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Organ Printing

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Organ printing is a branch of medicinal regeneration. Here, we try to illustrate to reduce the death rate of patients, who die at the right time only because of defective human organs. The research concerns the concept of organ printing, technological forms, materials and methods, advantages and challenges, projected marketing rate and how it can be applied. The most important advances in 3DPrinting have taken place in external prosthetics, cranial or orthopedic implants and custom airway stents. But it has also proved to be helpful in surgical planning and has been used in complex open planning and has been used in complex open heart surgery, and also the complete face transplant of Cleveland clinic. Human tissue printing talks suggested that transplants of organs would one day be obsolete.

Introduction

3D printing would have an effect on a broader variety of medical fields in terms of personalization and customization. This bio-printing is a way of artificially producing custom organs. Our future will surely depend on this bioprinting because only through bioprinting, stem cells can be particularly positioned in 3D in relation to other cell types and /or biomaterials [3]. Eventually, bio-printing may be the chosen medium for using human stem cells to create artificial solid tissues and organs. Bio-printing materials have to fit a wide range of criteria, one of the most important being biocompatibility. The resulting scaffolds formed by 3D printed materials should be suitable both physically and chemically for cell proliferation [7]. Another important factor is biodegradability, which ensures that the artificially formed structure can be broken down after successful transplantation to be replaced by a cellular structure that is completely natural. Because of the design of 3Dprinting, the materials used must be adaptable and flexible, suitable for small and adaptable, suitable for a wide variety of cell types and structural conformations [10].

Natural Polymers

Chitosan, hydroxyapatite (HA), collagen, and gelatin are natural polymers used for tissue and 3dorgan printing. Gelatin is a thermo-sensitive polymer with excellent wear properties Solubility, biodegradability and a mild immunological reaction. These qualities are advantages and result in high acceptance for invivo implantation of the 3D bio-printing organ [11].

Synthetic Polymers

Synthetic polymers are made by humans through monomeric chemical reactions. Their lack of functional groups and structural complexity has, however, restricted their use in organ printing [2]. Current synthetic polymers with excellent 3Dprintability and compatibility with in vivo tissue, include polyethylene glycol (PEG), Poly-lactic-GlycolicAcid (PLGA),and Polyurethane (PU). PEG is biocompatible, non-immunogenic synthetic polyether that has tunable mechanical properties for use in 3D bio printing and bio stabilization for use in complex bio-artificial organ printing and processing [7]. Such materials can be applied to organ printing in a number of complex ways, such as the brain, heart, lungs and kidneys, due to the high vascular and neural network construction.

Natural Synthetic Hybrid Polymers

Natural hybrid synthetic polymers are based on the synergistic effect between synthetic and biopolymeric components. Gelatine-meta-acryloyl (Ge IMA) has become a popular bio-printing biomaterial. