Patient-derived MicroOrganoSpheres (MOS)™ enable precision clinical decision-making for multiple myeloma patients

Rui Xi, Xiaobei Wang, Renuka Raman, Nicholas Baro, Shaima Jaibbar, Shaun Steele, *Shengli Ding*, Yubing Kang, Xiling Shen

Background

There are many equipoised multiple myeloma (MM) treatments and nearly all relapse patients undergo cycles of treatment, response, and relapse management. Selecting the right agents and right drug combination is thus of critical importance and an area of unmet need. We currently lack patient-derived MM models that can enable functional precision medicine to help real-time clinical decision-making to guide individual patient treatment.

Methods

We have created a method to grow MM patient avatars in MicroOrganoSheres (MOS)™, microscale droplet ECM that sustain the original tumor microenvironment (TME) including both stromal and immune compartments. MOS™ enable reliable testing of available drug combinations and experimental drugs within 10 days of bone marrow (BM) biopsy, making it feasible to guide treatment decisions in the clinic. In the current study, BMB-derived MM MOS were generated via droplet microfluidics and cultured *in vitro*, followed by live MOS staining and flow cytometry. Drug screen was performed on MOS with FDA-approved single agents and combinations.

Results

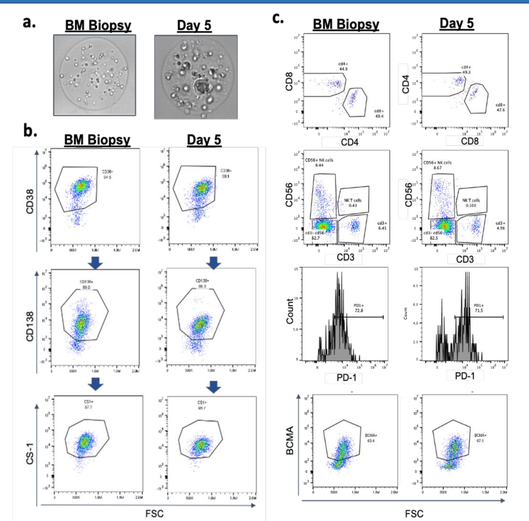

Figure 1. Patient-derived MM MOS from bone marrow (BM) aspirate retains MM markers and immune cells from TME. **(a)** Representative BF images of MM MOS. **(b)** MOS preserves MM tumor markers. **(c)** MOS preserves key immune cell populations.

Results

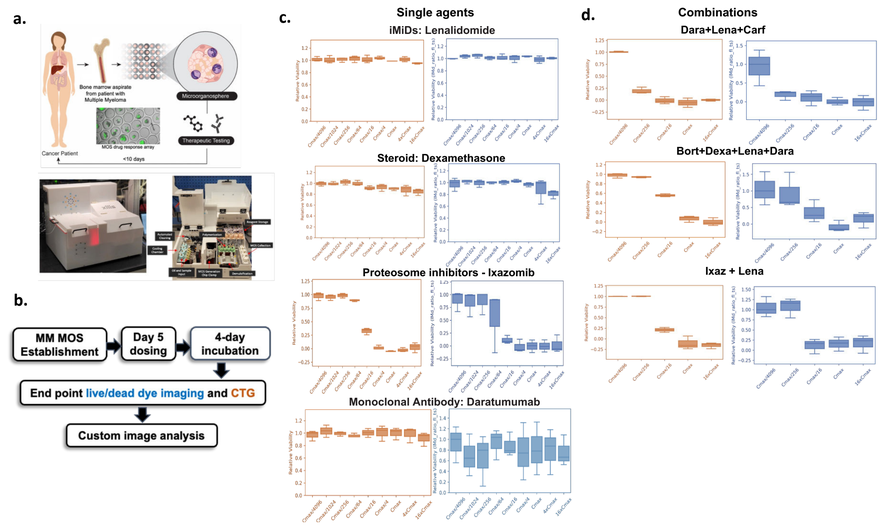

Figure 2. High throughput drug screen on MOS derived from MM biopsy sample. **(a)** Xilis MOS technology. **(b)** High throughput drug screen workflow. **(c)** Response to single agent dosing (CTG vs. live/dead imaging assay). **(d)** Response to combinations regimen.

a.

