3D bioprinted skin: the first 'to-be' successful printed organ?

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Industrial revolution brought in a transformation in the way things are manufactured. Hardly would have anybody thought that a second industrial revolution is coming when living tissues and organs are manufactured and sold in markets. The time is at hand. With the advent of 3D printing, the manufacturing sector is witnessing a second industrial revolution. 3D bioprinting, a subset of 3D printing is revolutionizing the field of tissue engineering and regenerative medicine. The unique advantage of this technology is the ability to fabricate customized patient-specific biomimetic structures out of living cells. There are three types of bioprinting processes, namely laser-based forward transfer, extrusion or robotic dispensing and ink-jet bioprinting. Successful early attempts at bioprinting various kinds of cells and tissues using all three types of bioprinting processes are reported in literature. Various types of bioinks, hydrogels and polymers are printed using these technologies. Smart hydrogels are a new group of materials that respond to various external stimuli, such as temperature, pressure or pH, and are being developed for 4D bioprinting, the fourth 'D' being time. While bioprinting of fully functional living organs is a herculean task to achieve, good news is that we are moving faster than ever to accomplish that feat. Many reports of bioprinting of liver, heart, bladder, skin and cartilaginous tissues are published [1], which demonstrate the rapid progress toward functional organ fabrication.

Though there are earnest attempts to print various organs, in my opinion, the first one to successfully reach the market would be the bioprinted skin. There are compelling reasons for this contention of mine. First, the need for bioprinted skin is not only limited to regenerative medicine and organ transplantation. There is a huge demand for artificial skin in the cosmetics and skin care industry for product testing as testing on animals is being banned in many countries. Popular players such as L'Oréal and Procter & Gamble are going in the technology of bioprinting 3D skin organotypic models [2]. Bearing in mind the challenges of passing the regulatory hurdles for bioprinted organs to be transplanted to humans, it is rather comparatively easier to use bioprinted skin for cosmetic testing. Second, the flat layered structure of skin is easy to print compared with other complex organs such as a heart or kidney. Third, the fact that there are skin substitutes commercially available in the market already for wound dressing and burn treatment (e.g., Apligraf®, INTEGRA® etc.), makes the regulatory approval pathways easier for bioprinted skin.

Bioprinting of skin involves six main process steps, namely imaging, design approach and modeling, selection of materials, selection of cells, bioprinting and finally transplantation/cosmetics or drug testing. If the intended application of the bioprinted skin is transplantation to humans or wound healing, imaging is the first step. Acquiring data about the type of wound, wound size, wound depth and

contour by techniques such as computed tomography, MRI, active dynamic thermography, converting the 2D images to 3D models are some of the critical steps involved in the imaging process. Capturing of the skin texture and color is also important. Based on the data acquired, design approach is decided as to single-layer or multilayer (depending on the depth of injury), scaffold-less or scaffold approach (depending on the wound area) and the like. For cosmetic testing, imaging and design approach might not be critical as standard organotypic models are preferred for testing. However, a database of skin types (normal, dry, oily, combination or sensitive), skin texture and skin color might be a starting point to have bioprinted skin models of various types enabling effective product testing. Selection of materials comes next. Natural polymers, synthetic polymers and decellularized extracellular matrix are some choices. Natural polymers such as collagen and chitosan resemble the native extracellular matrix and are more cell friendly, while synthetic polymers have good mechanical properties and structural integrity. Primary cells from patients or cell lines could be used depending on the application. More than one type of cells (fibroblasts, keratinocytes and melanocytes) is preferred to fabricate a multilayered biomimetic skin model. One of the three bioprinting processes could be then used to fabricate the skin based on the required resolution, precision and scalability. Postprocessing of the bioprinted construct involves tissue maturation in a bioreactor. Finally, the bioprinted skin is transplanted onto humans or used for drug or cosmetics testing.

Having explained all the steps involved in bioprinting of skin, there are challenges in each step that are to be addressed before bioprinted skin could successfully be translated into market. Bioprinting of skin with all the constituent cell types, appendages and hair follicles is the first challenge. Recently, a group of scientists from Japan reported fabricating bioengineered 3D skin with hair follicles and sebaceous glands [3], which is a remarkable achievement and a great leap to have fully functional bioprinted skin. Further research is needed to create functional skin with sufficient vascularization, innervation and functions such as touch sensation and perception. Reproducing the color and texture of the native skin is another important challenge. How does one fabricate dry skin and oily skin? How about

different textures of skin? How about European white skin, Asian moderate and African dark shades of skin? Scalability and affordability are two other snags to overcome. There are some ethical, social and legal challenges that need attention before the technology and the product can be successful [4].

I foresee that bioprinted skin will find its way into the market stage by stage, as given below:

- Cosmetics/skincare product testing: cosmetic companies would first test their products on skin models as an alternative to animal testing;
- *In vitro* assay system: pharma industries will then start testing their drugs and chemicals by using bioprinted skin as *in vitro* models;
- Organ transplantation: treating burn wounds and injuries using bioprinted skins; cells taken from the patient's own body will be used in the bioprinting process;
- *In vitro* 3D tumor models: tumor models with engineered tumor microenvironment for studying the modus operandi of cancer proliferation, metastasis and drug response; and
- Precision medicine: with the 3D skin model/tumor model, drug effectiveness can be studied for each patient and thereby aid in personalized medicine.

In conclusion, there has been a commendable progress in bioprinting of skin and we are almost there in fabricating a biomimetic functional skin. In less than a decade, we could see bioprinted skins put to use for various applications as stated above. A concerted research among various disciplines could be more productive and the effective time of translation from bench to bedside could be considerably shortened.

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