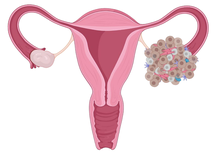
Engineering a physiologically relevant *ex vivo* 3D ovarian cancer culture (OC) model for precision-based drug screening



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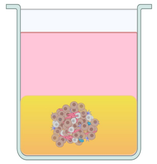

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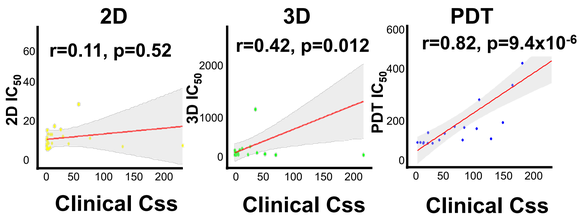
Introduction

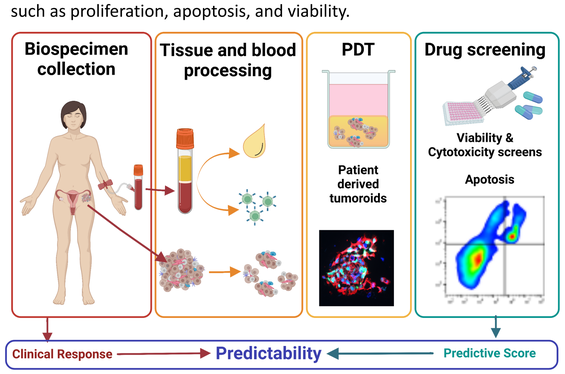
Ovarian cancer (OC) is one of the deadliest forms of cancer in women and is known as the "silent killer" due to a lack of symptoms and resistance to treatment that causes recurrence in 80% of patients within 5 years. Both *in vivo* and *in vitro* studies have demonstrated how various interactions affect tumor progression and therapy response. However, high cost and species-dependent differences make it challenging to isolate these mechanistic links. Tumoroids ("tumor-like-organoids") have been shown to retain both histological and genetic features of original tumors and are feasible for *in vitro* drug sensitivity assays, recapitulating clinical responses of the matched patients, but often lack physiologically relevant physical characteristics.

The overall objective of this investigation is to provide a translationally relevant 100% patient-derived ex vivo 3D culture platform with controlled physiologically relevant physical properties to perform clinically relevant analysis of OC treatment responses



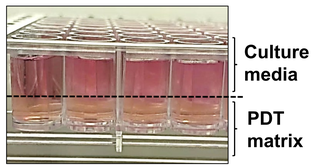
Methods

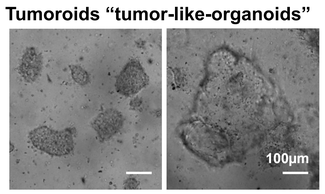
A biological model was developed through the crosslinking of patient-derived plasma fibrinogen to fibrin to better recapitulate the framework of *in vitro* tumors. This model contains patient-derived tumoroids within the 100% human patient-derived plasma 3D matrix which incorporates factors such as tumor cells and the tumor microenvironment as well as chemoresistance mechanisms under physiologically relevant oxygen levels. Minced biopsy tissue was enzymatically dissociated and embedded into the 3D matrix where the patient-specific tumoroids were grown and exposed to known standard-of-care treatments. Primary biospecimens were categorized as sensitive and resistant by Response Evaluation Criteria in Solid Tumors or RECIST score, and precision-based drug screens were performed in order to establish a predictive score that would be able to distinguish sensitive from resistant patients using several read-outs such as proliferation, apoptosis, and viability.

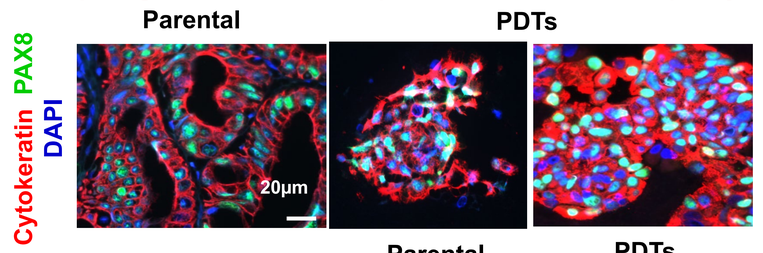


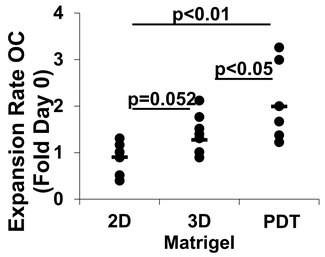
Results

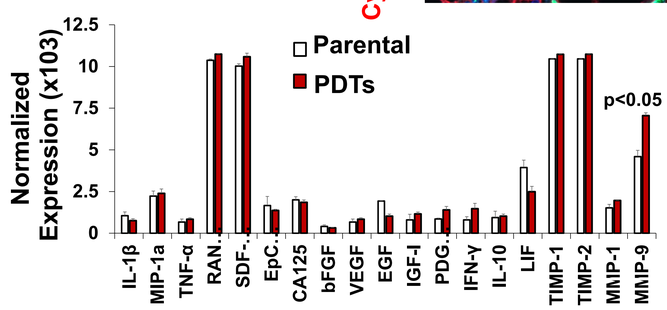
Figure 1: PDTs support primary OC growth better than traditional 2D and Matrigel cultures as well as preserve the biochemical signals involved in key cancer hallmarks, as well as successfully recreate morphological features and recapitulated the structural complexity of parental OC tumors

