Review Article

Prospects of emerging 3D bioprinting technologies: major technology components, technology developers, and end users—Part I

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Abstract

Bioprinting technology aims to create 3D structures with living cells to mimic real tissue and organ functions. The process involves various additive technologies, including 3D bioprinters and bioinks. Bioinks comprise hydrogels, scaffolds, additives, growth factors, and living cells. While much of the technology is still in the exploratory stages, it has successfully produced living tissue, blood vessels, and bones. Research suggests the potential for bioprinting whole organs to revolutionize medical procedures. Current major business components include various types of bioprinters and advanced bioinks. Advancements in technologies such as cellular reprogramming hold the potential to enhance the development of superior bioinks, thereby enabling the fabrication of 3D bioprinted tissues. 3D bioprinting technology offers significant benefits across research, personalized medicine, and other applications. This review provides a flavor of the potential benefits of using 3D bioprinting technology in various areas of usage, including Research and Development (R&D), and its applications on a wide spectrum, including personalized medicine.

Keywords: 3D bioprinting, bio-fabrication, bioinks, bioprinters, regenerative medicine, tissue engineering

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INTRODUCTION

It is possible to construct natural tissue-like three-dimensional (3D) structures through technology, using bioinks mixed with living cells and printed in a 3D manner to construct natural tissue-like 3D structures. This technology is evolving and is called 3D bioprinting technology.

The history of 3D printing dates back to the early 1980s when an American Engineer by the name of Hull,[1] popularly known as Chuck Hull, built the first 3D printer using acrylic-based photopolymer following a computer-aided design (CAD) and made the print 3D by simultaneously crosslinking the print with UV light. The then-new 3D printing technology, stereolithography, was applied to developing 3D bioprints using bioinks containing living cells.

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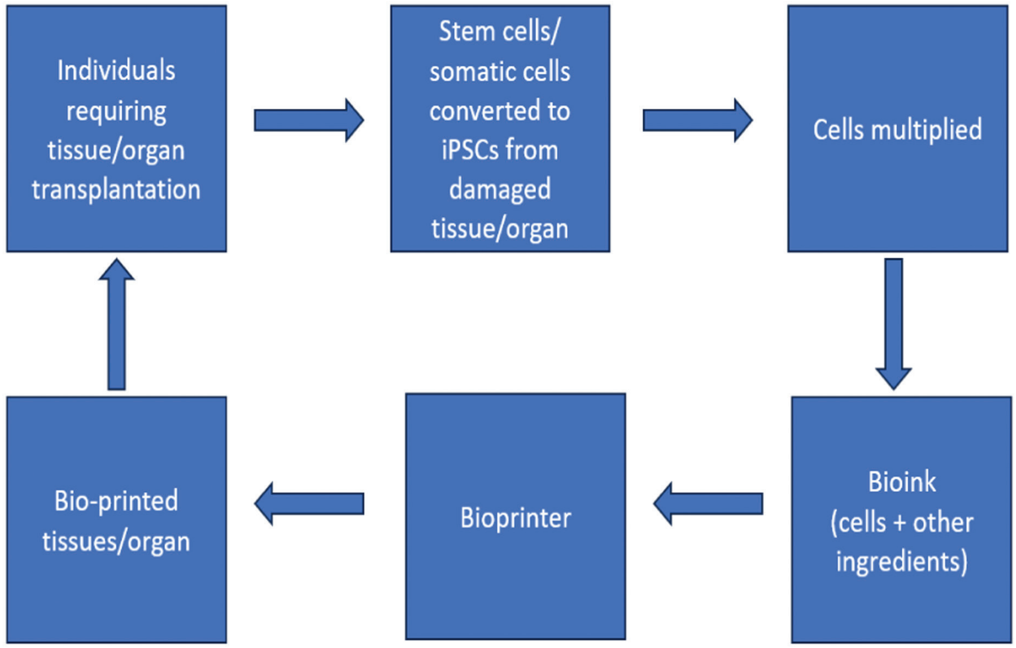

Figure 1: Essential steps in 3D bioprinting for tissues and organs

Bioprinting technology involves the creation of 3D structures using a combination of living and nonliving materials, primarily aimed at replicating the functionalities of real tissues and organs. These structures are produced by integrating various additive techniques, including stereolithographic printing guided by computer-aided design (CAD), resulting in bioengineered constructs. Such constructs find applications across numerous fields within cell biology research.

Adult stem cells are found in tissues or organs. Stem cells can be isolated from that place and multiplied *in vitro* to magnify their numbers. Somatic cells can also be converted into induced pluripotent stem cells (iPSCs), multiplied *in vitro*, and used instead of stem cells. Stem cells can differentiate and produce specialized cells, tissues, or organs from where the stem cells were isolated. Engineered extracellular matrices or scaffolds can be used with stem cells to regenerate tissues or organs outside the human body.

A primary objective of 3D bioprinting technology is to create *in vitro* tissues or organs that can replace damaged tissues or organs in individuals.

