Organoids Standardized to a Clinically Validated Drug Response Assay for Truly Predictive In Vitro Drug Response Profiling

#3086

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Abstract

Unlike cell lines, organoids maintain most of the biological properties of the parental tissue from which the starting cells were isolated including the histology and gene expression. When organoids include clinical annotation and follow-up, they become a useful, renewable tool for clinical correlation studies, but to be truly predictive the drug profiling assays utilized to screen organoid response must have measurable correlation with patient response. 3D Predict™ is a highly accurate assay that is 89% and 85% predictive of response in first-line ovarian cancer and high-grade gliomas (HGG) respectively. We have developed a panel of organoids that are clinically annotated, include correlative primary tissue 3D Predict™ drug response data, and have been assessed for the recapitulation of primary tissue histology and genomics. Additionally, our organoid models incorporate matched immune cells, a key component of the tumor microenvironment, making them an ideal model for immune-oncology studies. Here we present data on 15 available organoid models across HGG, breast, colorectal and bladder cancer. We have applied these models to drug response studies, including checkpoint inhibitors and shown correlation to primary patient response. The assurance of predictive capacity and the inclusion of clinical annotation and follow-up is unique to KIYATEC's organoids and is significant because it avoids the pitfalls of comparing drug responses across non-concordant assay platforms while providing assurance that the models are reflective of individual patient response and outcomes.

Methods

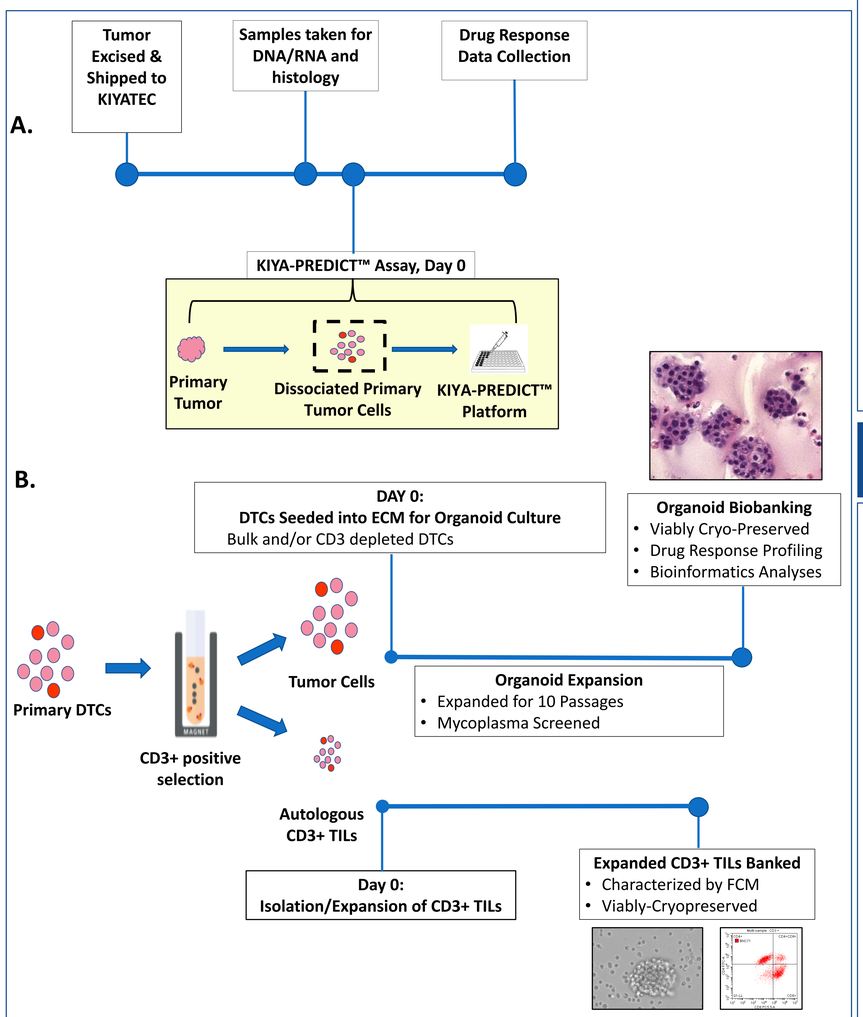
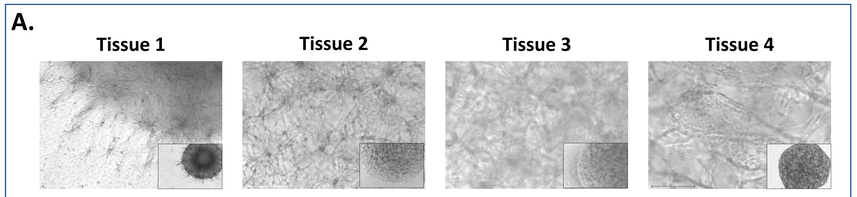


