A novel humanized multi-organoid disease model for early *in vitro* assessment and quantification of drug resistance

Raquel Sousa[1], Agne Vaitkeviciene[1], Marco P. Leu[1], Andreas R. Thomsen[1,2], Arne-C. Faisst[1]

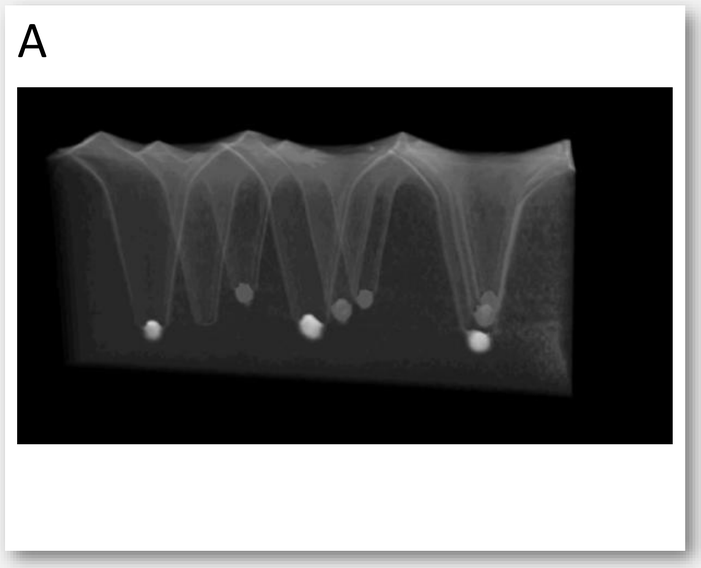
[1] abc biopply ag, Weissensteinstrasse 81, 4500 Solothurn ; [2] Department of Radiation Oncology, University Hospital of Freiburg, Germany

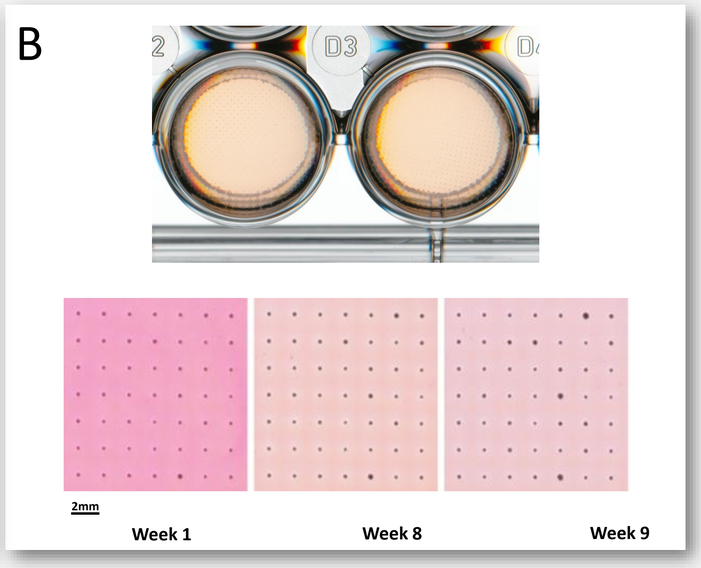
Introduction

Drug resistance remains one of the leading causes of treatment failure in oncology, with many therapies showing promising initial responses before disease progression driven by resistant cell populations. Detecting resistance mechanisms early during preclinical development is therefore critical for optimizing candidate selection, identifying effective combination therapies, reducing late-stage attrition, and ultimately improving patient outcomes.

Today, resistance is commonly investigated using 2D cell cultures, conventional organoid systems, and animal models. While 2D models offer high throughput, they fail to capture the complexity of human tumor biology. Conventional organoids provide greater physiological relevance but often suffer from variability, limited standardization, and insufficient representation of cellular interactions. Animal models add systemic complexity but frequently lack human-specific predictivity.