The development of biomedical scaffolds requires standardization and the use of tissue engineering techniques. Bioprinted scaffolds must sustain the diploid human cell proliferation with regular "G1-S-M-G2" cell cycles to produce many diploid cell progenies. Bioink is an essential and critical component in the development of biomedical scaffolds. Bioink is an appropriate hydrogel that should have numerous rheological, mechanical, and biological properties for producing appropriate tissue constructs. The development of a standardized bioink is a challenging factor in the success of bioprinting. Bioprinters and the printing processes are other critical components for the success of this emerging technology. Standardizing the quality of input materials is equally crucial, with various methods being employed to ensure consistency in critical variables, aiming for enhanced outcomes.[2-4]

3D bioprinted products include biomedical devices, tissues, and organs; bioengineered prosthetics and implants; and new drug development devices and biosensors. The above simplified flowsheet depicts the essential steps in the 3D biomanufacturing process for human tissues and organs [Figure 1].

By creating conditions that enable the 3D bioprinted tissues to change shape, size, and functionality over time, a new terminology of 4D bioprinting is also used for the 3D bioprinted materials in certain situations.

3D bioprinted technology is emerging to revolutionize the microfabrication industry. Microfabrication is fabricating miniature structures on micrometer scales and even smaller ones. Microfabrication applications include tools for molecular biology and biochemistry, tools for cell biology, medical devices, and biosensors. Such miniature structures can be used as biomedical devices, self-healing appliances, sensors, microfluidics applications, and microelectronics devices. The applications are anticipated to generate biomaterials that replicate parts that imitate natural tissues, blood vessels, several organ systems such as nervous, cardiovascular, skeletal, integumentary, endocrine, exocrine, gastrointestinal, respiratory, urinary systems, bones, cartilages, and other body parts[5] by layer-by-layer deposition using different types of biomaterials, stem cells, iPSCs, and biomolecules.[6]

3D bioprinting technology would enable precise control over compositions, spatial distributions, and architectural accuracy of bioprinted tissues using bioinks containing scaffolds and the use of homogenous cells derived from *in vitro* multiplied primary cells or stem cells, including induced pluripotent stem cells (iPSCs), depending on the intended application. The scaffolds used in the technology serve as 3D templates to support cells to attach, increase, and expand throughout the entire structure. Eventually, the composite structures develop their extracellular matrix (ECM). The ECM, after that, leads to the generation of mature cell-laden grafts with properties comparable to their native counterparts. In regenerative medicine, the fabrication and use of such 3D bioprinted composite structures as tissues for blood vessels, the heart, the liver, and cartilage are the aim of 3D bioprinting technology in the long run.[7]

3D bioprinting technology addresses a key challenge in tissue engineering by offering scalable and precise fabrication of vascularized tissue constructs. Several reviews have highlighted the advancements in 3D bioprinting technologies and generating biomaterials for future applications in vascularized tissue fabrication. Vascularization refers to the process of growing channels into tissues to improve oxygen and nutrient supply. Successful fabrication of vascularized tissue involves coordination and synergy among multiple operations, such as forming the growing perfusable channels during 3D printing with the deployed bioink containing the right living cells so that angiogenic sprouting of the growing nutrient channels occurs during the cell multiplication. There are major challenges in achieving the precise end objectives of vascularization. Vascularization is critical for the engineered tissues' prolonged survival and functional maturation. A number of recent reviews have addressed the challenges outlining the prospects in the field using 3D bioprinting technologies to promote vascularization, and to produce vascularized tissue constructs.[8,9] Integrating bioprinting with patient-derived stem cells and specific biomaterials shows promise for creating functional vasculatures, advancing personalized therapies, and drug discovery in regenerative medicine.[10]

Technology in its present forms of development can be immediately used in multiple research areas, such as new drug development[11] and tissue engineering research.[12]

New drug development is a highly expensive and time-consuming process. It takes nearly 14 years and requires an average expenditure of about USD 1.336 billion (at 2021 USD prices) to discover a new drug.[13] If 3D bioprinting technology can help speed up the drug development process to reduce the development time, it would be a boon for the pharmaceutical industry, as it could quickly identify the most promising drugs. In new drug development research, 3D bioprinted organoids and organs-on-chip assemblies have been increasingly used. The *in vitro* 3D bio constructs in drug development research hold multiple potentials. In some situations, these include replacing animal studies before clinical trials by developing organ-on-chips and microfluidic models for drug development and precision medicine. Drug development through better understanding in the cancer research area, *in vitro* respiratory models for toxicity studies in research in the lung research area, transport and metabolism of nutrients and drugs in intestinal biochemical processes, and aspects of brain research are examples of the potential use of *in vitro* 3D bio-constructs.

