Refractory colorectal cancer patient derived MicroOrganoSpheres (MOS)™ enables correlation of targeted therapy combination response with clinical outcomes

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Background

Metastatic colorectal cancer (CRC) patients who have become resistant to standard-of-care (SOC) treatments are often put on targeted therapies, including experimental drugs still in clinical trials. However, patients with targeted mutations still often do not respond to the targeted therapies alone, hence it remains a critically unmet need to explore potential combinatorial regimens that will enhance the efficacy.

Methods

We performed a high-throughput screen using MicroOrganoSpheres (MOS)™ derived from metastatic refractory patients to correlate with clinical outcomes and explore alternative combinations that might benefit the patients. Biopsies from metastatic CRC patients who became resistant to SOC and were about to receive targeted therapies in clinical trials were molecularly profiled and implanted into immunodeficient mice to generate patient-derived xenografts (PDX). MOS generated from PDX were treated with drug combination titrations based on physiologically relevant concentrations. Live/dead staining was performed on day5 post drug dosing and quantified via high-content imaging and a custom image analysis pipeline. Relative viability per drug concentration was calculated in triplicate as percent live (live / all fluorescence signal) and normalized to an empty control.

Results

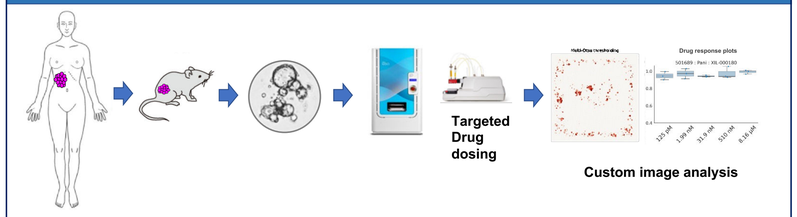


Figure 1. Scheme of targeted drug screen platform using MOS technology.

Table 1. Refractory CRC patient with experimental drugs in clinic

PDX ID	Mutation	Tissue source	Post treatment information	Response	RECIST %
B8239	KRAS G12C	Liver	AMG510 with Trametinib	Stable Disease	3%
B8292	BRAF V600E	Liver	Encorafenib + Cetuximab + Nivolumab	Progression	36%
B8293	BRAF V600E	Liver	Encorafenib + Cetuximab + Nivolumab	Progression	11.2%
B8281	WT	Liver	Panitumumab	Progression	
B8320	WT	Peritoneum	Panitumumab	Progression	

Results

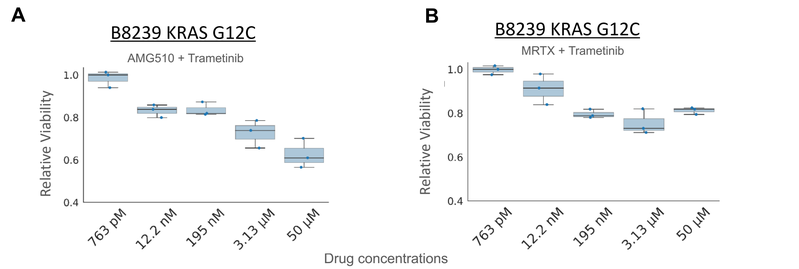


Figure 2. MOS derived from refractory CRC patient with KRAS G12C mutant response to experimental drugs (Amgen vs. Mirati). Response curve is plotted from MOS dosed with AMG510 or MRTX849 in combination with Trametinib **(A, B)** in 5-dose titrations. X-axis represents AMG510 titrations: 1/4096*Cmax, 1/256*Cmax, 1/16*Cmax, Cmax, 16*Cmax.

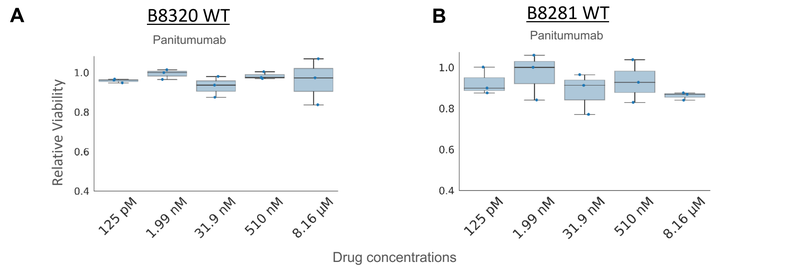


Figure 3. MOS drug response box plot graphs show correlation with clinical outcomes from refractory patients with no mutations. Response curve is plotted from MOS dosed with Panitumumab **(A, B)** in 5-dose titrations. X-axis represents Panitumumab titrations: 1/4096*Cmax, 1/256*Cmax, 1/16*Cmax, Cmax, 16*Cmax.

