A Rapid Digital Patient-Derived Organoid Guiding Therapy After Antibody Drug Conjugates (ADC)s In Patients with Metastatic Breast Cancer

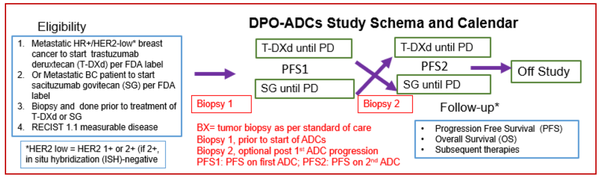
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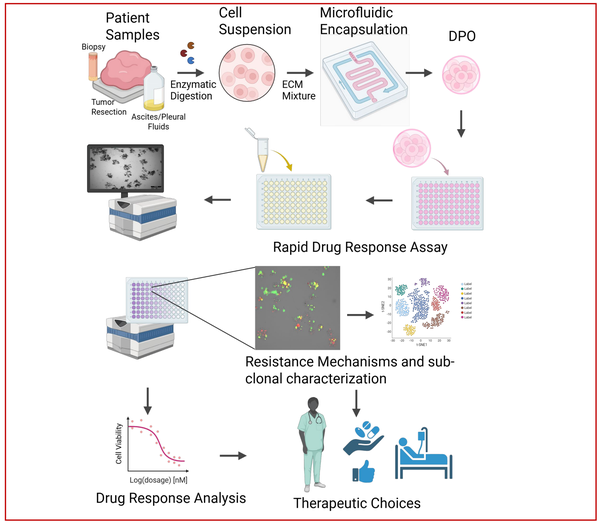
Background

- Metastatic breast cancer (MBC) remain incurable and multiple drug antibody conjugates (ADCs) such as trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) have shown promising efficacy.
- However, optimal sequencing of ADCs treatment strategies for individual patients is lacking with rising evidence of ADC cross resistance.
- With the fast-paced clinical development of multiple ADCs in the MBC space, there is a critical unmet need to guide subsequent therapy following initial ADC resistance.
- The current study aims to develop a clinical diagnostic assay using digital patient organoid (DPOs) to guide personalized treatment selection for patients with MBC undergoing ADCs therapy and to elucidate the mechanism of ADC resistance.

Study Schema



DPO Drug Assay Workflow



Results

Overall	Breast Cancer Subtype		
59%	HER2+	HR+	TNBC
	38%	67%	63%
Sites of Metastasis			
Ascites	Breast Surgery	Liver Metastasis	Pleural Fluid	Dermal met
75%	88%	20%	86%	42%

Table1. Drug Response Assay Success Rate in DPOs by BC Subtype and Site of Metastasis. Between 09/2024–11/2025, 56 fresh patient tissues were collected, of which 23 passed QC for DPO establishment and 16 failed, yielding a 59% success rate; in the past six months, this rate has improved to >70%.

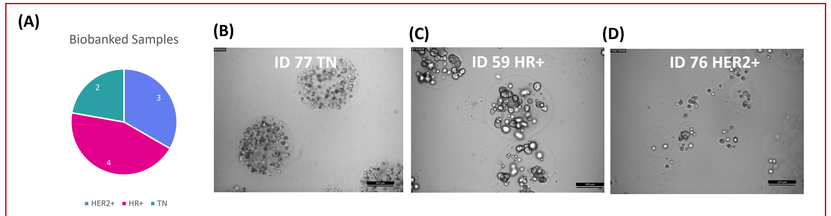


Fig 1. Breakdown of Biobanked DPOs and Representative Images
(A) Percentage breakdown of biobanked patient samples and their corresponding subtypes, spanning multiple tissue sources and treatment histories. (B-D) Representative images of DPOs in culture.

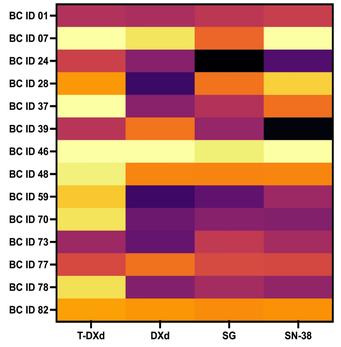


Table 2. ADC vs Payload Resistance	T-DXd	SG
Resistant to ADC only	29%	10%
Resistant to payload only	0%	5%
Resistant to both	12%	25%
Intermediate response to ADC only	21%	15%
Intermediate response to payload only	17%	10%
Intermediate response to both	0%	15%
Sensitive to ADC only	0%	5%
Sensitive to payload only	21%	10%
Sensitive to both	0%	5%