Organoids are 3D-cell cultures derived from pluripotent stem cells. Organoids mimic human organs' structure, function, and cellular complexity with remarkable details and accuracy. Organoids are made using an extracellular matrix that supports the cells. Human organoids enable the study of many human diseases, such as infectious diseases, noninfectious tissue and organ disorders, genetic disorders, and cancers. Data generated from human organoid composites complement[14] data generation in animal models. By creating innovative 3D bioprinted tissues, it is anticipated that evaluating new molecules will be speeded up with high-throughput capability, high reproducibility, and high precision, helping the pharmaceutical industry to quickly identify and focus on the most promising new drugs.[15] 3D bioprinting technology can create bioengineered tumor models *in vitro*, mimicking human tumor tissues. These models aid in anticancer drug screening and precision treatment regimens by replicating real tumor heterogeneity.[16,17] 3D tumor organoids created by using bioprinted tumor cells collected from patient tumors would be useful for studying gene expression profiles, and such models can be used for therapy development and selecting effective molecules in cancer research.[18] Organ-on-a-chip can match and imitate physiological conditions better than conventional cell culture models. Such chips can closely match tissue and organ physiology regarding crucial parameters like perfusion. 3D bioprinted organoids in hydrogels were found to be of better efficiency than non-bioprinted organoids. Organ-on-a-chip reduces labor costs, reagent usage, and human error by supporting automated operating systems.[19]

Tissue engineering aims to fabricate functional tissues useful for applications in regenerative medicine and drug testing. The basic elements of tissue engineering are living cells, scaffolds, and cell growth information. Biocompatible scaffolds are to be generated and are expected to support cell colonization, migration, growth, and differentiation. The fabricated scaffolds are usually in miniature structures, known as microfabrication structures. Such 3D structures are on the micrometer scale. Microfabrication applications include tools for molecular biology and biochemistry, tools for cell biology, medical devices, and biosensors. Although there have been considerable developments in the basic understanding, there is considerable scope for developing cell sources and cell support materials to enable unique immune modulation and vascularization. In these contexts, computer-aided mathematical modeling systems will be very useful for developing devices in individual patient care.[20,21] There is no approved tissue-engineered, bioprinted, or fabricated scaffold for human medicine, although research in this field is copious and vigorous.

The emphasis on the trend in academic research, the emerging and presently established technology hubs in industries, and the world's regions from the patent literature landscape provide clues to future market developments through the 3D bioprinting technologies integrated into certain current literature. It appears that successful industrial ventures that could combine and integrate engineering expertise in additive manufacturing technologies, including living cell handling and optimization of healthy cell growth and differentiation, together with biomaterial developments and expertise in biomedicine and pharmaceutics, would be able to reach the marketplace fast. The technology is predicted to grow initially in making cell scaffolds to help repair damaged personalized ligaments, joints, and body parts, as well as in drug discovery research.

In summary, 3D bioprinting technology would create innovative artificial biological structures and tissues resembling natural substances using appropriate cells, biopolymers, scaffolds, and bioinks. This technology is anticipated to revolutionize the basic understanding of life sciences and biology, as it can build multiple kinds of tissues from scratch. The 3D bioprinted structures shall enable not only the repair of damaged tissue of diverse kinds in various organs, besides enabling drug screening, but the technology shall also enable the exploration of cellular crosstalk and cellular morphogenesis.[22]

This paper aims to review the major published scientific literature on 3D bioprinting techniques and to highlight the importance and potential benefits of using the techniques in current and evolving personalized medicine in a wide spectrum and the evolution of 3D bioprinting start-up companies globally using these technologies. In Part I of the paper, the major technology components of 3D bioprinting technologies, the developers of the technologies, and the end users are profiled. Part II of the paper will discuss the major start-up companies and the regulatory issues required to be addressed and resolved for human use of 3D bioprinted scaffolds, tissues, and organs.

3D printing (not bioprinting) enables identifying pills from shapes, and prints are produced for treating the individual condition of the patient; pills can be printed by 3D printing technology, which is loose in texture and, therefore, would reduce swallowing difficulties; the technology can also be used to make transdermal microneedle patches to reduce the pain of patients. Multiple such applications[23-25] can be had through 3D printing of dispensed medicines and medical devices, which have many advantages. Various 3D-printed devices have been approved for use by the regulatory authorities. However, this paper does not discuss 3D printing technologies, where living cells are not used.

MAJOR POTENTIAL APPLICATION AREAS OF 3D BIOPRINTING TECHNOLOGY

3D bioprinting technology shall be applied in various biomedical fields, including developing biomedical devices, medicines, bioengineered prosthetics, implants in dentistry, drug testing, and new drug development devices and biosensors. Briefly, these areas are further explained and elaborated.

