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Editorial

Biomaterials for Personalized Disease Models[☆]

The rise of precision medicine in modern healthcare has been driven by innovations in molecular profiling and the establishment of better models of development and disease. Heterogeneity across patients, including each patient's unique genetics and lived experiences, can have significant effects on both the clinical presentation of a particular pathology and how each patient responds to medical treatment [1]. Such diversity necessitates the use of personalized strategies during discovery, development, preclinical evaluation, and implementation of new clinical approaches. Personalized approaches are particularly valuable for study and therapeutic development in rare genetic diseases, for which there are not enough patients from which to collect meaningful clinical data [2]. Advanced strategies for organ and tissue regeneration and transplantation would also benefit from personalized therapies, as growing new tissues from the patient's own cells would eliminate the need for taking immunosuppressant medications, which often have harmful side effects.

A key aspect of developing a personalized model is selection of the appropriate cell type, necessitating either primary somatic cells, adult stem (progenitor) cells, or multipotent cells reprogrammed from easily accessible somatic sources. A promising cell type from this latter category are the so-called induced pluripotent stem cells (iPSCs), which have garnered interest for personalized therapies, as theoretically an individual's cells can be easily and noninvasively harvested, converted to stem cells, and then directed to re-differentiate into any organ or tissue in the body [3]. Generation of organoids, defined as relatively small clusters of cells with three-dimensional (3D) organization that recapitulate key features of full-scale organs, from iPSCs represents a huge step for personalized medicine. For example, organoids have enabled creation of microphysiological systems with improved clinical relevance for treatment discovery, screening, and preclinical evaluation [4,5]. Strategies to yield personalized tissues, for microphysiological systems or clinical transplantation, depend on the ability to guide development of stem cells into the specialized cells of that tissue. The microenvironment surrounding cells is key to directing differentiation and organization of stem cells into functional tissues. Together, microenvironmental features, including geometry (e.g., dimensionality), topography, mechanical forces, spatial and temporal availability of soluble biomolecules, and neighboring cells, drive fate specification and tissue formation.

The biological materials in the microenvironment are central to orchestrating cellular assembly towards tissue and organ development. For personalized models, the design of biomaterials re-

quires similar considerations to the cellular components, with heterogeneity in composition and structure dictating patient-specific form and function. In general, researchers have worked towards biomaterials that recreate various aspects of the extracellular matrix (ECM), which is tissue-specific and provides a scaffolding for cells in the body [6]. Matrigel, ECM derived from mouse sarcomas, is perhaps the most widely used biomaterial for interfacing with iPSCs and organoids. However, this and other natural materials have limitations, including batch-to-batch variability, potential for pathogen transmission or immunorejection due to a non-human source, and an inability to tailor the biomaterial for application to a specific tissue or organ function. In contrast, synthetic biomaterials systems have controllable physicochemical properties, batch-to-batch uniformity, and with careful design can be organized to provide spatiotemporal cues to coax cellular organization into biomimetic hierarchies.

In this special issue of *Acta Biomaterialia*, we evaluate the current state and future promise of using biomaterials for development and translating personalized disease models. Chemically defined biomaterials have improved control over stem cell fate and mature cell functions. Additionally, advanced techniques in biofabrication, additive manufacturing, and microfluidics have been combined with defined biomaterials to yield larger and more complex structures with the ultimate goal of creating full-scale human organs *ex vivo* [4,7]. On the other hand, similar techniques in these fields have been used to miniaturize organs and tissues, creating "organ-on-a-chip" devices compatible with high-throughput assays. Organ-on-chip platforms enable high-throughput screening of drug treatments for both efficacy and toxicity [8]. This special issue includes both review (12 contributions) and original research (9 contributions) articles that cover core biomaterial technologies being applied for personalized medicine, including for high-throughput screening, and biomaterial-centered approaches for a range of specific organ and tissue sites, including their pathologies and cancers.

Focused on core biomaterial technologies, Tayler, *et al.* review how hydrogel biomaterials can be engineered to represent distinct microenvironments through which they can direct stem cell fate for applications in tissue engineering and disease modeling [7]. In addition, they describe how advanced imaging and bioprinting techniques can be used to further develop biomaterial-centered platforms. In a complementary review article, Hoang and Ma outline biomaterial-based strategies for biomaterial manufacturing of organoids, including 3D printing into larger constructs, and organoid-on-a-chip platforms [4]. Kim, *et al.* provide a more focused review on engineering organoids to recapitulate for specific pathologies for use as disease models and drug development [5].

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In particular, they focus on tissue sites where mass transport is critical (e.g., highly vascularized liver tissues) and discuss how microfluidics can be used to add such dynamic features to organoid cultures. More broadly, Grubb and Caliri review techniques for adding biological complexity to biomaterial-based disease models for high-throughput screening [8]. While most research articles in this special issue focus on tissue- or disease-specific applications, Homma, *et al.* developed a technique enabling dynamic stiffening of a hydrogel substrate on which live cells were cultured [9]. As dynamic stiffening of tissues occurs during development, aging and progression of many diseases (e.g., cancer and fibrosis), techniques to control this progression will likely be very valuable for personalized disease models.

