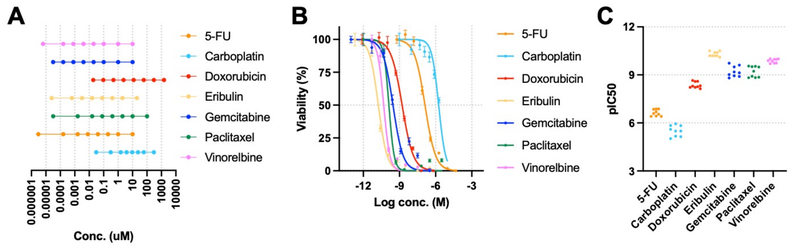


A patient's breast sample (primary or metastatic) is dissociated and packaged into MOS using our emulsion-based microfluidic device. MOS are established over a period of 1-2 weeks. Brightfield images showing established breast MOS growing over 4 days. Established samples are dosed using an automated workflow. Drug response is tracked and quantified using longitudinal imaging and viability measures.

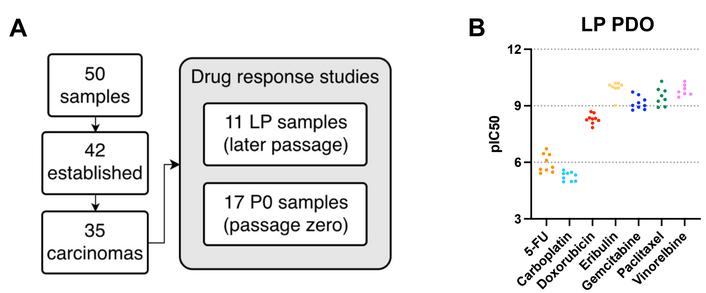
Results

Established breast cancer PDO samples

A total of 42 out of 50 breast PDO samples were established (84% success). Molecular subtypes (left) and tumor types (right) from the 42 PDOs are shown. IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, DCIS = ductal carcinoma in situ, MET = metastatic carcinoma, Other = largely Phyllodes and fibroadenoma tumors.

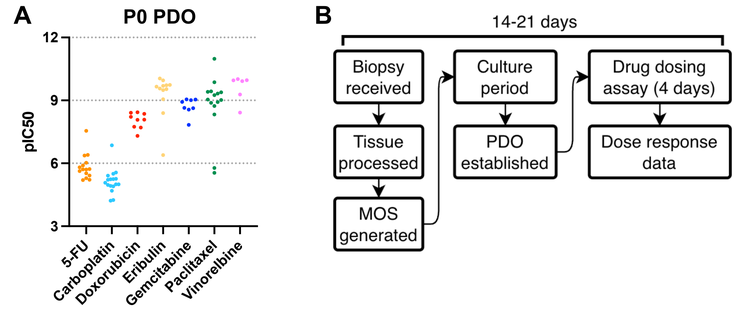


A semi-automated workflow was created to measure drug responses of PDO samples to **(A)** standard-of-care chemotherapies broadly prescribed as first line treatments across all subtypes of advanced breast cancer. Dose response curves showing **(B)** % viability and **(C)** pIC50 (negative log of IC50) from a representative PDO line dosed in technical and biological triplicate across all drugs. Our dosing assay showed high reproducibility (CV<8%; MAD<0.5) and excellent signal-to-noise (z-prime=0.56, SSMD=-7.64).



Of the 42 established breast PDO samples, 35 of these were carcinomas **(A)**. To date, we have dosed 28 of these samples with 11 from later passage samples ("LP"; defined as samples dosed at passage 1 or older) and 17 from passage zero samples ("P0"). **(B)** Dose response pIC50 values shown for all 11 LP PDO samples across all drugs**.**

Results



Dose response pIC50 values for all 17 of the P0 PDO samples **(A).** Collectively, these samples were all processed, established, and completed drug dosing with analysis within 14-21 days **(B)** with some samples completed within 7 days. Number of drugs dosed varied based on available biomass.

Conclusions

Our data demonstrate the feasibility of:

- Efficiently establishing PDO from breast cancer patient tumor samples from different subtypes using MOS.
- Performing drug dosing studies on MOS that results in improved turnaround times that are in line with clinical timescales.

Future directions

- Continue expanding our breast cancer PDO biobank, generating full dose response profiles across chemotherapies with rapid turnaround times
- Develop a predictive model using MOS to determine patient sensitivity to chemotherapy.

References

1. Sachs N, de Ligt J, Kopper O,…, Clevers H. A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity. Cell. 2018 Jan 11;172(1-2):373-386.e10.
2. Guillen KP, Fujita M, Butterfield AJ, …, Welm AL. A human breast cancer-derived xenograft and organoid platform for drug discovery and precision oncology. Nat Cancer. 2022 Feb;3(2):232-250.