BIOMEDICAL DEVICES AND MEDICINES

Tissue-engineered organs

3D bioprinting is being explored to create 3D structures of organs and tissues. This can potentially revolutionize organ transplantation by providing an alternative source of organs for transplantation. The restoration of damaged or dysfunctional cells, tissues, or organs for various reasons is anticipated to be possible by using appropriate 3D technologies. Such technologies would be part of regenerative medicines. The developmental areas include wound care, burn care, scar treatment, nerve regeneration, fat grafting and adipose stem cell therapy, face transplantation, generation of new skin via tissue expansion, bone regeneration, and many more. The work would involve using a person's cells and tissues. 3D bioprinting is being used to create skin tissue for wound healing applications. This includes the development of skin grafts with the patient's cells. Artificial skin (AS) is a skin substitute for wound healing. While there is copious research in many parts of the world on the manufacture of AS, there are multiple challenges, which include standardization of complicated preparation conditions, stability and robustness issues of the printed skins, and several others. However, publications claiming to solve such issues are coming out quickly.[26] The hematoxylin, eosin (H&E), and immunofluorescence-stained AS have shown that the bioprinted skins were morphologically close to the human skin.[27]

The technology promises to produce personalized medicines tailored to individual patients' needs. Tissue-engineered medical products (TEMPs) are biomaterial-based products containing living cells that are to be implanted during a therapeutic procedure into the body of the treating patients. TEMPs are personalized medicines and hold enormous potential for treating individuals. TEMPs are quickly developing globally[28] and are currently in the R&D stage. Among the TEMPS, those with hollow structures and simple geometry, like different kinds of skin, cartilage, and bladders, are anticipated to be the easiest 3D bioprinted organs to emerge fast in the market.

Bioengineering prosthetics and implants in dentistry

Customized prosthetics and dental implants can be created using 3D bioprinting to match the specific anatomy of individuals, leading to better functionality and comfort. Dental tissue engineering and regenerative dental medicine hold enormous potential to treat edentulism (without natural teeth) and other dental-related diseases.[29] Heavy R&D investments are being made in certain parts of the world to enable the development of effective, biocompatible dental scaffolds for use in dentistry.

Drug testing and new drug development

As mentioned in the text earlier, the 3D bioprinted tissues can be used for drug testing, allowing researchers to study the pharmacokinetics of new drugs on human tissues more accurately than traditional cell culture methods.

Biosensors

Biomedical sensing devices are characterized[30]by the miniaturization, customization, and elasticity of bioprinted devices, enabling the quantification of biomarkers in complex medical areas. Other areas of interest include rapidly sensing pathogens and pathogen biomarkers enabled by 3D printing. Researchers in academia and industry shall benefit when a wide range of bioprinted biosensors are available for use in multiple areas of exploration. Bioprinted biosensors are being devised with high performance in real-time monitoring of physiological events, detection of adverse events, detection of toxins, and performing several other functions.[31] Biosensor fabrication and scaling up are important considerations for biosensor devices, where the focus is on optimizing bioprinting techniques such as microcontact printing, inkjet printing, and laser-direct-write to expand the utility and availability of biosensors widely.

MAJOR COMPONENTS OF 3D BIOPRINTING TECHNOLOGY

In the emerging 3D bioprinting technology, bioprinters and materials used in printing are critical for creating functional and biocompatible structures. These materials are designed to accommodate living cells and provide an environment conducive to cell growth and tissue development. Here are some key components and materials used in 3D bioprinting on which brisk R&D work and continuous developments occur.

Bioprinters

Based on their working principles, the 3D bioprinters can be classified into four groups[32] such as (a) droplet-based, (b) extrusion-based, (c) laser-assisted, and (d) stereolithography technique-based. At present, commercially, seven types of bioprinters are available, which include (1) inkjet types, (2) laser-assisted types, (3) extrusion-based types, (4) stereolithography types, (5) acoustic-based types, (6) microvalve-based types, and (7) needle array-based bioprinter types. Inkjet-based, laser-assisted, and extrusion-based are the three most common types of widely used bioprinters.

These bioprinters have unique advantages and disadvantages compared with cost, cell viability, cell density, resolution, and more. All these bioprinters are fabricated to print liquid- and gel-based materials. These printers can additionally perform non-contact droplet printing. Various authors used inkjet bioprinters to carry out analyses of several parameters, such as live cell analysis and cell behavior analysis of bioprinted human colorectal carcinoma cells, human dermal fibroblast cells, porcine cells, and rat cells, and it was found in a review[33] that the printer performance was satisfactory. Laser-assisted bioprinters are the most expensive, although such printers have several advantages, such as high cell viability in the bioprinted products. Laser-assisted bioprinters have five main elements: a pulsed laser beam, a focusing system, a ribbon-structure donor layer containing an energy-absorbing layer, a liquid bioink solution layer, and a receiving substrate layer. Laser-assisted bioprinters are compatible with different types of bioinks and are, therefore, more versatile. The advantages and disadvantages of the three types of bioprinters have been compared.[34] Different bioprinters are available in the market and are supplied from various countries at different prices.[35-37] Biologists in different countries can procure one or more of the best ones according to their requirements and conduct developmental work using bioprinters.

