Tumor-on-Chip as a Personalised Platform for Rapid Drug-Testing in Breast Cancer

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BACKGROUND

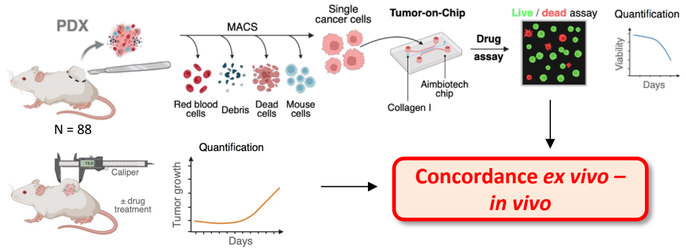
- **Chemotherapy remains the mainstay of treatment** in the later-line **metastatic setting of breast cancer** (BC) but response rates are highly variable (10 to 50%) and **no robust predictive biomarker** exists to **guide chemotherapy selection**
- Patient-derived xenografts (**PDXs**) and organoids (**PDOs**) have demonstrated strong **predictive value** for drug response in BC but **variable success rates of establishment** and **prolonged culture timelines** limit their clinical application
- Tumor-on-Chip (**ToCs**) are **miniaturized 3D platforms** which replicate ***ex vivo*** essential features of tumors but no BC ToC model has been clinically evaluated for its predictive accuracy

OBJECTIVES

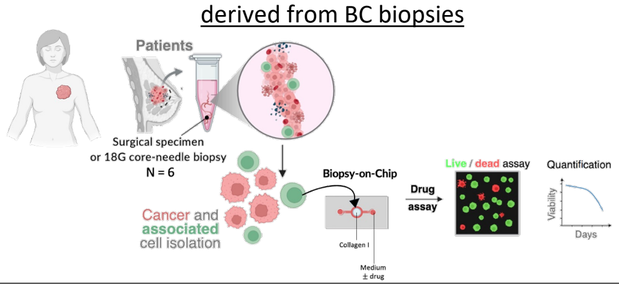
To develop **patient-specific ToC models of breast cancer** as ***ex vivo* platforms** enabling **drug sensitivity profiling** from minimal **biopsy** material and delivering results within a **clinically actionable timeframe,** with the long-term objective of **supporting real-time therapeutic decision-making**

METHODS

Part 1: Validation of *ex vivo* drug profiling on ToC versus matched PDX models *in vivo*

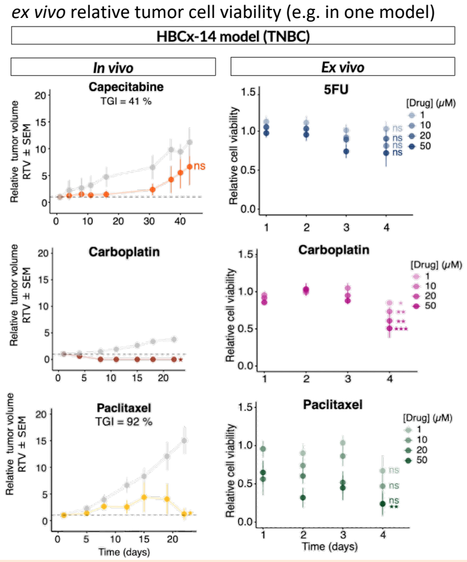


Part 2: Establishing patient-specific Tumor-on-Chip models derived from BC biopsies



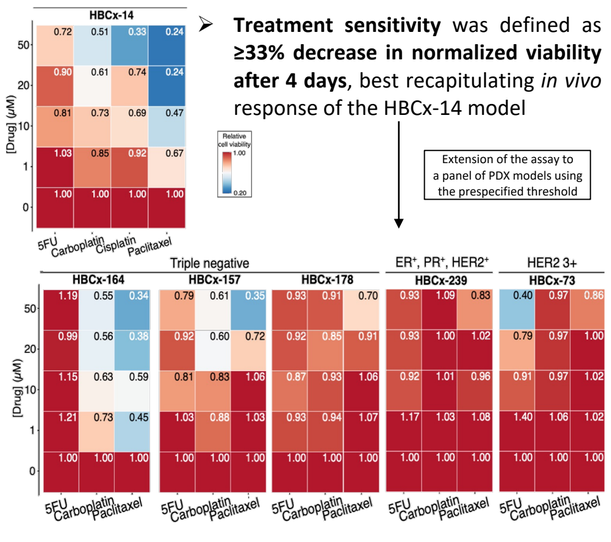
RESULTS (Part 1)

Figure 1. *In vivo* tumor growth kinetics and corresponding *ex vivo* relative tumor cell viability (e.g. in one model)



➢ **On-chip** assay yields drug-response profiles within **4 days** — a **5–10× reduction in assay time**

Figure 2. Heatmaps of relative tumor cell viability after 4 days of drug exposure in several PDX-derived ToC models of breast cancer.

