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Overview Description of Existing Bioprinting Technologies and Comparison of Their Characteristics

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Abstract:

3D bioprinting is a new revolutionary branch of regenerative medicine. Bioprinting can be defined as the layer-by-layer formation of an object from various biomaterials (living cells) based on a previously created computer model. Today, the production of three-dimensional structures loaded with cells to mimic body tissues plays an important role not only in tissue engineering, but also in drug delivery research and cancer research. The lack of donors is a serious medical problem, and the tendency is that donors are becoming fewer and fewer patients needing donor organs. This work aims to review existing bioprinting technologies and give them a comparative description, taking into account advantages and disadvantages.

Keywords **—Regenerative medicine, 3D printers, printing, bioprinting, 3D bioprinting.**

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I. INTRODUCTION

The problem of the lack of donor organs for transplantation forces цus to look for biomedical solutions that do not require the use of donor material. Regenerative medicine technologies are currently considered the most promising. These include gene and cell therapy and tissue engineering [1,2,3]. Recently, another area of regenerative medicine – 3D modeling and 3D bioprinting – has received rapid development. Nowadays, 3D printers are successfully used in orthopedic dentistry, where prostheses, models, braces, and implants are produced by 3D printing without the need to use traditional materials, in the shortest possible time, compared to classical production technology. In addition, scientists have started the practice of growing whole tissues and even organs with the help of 3D technologies by layer-by-layer printing. Bioprinting can be defined as the layer-by-layer formation of an object from various biomaterials (living cells) based on a previously created computer model.

II. PROBLEM ANALYSIS

The technology of 3D printing with living cells promises incredible possibilities. However, in order to fully reveal its potential, it is necessary to increase the speed and quality of printing, the viability and controllability of cells, the availability of the technology itself, and also to think about the discovery of new technologies for printing with bioinks. In this regard, we consider it expedient to consider in detail the possibilities and promising directions of using 3D modeling and 3D printing [4,5].

Therefore, the purpose of this work is to compare different operating principles of bioprinters for printing organs, to determine their advantages and disadvantages.

III. COMPARISON OF TECHNOLOGIES

The extrusion bioprinting method usually uses mechanical microextrusion, so the hydrogels used in it are usually defined as non-Newtonian fluids [6], in which the viscosity depends on the shear rate. In addition, bio-ink should have properties of low adhesion and surface tension, in order to exclude its adhesion to the surface of the nozzle tip. In addition, it should have a fast gelling ability to maintain its shape without spreading.

The method of droplet bioprinting uses such types of energy as electricity, heat, or sound [7,8]. This allows you to extrude bioink with high throughput. Bio-inks should have a low viscosity and not have a fibrous nature, in order to easily pass through the nozzle without clogging it. That is, the liquid must have a rheopectic property, in rheopectic liquids, the viscosity of the liquid increases with the application of shear stress over time [7]. Another important feature is having sufficient wettability so that the liquid passes freely through the cartridge without flooding either the outer part of the nozzle or the print head. In addition, the liquid must solidify immediately after pouring it into the mold.

The laser printing method, as its name implies, uses laser energy. It is divided into two types: the first is the transfer of cells from the substrate of the "donor" slide directly to the "recipient" slide; the second, the use of the photopolymerization process, where the laser beam is selectively directed to certain areas, which as a result harden [7]. Therefore, in the first case, the bioink must have a sufficient degree of adhesion and low surface tension in order to be evenly distributed over the intermediate layer and stick. Also, the substance must convert thermal energy into kinetic energy and be characterized by high viscoelasticity. As for other methods, it must have the ability to quickly gel, so that the liquid streams can solidify without spreading. In addition, the interaction of the jet and the substrate is also important, it is necessary to choose the right substrate so that the substance does not splash. For the second type, it is worth choosing hydrogels with the ability to photopolymerize. Bioink should be additionally strengthened with non-toxic water-soluble photoinitiators and light absorbers to initiate photopolymerization and ensure the possibility of manufacturing fabric structures with a uniform layer thickness [8, 9]. In addition, the bioink must possess an appropriate mechanism of gel formation due to chemical, physical or enzymatic crosslinking. Stability and high mechanical strength are also important, as well as the ability to retain cells evenly distributed in the precursor solution.

