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Editorial: Special Issue on Tissue Engineering and Biomaterials Approaches to Tumor Modeling

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It is encouraging that cancer mortality rates continue to decline. However, almost 40% of men and women will be diagnosed with cancer at some point during their lifetimes and approximately 609,000 people are expected to die of cancer in 2018 alone. To address the unmet need for improved therapies, research has historically focused on the tumor cells themselves. This approach elucidated many molecular perturbations that are now being explored clinically. Yet tumor cells do not exist in isolation and the role of the microenvironment in regulating cancer development and progression is now widely accepted. In fact, the recent successes of immuno-oncology are based on the premise that treating the microenvironment, rather than the tumor cells directly, can effectively inhibit tumor progression and recurrence. Nevertheless, the tumor microenvironment is complex and includes altered cellular composition, extracellular matrix (ECM) deposition, and mechanical cues, many of which we still do not understand. It is obvious: to gain a better understanding of how these diverse biochemical and biophysical components modulate tumorigenesis, model systems are required that allow recapitulating tumor-microenvironment interactions *in vitro*.

While Matrigel®-based 3D tumor models have yielded many important insights in the past, the intrinsic limitations of this sarcoma-derived basement membrane mix have catalyzed the development of biomaterials-inspired approaches. For example, exploring natural or synthetically-defined ECM components as biomimetic scaffolds for 3D tumor models can circumvent challenges related to batch-to-batch variations and the limited range of mechanical properties associated with Matrigel®. In fact, integrating cancer research with biomaterials and tissue engineering has started the new field of ‘tumor engineering’ that blossomed over the past 2 decades. While the search term ‘tumor engineering’ only yielded 87 Pubmed hits in 2000, 1749 articles were reported in 2017, an impressive 20-fold increase. Most major biomaterials and tissue engineering-related conferences, such as meetings organized by the Society of Biomaterials (SFB), Tissue Engineering and Regenerative Medicine International Society (TERMIS), and Biomedical Engineering Society (BMES), now routinely organize sessions dedicated to cancer. Vice versa, conferences focused on cancer or cell biology such as the annual meeting of the American Society of Cell Biology (ASCB) and the American Association of Cancer Research (AACR) now include events related to engineered tumor models. Last but not least, new federal funding mechanisms have been implemented to support biomaterials-based approaches for cancer research (e.g.

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Cancer Tissue Engineering Collaborative: Enabling Biomimetic Tissue-Engineered Technologies for Cancer Research by the NCI).

Clearly, biomaterials scientists are at the forefront of developing advanced culture microenvironments for improved basic research and translational applications in cancer research. This special issue is timely and highlights some of the most recent developments in the field of tumor engineering in the context of cancer types ranging from mammary to pulmonary to hepatocellular carcinomas, as well as sarcomas and blood cancers. A combination of review and original research articles summarizes key design parameters for engineering culture microenvironments to study tumor cell interactions with various stromal compartments including vasculature, bone, and immune cells. Furthermore, it describes specific applications for engineered tumor models in the context of drug and bioactive agent testing and outlines the role of mechanical and matrix cues in regulating malignancy. Last but not least, when culturing tumor and stromal cells within complex culture models, new technologies are required that allow monitoring and manipulating cellular responses to their microenvironment. Two articles will emphasize such new technologies in the context of analyzing cell-ECM interactions.

Particular design considerations for complex tumor models include physical and biochemical properties, cellular composition, biomaterials and bioreactors, cost considerations, and imaging constraints. Many of these parameters are discussed within this special issue. For example, a review by Werner et al. addresses advances in combining materials science, engineering, and cell biology to define promising scaffolds for vascularized tumor engineering[1]. West et al. describe a specific example for vascularized tumor engineering by exploring a PEG-based synthetic hydrogel to generate vascularized lung cancer spheroids[2]. The Spagnoli laboratory reviews *in vitro* models to study cancer cell-immune cell interactions and elaborates on how these may be useful for identifying new therapeutics or biomarkers for the patient population best suited for certain immunotherapies[3]. The Reagan laboratory summarizes current options for modeling bone- or bone-metastatic cancers *in vitro*, including biomaterials, relevant cell types, and scaffolds, and summarizes the differences observed between 2D and 3D cultures[4]. Finally, Kong et al. describe their development of decellularized 3D mesenchymal stroma cell (MSC) matrix in the generation of hepatocarcinoma cultures and the resulting functional effects on tumor cells[5].

