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RESEARCH INVENTION JOURNAL OF BIOLOGICAL AND APPLIED SCIENCES 3(3):13-16, 2024

©RIJBAS Publications Online ISSN: 1115-6171

Print ISSN: 1597-2879

Bioprinting: 3D Printing Organs and Tissues

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ABSTRACT

Bioprinting is an advanced 3D printing technology that enables the fabrication of functional tissues and organs by layering living cells and biomaterials in a precise, scaffold-like structure. This innovative approach offers potential solutions to address the shortage of donor organs and to advance tissue engineering and regenerative medicine. Bioinks, comprising natural or synthetic biomaterials, are essential in the bioprinting process and must meet strict standards of biocompatibility and printability. Despite its promising future, bioprinting faces challenges in terms of bioink optimization, cell viability, vascularization, and large-scale tissue production. This paper explores the technologies, materials, applications, and future directions of bioprinting in the context of medical research, organ replacement, and pharmaceutical testing.

Keywords: Bioprinting, 3D printing, Tissue engineering, Bioinks, Regenerative medicine.

INTRODUCTION

Bioprinting is an innovative technology that utilizes 3D printing techniques to fabricate biological structures. Bioprinting involves the layer-by-layer deposition of living cells and biomaterials to create functional tissues and organs. An important aspect of bioprinting is the need for biocompatibility of the materials used, as they must provide a suitable environment for cell survival, proliferation, and differentiation. In addition to cells, bioinks often contain hydrogels or other biopolymers that can create a scaffold for the cells and mimic the extracellular matrix of natural tissues. Bioprinting has the potential to revolutionize the field of regenerative medicine, offering new solutions for the treatment of organ failure, tissue defects, and other medical conditions [1]. The human body has approximately 37.2 trillion cells of about 100 different types and 78 organs of various forms and functions. Biofabrication is the technique to replicate natural nano bioenvironments, allowing for the creation of biofabricated tissues and organs. 3D bioprinting, a computer-assisted technique, is used to create these constructs with desired features at the cellular level. Key components of bioprinting include cells, bioink, bioprinter, and computer-aided design. Bioprinting technologies include extrusion-based, laser-assisted, inkjet, microvalve, and light-based methods. Important research areas in 3D bioprinting include live cell survival, bioink design, printing fidelity, and construct performance. The application of 3D bioprinting extends to bioinks, cells, and biomaterials. Bioprinted constructs address heterogeneity, vascularization, integration, and in vivo performance. Additionally, 3D bioprinting is used in biotechnology for the production of peptides, proteins, microbioreactors, and biosensors [2]. The history of bioprinting dates back to 1999 when the first bioprinters were described. At that time, mainly extrusion and inkjet-based technologies were employed. Due to rapid advancement in technology, bioinks and the use of stem cells, bioprinting became an important technique in tissue engineering and regenerative medicine. Since the advent of bioprinting, it became possible to 3D biofabricate tissues and organs that mimic natural ones both structurally and functionally. Bioprinting technology has the potential to eliminate the gap between supply and demand of donor organs and tissues, to substitute missing body parts, and to create organ models for drug testing, toxicity, and biocompatibility studies [3].

DEFINITION AND HISTORY

Bioprinting uses 3D printing to create tissues and organs. Different techniques include extrusion, laser-induced, inkjet, and light-based approaches. It combines with tissue engineering to produce functional tissues using stem cells, growth factors, and biomaterials. These constructs can be transplanted to replace damaged tissues or used for drug testing. Bioprinting falls under additive manufacturing, which includes rapid prototyping. It has expanded to include metal, glass, and ceramics. The term was introduced in 2002 and has since seen significant growth in publications and patents. Bioprinting is a rapidly growing field in tissue engineering, regenerative medicine, and 3D printing [4].

TECHNOLOGIES AND PROCESSES

Bioprinting uses additive manufacturing to create 3D structures resembling biological systems with living cells, biomaterials, and growth factors. There are three main types of bioprinters: inkjet, microextrusion, and laser-assisted. Inkjet bioprinters offer high-resolution prints but have limitations with bioinks and cell viability. Microextrusion bioprinters enable rapid printing and complex structures but face issues with resolution and cell viability. Laser-assisted bioprinters provide flexibility and precision but have cost concerns and biomaterial deposition limitations. Advances are being made to enhance resolution, viability, cost-effectiveness, and versatility. Bioprinting has the potential to revolutionize tissue engineering, regenerative medicine, and drug discovery. The future holds promise for personalized medicine and biomedical innovation [5].

