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EDITORIAL

Biomaterials and emerging technologies for tissue engineering and in vitro models

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The latest advances in the field of biomaterials have opened new avenues for scientific breakthroughs in tissue engineering which greatly contributed for the successful translation of tissue engineering products into the market/clinics. Biomaterials are easily processed to become similar to natural extracellular matrix, making them ideal temporary supports for mimicking the three-dimensional (3D) microenvironment required for maintaining the adequate cell/tissue functions both in vitro and in vivo [1]. The integration of functionalized biomaterials with emerging technologies such as microfluidics and 3D printing brings a myriad of advantages for manufacturing complex tissue designs with broad applications in cell/tissue engineering and regenerative medicine, and in vitro tissue/disease models (Fig. 1).

The special issue gathers two excellent reviews and five original works dealing with design and functionalization of biomaterials, advanced manufacturing, and applications in tissue engineering and in vitro models. The recent progresses in 3D printing of Israel are summarized. Moreover, the latest scientific developments related to the biodesign and functionalization strategies of (nano) biomaterials, in particular hydrogels/bioinks and semicrystalline polymers for both enhancing and controlling cell functions, are also provided. An overview of the cellular interplay in 3D in vitro microphysiological disease models with a special focus on microbiota–gut–brain axis is also presented. Finally, the important research achievements involving the biofabrication of complex in vitro 3D tissue/tumor models are also highlighted.

In particular, Gao et al. [2] provided an interesting and comprehensive overview of the advancements in 3D printing/bioprinting in Israel, highlighting the various scientific research areas that include printable components, soft device fabrication, and tissue engineering applications. The translation to the market of artificial meats produced using 3D printing technology was also discussed. The review deeply explores the development of functional hydrogels/bioinks, printed electronics and soft actuators, and use of peptides in self-assembly and biofabrication of supramolecular architectures.

Three interesting works innovatively proposed engineering approaches to unprecedently address the current challenges posed by tissue engineering, in particular on how to better address the tissue complexity, cytocompatibility, biofunctionality, sensing properties, and reproducibility requirements.

De Nitto et al. [3] proposed the development of poly(2-hydroxyethyl methacrylate-co-methacrylic acid) (pHEMA-co-MAA)-based hydrogel loaded with conductive poly(3,4-ethylene-dioxythiophene) (PEDOT) and polypyrrole (PPy) nanoparticles (NPs) for finding applications as patches for wound healing, sensors, and peripheral nerve regeneration. The hydrogels were processed as bioinks via photopolymerization of monomer mixtures for 3D printing. The effect of NPs loading into the structural stability of the proposed hydrogels, conductivity, and its antimicrobial properties was investigated. Undoubtedly, the in vitro studies using a glial cell line showed that the NP-loaded hydrogels present an adequate cytocompatibility opening up several potential uses in different electroactive tissue engineering strategies.

In a proof-of-concept study, Beeren et al. [4] have addressed the challenges related to the need to improve the biological activity of semicrystalline polymers. The interesting strategy was pursuit to tune the surface density of bioactive groups by means of blending a low

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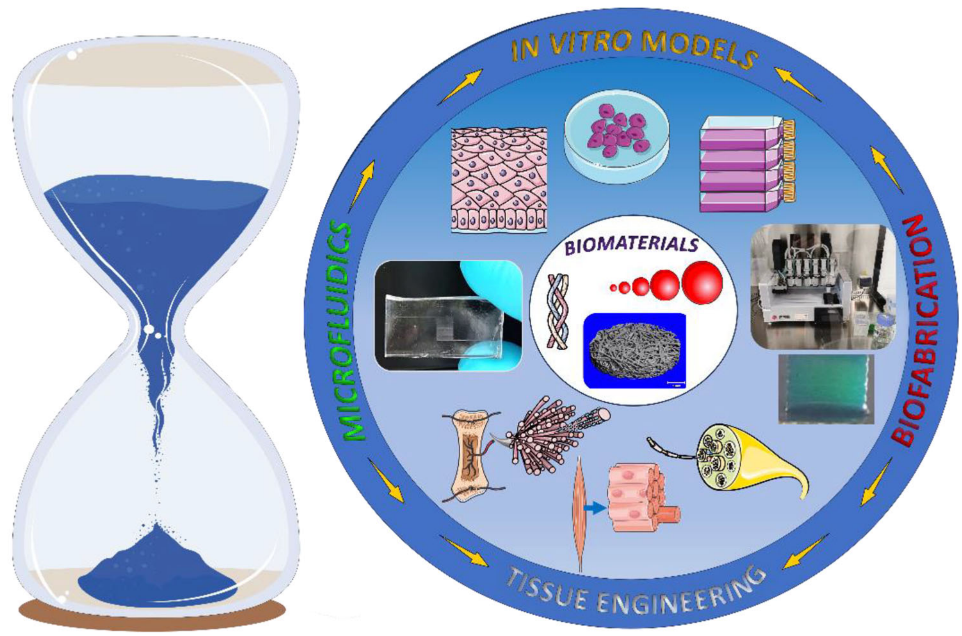