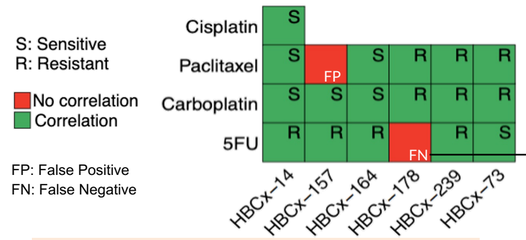


➢ **Treatment sensitivity** was defined as **≥33% decrease in normalized viability after 4 days**, best recapitulating *in vivo* response of the HBCx-14 model

Extension of the assay to a panel of PDX models using the prespecified threshold

➢ **Heterogenous drug-response profiles mirroring clinical history** of source patients

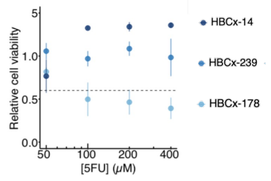
Figure 3. Concordance between tumor volume change *in vivo* (PDX) and cell viability change *ex vivo* (ToC, at 50 µM).



➢ **Strong *ex vivo* - *in vivo* concordance:**
- Sensitivity 88%
- Specificity 91%

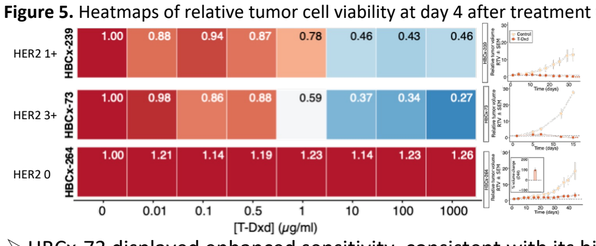
➢ **No false positive at clinically relevant concentrations**

Figure 4. Relative tumor cell viability of different PDX models when increasing 5-FU concentrations up to 400 μM (approaching Cmax observed in plasma patients).



➢ Misclassification of the HBCx-178 model as resistant to 5-FU was due to *ex vivo* underdosing; higher concentrations—within the range of *in vivo* exposure—confirmed drug sensitivity

Figure 5. Heatmaps of relative tumor cell viability at day 4 after treatment with trastuzumab-deruxtecan.



➢ HBCx-73 displayed enhanced sensitivity, consistent with its higher HER2 expression

➢ **ToC technology also enables the study of drug-response to antibody-drug conjugates (ADC)**

RESULTS (Part 2)

Figure 4.A Schematics of a novel PDMS custom chip with a design specifically engineered for biopsies (top) and the corresponding mold (bottom).

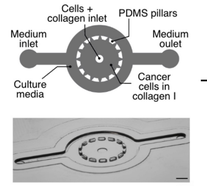
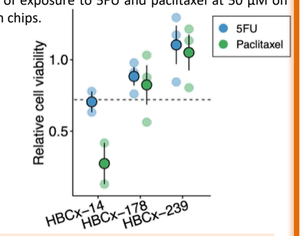


Figure 4.B Relative cell viability of simulated biopsies performed *ex vivo* upon arrival of PDX specimens after 4 days of exposure to 5FU and paclitaxel at 50 µM on custom chips.



➢ ToC models can be established from **minimal cell input**

➢ **Drug-response profiles are consistent** with those obtained from whole tumor dissociation

Figure 5.A Images of PDMS chips seeded with patients cells (top) and confocal staining (bottom) of patient sample #1.

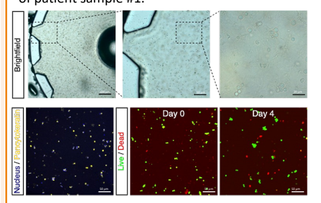
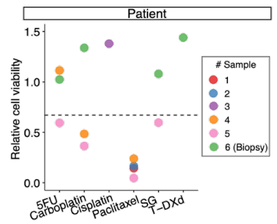


Figure 5.B Relative cell viability of **patient-specific** ToC models



➢ **ToC models can be successfully generated from human primary tumors of breast cancer including daily practice biopsy**

➢ **Heterogenous drug-response profiles are identified on-chip within 4 days**

CONCLUSIONS

***Ex vivo* drug profiling** of PDX-derived breast cancer on-Chip models revealed:

- a **high success rate of establishment (n=86 ToC established from 88 PDX tumors)**
- a **high reproducibility** of drug response patterns
- a **strong concordance** with *in vivo* responses
- a **rapid turnaround time of only 4 days**

Patient-specific ToC models of breast cancer:

- Can be **successfully established** from **routine core-needle biopsies**
- Using **both primary and metastatic human samples**
- And deliver **individualized *ex vivo* drug response profiles within 4 days**, a **clinically actionable timeframe**

→ Strong potential for ToC platforms in **real-time functional precision oncology**

→ Robust evaluation of their predictive accuracy in larger patient cohorts is now required

AKNOWLEDGEMENTS

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