One of well-known 3D printing technologies is also stereolithography. This technology is widely recognized as the world's first mass-produced 3D printing process. Stereolithography is a technology that uses the effect of a laser on photopolymer resin, as a result of which the resin vulcanizes and forms solid layers of the future model. With the help of stereolithography, you can create objects with high precision. It's a complex process, but in simple terms, photopolymer objects are formed in a container with a moving platform inside. The laser beam is directed along the XY axes over the entire surface of the resin, according to the 3D data entering the printer, as a result of which the photopolymer hardens exactly where the laser hits the surface. After a layer is completed, the platform moves along the Z-axis and the laser passes through the next layer. This continues until the entire object is completed and the platform can be lifted from the container. Due to the nature of stereolithography, prototyping requires auxiliary supports for some parts, in particular, for protruding or overhanging elements. In the future, the supports are removed manually. Other post-processing steps include cleaning and adjusting the model. It is generally accepted that stereolithography is one of the most accurate 3D printing technologies with excellent surface quality. However, limiting factors include post-processing steps that ensure the stability and stability of materials over time.

Describing different types of printing, we will give the advantages and disadvantages of each of them.

Among the advantages of droplet bioprinting is low cost, high resolution, high printing speed, and the ability to create gradient concentrations of cells, tissues, or growth factors across the entire area of 3D structures by changing the size and density of droplets. Among its disadvantages are limitations in the viscosity of biomaterials, the need for materials to be in liquid form, clogging of the nozzle or accumulation of "cellular debris", as well as damage and death of cells.

Extrusion bioprinting has the following advantages: superimposition of cells with very high density, low price and a wide range of bioprinters, extrusion has a faster deposition and printing speed than others, which can facilitate scaling up in a relatively short period of time. Such printers allow bioprinting of a wide range of materials, as well as bioprinting of anatomically correct porous structures, which is a very difficult task. Among the disadvantages of this technology are the problem of nozzle clogging and limited resolution. Also, bioink in a liquid or sol-gel state must have the ability to shift to overcome surface tension. Also, the shear stress on the nozzle tip wall can cause a significant drop in the number of living cells at high cell density.

As for laser bioprinting, its advantages are as follows: high cell viability, no nozzle clogging problem, allows bioprinting of cells in larger quantities, high resolution and non-contact nature. Disadvantages include: due to the high shear stress and droplet formation mechanism, a very limited number of cells can be encapsulated in each droplet. Also, the preparation of different materials for different types of cells takes some time, and this technology has a high cost.

The stereolithographic method raises questions about its wide application in bioprinting precisely because of its features. Among its advantages, it has a solid freeform and nozzle technology, the highest manufacturing accuracy, compatibility with an increase in the number of materials, and the ability to print light-sensitive hydrogels layer by layer. Among its disadvantages are the following: it is used only for photopolymers, the lack of biocompatible and biodegradable polymers, the harmful effects of residual toxic photocuring reagents and the possibility of damage to DNA and printing products by ultraviolet light.

Despite significant progress in the development of biomaterials for tissue engineering and regenerative medicine, a relatively small amount of research is devoted to the development of biomaterials for bioprinting. Most researchers do not consider the possibility of improving biomaterials, so further efforts should be directed to the development of new materials for bioprinting. To develop such materials, it is first necessary to determine the existing methods and processes of bioprinting, since each methodology makes different requirements for materials. The development of new bioinks for extrusion printing is crucial, as most researchers use this method due to its practicality and ability to produce large-scale tissue structures [8, 10]. Bio-inks used in extrusion printing must possess various properties, but the most important characteristics are shear thinning, curing ability and fast cross-linking. Hydrogels lacking the ability to harden quickly tend to blur during extrusion and cannot retain their original shape. Currently, there are only a few types of hydrogels that exhibit such properties as Pluronic ® and sodium alginate, but these materials do not support cell growth and tissue regeneration [11]. Therefore, new bioink materials possessing all these characteristics will be most valuable.

IV. CONCLUSIONS

Each bioprinting technique has different requirements for the bioinks, which can create different effects on the encapsulated cells. Bioprinting is still in development and has many steps to go before entering the clinical world, especially as a direct in situ application. From this brief overview, it is concluded that different applications require different fabrication techniques, depending on the required resolution, speed, cost, vertical printing capability, etc. Future developments are now focused on a combination of

complementary techniques to optimize the process of creating tissue-mimicking structures.

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