An exciting prospect in the field of personalized models is the modularity of these materials and technologies, where tailoring the cells and matrices used can yield platforms that span diverse tissues and disease states. There are many tissue-specific models that have been developed in recent years. Tonti, *et al.* review considerations for designing biomaterials that mimic the ECM of a range of specific organs and tissues [6]. Additional articles in this special issue delve into these tissue-specific models spanning five important systems: *cardiovascular*, *musculoskeletal*, *gastrointestinal*, *reproductive*, and *neural*. The cardiovascular section begins with a review article by Lust *et al.* describing the design considerations for modeling vascular pathologies, governed by the central tenet that biomaterials, cellular organization, and fluid forces all influence normal versus pathological function [10]. Chatterjee *et al.* examines the origin of blood cells and the important parameters for constructing accurate mimics of the hematopoietic stem cell niche [11]. This review article highlights two biomaterials-driven areas: *in vitro* blood production and models to explore niche pathology. The cardiovascular section continues with original research articles by Williams *et al.* describing a tissue model for cardiac arrhythmias [12], Lau *et al.* demonstrating perlecan-functionalized silk fibroin biomaterials for blood-contacting applications [13], and Kim *et al.* reporting a cell sheet engineering approach to support models with vascularized tissue [14]. The musculoskeletal section includes a review article by Alcalá-Orozco *et al.* exploring the current state of 3D biofabrication for musculoskeletal tissue [15], followed with original research by Mirkhalaf *et al.* on using Baghdadite for personalized bone scaffolding [16], Ebrahimi *et al.* describing a skeletal tissue model of Duchenne muscular dystrophy [17], and Ma *et al.* presenting a model of ischemic osteonecrosis [18].

Moving to softer tissues, Hirota *et al.* review the current state of biomaterials for personalized intestinal organoid models [19] and Swaminathan *et al.* explore the influence of biomaterials stiffness on enteroids when interfaced with *E. coli* [20]. The next section begins with a review by Stejskalova *et al.* on *in vitro* models of the female reproductive system [21] followed by original research by Tomaszewski *et al.* demonstrating a synthetic biomaterials sequestering approach to build mature ovarian follicular organoids [22]. Finally, this special issue includes two review articles on engineered models of neural tissues and neural pathologies. First, Bang, *et al.* review techniques used to fabricate, stimulate and measure engineered neural circuits and how these models can facilitate advances in neuroscience and neuropharmacology [23]. Then, Bindas *et al.* review current technologies and limitations to engineering neural tissues, specifically in the context of Parkinson's disease [24]. Then they discuss the need for modeling interactions of the brain and gut microbiota to better understand neurodegeneration, which would require integrating cultures of brain, intestinal, and bacterial cells. Central to each of these systems is a need for careful control of cells and biomaterials to re-create the biology of both normal and disease states and ensure personalized models reveal physiologically meaningful results.

Representing a common pathology across organs and tissues, cancer is the leading cause of death worldwide [25]. Genetic and non-genetic phenotypes of cancers vary significantly depending on the tissue of origin, any metastatic site(s), and the individual patient. Thus, large efforts have been made to develop patient-tailored therapies, including using molecular pathology to select the treatment plan most likely to be effective for a particular patient (e.g., precision medicine) and other and personalized approaches where a patient's own tumor cells are screened for treatment response *ex vivo* to inform treatment plans. This special issue includes several studies focused on developing personalized, biomaterial-based models of cancer. Ando *et al.* review cell-based strategies for cancer immunotherapies, where a patient's own immune cells are deputized to attack tumor cells, and development of engineered microphysiological models of immune-tumor interactions [26]. Additional review articles provide more focused discussions on recent progress in biomaterial-based models of specific cancers, where Costard *et al.* examine personalized models of lung, breast, and prostate cancers [27], Horst *et al.* evaluate models of ovarian cancer [28], and Hatlen and Rajagopalan discuss models of glioblastoma [29]. Original research articles investigate effects of incorporating different aspects of the tumor microenvironment into *in vitro* tumor models. Hill *et al.* characterize how independently tuning various bioactive features of a biomaterial affected how glioblastoma tumor cells respond to chemotherapy [30]. Cao *et al.* investigate how biomaterial stiffness affects stromal cells, specifically cancer-associated fibroblasts (CAFs), which are highly influential in epithelial cancers [31]. Creating tumor models with highly complex microenvironments, Luo, Fong *et al.* combined CAFs and a defined biomaterial matrix with colorectal cancer cells [32] and Berger Friedman *et al.* incorporated a biomaterial matrix and macrophages into a microfluidic chip for dynamic co-culture with breast cancer cells [33].

Collectively, this special issue represents the state-of-art technologies for leveraging biomaterials that, when combined with a patient's cells, can be used for personalized engineering of functional organs and tissues and diseases affecting these tissues. The value of adding complexity to the microenvironment by incorporating multi-functional biomaterials, multiple cell types, and dynamic changes in the system is discussed throughout this special issue. In the near future, we expect advances in additive manufacturing, biomanufacturing, biomaterials, and microfluidics to further facilitate the development of platforms in which multiple engineered tissues can interact (e.g., multi-organ-on-a-chip). Such platforms will be valuable for exploring systemic aspects, including the immune system, of diseases and drug treatments.

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