ID	Treatment in the clinic	C_{max} %Killing	MOS prediction	Patient clinical outcome following treatment
01	Lenalidomide	1.7%	Resistant	Resistant to multiple rounds of treatment
01	Pomalidomide	23.4%	Partially responsive	Short-term and partial response to Pomalidomide treatment.
01	DCEP	96.5%	Responsive	Responsive to DCEP as measured by reduction in M Protein from 1.74g/dl -> 0.91g/dl (d17); Kappa light chain: 121.5mg/dl -to 16.99mg/dl (d17))
02	Lenalidomide and Ixazomib	100%	Responsive	Patient has stable disease
03	Dara-Velcade-Dex	97.8%	Responsive	Responsive to Dara-Velcade-Dex and M protein reduced from 1.32g/dl to 0.5g/dl; Kappa light chain level reduced from 2.97 to 1.15 mg/dl
04	DCEP	40.5%	Partially responsive	Decreased size of heterogeneously hypoenhancing soft tissue inferior to the right renal pole measuring 6.6 x 3.6 cm previously measuring 8 x 5.2 cm (3/104)*

b.

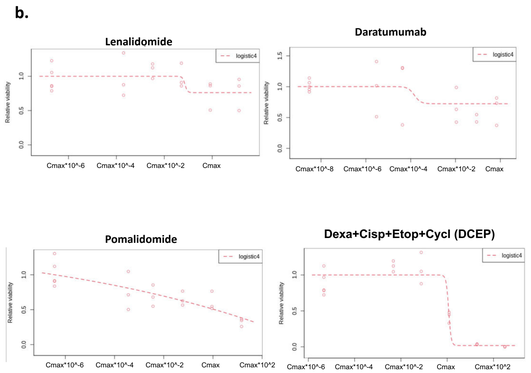

Figure 3. Multiple myeloma patient-derived MOS response was consistent with clinical outcome. **(a)** Table depicting MOS readouts correlations with clinical outcomes. **(b)** Representative drug response curve from CTG data.

Results

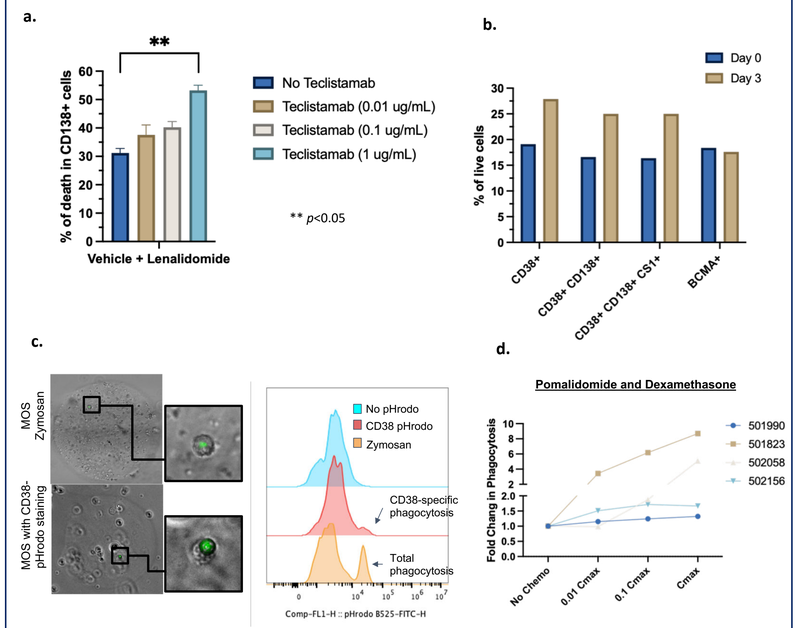

Figure 4. Advance MM MOS assay for novel first-in-class immunotherapies. **(a)** MM MOS responds to CD3/BCMA BsAb and Lena combo treatment **(a)** The same patient sample showed decent BCMA expression in MOS. **(c)** Antibody based pHrodo phagocytosis assay established in MM MOS. **(d)** Pomalidomide and Dexamethasome combo regimen induces phagocytosis in patient MM MOS.

Conclusion and future directions

MOS technology could enable clinical decision in multiple myeloma patient treatment. A clinical trial including 40 patients is starting in a month to further validate the predictability of the MM MOS assay for therapeutic decision-making in the clinic.

References

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.