Bioinks

Bioinks are biomaterials that provide living cells with temporary or permanent support while the cells multiply and produce their extracellular matrix resembling body tissues. The properties of bioinks closely relate to the properties of bodily tissues. There are presently a variety of bioinks used in different aspects and conditions of biomedical research. Each bioink is a crucial component in 3D bioprinting, serving as the "ink" used to create the 3D structures of living tissues and organs. The main kinds and types of bioink materials are hydrogels, microcarriers, cell aggregates (in the forms of cell pellets, tissue spheroids, and tissue strands), and an extracellular matrix.

Unlike traditional 3D printing, which uses materials like plastic or metal, 3D bioprinting requires a special type of ink compatible with living cells and tissues. Bioink is designed to provide a supportive environment for cells to thrive and interact, allowing for the creation of complex biological structures.

Some key characteristics and components of bioink are biocompatibility, viscosity, and printability; structural support issues; biodegradability; cell encapsulation characteristics and properties; cross-linking ease; and tolerability.

Biocompatibility: Bioink must be biocompatible, meaning it is not harmful to living cells and can support their growth and function. This is essential for maintaining the viability of cells during and after the printing process.

Viscosity and Printability: The viscosity of bioink is important for its printability. It needs to have a consistency that allows it to flow through the 3D printer's nozzle and be deposited in a controlled manner layer-by-layer. Different bioinks may have varying viscosities depending on the specific application.

Structural Support: Bioink should support printed tissue or organs. It must maintain its shape during and after printing to create stable and functional structures.

Degradability: In some cases, it's desirable for the bioink to be biodegradable or have controlled degradation properties. This allows the printed tissue to integrate with the host tissue over time as the bioink breaks down, promoting natural tissue regeneration.

Cell Encapsulation: Living cells play a pivotal role in the composition of materials used in 3D bioprinting. Bioink, comprising living cells, which may be either primary or stem cells, depending on the intended purpose, is employed. These cells are suspended within the bioink and are meticulously deposited to create the desired tissue architecture. Cellular reprogramming techniques can reset cell aging clocks, transforming human somatic cells into a pluripotent embryonic stem cell-like state. This transformation empowers the cells to differentiate into diverse tissues and organs.[38-40] Utilizing such cells facilitates the development of 3D bioprinted structures and tissues, which hold significance in investigating human diseases, the advancement of novel drug therapies, and personalized regenerative cell treatments.

Crosslinking: After printing, bioink may undergo a crosslinking process to solidify the structure and enhance its stability. Crosslinking methods can include chemical, physical, or biological processes.

Tailorability: Bioink formulations can be tailored to specific tissues or organs, considering the unique requirements of different cell types and tissues in the human body.

In summary, it needs to be emphasized that bioinks form special materials for the success of 3D bioprinted products, using which living tissue, bone, blood vessels, and other tissues are constructed. Bioinks shall also be one of the most crucial materials in constructing whole organs when such technologies mature and when bioprinted whole organs are deployed for medical procedures. The crucial roles of bioinks focusing on bio-fabrication techniques have been reviewed in recent literature.[41-43]

Hydrogels in bioinks

Hydrogels are a common base for bioinks. They are water-absorbent materials that provide a 3D environment for cells. Hydrogels mimic the extracellular matrix (ECM) found in natural tissues and can be modified to support specific cell types. Hydrogels are soft materials that can be engineered to mimic the extracellular tissue microenvironment. As a result, these can have medical applications such as biosensors, scaffolds for tissue regeneration, and drug delivery technology. Hydrogels include[44] purified natural polymers made from agarose, alginate, collagen, gelatin, fibrin, hyaluronic acid, and Matrigel. Matrigel is a gelatinous protein mixture derived from mouse tumor cells and is used in cell culture and *in vivo*. Mulberry silk-based and Indian nonmulberry silk-based proteins, such as fibroin and sericin, are useful in various bioprinting applications, including bioinks. Hydrogels, such as polyethylene glycol, and certain poloxamers, which are synthetic polymers, have also been used. Properly chosen hydrogel-based bioinks are promising options for the development of bioprinting technology. The development of new hydrogels is a continuous process.

In summary, developing advanced bioinks is an active area of research in 3D bioprinting. Researchers are working on improving the properties of bioinks to enhance cell viability, structural integrity, and the overall functionality of the printed tissues. These advancements are critical for the potential future use of 3D bioprinting in regenerative medicine and organ transplantation.

Other support materials in bioink

Scaffolds

Scaffolds are biodegradable materials. These act as temporary templates.[45] Scaffolds interact with cells and integrate with native tissues.

Crosslinking agents

Chemical crosslinkers: These substances promote the crosslinking or solidification of bioinks. Crosslinking is often required to stabilize the printed structure. UV Light or Temperature-Based Crosslinking: Some bioprinting techniques use external stimuli, such as UV light or temperature changes, to induce crosslinking.

Proteins and growth factors as additives

These materials are sometimes incorporated into bioinks to provide signals that promote cell differentiation, proliferation, and tissue development.