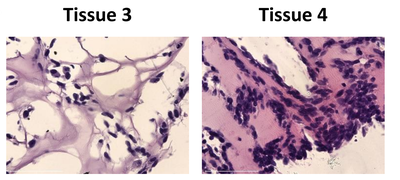
Figure 1. Workflow Schema of Organoid Establishment and Autologous T-cell Isolation and Expansion from Primary Tissue Samples. **(A)** Sample acquisition and processing for KIYA-PREDICT™ Drug Response Profiling Assay. **(B)** Tissue samples designated for organoid development, including the isolation and expansion of autologous CD3+ T-cells undergo a rigorous process of expansion and characterization.

High-Grade Glioma Organoids



B.

Sample ID	Tumor Type
Tissue 1	High-grade Glioma
Tissue 2	Glioblastoma
Tissue 3	High-grade Glioma
Tissue 4	High-grade Glioma



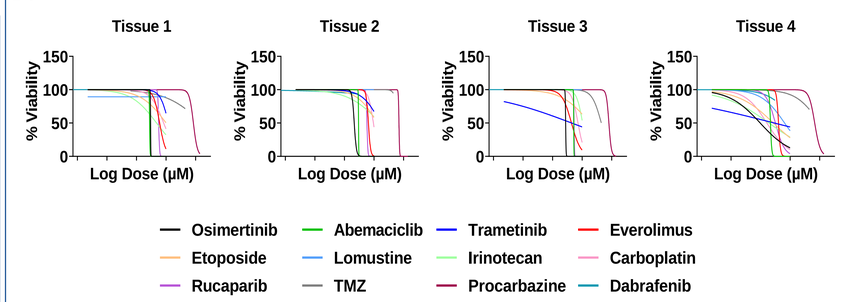
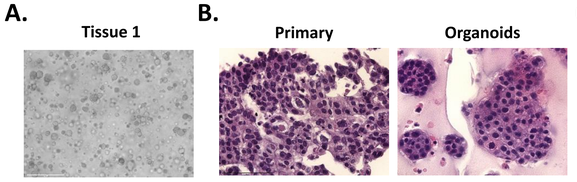


Figure 2. High-grade Glioma Organoids (HGG) (A) Representative Bright-field images of established HGG Organoids, 10x magnification. Inset: 4x Bright field images of organoid ECM domes. **(B)** Table of tumor organoid subtypes. **(C)** Hematoxylin and eosin (H&E) stained organoids, 40x magnification**. (D)** HGG organoid drug response profiling using KIYAYEC's HGG KIYA-PREDICT™ assay platform.

Bladder Tumor Organoids



C.

Sample ID	Tumor Type
Tissue 1	Urothelial carcinoma
Tissue 2	Urothelial carcinoma
Tissue 3	Transitional Cell Carcinoma (Papillary)
Tissue 4	Transitional Cell Carcinoma (Papillary)
Tissue 5	Urothelial carcinoma
Tissue 6	Urothelial carcinoma
Tissue 7	Urothelial carcinoma
Tissue 8	Papillary-urothelial carcinoma low grade
Tissue 9	Invasive papillary-urothelial carcinoma, high grade

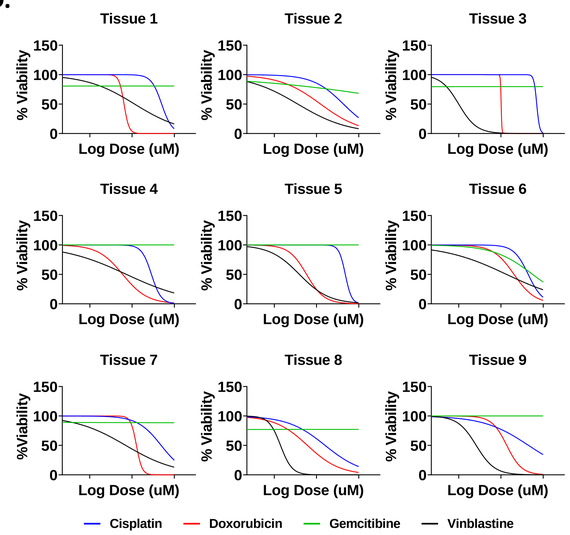
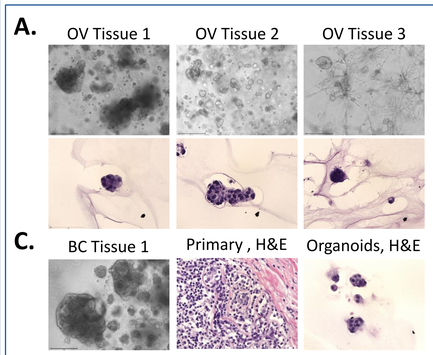