Fig. 1 Schematic representation of the biomaterials (e.g., hydrogels, scaffolds, and nano-/microparticles) and emerging technologies (e.g., microfluidics and biofabrication) integration toward the development of advanced strategies to tackle the current challenges of tissue engineering and in vitro tissue/disease models. The figure partially used material freely available under the Creative Commons 3.0 license

molecular weight poly(ε-caprolactone) (PCL5k) containing orthogonally reactive azide groups with an unfunctionalized high molecular weight poly(ε-caprolactone) (PCL75k). That strategy allowed the grafting of a bone morphogenetic protein 2 (BMP-2) derived peptide, for example. The study revealed that grafting density modulates osteogenesis, thus highlighting the advantage of surface functionalization of polymers and use of scaffolds with compositional gradients in tissue engineering applications.

Importantly, Grasso et al. [5] proposed a new strategy for the fabrication of ratiometric oxygen-sensing biomaterials made of poly(ε-caprolactone)/poly(dimethyl)siloxane (PCL/PDMS) nanofibers embedding the oxygen-sensing Ru(II) tris-heteroleptic polypyridyl complex ($Ru(dpp)_3{}^{2+}$) probe and the oxygen non-sensitive Rhodamine *B* isothiocyanate fluorophores for real-time monitoring of oxygen consumption in 3D cultures. The electrospinning processing was extensively optimized, and the nanofibers' sensing performance was investigated. The work provided interesting results demonstrating that for all the sensing systems, intensity ratios were linearly correlated to the dissolved oxygen concentrations in the surrounding environment. This suggests that the proposed sensing platforms may be applied for precisely and spatiotemporally monitoring oxygen extracellular changes and metabolism of cells in in vitro disease models and tissue engineering strategies.

It is noteworthy that it would be interesting if the aforementioned strategies proposed by Beeren et al. [4] and Grasso et al. [5] could be combined as it would innovatively provide a sensing PCL scaffold possessing compositional gradients and improved biological performance for tissue engineering applications.

By its turn, Nair et al. [6] provided a concise review on cellular interplay to 3D in vitro microphysiological disease models focusing on cell patterning microbiota–gut–brain axis. This review briefly discusses the communication pathways between the gut microbiome and brain, and the importance of in vitro models and technology integration (e.g., bioprinting and microfluidic chips) for in-depth understanding of different diseases such as autism spectrum disorder, Parkinson, and Alzheimer.

Then Wang et al. [7] reported a 3D brain tumor model fabricated by means of encapsulating U87 MG glioma (U87) cells in a hydrogel containing type I collagen. The authors investigated the effect of oxygen concentration on cell functions. Interestingly, the in vitro studies revealed that the oxygen concentration can affect cell functions, and the constructed 3D tumor is more representative as compared to two-dimensional (2D) culture systems, making it a valuable in vitro 3D model for studying glioblastoma.

Finally, Jeong et al. [8] from Harvard Medical School reported an oxygenating colloidal bioink for the engineering of biomimetic tissue constructs.

Ultimately, the works highlighted in the special issue offer only a handful of significant contributions at a time when strategies involving the functionalization of biomaterials and their integration with emerging technologies can have a transformative impact in fields of tissue engineering and in vitro 3D models.

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Declarations

Conflict of interest JMO is an editorial board member for *Bio-Design and Manufacturing* and was not involved in the editorial review or the decision to publish this article. The authors declare that they have no conflict of interest.

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