Nanoparticles

Biocompatible nanoparticle materials are added in certain situations in bioinks to enhance the mechanical properties or introduce specific functionalities to the printed structures.

Synthetic polymers

Certain synthetic polymers, such as polyethylene glycol (PEG) of certain chain lengths, polylactic acid (PLA), and others, are sometimes added to the bioinks to impart certain mechanical properties of the printed structures.

It's important to note that the choice of materials depends on the specific application, the type of tissue or organ being printed, and the 3D bioprinting technique used. Researchers continue to explore and develop new materials to improve the biocompatibility, mechanical properties, and overall performance of 3D bioprinted structures.

End users of 3D bioprinting technology

The end users of 3D bioprinting technology span various sectors within healthcare, research, and industry. Here are some key end users of 3D bioprinting technology:

Medical professionals and hospitals

Surgeons can benefit from 3D bioprinting technology for pre-surgical planning and practicing complex procedures on patient-specific models. 3D bioprinting holds the potential to provide organs and tissues for transplantation, reducing the need for donor organs.

Pharmaceutical and biotechnology companies

Drug Development Researchers can use 3D bioprinting technologies in drug development to test new pharmaceutical compounds' efficacy and toxicity on bioprinted tissues, offering a more accurate representation of human physiology than traditional cell culture methods.

Market success in setting up start-ups and expansion in the existing companies in 3D bioprinting technology as new divisions are yet highly competitive and uncertain.

The author observed that start-up companies are hovering around features of new product developments; many are seeking collaborations and partnerships for sustainability; many are seeking funds for sustenance; and many others are adopting more such strategies to remain in the market. Concurrently, mergers, purchases, and acquisitions are happening too fast in this sector, where the successful key players are enhancing and strengthening their positions. The author shall deal with more of these aspects in Part II of the paper.

Academic and research institutions

Researchers in universities and research institutions use 3D bioprinting to study tissue engineering, regenerative medicine, and other biomedical applications. Scientists in various disciplines utilize 3D bioprinting to advance their understanding of cell behavior, tissue formation, and disease mechanisms. Professionals in the field of biomedical engineering use 3D bioprinting to develop and optimize bioprinting technologies and materials. Those focused on tissue engineering leverage 3D bioprinting to create functional tissues and organs for transplantation and regenerative medicine. The tissue engineers assemble functional constructs that restore, maintain, and may even improve damaged tissues or whole organs. They work primarily on musculoskeletal tissues like the bones, cartilage, and tendons (connective tissue between muscles and bones). 3D bioprinting is applied to create customized dental implants, crowns, and other oral structures. The technology has applications in veterinary medicine, allowing for the creation of custom implants or tissues for animals.

Bioprinting service providers

Companies Offering Bioprinting Services: Some companies specialize in providing 3D bioprinting services to researchers, pharmaceutical companies, and other clients who may or may not have in-house bioprinting capabilities. Such service providers are linking up among organizations, including institutions and industry, through collaborations and opening up opportunities among collaborating partners to speed up the developmental process.

Patients

Individuals Requiring Transplants: Patients needing organ or tissue transplants may be end users indirectly benefiting from 3D bioprinting as the technology progresses toward creating functional, transplantable organs. Accruing from such benefits requires legal requirements for operating the system among the patients and the caregivers providing the transplanting materials. Presently, legal requirements are not yet in place anywhere in the world, but they will soon be developed as success from the use of 3D bioprinting technology emerges. The legal aspects shall be dealt with in Part II of the paper.

As 3D bioprinting technology advances, its applications will likely expand, and new end users will emerge. The collaboration among researchers, medical professionals, industry, and regulatory bodies is crucial for the responsible development and implementation of 3D bioprinting in various domains.

CONCLUDING REMARKS

Bioprinting is an intelligent and innovative extension of traditional 3D printing. By using 3D bioprinting technology, it has been possible to produce living tissue, blood vessels, cartilage, and bones. Several research leads have shown the potential of this technology for 3D bioprinting of whole organs, which, with further developments and perfection, would enable their use in medical procedures. The complexities of the living body have been understood more comprehensively over time through intense research efforts. Once such complexities are mastered, the 3D bioprinted whole organs shall be utilized to treat patient-specific organ disorders. Although fully functional and viable organs for human transplants are not yet ready, the technological leads in certain institutions and countries provide hope that those days are not far away. As 3D bioprinting technology is perfected, it would be one more addition to ensuring healthy lives and promoting the well-being of human lives for all ages.

Current business components include 3D bioprinters, categorized into droplet-based, extrusion-based, laser-assisted, and other stereolithography techniques. The most common bioprinters in use are inkjet-based, laser-assisted, and extrusion-based. Bioinks, crucial for constructing living tissues, organs, and other structures, comprise hydrogels, biodegradable scaffolds, less toxic crosslinking agents, additives, and living cells. Global developmental progress analysis indicates a promising global outlook for 3D bioprinting technology and its products.