Figure 3. Bladder Tumor Organoids (A) Representative Bright-field image of established bladder tumor organoids derived from Tissue 1, 10x magnification. **(B)** On the left, H&E-stained tissue section of primary bladder tumor, Tissue 1 and (right) corresponding H&E-stained organoids. **(C)** Table of established bladder tumor organoid samples . (D) Bladder tumor organoid drug response curves profiled using KIYATEC's KIYA-PREDICT EV3D platform.

Breast / Ovarian / CRC Tumor Organoids



B.

Sample ID	Tumor Type
OV Tissue 1	High-grade Serous Carcinoma
OV Tissue 2	High-grade Serous Carcinoma
OV Tissue 3	High-grade Serous Carcinoma

D.

Sample ID	Tumor Type
BC Tissue 1	TNBC
BC Tissue 2	HER2+
BC Tissue 3	HER2+

F.

Sample ID	Tumor Type
CRC Tissue 1	Adenocarcinoma
CRC Tissue 2	Adenocarcinoma

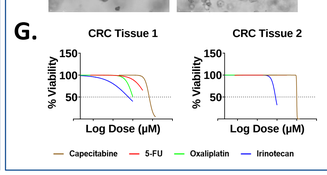
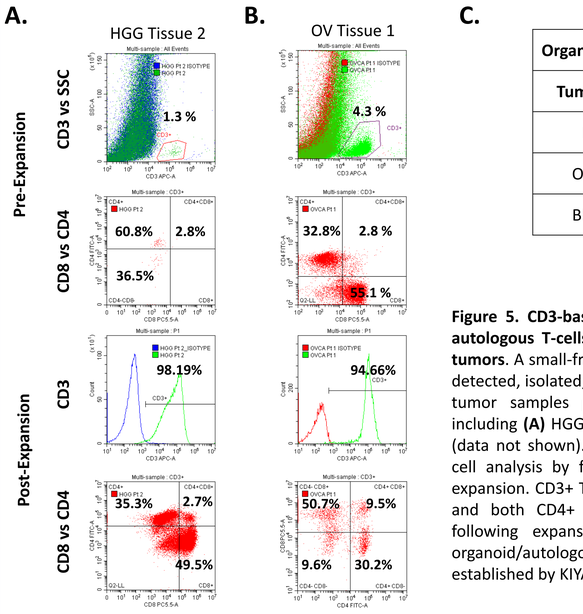


Figure 4. Additional organoids representing breast (BC), ovarian (OV) and colorectal (CRC) cancers. (A) Representative bright-field images of ovarian cancer organoids, 10x Magnification. **(B)** Table listing ovarian cancer subtypes of organoids. **(C)** Breast cancer Tissue 1 Representative images Left- Brightfield image of established organoids, 10x magnification. Middle- H&E stained tissue section of primary tumor, 40x magnification. Right- H&E-stained section of corresponding established organoid. **(D)** Table listing breast organoid subtypes. **(E)** Representative brightfield images of CRC organoids, 10x magnification. **(F)** Table of CRC organoid subtypes. **(G)** CRC organoid drug response curves.

Matched Organoid-Immune Cell Models



C.

Organoid & Autologous T-cell Sets	
Tumor Type	**# of Models**
HGG	5
Ovarian	3
Bladder	2

Figure 5. CD3-based selection and expansion of autologous T-cells from bulk dissociated, primary tumors. A small-fraction of CD3+ immune cells were detected, isolated, and expanded from bulk primary tumor samples prior to organoid development including **(A)** HGG, **(B)** Ovarian, and Bladder tissues (data not shown). Characterization has included T-cell analysis by flow cytometry before and after expansion. CD3+ T-cells are preferentially expanded and both CD4+ and CD8+ T-cells are detected following expansion. **(C)** Table listing available organoid/autologous T-cell models currently established by KIYATEC.