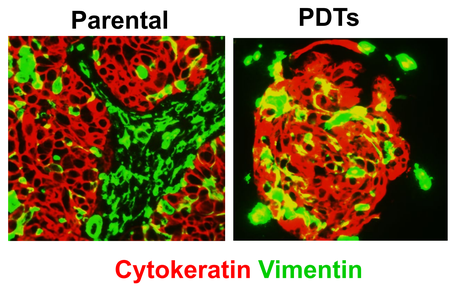


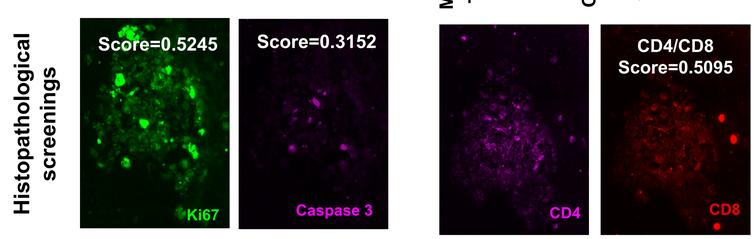












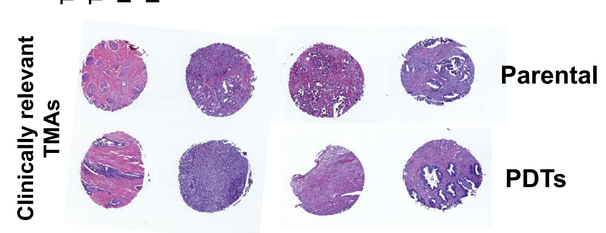
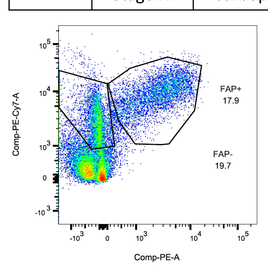
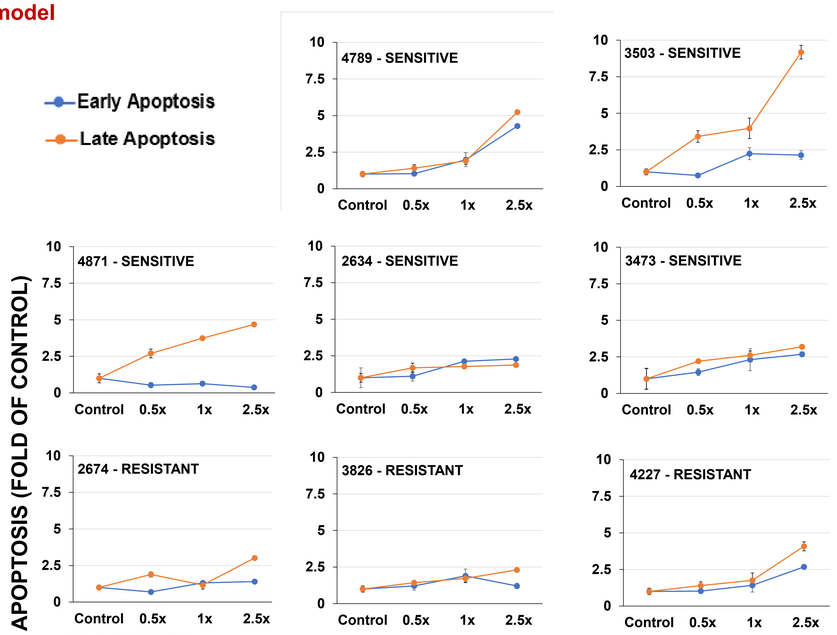


Figure 2: Diagnosis, treatment history, RECIST score, and response group were provided for each biospecimen and chemotherapeutic responses were retrospectively confirmed in the PDT model

Clinical Information of Biospecimens				
ID	**Diagnosis**	**Treatment History**	**RECIST**	**Group**
2674	Stage IIIB	Carboplatin/Taxol	PD	**Resistant**
3826	Stage IV	Carboplatin/Taxol	PD	**Resistant**
4227	Stage IV	Carboplatin/Taxol	PD	**Resistant**
4789	Stage IIIC	Carboplatin/Taxol	SD	**Sensitive**
3503	Stage IIIC	Carboplatin/Taxol	CR	**Sensitive**
4871	Stage IIA	Carboplatin/Taxol	CR	**Sensitive**
2634	Recurrent	Carboplatin/Taxol	PR	**Sensitive**
3473	Stage IV	Carboplatin/Taxol	CR	**Sensitive**





Conclusions

- We confirmed the recapitulation of key parameters of OC including biochemical, structural complexity and morphological features as well as verified growth of OC biopsy tumoroids within our 3D model confirming it as a **well-suited platform to study chemotherapeutic response of OC patients in a biologically relevant matter**.
- These retrospective patient studies are providing us with a training cohort of samples with known therapeutic responses to help us establish our baseline cutoff for categorization of patients as sensitive or resistant.
- Our results present a **reproducible and clinically translatable preclinical model assessing effective treatment options by predicting therapeutic efficacy** and avoiding treatment with drugs that the tumor will be resistant to. Moreover, our results are expected to have an **important positive impact** because they will provide a valuable tool in predicting each individual patients' response to therapy and permit a much more in-depth and clinically relevant analysis of OC treatment responses than is currently possible.

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