Reprogramming aged somatic cells involves resetting their aging clock and lengthening telomeres, transforming them into cells that mimic pluripotent stem cells. This process is a vital aspect of emerging technology that enhances bioink development and facilitates the creation of 3D bioprinted tissues, potentially for organ replacement.

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There are no conflicts of interest.

REFERENCES

1. Hull CW. SCV's Charles W Hull (Chuck Hull), the inventor of the 3D printer, revolutionized technology. Valencia, CA: The Signal: Santa Clarita Valley (SCV); 2020. Available from: https://www.msn.com/en-us/news/technology/scv-s-charles-hull-inventor-of-3d-printer-revolutionizes-technology/ar-AA1kwTMn. [Last accessed on 20 Jan 2024].
2. Udofia EN, Zhou W. Micro extrusion based 3D printing–A review. In: Solid Freeform Fabrication 2018: Proceedings of the 29th Annual International Solid Freeform Fabrication Symposium – An Additive Manufacturing Conference Reviewed Paper. Austin, Texas: The

University of Texas; 2018. 28p. Available from: https://repositories.lib.utexas.edu/server/api/core/bitstreams/3f122912-7900-4083-9add-268872eed30d/content. [Last accessed on 20 Jan 2024].

3. Santoni S, Gugliandolo SG, Sponchioni M, Moscatelli D, Colosimo BM. 3D bioprinting: Current status and trends—A guide to the literature and industrial practice. Bio-des Manuf 2022;5:14-42.
4. Dey M, Ozbolat IT. 3D bioprinting of cells, tissues, and organs. Sci Rep 2020;10:14023.
5. Jain P, Kathuri H, Dubey N. Advances in 3D bioprinting of tissues/organs for regenerative medicine and in-vitro models. Biomaterials 2022;287:121639.
6. Panja N, Maji S, Choudhuri S, Ali KA, Hossain CM. 3D bioprinting of human hollow organs. AAPS PharmSciTech 2022;23:139.
7. Zhang YS, Yue K, Aleman J, Moghaddam KM, Bakht SM, Yang J, *et al*. 3D Bioprinting for tissue and organ fabrication. Ann Biomed Eng 2017;45:148-63.
8. Richards D, Jia J, Yost M, Markwald R, Mei Y. 3D Bioprinting for vascularized tissue fabrication. Ann Biomed Eng 2017;45:132-47.
9. Chae S, Ha DH, Lee H. 3D bioprinting strategy for engineering vascularized tissue models. Int J Bioprint 2023;9:748.
10. Gentile C, Lim KS, Vozzi G. Editorial: 3D bioprinting of vascularized tissues for in vitro and in vivo applications. Front Bioeng Biotechnol 20216;9:754124.
11. Prina-Mello A, Bonacina L, Staedler D, Movia DE. Use of 3D models in drug development and precision medicine – Advances and outlook. Front Bioeng Biotechnol 2021;9:658941.
12. Richards Richards DJ, Tan Y, Jia J, Yao H, Mei Y. 3D Printing for tissue engineering. Isr J Chem 2013;53:805-14.
13. Ghosh PK. Revisiting Novel Active Pharmaceutical Ingredients from India Achievements and Future Challenges. New Delhi: RIS: Research and Information System for Developing Countries; 2021. p. 136.
14. Kim J, Koo BK, Knoblich JA. Human organoids: Model systems for human biology and medicine. Nat Rev Mol Cell Biol 2020;21:571-84.
15. US National Science Foundation. Productive 3D Bioprinter Could Help Speed Up Drug Development: The Pharmaceutical Industry Could Quickly Identify the Most Promising Drugs. Alexandria, VA: NSF; 2021. Available from: https://new.nsf.gov/news/productive-3d-bioprinter-could-help-speed-drug. [Last accessed on 12 Mar 2024].
16. Augustine R, Kalvaa SN, Ahmada R, Zahida AL, Hasana S, Nayeemc A, *et al*. 3D bioprinted cancer models: Revolutionizing personalized cancer therapy. Transl Oncol 2021;14:101015.
17. Gnatowski P, Piłat E, Kucińska-Lipka J, Saeb MR, Hamblin MR, Mozafari M. Recent advances in 3D bioprinted tumor models for personalized medicine. Transl Oncol 2023;37:101750.
18. Tebon PJ, Wang B, Markowitz AL, Davarifar A, Tsai BL, Krawczuk P, *et al*. Drug screening at single-organoid resolution via bioprinting and interferometry. Nat Commun 20236;14:3168.
19. Baptista LS, Porrini C, Kronemberger GS, Kelly DJ, Perrault CM. 3D organ-on-a-chip: The convergence of microphysiological systems and organoids. Front Cell Dev Biol 2022;10:1043117.
20. Howard D, Buttery LD, Shakesheff KM, Roberts SJ. Tissue engineering: Strategies, stem cells and scaffolds. J Anat 2008;213:66-72.