In this study we used the 3D CoSeedis Humanized In-Chip Technology™ to address these limitations by enabling highly standardized micro-tissues composed of hundreds of communicating organoids. This unique platform combines scalability, reproducibility, and human relevance, allowing long-term monitoring of treatment response, resistance emergence, relapse, and biomarker dynamics. By bridging the gap between simple in vitro assays and complex in vivo studies, 3D CoSeedis™ provides a powerful fit-for-purpose solution for earlier and more predictive assessment of drug resistance including a unique chance to compare resistances via a standardized quantification.



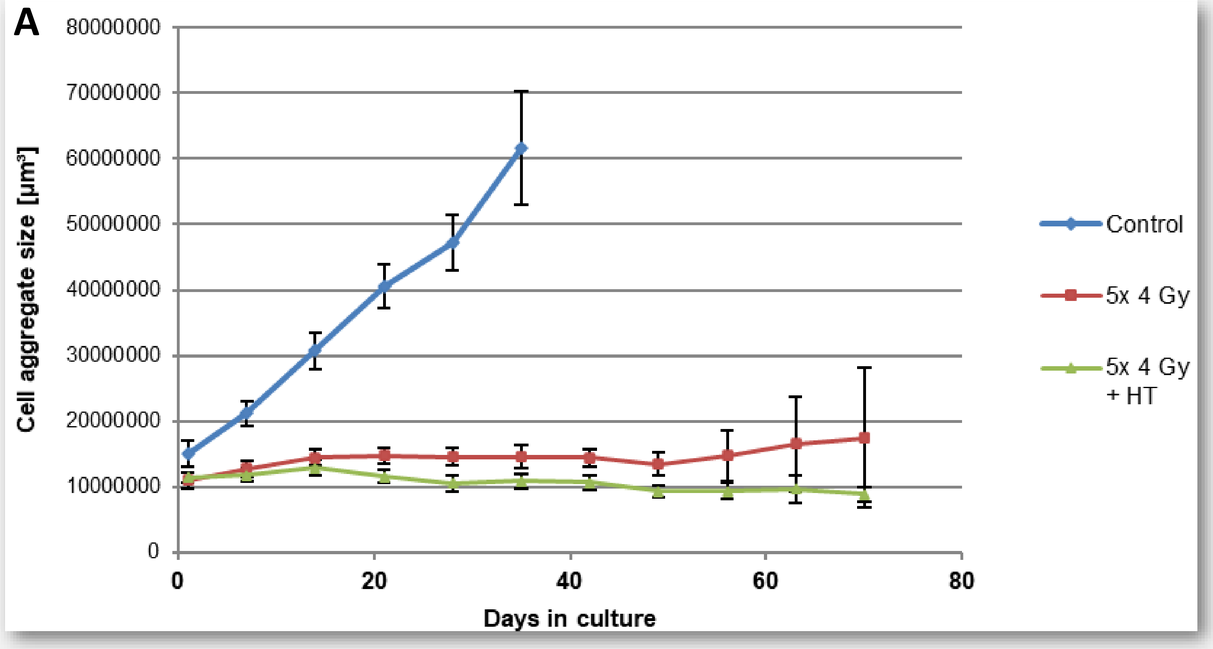


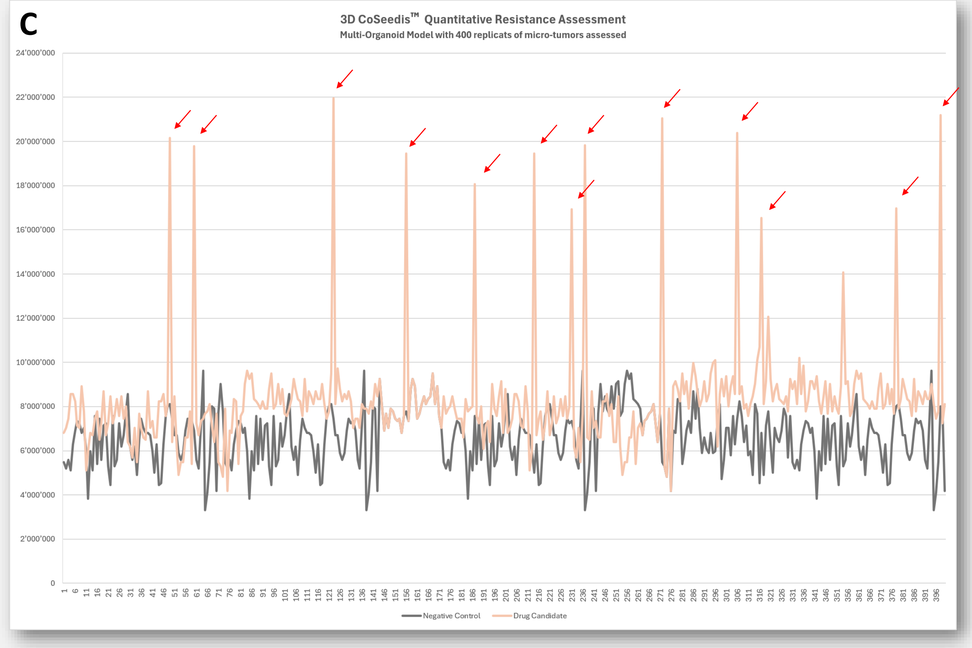
The foundation: **3D CoSeedis Multi-Organoid *in chip* Technology™**

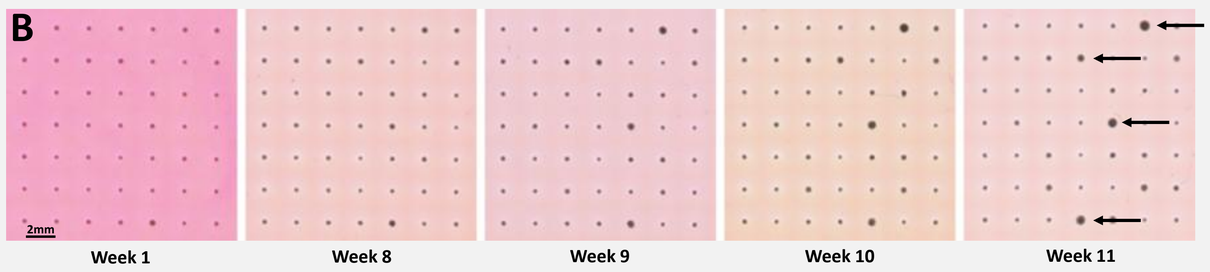
