Better Bioprinting Ahead

Breakthroughs and Remaining Challenges

Brian Gazaille

Bioprinted organs soon could revolutionize clinical trials, transplantation, and regenerative medicine. But as Chris Lo reminds us in a new *GlobalData* report (**1**), several technical hurdles must be negotiated before biopharmaceutical companies can harness three-dimensional (3D) printing for such purposes. BPI explores persistent printing problems and promising solutions below by analyzing Lo's report alongside commentary from founding editorial advisory board member **Bill Whitford** (bioprocess strategic solutions leader at GE Healthcare Life Sciences), **Lev Gerlovin** (vice president in the life sciences practice at Charles River Associates, CRA), and **Andrew Thomson** and **Jack Vailas** (both associates at CRA).

Handy Hardware

Until recently, technical gaps made 3D bioprinting slow and inefficient. But new hardware is improving the handling of cellular substrates. Lo highlights Cellink's BIO X6 printer (**2**) as a particularly promising model, noting that the technology "incorporates six electromagnetic droplet printheads to enable faster printing of complex structures with mixed biomaterials and cell types."

Whitford adds, "Commercially available bioprinters increasingly are supplying features that increase control over the printing process: temperature and humidity controls; multiple head-motion mechanisms (e.g., liner actuators); multiple effectors with different levels of interchangeability, including components that can be changed midprocess; effectors with different degrees of articulation; and printing trays of different sizes."

Shaping the Future

"Bioinks" are improving equally quickly. Whitford states that companies now offer a strong selection of "ready-to-use" formulations that include buffers and nutrients. "These bioinks boost printing resolution, limit sheer, increase mechanical strength, and improve cytocompatibility and crosslinkability."

But bioink components still need to be adequately adhesive. Lo explains, "Synthetic polymers are mechanically strong, but they are nondegradable and can lack the adhesive qualities [needed] to support adequate cell growth." Natural polymers are "not as strong as their synthetic counterparts but are much better suited to cell attachment, proliferation, and differentiation." Plant-based materials promise the best of both worlds.

In April 2019, researchers from Swansea University in Wales, UK, published an article to support plant-based applications (**3**). Lo reports, "The team highlighted nanocellulose and alginate," noting how they "combine the strength of plant microarchitecture with the natural benefit of cell-growth support."

Maintaining the shape of bioprinted tissue remains a challenge. Scaffolds often are used to bolster tissue and seed-cell integrity. But Lo suggests that scaffold degradation can provoke immunogenic or cytotoxic side effects. In March 2019, teams from Japan's Nagasaki and Saga Universities proposed eliminating scaffolds (**4**). Using a multicellular spheroid technique, they fabricated 3D esophageal tissue. A few months later, researchers from the University of Illinois at Chicago (**5**) and the University of Birmingham, UK (**6**), publicized their respective scaffold-free processes, which use hydrogel beads to support printed constructs.

Capillary Action

Without vessels to supply oxygen and nutrients and to remove waste products, printed organs cannot survive. Thus, microfluidic research is critical to the success of organ printing. Cellink and Prellis Biologics are addressing vascular challenges with their Holograph X bioprinter (**7**). Lo states that the device "is designed to facilitate manufacture of capillary-containing organ structures for transplantation using ultrafine resolution and laser-based holographic projection printing."

Lo adds that teams at Harvard University's Wyss Institute for Biologically Inspired Engineering (MA) are developing a similar technique called "sacrificial writing into functional tissue" (SWIFT) (**8**). "[It] works by placing a network of vascular channels into a living matrix of stem cell-derived organ building blocks, creating a structure that mimics the cellular density of human organs while allowing for the supply of nutrients and oxygen through vascular channels." Lo notes that "channels are created by a thin bioprinting nozzle, which prints the titular 'sacrificial ink' into the matrix, moving other cells out of the way without damaging them."

Back to the Future

Gerlovin, Thomson, and Vailas spoke as one: "Even though scalable manufacturing of replacement organs and tissues remains a visionary ambition, bioprinting already has begun to revolutionize healthcare." Several pharmaceutical companies and research institutions "are capitalizing on the accuracy, scalability, and cost efficiency of bioprinting to increase the volume and complexity of regenerative therapeutics and diagnostic tests." Mechanically derived organic constructs are enhancing the precision and accuracy of preclinical testing. "Commonly referred to as *organoids*, these constructs closely resemble in vivo drug response, toxicity, and pathophysiology given their

heterogenous microarchitectures, which mimic the cell–cell and cell–matrix interactions of native tissue environments." By developing such technologies further, bioprinting pioneers are "spearheading the development of in vitro platforms for pharmacokinetic testing."

Although analytical and diagnostic applications abound, therapeutic constructs are garnering significant attention. "Several patients within a limited number of clinical trials already have received engineered skin, urethras, blood vessels, and bladders. 2D tissue constructs such as bone, skin, and cartilage present researchers with early therapeutic targets, aided by their lack of structural complexity as compared to more highly vascularized tissues." Acellular organic scaffolds also hold promise for in situ tissue generation. "Because that process does not involve the direct incorporation of living cells, therapeutic scaffolds represent bioprinting's initial route of entry toward the scalable manufacturing of tissue engineered medical products (TEMPs) for therapeutic use." Thus, bioprinting now is poised to generate "simple therapeutic structures that could supplant current gold standards of treatment."

Whitford adds that preclinical testing of vascular implants, miniature-liver models, and regenerative esophageal structures has progressed rapidly. Current applications are even more exciting: e.g., bioprinted microfluidic devices, commercially available human-tissue kits that support animal-free drug and materials testing, and multiple–cell-type organoids for personalized diagnostic applications. Regardless of application, regulatory agencies are recognizing the promise of 3D bioprinting. That confidence, Whitford points out, is "reflected in the now two-year-old US Food and Drug Administration (FDA) guidance on *Technical Considerations for Additive Manufactured Devices*."

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