BIOPRINTING MATERIALS

Bioprinting is a significant advance in the field of regenerative medicine and tissue engineering that enables the generation of functional living tissues and organ substitutes. This is achieved via the structuring of cells, growth factors, and supportive biomaterials as 'bioinks', which are then bioprinted into 3D constructs resembling the architecture and functionality of the target tissue or organ. However, bioink composition remains a major barrier to relevant clinical translations due to the absence of standardized bioinks among the various bioprinting platforms and an incomplete understanding of the in situ bioink printability and post-printing fate [6, 7]. A bioink is crucial for bioprinting and must meet printability, biocompatibility, and bioactivity requirements. Bioinks can be categorized based on composition (natural, synthetic, or composite) and have different applications. The selection and functionalization of bioinks are important for successful bioprinting, post-processing, and the impact on biological and physiological aspects in constructs [8]. Bioink Printability Criteria and Considerations include: 1. Parameterization of 'Printability' as Composed of Fidelity and Functionality Considerations 2. Bioprintability of Bioink Systems in Terms of Fidelity and Functionality Considerations 3. Establishing Strategic Guidelines for Selection of Bioprinting Technologies 4. Considerations in Assessing Fidelity and Functionality Performance Post-Bioprinting 5. Consideration on Initial Material Characteristics of Bioinks Prior to Bioprinting

TYPES OF BIOINKS

The bioink is the most important component of a bioprinter. Composed of biological, synthetic, natural, cell, and tissue components, bioinks are carefully prepared by adding cells, biomolecules, and nutrients to a suitable 3D scaffold to support tissue formation. Generally, bioinks can be classified into three main categories: natural bioinks, synthetic bioinks, and hybrid bioinks [9]. Natural bioinks are composed of bioactive, biodegradable, and biocompatible materials. They can be plant-based, animal-derived, or algae-based. Plant-based bioinks contain cellulose, a bioink with potential as it is biocompatible and made from renewable resources. Alginate and chitosan, derived from seaweed and shrimp shells respectively, are also commonly used natural bioinks. Gelatin and collagen are popular animal-derived bioinks, known for their gel-forming properties and abundance. Silk fibroin bioinks have high mechanical strength and thermal stability. Algal bioinks, such as agarose and carrageenan, are praised for their porosity, low density, stiffness tunability, and biocompatibility. Synthetic bioinks, made of artificial chemicals like PLA, PEEK, and PCL, offer reproducibility and controllable properties but lack bioactivity. They can be thermosensitive, UV-curable, photocurable, or osteogenic. Thermosensitive bioinks gel at higher temperatures, while UV-curable bioinks require ultraviolet light for hydrogel formation. Gelation inhibitors can be used to prolong gelation time. Photocurable biocompatible bioinks stabilize gelation and promote stem cell proliferation. Hybrid bioinks combine natural and synthetic materials, improving printability and mechanical properties. The formulation of natural and synthetic bioinks can be optimized according to bioink properties. Various bioink formulations exist, each with unique contents and bioprinting technologies [10].

APPLICATIONS OF BIOPRINTING

Tissue engineering is an interdisciplinary field that aims to develop biological substitutes to restore, maintain, or improve tissue and organ functionality. Engineering these substitutes may involve the use of appropriate scaffolds, cells, and biologically active substances. The choice of scaffold is crucial as it strongly influences cell behavior. A wide variety of scaffolds can be employed in tissue engineering, including biopolymers, ceramics, metals, and combinations of these. The development of biomaterials for tissue engineering applications requires a multidisciplinary approach, involving material sciences, biochemistry, and medicine [11]. Scaffolds for tissue engineering must meet specific requirements: biocompatibility, biodegradability, stiffness, porosity, and pore size. Various techniques, such as phase separation, foaming, and 3D printing, are used to create scaffolds with precise structures and interconnecting pores. Pore size affects cell attachment and nutrient exchange, while porosity affects scaffold rigidity. Complementary techniques, like electrospinning and reaction-based approaches, offer wider design possibilities but have limited application with biopolymers [12]. With the advance of tissue/organ bioprinting technology, a new biofabrication technique emerged, based on the controllable deposition of cells and biomaterials into spatial 3D structures. This ability of bioprinting to fabricate complex scaffolds with high precision and reproducibility has drawn wide attention from the scientific community in tissue/organ engineering applications. Furthermore, emerging bioprinting technologies such as inkjet-based, laser-induced, and robotic bioprinting have made it possible to fabricate scaffolds with high cellular density and viability, allowing for cellular self-organization and tissue maturation. However, physicians' concerns regarding the practice of biofabricating tissues and organs in animals remain to be solved [13].