This technology is a fully humanized, physiologically relevant ex vivo platform designed to combine biological complexity with industrial-grade standardization. The technology enables the parallel generation of hundreds of highly uniform microtissue replicates under identical growth, maintenance, and treatment conditions, creating a robust basis for quantitative assessment of treatment response and resistance (Fig A).

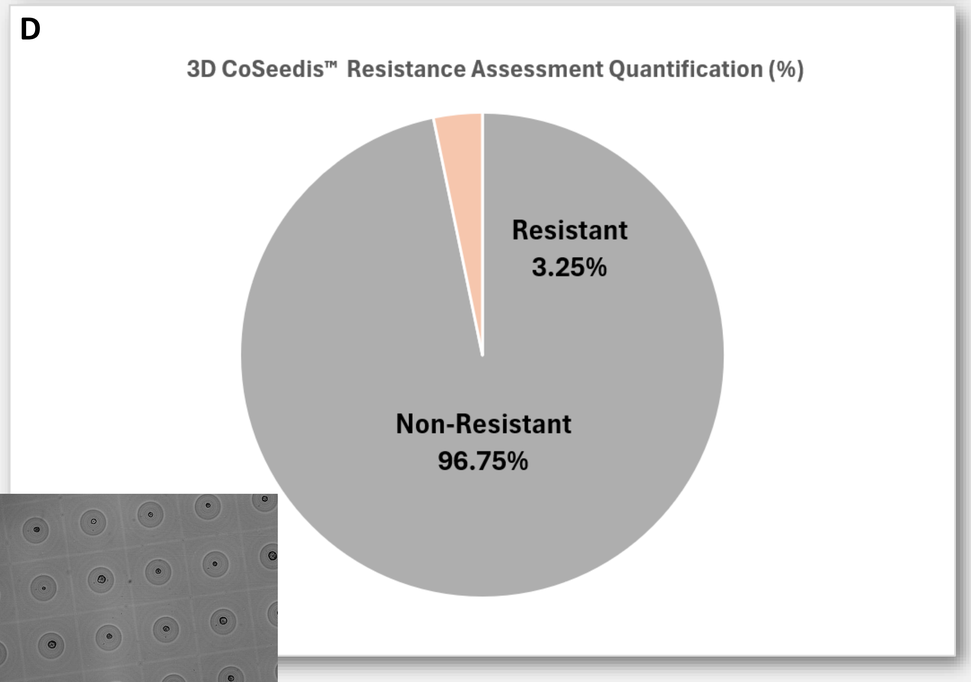
Unlike conventional organoid systems that often rely on limited numbers of variable organoids, 3D CoSeedis™ produces large numbers of directly comparable replicates, enabling statistically meaningful detection of rare resistant clones and subtle treatment-induced changes. The platform supports the investigation of resistance mechanisms within a biologically relevant microenvironment.

