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Engineered Biomaterials for Developing the Next Generation of In Vitro Tumor Models

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The field of in vitro tumor modeling has undergone rapid advances in the past few decades, marked by our increased understanding of the composition and architecture of human tumors. Chronologically, in vitro tumor models have evolved from simple 2D monolayer cultures to 3D spheroids, and most recently, to organotypic assemblies comprising cancer and/or stromal cells. Advances in biomaterials and biomanufacturing technologies have further improved these 3D models to recapitulate the dynamic interplay between cancer and stromal cells, their interactions with the extracellular matrix (ECM), and enable precise control over spatial positioning of different cell types in the tumor microenvironment. In parallel, the cancer research community has recognized the importance of cell source, moving away from immortalized cancer cell lines to primary cells, organoids, and patient-derived xenografts (PDX). Integrating these different cellular and tissue models with engineering approaches has enabled researchers to more accurately capture both intra- and inter-tumoral heterogeneity, thereby allowing for more nuanced studies of cancer progression. However, despite these advances, questions surrounding the role of the tumor microenvironment in cancer progression, metastasis, and therapy response, remain largely unanswered. In this special issue, we have compiled 14 research articles representing both fundamental and translational studies, as well as four review articles from leaders in the field. Collectively, these articles highlight how bioengineered tumor models have become indispensable tools for resolving these questions and to realize personalized medicine for cancer patients.

Understanding how cancer cells interact with the ECM may open new opportunities to halt the initiation of cancer growth and metastasis. In a study by Shyni Varghese and co-workers (article 2201842), a microfluidic platform was leveraged to mechanically probe growing spheroids and the surrounding 3D matrix non-destructively. The authors demonstrate the importance of matrix stiffness in determining spheroid growth as spheroids in softer matrices were found to depend on local matrix degradation to grow, while spheroids in stiffer matrices rely on volumetric expansion. To elucidate the differences between how cancer cells with varying invasive phenotypes interact with the ECM, Umber Cheema, Emad Moeendarbary, and co-workers (article 2201749) developed a tumoroid assay that implicated matrix metalloproteinases (MMPs) as a potential mechanism through which more invasive cells manipulate their environment. Interestingly, the authors show that while poorly invasive cancer cells stiffen the surrounding matrix, highly invasive cancer cells soften the surrounding matrix using MMPs to create space for cell invasion. Given the known role of hyaluronan (HA) in facilitating cancer cell invasion, Stephanie K. Seidlits and co-workers (article 2203143) developed bioengineered matrices with precisely varied HA concentrations to elucidate how HA-CD44 interactions influence the invasiveness of glioblastoma (GBM) tumors. The authors demonstrate how HA concentration affects the invasiveness of GBM cells, identifying HA-CD44-ezrin interactions as a key mediator of GBM cell migration. In another study investigating the role of HA in facilitating cancer cell invasion, Claudia Fischbach and co-workers (article 2202224) leveraged multiple multidisciplinary approaches, including in vitro tumor models, computational metabolic modelling and genomic tools, to reveal how HA overproduction may result in metabolic adaptations to meet the energy demands for 3D invasion of breast cancer stem cells. Given the role of tumor dormancy in the invasion–metastasis cascade and the need for improved methods to study this phenomenon, Shelly R. Peyton and co-workers (article 2202275) developed a platform to enable the identification and study of dormant cancer cells, where they showed that long-term quiescence is modulated by both cell intrinsic and extrinsic factors. Lastly, Martina H. Stenzel, Kristopher A. Kilian, and co-workers (article 2201696) used hydrogel micropatterning to create pseudo-3D cancer aggregates harboring both cancer cell and cancer stem-like cell subpopulations to model cancer heterogeneity. Interestingly, the authors show that cancer stem-like cells were more susceptible to nanoparticle uptake as a result of increased membrane deformability, opening up a potential avenue to target this cell population which contributes to metastasis and recurrence.