MEDICAL APPLICATIONS

Bioprinting in medicine involves various fields and approaches to tissue engineering and bone reconstruction. With living cells and bioinks, bioprinting creates biomimetic structures for tissue regeneration. These structures have specific properties tailored to their use, thanks to a range of biocompatible materials. Bioprinted constructs can replace damaged tissue or act as support for transplanted cells. Bone regeneration using bioprinting has improved through the use of hydrogel bioinks containing cells. However, challenges remain, such as creating large grafts with proper nutrient supply. Advances in bioprinting techniques have allowed for the fabrication of complex scaffolds that enhance bone regeneration. Current trends include optimizing printing parameters and creating composite scaffolds from different materials [14].

RESEARCH AND DEVELOPMENT

Bioprinting has evolved to support research and development, particularly in drug testing. Compound libraries have grown in size, enabling high-throughput screening processes. Automation in cell culture and seeding processes improves precision and speed. 3D bioprinting technology can fabricate filaments for cell-laden hydrogels, but conflicts with printing speed. A solution could be to use sacrificial bio-paper. Various tissue culture and drug response studies have been demonstrated. The combination of bioprinting and modeling could be implemented in large-scale projects for drug discovery R&D [15].

CHALLENGES AND FUTURE DIRECTIONS

Bioprinting, although an innovative technology with wide applications, presents challenges to its development. The biocompatibility of the printed materials, including both hydrogels and supporting materials, is crucial for the bioink and frame material. Several studies have shown that some biomedical applications of bioprinting require improving the biocompatibility of the bioink or the supporting material. For example, cell-laden constructs are usually bioprinted using photo-crosslinkable hydrogels, which need to be crosslinked using UV light. However, UV light can induce cell death due to DNA damage. To improve the biocompatibility of the bioprinted construct, bioinks were crosslinked by using other light sources, like blue light, which goes through the cells partially and thus reduces the cell damage of the printed construct while maintaining printability, structural integrity, and stability. Another example is using hydrogels with lower concentrations of materials, so the bioink would have lesser shear stress during printing; however, in this case, the strength of the construct would be weaker. Therefore, there is a trade-off between the printability of the bioink and its biocompatibility [16]. Bioprinting has limited functionality due to lack of extracellular matrix (ECM) in printed constructs. ECM formation can be promoted by adding cells that secrete ECM components in cell-laden bioinks, increasing tissue-specific functionality. Future bioprinting relies on developing bioinks with ECM-secreting cells, like stem cells. Specific cells for certain tissues, such as neurons for neural tissues, should also be investigated. Bioprinting creates 3D structures with living cells and scaffolds in one step and has applications in tissue engineering and organ replacement. Research on bioprinting holds promising outcomes for medicine [17].

CONCLUSION

Bioprinting represents a groundbreaking advancement in the field of tissue engineering and regenerative medicine. By utilizing 3D printing technologies and bioinks, bioprinting enables the precise creation of biological structures that mimic the complexity of human tissues and organs. While the potential applications in medicine, including organ replacement and drug testing, are vast, bioprinting still faces significant challenges such as bioink development, vascularization, and ensuring the long-term functionality of printed constructs. Continued research and technological improvements in these areas are essential for bioprinting to fully realize its transformative potential in healthcare.

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CITE AS: Kibibi Wairimu H. (2024). Bioprinting: 3D Printing Organs and Tissues. RESEARCH INVENTION JOURNAL OF BIOLOGICAL AND APPLIED SCIENCES 3(3):13-16.