Specific applications of 3D tumor models are also highlighted within this issue. For example, the Peyton lab has evaluated drug responses of 3D multicellular tumor spheroids (MCTS) as a function of the particular MCTS formation method[6]. The Sant group developed elegant 3D microsized tumors to test drug responses in different stages of breast cancer (early and late/advanced stages)[7]. In addition to examining effects on the tumor cells themselves, Verbridge et al. shows that 3D collagen-based culture models can also help define differences in stromal cell behavior[8]. His lab studied the effect of lipopolysaccharide on endothelial cells. Given the key role of chronic inflammation in tumorigenesis such studies will further advance our understanding of how altered vascular properties may promote tumorigenesis.

Mechanical alterations of the tumor microenvironment include growth-induced solid stress, but also interstitial pressure, and the forces that cells are exposed to in the blood stream. A review by Kamm & Moeendarbary et al. summarizes the role of these different forces with a specific focus on cancer metastasis and provides an outlook on the emergence of novel *in vitro* assays to probe and recapitulate tumor mechanics[9]. A study by Mikos et al. builds on this topic and provides a compelling example of how 3D printing may be explored to generate shear stress gradients within tissue culture scaffolds to evaluate their effect on Ewing Sarcoma cells[10]. Lin et al., on the other hand utilized micrometer-sized cylindrical pores with precisely controlled wall stiffness to examine the effect of stress buildup on the growth dynamics of human lung epithelial cells[11].

The ECM itself is another key regulator of tumor mechanical properties. A review by Chauduri et al. provides a comprehensive overview of how cells sense and respond to ECM mechanics and which materials and material modifications may be used to mimic these properties for culture studies[12]. An article from the Lelièvre lab further highlights the importance of ECM stiffness by studying its effect on cellular hypoxia response and nuclear size and shape[13]. These studies were made possible with the help of a microfluidic device that allows the development of reactive oxygen gradients within collagen. Finally, findings from the Gerecht laboratory further complement these findings by investigating how collagen fiber characteristics regulate sarcoma cell migration in response to hypoxia[14].

One key mechanism that tumor cells use to adjust their interactions with the ECM is through their glycocalyx, a sugar and protein coating on cell membranes that influences integrin engagement. However, the underlying mechanisms remain poorly understood. The Paszek laboratory developed a toolbox to genetically engineer a cancer-like glyocalyx onto cells and studied the resulting effects on tumor cell adhesion[15]. Another mechanism that tumor cells explore to respond to their surrounding ECM is through proteolytic degradation. To monitor such interactions, the Anseth laboratory developed FRET-based microgel sensors and used these for spatial and temporal monitoring of protease activity of melanoma cells[16]. This important tool may be useful for researchers studying variables or testing drugs related tumor invasion and metastasis.

In summary, 3D tissue-engineered tumor models promise to advance our current understanding of cancer by providing tools to recapitulate and monitor relevant properties of tumor-microenvironment interactions. While targeting aspects of tumors other than the tumor cells directly has shown success in the clinic, better, more intricate models are needed to more fully understand drivers of tumor initiation, growth, metastasis, metabolic adaptation, and immune evasion. Tissue engineering bears tremendous potential towards gaining a more complete understanding of the underlying biological and physical mechanisms ultimately advancing the treatment of cancer patients. The contributions presented in this special issue are examples for progress towards this end.

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