Fig 2. ADC (T-DXd & SG) and payload (DXd & SN-38) response diversity across breast cancer DPOs.
This figure highlights the heterogeneity of ADC and payload responses. **Table 2** illustrates overall resistance patterns, forming the foundation of a developing ADC-resistance biobank. The heatmap summarizes the area-under-curve (AUC) values for each tumor's response to T-DXd, SG, and their payloads DXd and SN-38. While most ADC resistance tracked with payload resistance, several tumors—PT 37, 70, 78, 28, and 59 --- remained DXd-sensitive yet T-DXd–resistant, likely due to low HER2 expression limiting ADC uptake.

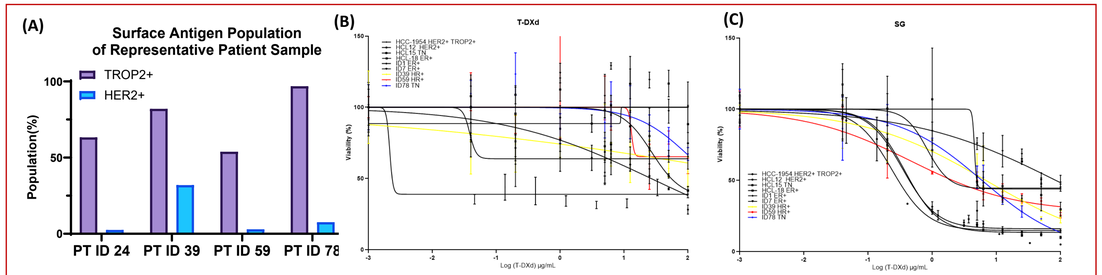


Fig 3. Differential ADC responses aligned with surface antigen profiles.
Drug response corresponded closely with surface antigen levels. PT 39, the only sample with moderate HER2+ (31.9%), showed moderate T-DXd sensitivity, consistent with the patient's stable disease with ongoing treatment, whereas PT 24, 59, and 78 were all resistant to T-DXd. All four tumors expressed TROP2 >50% and demonstrated moderate SG responses. Collectively, these findings indicate that ADC resistance can arise through antigen loss or reduction. Cells not responding to the treatment remains in both cases, highlighting potential sub-clonal heterogeneity.

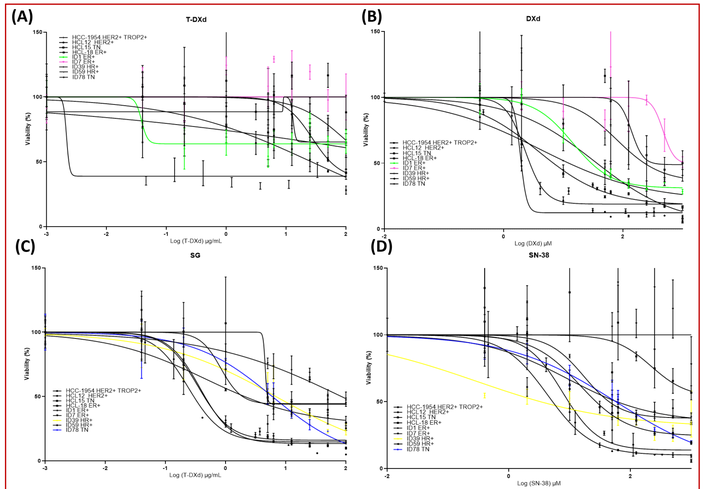


Fig 4. Patients who received ADC develop resistance via various paths.
Among T-DXd–treated cases, ID1 (10.81 months) remained DXd-sensitive but showed poorer ADC response, while ID7 (1.39 months) demonstrated high resistance to both DXd and T-DXd. For SG-treated patients, ID78 (25.65 months) responded to SG/SN-38 but retained a resistant subpopulation, and ID39 (11 months) remained payload-sensitive especially at lower dosages yet showed reduced SG response.

Conclusions and Future Directions

- Our DPO models rapidly capture patient-specific drug responses and reveal clinically relevant ADC resistance mechanisms. This approach enables potential rational selection of ADCs and chemotherapies.
- Overall, payload sensitivity emerged as a major determinant of response, with surface antigen levels and treatment history also shaping ADC effectiveness.
- These findings support incorporating patient-derived organoids into clinical decision-making to better guide therapy after ADC resistance.
- For future direction, we plan to use single-cell RNA sequencing to characterize transcriptional changes and sub-clonal heterogeneity associated with resistance.

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