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Closing the loop: A dynamic “sample-to-answer” Ecosystem for vascularized tumor modeling and real-time therapies

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1. Introduction

Advances in patient-derived organoid technologies have significantly improved our ability to model tumor-specific biology and therapeutic response in vitro. However, most current platforms remain limited by incomplete representation of the tumor microenvironment and reliance on static, endpoint-based analytical workflows [1]. Addressing these limitations is essential for improving the translational relevance of organoid-based cancer models. In this context, the study by Ruan et al. introduces an integrated microfluidic platform that enables continuous vascularized tumor modeling coupled with real-time biomarker monitoring [2].

2. The “Black Box” Challenge in oncology models

Patient-derived organoids (PDOs) have emerged as powerful experimental systems for modeling patient-specific tumor biology and therapeutic response [1,3–5]. Despite their growing use, most organoid platforms remain constrained by two fundamental limitations: incomplete representation of the dynamic cross-talk among the tumor microenvironment components and fragmented analytical workflows. Biologically, conventional PDOs are typically avascular and diffusion-limited, lacking the endothelial and stromal components that critically influence tumor growth, metabolism, and drug response in vivo. Analytically, organoids are commonly interrogated through intermittent endpoint assays, which offer static snapshots of processes that are inherently dynamic. Together, these constraints limit the predictive value of organoid-based models and contribute to their characterization as experimental “black boxes.” In this context, the study by Ruan, Gao, Wang, Hu, Liao, and colleagues introduces a notable conceptual advance [2].

3. Breaking boundaries: from Bench to Bedside in one stop

A key feature of this work is its holistic, "all-in-one" engineering philosophy. By combining a vascularized organoid-on-a-chip (VOoC) platform with an inline, real-time microfluidic ELISA module, the authors bridge the long-standing divide between tumor modeling and molecular readout. This integrated, dual-effect bimodal system enables continuous biological monitoring within a single microfluidic architecture, establishing a streamlined “sample-to-answer” workflow that connects tumor culture, therapeutic interventions, and biomarker detection.

4. Vascularization as a functional requirement for tumor fidelity

A key contribution of this work is the explicit use of vascularization as a functional necessity rather than an optional implementation. Tumor vasculature regulates oxygen and nutrient delivery, metabolic gradients, interstitial pressure, drug penetration, and paracrine signaling, all of which shape tumor behavior and therapeutic response. Organoids lacking perfusable vasculature inevitably diverge from the physiological and molecular states of the tumors from which they derive, thus limiting their reliability in testing treatment responses.

Using a microfluidic co-culture system, the authors generate squamous cervical cancer organoids surrounded by self-assembled, lumen-

Abbreviations: ceRNA, Competing Endogenous RNA; PDO, Patient-derived organoid; VOoC, Vascularized organoid-on-a-chip; ELISA, Enzyme-linked immunosorbent assay; PI3K, Phosphoinositide 3-kinase; Akt, Protein kinase B; SCCA1, Squamous Cell Carcinoma Antigen 1; CA125, Cancer Antigen 125; CEA, Carcinoembryonic Antigen; CA19-9, Carbohydrate Antigen 19-9.

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containing vascular networks formed through interactions between tumor cells, endothelial cells, and fibroblasts. Perfusion assays confirm that the vasculature remains patent, while histological analyses demonstrate that proliferative and differentiation markers, which are decreased in non-vascularized cultures, are restored. Importantly, transcriptomic profiling reveals that vascularized organoids more closely resemble primary tumor tissues than their avascular counterparts, with reactivation of key oncogenic and disease-relevant pathways, including PI3K/Akt signaling and HPV-associated transcriptional programs. These findings underscore the importance of heterotypic cell–cell interactions in maintaining malignant identity and functional relevance.

5. High-fidelity modeling meets precision sensing

Beyond biological fidelity, the most distinctive feature of this platform lies in its analytical integration. Traditional organoid workflows require manual sampling of culture supernatant followed by offline biochemical assays, introducing experimental disruption, temporal delay, and loss of dynamic information. In contrast, the authors directly couple the VOoC to a downstream microfluidic ELISA module via a bi-pitch Y-shaped connector, enabling automated and continuous sampling of culture effluent.

In this configuration, tumor-derived secreted factors serve as a real-time proxy for tumor state, enabling longitudinal quantification of clinically relevant biomarkers, including SCCA1, CA125, CEA, and CA19-9. This continuous monitoring transforms experimental assessment from endpoint analysis to dynamic surveillance, capturing transient molecular responses and early indicators of treatment efficacy or resistance that would otherwise be missed. The result is a platform that links structural, cellular, and molecular readouts within a single experimental system.

6. Drug response as a temporal and multidimensional process

The translational potential of this closed-loop platform is illustrated through drug-response studies involving cisplatin, bevacizumab, and their combination. Unlike static culture assays, the perfusion-based VOoC allows simultaneous assessment of tumor viability, vascular integrity, perfusion dynamics, and biomarker release. Cisplatin primarily induces direct cytotoxic effects on tumor organoids while also perturbing vascular stability at higher concentrations. In contrast, bevacizumab selectively disrupts angiogenic networks, indirectly suppressing tumor growth through vascular deprivation.

Notably, combination treatment produces synergistic anti-tumor and anti-angiogenic effects at substantially lower drug concentrations than either agent alone. These effects are evident not only at the cellular level but also in real-time biomarker trajectories, highlighting the value of continuous monitoring. Such observations emphasize that therapeutic response is inherently temporal and multidimensional, shaped by drug scheduling, vascular remodeling, and adaptive tumor signaling. By capturing these evolving dynamics, the platform provides insights that extend beyond those obtainable from conventional endpoint assays.

7. Implications for precision oncology and experimental modeling

More broadly, this work aligns with a growing recognition that cancer progression and treatment response are dynamic processes characterized by temporal heterogeneity and adaptive molecular states [6–9]. As precision oncology increasingly incorporates multi-omics profiling and functional stratification, experimental platforms must evolve to reflect not only molecular composition but also biological dynamics.

The dual-effect bimodal chip described here provides a framework for such evolution. By unifying vascularized tumor culture with real-time molecular sensing, it approximates key features of clinical oncology, where diagnosis, treatment, and monitoring occur as a continuous process. While demonstrated in cervical cancer, the modular design of the platform allows extension to other tumor types and incorporation of additional microenvironmental components, including immune and stromal populations.

8. Conclusions and future directions

The conceptual significance of this work lies in its emphasis on integration and continuity. By restoring vascular context and embedding real-time sensing within tumor models, Ruan et al. close the loop between biological modeling and analytical measurement. This approach not only enhances biological fidelity but also enables dynamic assessment of therapeutic response within a single system. Future studies may expand on this foundation by incorporating computational modeling and AI-based analytical tools to further refine predictive capacity. Collectively, this platform represents a meaningful step toward experimental systems that better reflect the complexity and dynamic nature of cancer in patients.

CRediT authorship contribution statement

Ciro Isidoro: Conceptualization, Validation, Writing – review & editing. **Yong Sang Song:** Writing – review & editing, Validation. **Danny N. Dhanasekaran:** Conceptualization, Writing – original draft, Validation, Writing – review & editing.

Data availability statement

All data relevant to the study are available either in the main article or the cited references.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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