21. Khademhosseini A, Langer R, Borenstein J, Vacanti JP. Microscale technologies for tissue engineering and biology. Proc Natl Acad Sci U S A 2006;103:2480-7.
22. Daly AC, Prendergast ME, Hughes AJ, Burdick JA. Bioprinting for the biologist. Cell 2021;184:18-32.
23. Zhu X, Li H, Huang L, Zhang M, Fan W, Cui L. 3D printing promotes the development of drugs. Biomed Pharmacother 2020;131:110644.
24. Wang S, Chen X, Han X, Hong X, Li X, Zhang H, *et al*. A review of 3D printing technology in pharmaceutics: Technology and applications, now and future. Pharmaceutics 2023;15:416.
25. Mamo HB, Adamiak M, Kunwar A. 3D printed biomedical devices and their applications: A review on state-of-the-art technologies, existing challenges, and future perspectives. J Mech Behav Biomed Mater 2023;143:105930.
26. Admane P, Gupta AC, Jois PS, Roy S, Lakshmanan CC, Kalsi G, *et al*. Direct 3D bioprinted full-thickness skin constructs recapitulate regulatory signaling pathways and physiology of human skin. Bioprinting 2019;15:e00051.
27. Liu J, Zhou Z, Zhang M, Song F, Feng C, Liu H. Simple and robust 3D bioprinting of full-thickness human skin tissue. Bioengineered 2022;13:10087-97.
28. Sekar MP, Budharaju H, Zennifer A, Sethuraman S, Vermeulen N, Sundaramurthi D, *et al*. Current standards and ethical landscape of engineered tissues-3D bioprinting perspective. J Tissue Eng 2021;12:20417314211027677.
29. Yelick PC, Sharpe PT. Tooth bioengineering and regenerative dentistry. J Dent Res 2019;98:1173-82.
30. Ali MA, Hu C, Yttri EA, Panat R. Recent advances in 3D printing of biomedical sensing devices. Adv Funct Mater 2022;32:2107671.
31. Dias AD, Kingsley DM, Corr DT. Recent advances in bioprinting and applications for biosensing. Biosensors (Basel) 2014;4:111-36.
32. Yu J, Park SA, Kim WD, Ha T, Xin YZ, Lee J, *et al*. Current advances in 3D bioprinting technology and its applications for tissue engineering. Polymers (Basel) 2020;12:2958.
33. Kumar P, Ebbens S, Zhao X. Inkjet printing of mammalian cells – Theory and applications. Bioprinting 2021;23:e00157.
34. Zhang J, Wehrle E, Rubert M, Müller R. 3D bioprinting of human tissues: Biofabrication, bioinks, and bioreactors. Int J Mol Sci 2021;22:3971.
35. O'Neill B. 3D Bioprinting: Comprehensive Guide and Product Selection. Bayonne, France: Aniwaa SAS – Technocite; 2022. Available from: https://www.aniwaa.com/buyers-guide/3d-printers/3d-bioprinting-3d-bioprinters/. [Last accessed on 25 Jan 2024].
36. 3D Natives. 3D Bioprinters: The Main Manufacturers on the Market. Paris, France: Carlota V; 2022. Available from: https://www.3dnatives.com/en/3d-bioprinters-main-manufacturers-081020194/#!. [Last accessed on 25 Jan 2024].
37. Gama JFG, Dias EA, Aguiar Coelho RMG, Chagas AM, Aguiar Coelho Nt J, Alves LA. Development and implementation of a significantly low-cost 3D bioprinter using recycled scrap material. Front Bioeng Biotechnol 2023;11:1108396.
38. González F, Boué S, Izpisúa Belmonte JC. Methods for making induced pluripotent stem cells: Reprogramming à la carte. Nat Rev Genet 2011;12:231-42.
39. Takahashi K. Cellular reprogramming. Cold Spring Harb Perspect Biol 2014;6:a018606.
40. Saito S, Lin YC, Nakamura Y, Eckner R, Wuputra K, Kuo KK, *et al*. Potential application of cell reprogramming techniques for cancer research. Cell Mol Life Sci 2019;76:45-65.
41. Derakhshanfar S, Mbeleck R, Xu K, Zhang X, Zhong W, Xing M. 3D bioprinting for biomedical devices and tissue engineering: A review of recent trends and advances. Bioact Mater 2018;3:144-56.
42. Dey M, Ozbolat IT. 3D bioprinting of cells, tissues, and organs. Sci Rep 2020;10:14023.
43. Yang Y, Jia Y, Yang Q, Xu F. Engineering bio-inks for 3D bioprinting cell mechanical microenvironment. Int J Bioprint 2022;9:632.
44. Dell AC, Wagner G, Own J, Geibel JP. 3D bioprinting using hydrogels: Cell inks and tissue engineering applications. Pharmaceutics 2022;14:2596.
45. Ze Y, Li Y, Huang L, Shi Y, Li P, Gong P, *et al*. Biodegradable inks in indirect three-dimensional bioprinting for tissue vascularization. Front Bioeng Biotechnol 2022;10:856398.