To better understand how the tumor microenvironment influences cancer progression and drug resistance, in vitro tumor models which incorporate stromal elements may be very useful. However, it remains highly challenging to develop conditions that permit co-culturing of different cell types with an in vivo-like spatial architecture. Using a state-of-the-art microfluidics-based perfusion device, Daniel A. Harrington and co-workers (article 2201434) demonstrated the feasibility of culturing multiple

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prostate cancer-derived PDX models as 3D clusters within engineered hydrogel matrices, together with bone marrow-derived stromal cells and endothelial cells, to model bone metastatic prostate cancer. In another study, Nathalie Bock and colleague (article 2201701) leveraged GelMA-based hydrogels to develop the first humanized bone tumor models incorporating human bone marrow-adipocytes. Given recent interest in leveraging immunotherapies as a therapeutic strategy, Daniela Loessner and co-workers (article 2201907) developed a multicellular cancer model using rationally designed hydrogels to support human pancreatic cancer cells, cancer-associated fibroblasts, and myeloid cells for assessing the efficacy of immune checkpoint blockade-based therapies. To further mimic how immune cells traffic and infiltrate tumors, Chenguang Xu, David A. Barbie, Roger D. Kamm and co-workers (article 2201784) developed a microfluidic-based vascularized tumor spheroid model. They found that the addition of fibroblasts to a pre-formed tumor spheroid better supported tumor vascularization as compared to co-mixed spheroids, enabling the use of this model for preclinical CAR-T cell evaluation. Single-cell analyses have revealed the importance of spatial organization or architecture, in human tumors. To create highly controllable tumor architectures, Hartland Warren Jackson, Alison P. McGuigan and co-workers (article 2201846) developed co-cultures of primary patient-derived organoids with pancreatic stellate cells using an engineered paper-based platform to recapitulate gradients of oxygen and other small molecules in 3D cultures. In this study, tissue architecture was shown to impact oxygen tension, consequently creating gradients in hypoxia which influenced cell proliferation. In another approach, Tim Woodfield and co-workers (article 2201581) demonstrated the feasibility of using an automated and integrated biofabrication system comprising spheroid and microsphere modules, to modularly construct tumors that mimic the tumor architecture. Finally, Scott S. Verbridge and co-workers (article 2300671) designed a dual layer hydrogel platform to study how gradients of CXCL12 regulate the migration of glioma and glioma stem-like cells.

While reductionist approaches to reconstruct human tumors in vitro are highly controllable for mechanistic studies and drug development, these bottom-up tumor models may not adequately recapitulate the complex composition and heterogeneous architecture of patient tumors. This is especially problematic if these models are used for assessing stromal-targeting drugs such as immunotherapies. In contrast, holistic tumor models based on patient-derived tumor explants, which potentially retain the entire tumor microenvironment ex vivo, may be very useful for personalized drug testing. Although developed decades ago, patient-derived tumor explant cultures have not been widely adopted likely because of their low-throughput and poor long-term viability. In a review by Eliza Li Shan Fong and co-workers (article 2202279), the authors outline key limitations of patient-derived tumor explant cultures and discuss strategies that could be leveraged to address current bottlenecks limiting the use of these models. One such strategy involves the use of bioengineered hydrogels to provide structural support to explant cultures. In a study by Laura J. Bray and co-workers (article 2202202), the authors demonstrate how mechanical support provided by hydrogels prevented the disintegration of tissue structures including the epithelium and stroma, thereby enabling the long-term maintenance of patient-derived breast explant tissues. A review by Carsten Werner, Anna Taubenberger, and co-workers (article 2202514) further emphasizes the importance of mechanical cues in the tumor microenvironment and their role in regulating disease progression. In their article, they describe strategies that allow mimicking the dynamic architectural and mechanical properties of hydrogel matrices for studies of tumor mechanobiology.

As a final piece to the puzzle, it is necessary to consider the integration of engineered tumor models with other advanced multidisciplinary approaches to truly maximize the insights that can be generated. Therefore, we have also selected review articles on emerging technologies to aid in vitro tumor modeling. Subhas C. Kundu, Rui L. Reis, and co-workers (article 2201442) describe the use of photonics paired with microfluidics and biosensing for improved assay development and analysis of 3D tumor models. Mai Chan Lau, Joe Poh Sheng Yeong, and co-workers (article 2202457) present a review on artificial intelligence as a tool for tumor modeling and characterization of the tumor microenvironment.

It has been our greatest pleasure to curate this special issue for *Advanced Healthcare Materials*. The fight against cancer is a long and arduous journey. By providing innovative platforms mimicking microenvironmental conditions for mechanistic studies of cancer, tumor engineers enable novel insights that will ultimately advance therapeutic strategies to treat cancer patients. Although this special issue is only a snapshot of recent advances in the field, we believe it represents the ongoing tremendous efforts that will eventually realize this possibility. With this, we would like to thank all authors for contributing to this issue, and Dr. Irem Bayindir-Buchhalter for the opportunity to contribute to *Advanced Healthcare Materials* and her assistance throughout commissioning of this special issue.

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