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Micro-OrganoSpheres™ as a Novel Precision Oncology Platform in Colorectal Cancer

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Abstract

Background: Patient-derived organoids (PDO) have been shown to have a high degree of similarity to the original patient tumors. PDO have also been used to perform high throughput drug screens and shown to correlate with patient response to therapy. Unfortunately, PDO require too much tissue and are too inefficient and costly for adoption into the clinic. The ideal assay would be one that could be performed <14 days from a core biopsy to minimize delay in therapy. We have now circumvented these barriers by leveraging recent technological advances in emulsion microfluidics and droplet generators to develop Micro-OrganoSpheres™ (MOS) that can be established and used to predict drug sensitivity within 14 days of biopsy.

Experimental Design: 18-gauge core biopsy specimen from patients with metastatic colorectal cancer who subsequently received an oxaliplatin based therapy were first obtained. Biopsy specimen was minced, enzymatically digested and mixed with basement membrane matrix. The mixture was then processed through a custom fabricated, flow-focusing droplet microfluidic chip to generate MOS. After culturing for 8-10 days, MOS were used to perform drug screen with oxaliplatin.

Results: A total of 12 CRC samples were processed with a success rate of 12/12 (100%) in generating MOS. Furthermore, drug screen was performed on all 12 samples with an average time to drug screen of 10.1 days. For the first eight patients, MOS was used to predict sensitivity to oxaliplatin. 4 patients were predicted to be sensitive to oxaliplatin and 4 patients were predicted to be resistant. 3 of the four patients predicted to be sensitive to oxaliplatin continue to be on treatment (> 6 months), whereas 3 of the four patients predicted to be resistant to oxaliplatin progressed on oxaliplatin based therapy within 8 weeks (sensitivity = 75%, specificity = 75%, positive predictive value = 75%, negative predictive value = 75%).

Hypothesis

We hypothesize that Micro-OrganoSpheres™ (MOS) are a novel platform that can be used as a potential therapeutic diagnostic assay to guide treatment for patients with metastatic colorectal cancer.

Methods

Figure 1. Micro-OrganoSphere™ Drug Screen to Lead Care (MODEL)
The MODEL clinical trial for colorectal cancer was established as a proof-of-concept trial to show that Micro-OrganoSpheres™(MOS) can be used to guide treatment. In this trial, patient tumor biopsies are used to generate MOS and perform a drug screen in < 14days. Primary objectives are to 1. Establish MOS from biopsies (>90% success) and 2. Perform a drug screen (<14 days). Secondary Objective is to correlate MOS drug response to patient clinical outcome.

Figure 2. Micro-OrganoSpheres™ from Patient Biopsy Samples are Established < 14d
Patient biopsy samples are processed through the Xilis Micro-OrgnaoSpheres™ Chip which generates droplet Micro-OrganoSpheres™ that are <300 micro in size and allows for rapid establishment and growth.

Results

Table 1. Patient Demographics of MODEL CRC Trial

	CRC-MOS-001	CRC-MOS-002	CRC-MOS-003	CRC-MOS-004	CRC-MOS-005	CRC-MOS-006	CRC-MOS-007	CRC-MOS-008
Gender	Female	Male	Male	Female	Male	Female	Male	Male
Histology	Adenocarcinoma	Adencoarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Grade	moderately differentiated	moderately differentiated	moderately differentiated	moderately differentiated	moderately differentiated	poorly differentiated		moderately differentiated
Primary Site	Rectal	Colon	Colon	Colon	Colon	Rectal	Colon	Colon
Metastatic Site	Lung	Liver	Liver	Liver	Liver	Pelvis	Liver	Liver
Microsatellite Status	MSS	MSS	MSS	MSS	MSS	MSS	MSS	MSS
KRAS	N/A	G12V	G12V	WT	G12D	G12D	G12D	WT
BRAF	N/A	WT	WT	WT	WT	WT	WT	WT

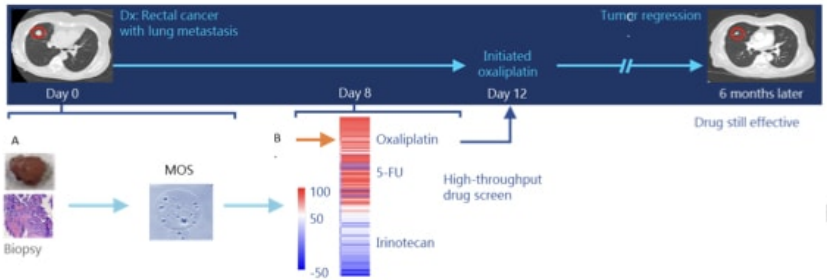

Figure 3. Patient 1 (CRC-MOS-001) had a biopsy of her tumor performed and MOS generated in 7 days (A). High throughput drug screen performed on Day 8 revealed MOS to be sensitive to oxaliplatin, 5-FU and resistant to irinotecan (B). Patient initiated on oxaliplatin based therapy on Day 12 and 6 months later, continued to have response to treatment (C).

Table 2. Drug Screen Results and Patient Outcome

Patient ID	Time to Drug Screen	MOS Prediction	Clinical Outcome	Time on Treatment
CRC-MOS-001	8 days	Sensitive	Response	46 weeks
CRC-MOS-002	9 days	Resistance	Response	28 weeks
CRC-MOS-003	12 days	Sensitive	Response	38 weeks
CRC-MOS-004	8 days	Resistance	No Response	8 weeks
CRC-MOS-005	8 days	Sensitive	Response	36 weeks
CRC-MOS-006	10 days	Resistance	No Response	3 weks
CRC-MOS-007	11 days	Sensitive	No Response	24 weeks
CRC-MOS-008	13 days	Resistance	No Response	6 weeks

A.

1 μM oxaliplatin	Response	No response	Total
Sensitive >50% killing	3	1	4
Resistant <50% killing	1	3	4
Total	4	4	8

B.

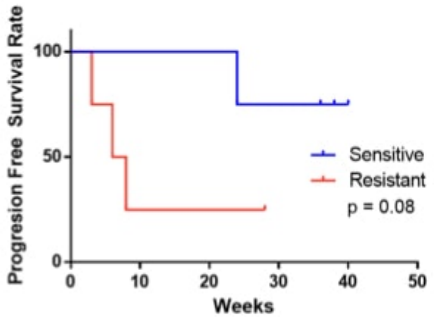

Figure 4. Results from MODEL CRC Trial (n=8)
A. Sensitivity = 75% Specificity = 75%, Positive Predictive Value (PPV) = 75% and Negative Predictive Value (NPV) = 75%
B. Progression Free Survival Curve demonstrates increase time on treatment for patient's whose MOS is sensitive to oxaliplatin (p=0.08)

Conclusions

We conclude that MOS can be generated from patient core biopsies and correlates to time on treatment. The ability to generate MOS and perform a drug screen in <14 days will allow for the development of a precision oncology platform that can be rapidly used in the clinic to guide therapy.

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