Advancing personalized treatment of patients with metastatic breast cancer by functional drug screening and IMC profiling

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Background

Worldwide, nearly 2.6 million women are diagnosed annually with breast cancer and 685 000 lives are lost to the disease, the vast majority due to drug-resistant metastases. Although new therapies significantly increased cure rates for early-stage breast cancer, the situation for metastatic disease has hardly changed. Cutting-edge technologies may help characterize the cancer better and tailor therapy decision. Testing drugs on ex-vivo avatar models of patients' tumors (i.e., personalized treatment) coupled with their in-depth characterization raises the hope of identifying more efficacious treatments. This should also spare the patients the side effects of ineffective treatments.

Methodes

We have initiated the nation-wide Swiss Personalized Oncology National Data Stream (SPO-NDS) study that uses a variety of OMICs to inform clinical decision making for patients with advanced breast cancer. We have been using high-resolution image-based functional drug screening on patient-derived organoids (PDO). We pre-emptively tested drug's efficacy, alone or in combination, on tissue biopsies taken upon disease progression on standard-of-care treatment (any line). Freshly isolated tumour cells were grown in 3D-culture, which retain the patient's molecular and cellular characteristics. (Fig 1-4) This has been combined with high-resolution imaging mass cytometry (IMC) which enables the analysis of dozens of markers at single-cell resolution while preserving spatial tumor architecture, and informing about tumor content, immune cell infiltration, presence of a specific target, or activation of specific pathways. The results of our studies were integrated into a molecular summary report, discussed at a swisswide interdisciplinary molecular tumour board, yielding patient-specific cancer vulnerabilities and informing highly-personalized treatment recommendations. The future development of these technologies as a routine tool in the clinics could be of paramount importance to provide tailored therapies to the unique genomic, molecular, and clinical characteristics of each patient's disease.

Figures 1-4

Figure 1: SPO workflow : from the clinics to the lab, and back to the clinics

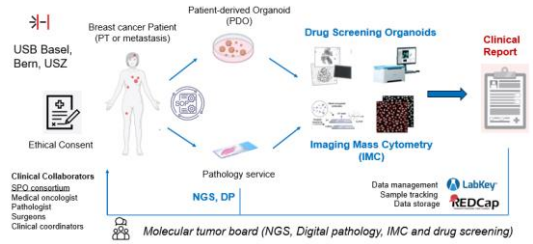


Figure 1: Workflow for generating personalized therapeutic insights from breast cancer patient samples. Tumor tissue from primary or metastatic sites is collected with ethical consent and used to establish patient-derived organoids (PDOs). These PDOs undergo parallel drug screening and imaging mass cytometry (IMC), complemented by next-generation sequencing (NGS) and digital pathology. Data are integrated through pathology services and managed in LabKey/REDCap. Results are reviewed by the molecular tumor board to produce a clinical report.

Figure 2: Drug screening on 3D grown biopsy derived metastatic breast cancer cells

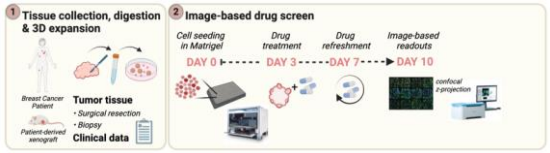


Figure 2: Schematic overview of the workflow for generating image-based drug-response profiles from breast cancer tissues.
(1) Tumor samples obtained from patients or patient-derived xenografts are collected, enzymatically digested, and expanded in 3D culture.
(2) Cells are embedded in Matrigel and seeded into multi-well plates (Day 0), followed by drug treatment (Day 3) and subsequent drug refreshment (Day 7). On Day 10, high-content confocal imaging and z-projected readouts are acquired to assess treatment responses.

Figure 3: AI-based live nuclei segmentation and count to infer drug efficacy

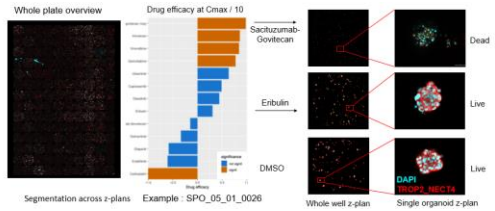


Figure 3 Image-based assessment of drug responses in patient-derived organoids. Left: Whole-plate overview showing segmentation across z-planes. Middle: Ranked drug efficacy profile at Cmax/10 for sample SPO_05_01_0026, with statistically significant responses highlighted. Right: Representative confocal z-projections from wells treated with Sacituzumab-Govitecan, Eribulin, or DMSO. Insets show single-organoid views stained for DAPI (nuclei) and TROP2/NECT4, illustrating treatment-induced cell death or survival.

Figure 4: Image-based drug screening: SPO #13

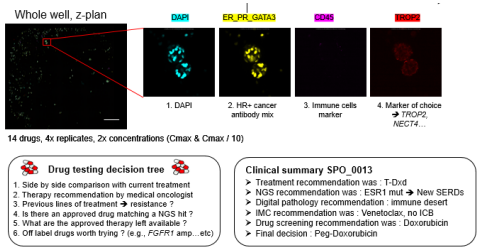


Figure 4: Multiplexed imaging and clinical decision integration for patient-derived organoids. A whole-well z-projection image shows organoid detection, with magnified views illustrating staining for DAPI (nuclei), an HR+ cancer antibody mix (ER/PR/GATA3), CD45 (immune cell marker), and a selectable marker of interest such as TROP2. Drug screening was performed using 14 drugs at two concentrations (Cmax and Cmax/10) in four replicates. A decision tree outlines how drug-screening results are integrated with clinical, NGS, digital pathology, and IMC findings. An example clinical summary (SPO_0013) demonstrates how multimodal data contribute to treatment recommendations.

Conclusions

This trial-in-progress supports the feasibility of using functional drug screening and multi-OMIC profiling to inform personalized treatment in advanced breast cancer. Early experience from the SPO-NDS framework demonstrates that integrating high-resolution phenotypic drug response data with comprehensive molecular and spatial profiling is technically achievable within clinically relevant timelines. Moreover, the convergence of PDO-based drug testing with IMC-derived single-cell and spatial insights has the potential to reveal patient-specific therapeutic vulnerabilities that are not apparent from genomic data alone. As the study expands, longitudinal follow-up and clinical correlation will be essential to determine the predictive value of these ex-vivo platforms and their ultimate impact on patient outcomes. If validated, this approach could pave the way toward a new paradigm in breast cancer management in which therapy selection is increasingly guided by individualized functional responses, thereby reducing exposure to ineffective treatments and improving the prospects for durable disease control in the metastatic setting.

Inclusion Criteria

Inclusion of patients with <u>advanced</u> breast cancer:

PLEURAL EFFUSION, BRAIN, LIVER, LYMPH NODE, soft tissues, BONE*** METS or PRIMARY RECURRENCE

(1) HR+/HER2 neg: progress on CDK4/6i + endocrine therapy
(2) HR+/HER2 low: progress on ADC (e.g. Trastuzumab deruxtecan)
(3) HER2+: progress on 2nd line or ADC (e.g. Trastuzumab deruxtecan)
(4) TNBC: progress on 2nd line
(5) Neoadjuvantly treated tumors with non (or insufficient) clinical response

Inclusion of patients with <u>early</u> breast cancer:

PRIMARY TUMOR

(1) TNBC: Neoadj. treated + immunotherapy with RCB 0-III → Before/after therapy tissue sample

Contact

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