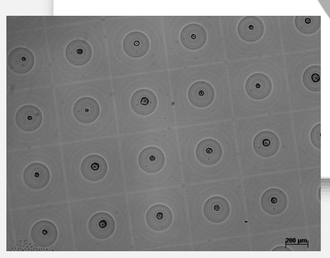
A key advantage is its ability to perform long-term studies for up to 12 weeks, enabling continuous monitoring of treatment response, resistance emergence, clonal evolution, relapse, and biomarker dynamics (Fig B). By combining scalability, reproducibility, long-term observation, and human-relevant tissue complexity, 3D CoSeedis™ provides a unique and powerful platform for the quantitative evaluation of resistance in novel drug candidates.











The biological manifestation: ex vivo drug resistance quantification using the 3D CoSeedis™ Drug Resistance Assay:

Using 3D CoSeedis *in chip* Technology™, a novel *ex vivo* assay has been established to quantify drug resistance with high accuracy, reproducibility, and temporal resolution across diverse disease models and treatment regimens.

In an exemplary study, the novel assay enabled optimization of hyperthermia combined with radiation therapy based on reduced tumor relapse (panel A). High-resolution 3D CoSeedis™ tumoroid scanning further revealed individual resistant tumor clones within the culture system, providing insights into clonal dynamics (panel B). Longitudinal analysis of large cohorts of identically cultured and treated organoids enables the identification and quantification of therapy-resistant clones. Volumetric analysis of individual tumoroids over time allows the detection (panel C, red arrows) and quantification of resistant clones, expressed as the percentage of tumors exhibiting resistance to a given therapy (panel D).

Conclusion

- 3D CoSeedis in chip Technology™ combines high statistical power with extended culture periods, enabling the detection and quantification of rare, stochastic events associated with tumor resistance.
- 3D CoSeedis™ Multi-Organoid Models provide physiologically relevant and scalable platforms for the identification, monitoring, and quantification of treatment resistance in complex therapeutic settings.
- 3D CoSeedis™ Drug Resistance Assessment offers a robust ex vivo quantification to identify the susceptibility of drugs to inducing resistance, thus supporting drug developers in making early decisions.

Outlook

- **Assessing physiological relevance:** Evaluating tumoroid models with increasing biological complexity enables correlation of resistance development with physiological relevance.
- **Fit-for-purpose model design:** Model complexity can be tailored to compound-specific requirements and mechanisms of action, enabling an optimized disease model for each application.
- **Qualitative resistance analysis:** In a second step automated differential clonal analysis of resistant versus susceptible tumoroids enables the qualification and characterization of resistance including underlying mechanisms and enables developers to respond to it early on.

[1] J. M. Waldschmidt et al., JCRCO, Volume 148, pages 1045–1055, (2022); [2] A. R. Thomsen et. al., Lab chip, 2018, 18, 179

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