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Guest Editorial

Special Issue on Three-Dimensional Bioprinting

Additive manufacturing, or commonly known as three-dimensional (3D) printing, is a layer-by-layer manufacturing approach enabling fabrication of highly complex objects made of plastics, ceramics, metals, composites, and other emerging materials. 3D bioprinting is an extension of tissue engineering, as it intends to create de novo tissues and organs combining biomaterials, tissue engineering, and 3D printing. It uses bioadditive manufacturing technologies such as laser-based writing, inkjet-based printing, and extrusion-based deposition to print constructs for generation of engineered tissues, tissue constructs, organ modules, and organs. Bioprinting offers great precision on spatial placement of cells, proteins, genes, drugs, and biologically active nano- and micro-particles to better guide tissue generation and formation. This emerging technology appears to be more promising for advancing tissue engineering toward functional tissue and organ fabrication for transplantation, ultimately mitigating organ shortage, and saving lives. In this regard, exploring novel bioprinting processes and next-generation bioprinter technologies, development of new bioink materials and understanding functional tissue and organ formation is of growing importance. This Special Issue selected seven Research Papers and an Expert View article on recent advances, research, and development in 3D printing and bioprinting technologies for tissue engineering and medicine.

Integration of 3D printing of hard polymers with cell-laden hydrogels has recently gained great interest due to the generation of structurally integrated, mechanical stable scaffolds loaded with high density of cells, which is not feasible using conventional means of loading cells on hard scaffolds. Ovsianikov and colleagues at Vienna University of Technology demonstrated loading of gelatin-based hydrogels into 3D printed poly(lactic) acid (PLA) using two-step approach, where PLA scaffold was first 3D printed using fused deposition modeling approach followed by infiltrating gelatin hydrogels loaded with mouse calvaria-derived preosteoblast cells (MC3T3). After infiltration of the hydrogel solution, the scaffolds were exposed to photopolymerization to crosslink the hydrogel solution. This study revealed generation of hybrid scaffolds with uniform distribution and high seeding efficiency of MC3T3 as well as their long-term survival and proliferation. Using a similar hybrid concept, an interesting approach and application was introduced, and a new 3D cell culture method was presented by Soman's research group at Syracuse University. In their approach, 3D printing was used to create a PLA device to hold a membrane made of photosensitive gelatin methacrylate (GelMA). The device, termed "suspended hydrogel membrane," supported 3D culture of murine mesenchymal 10T1/2 cells through seeding and encapsulating them in GelMA membrane with enhanced viability and spreading of cells. The presented study revealed a practical platform, which has a potential in development of in vitro essays to investigate complex cell-to-cell and cell-extracellular matrix interactions. In another article, Shirwaiker and his coworkers at North Carolina State University integrated 3D printed polycaprolactone (PCL) hard scaffolds with cell-encapsulating alginate spheroids to demonstrate the capability of loading cells with high cell density on scaffold constructs. In their study, electrostatically generated calcium alginate spheroids encapsulating MG-63 model bone cells were pipetted onto the scaffolds, and porous architecture of the scaffolds was controlled to entrap spheroids. Uniform distribution of calcium alginate spheroids was observed, and encapsulated cells remained viable over a week incubation time. Another interesting hybrid bioprinting approach was presented by Starly's research group at North Carolina State University for neural tissue engineering. In their new approach, PCL was first printed in two-layer mesh structure in microscale followed by electrospinning PCL material onto the micromesh structure generating a layer of nanofiber mesh structure. The fabricated multiscale hybrid constructs were later used to bioprint alginate strands on them, where alginate strands encapsulated cells from PC12 neural cell line. The structure was then rolled to create conduit shape to mimic the morphology of nerve tissue. Their study revealed that PC12 nerve cells demonstrated high cell viability and proliferation at a rate consistent with traditional two-dimensional (2D) culture.

In addition to advances in biofabrication and biomaterial science, novel developments in bioprinter technologies are also highly crucial to push the emerging field forward. Particularly, bioprinters enabling bioprinting of multiple bioink materials into hybrid tissue constructs is a great need to recapitulate complex tissue biology. In this regard, Campbell et al. at Fraunhofer USA presented a new multimaterial multiscale 3D bioprinter comprising three components including syringe pumps, a high velocity/high precision motion stage, and a temperature control unit. The presented development was verified by bioprinting heterocellular vascular tissue construct by localizing endothelial and smooth muscle cells in the inner and outer region of the construct, respectively. Moreover, versatility of the presented bioprinter was demonstrated by bioprinting various hydrogels using extrusion-based layer-by-layer deposition approach in 3D.

In addition to extrusion-based bioprinting, laser-assisted bioprinting (LAB) has been used in bioprinting of living tissue constructs and is preferred due to its high resolution and accuracy capability in patterning living cells very precisely. Although LAB technology has been predominantly used in 2D patterning of cells, recent advances in LAB enable bioprinting of tissue constructs in 3D. In this regard, Guillemot and colleagues at the Bordeaux University demonstrated a LAB technology enabling bioprinting a cell solution with 100×10^6 cells/ml density achieving $138 \pm 28\ \mu m$ in resolution and $16 \pm 13\ \mu m$ in precision.

Although 3D printing has been widely used in tissue engineering, it demonstrates great potential in other fields such as orthopedics, pharmaceutics, prosthetics, and biomedicine. Apart from the presented articles, Gurkan's group at Case Western Reserve University demonstrated 3D printing of microfluidic devices used in medical applications, where a hybrid manufacturing approach complementing strengths of 3D printing and laser machining was implemented to offer a new way of fabricating complex microfluidic devices with integrated manifolds. The presented approach generated high-level complexities, and the authors validated their approach by successfully perfusing microbeads and CD4+ T cells with uniform distribution among all channels.

In his Expert View paper, Ozbolat from the Pennsylvania State University presented his opinion on scaffold-based and scaffold-free approaches used in bioprinting of living tissue models. In scaffold-based approach, cells are seeded on scaffold surface or encapsulated in scaffold matrix enabling growth of new tissues; however, several impediments such as degradation and limited cell density and cell-to-cell interactions still exist. Although, scaffold-free bioprinting, where no exogenous material is used to support cell growth and proliferation, overcomes the abovementioned limitations and has recently gained great interest while it enables fabrication of biologically recapitulated tissue models, bioprinting of large-scale tissues and organs is still elusive. In his article, Ozbolat discussed the advantages and disadvantages of both approaches and presented a new conceptual framework in how both approaches can complement each other toward bioprinting of scale-up tissues.

I would like to thank all the authors for their contributions, reviewers for their valuable time and effort in ensuring high quality publications, and the ASME JNEM Staff and Editorial Board for support in completing this Special Issue. The collection of the papers presented recent advances in bioprinting science and technology, which will stimulate new research directions and prospects in this emerging interdisciplinary field. I hope you enjoy reading this special issue.

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