Pilot Study of a Micro-Organosphere Drug Screen Platform to Lead Care in Advanced Breast Cancer (MODEL-ABC)

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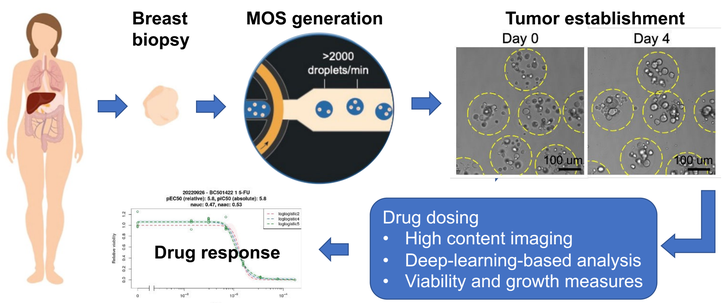
Background

ASCO guidelines suggest using single agent chemotherapy for patients with advanced breast cancer (ABC). Single agent chemotherapy provides modest response rates in ABC, causing patients to be exposed to unnecessary toxicity without benefit. Thus, there is an unmet clinical need to develop a clinically applicable assay to guide treatment.

We recently reported the use of MicroOrganoSpheres (MOS), which are gel droplets that encapsulate tumor cells creating miniature avatars of a patient's tumor and are amenable to high throughput dispensing and drug studies[1]. In our current study, we evaluated the feasibility of generating and dosing MOS from ABC samples as a novel drug screen platform that led to the development and enrollment of a precision oncology trial, known as MODEL-ABC.

Technology

MOS rely 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.

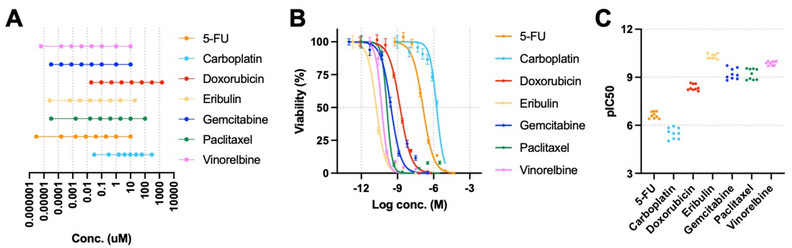


A patient's breast sample (primary or metastatic) is dissociated and packaged into MOS using our emulsion-based microfluidic device. MOS are established over a period of 1-2 weeks. Brightfield images showing established breast MOS growing over 4 days. Established samples are dosed using an automated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

Proof-of-concept

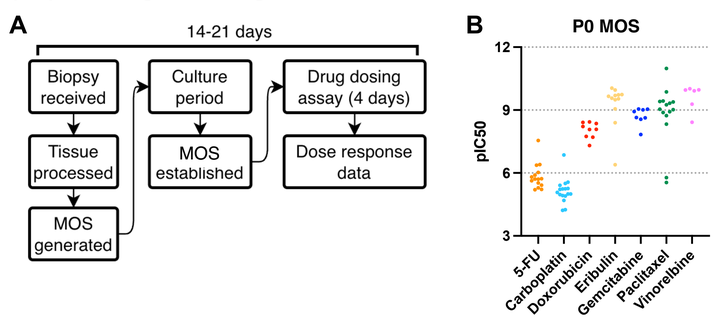
Samples from patients with ABC were dosed across 7 standard of care chemotherapies commonly prescribed for ABC. These data resulted in a platform for the MODEL-ABC study that enrolled patients with ABC of any ER, PR, or HER2 subtype who were eligible for single agent chemotherapy to determine the feasibility of using MOS to predict response to therapy.

Creating a dosing platform



A semi-automated workflow was created to measure drug responses of MOS 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 MOS 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).

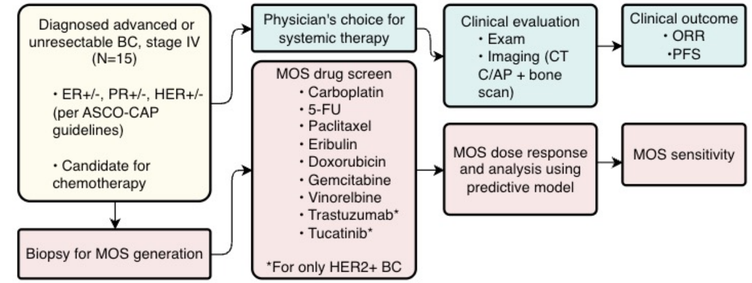
Rapid processing and dosing



Dose response pIC50 values for all 17 of the P0 MOS 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.

MODEL-ABC

Clinical protocol for MODEL ABC validation study

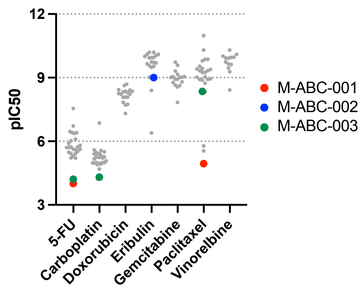


Objective 1: Determine feasibility of generating MOS from patient biopsies and dosing
Objective 2: Assess the association between chemotherapy sensitivity in MOS and clinical outcome of the patient using predictive model.
This study will not guide therapeutic decisions

Preliminary results

	pIC50				
	5-FU	Carboplatin	Eribulin	Paclitaxel	Days to dose
M-ABC-001	4.01			4.95	28
M-ABC-002			9.00		15
M-ABC-003	4.21	4.31		8.35	16

pIC50 values for MODEL-ABC samples relative to 35 established breast MOS lines across all breast subtypes.



Conclusions

Our platform enables efficient establishment of MOS from ABC patient samples and allows for drug dosing studies to be performed in a clinically meaningful timeframe. Our preliminary data suggests it is feasible to generate MOS and perform drug screens within weeks. These findings provided the foundation for evaluating this technology as a potential ABC diagnostic tool and warrants further clinical development in ABC.

References

[1] Ding, Shengli et al. "Patient-derived micro-organospheres enable clinical precision oncology." Cell stem cell vol. 29,6 (2022): 905-917.