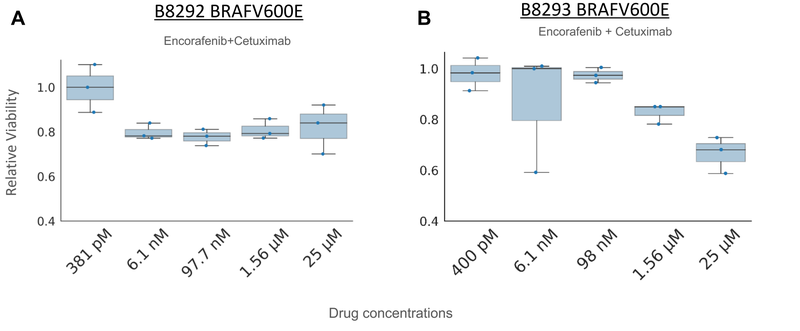
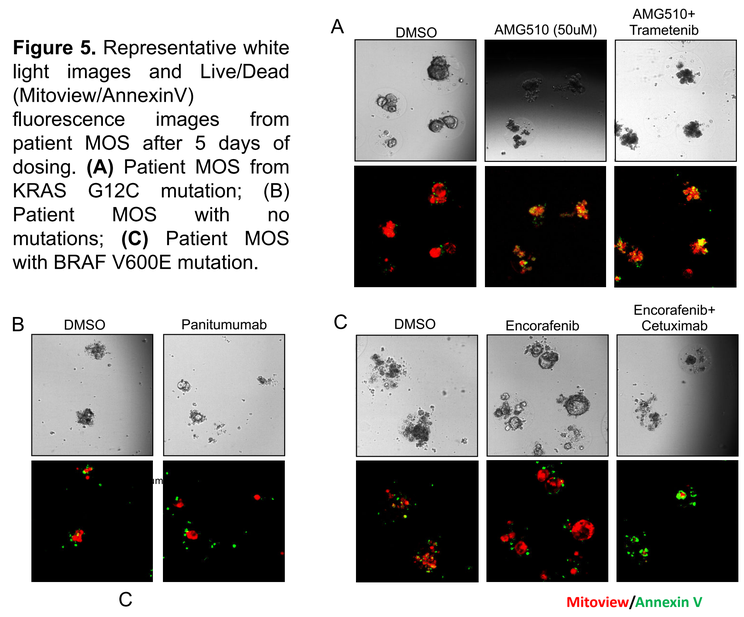


Figure 4. MOS drug response box plot graphs show correlation with clinical outcomes from refractory patients with BRAF 600E mutations. Response curve is plotted from MOS dosed with Encorafenib with Cetuximab **(A, B)** in 5-dose titrations. X-axis represents Encorafenib titrations: 1/4096*Cmax, 1/256*Cmax, 1/16*Cmax, Cmax, 16*Cmax.

Results

Figure 5. Representative white light images and Live/Dead (Mitoview/AnnexinV) fluorescence images from patient MOS after 5 days of dosing. **(A)** Patient MOS from KRAS G12C mutation; (B) Patient MOS with no mutations; **(C)** Patient MOS with BRAF V600E mutation.



Conclusion

Refractory patients may benefit from a MOS™-based high-throughput screen assay to select the optimal combination regimen containing targeted therapy.

Future Directions

- SOC or targeted drug screen response in MOS from CRC patient correlates with clinical outcome.
- Use MOS drug response platform to predict patient outcome.

References

1. Kanikarla Marie P, Sorokin AV, Kopetz S. Autologous humanized mouse models to study combination and single-agent immunotherapy for colorectal cancer patient-derived xenografts. *Front Oncol* (2022) doi: 10.3389/fonc.2022.994333.
2. Ding S, Clevers H, Hsu D, Shen X. Patient-derived micro-organospheres enable clinical precision oncology. *Cell Stem Cell* (2022) 29(6):905-917. doi: 10.1016/j.stem.2022.04.006.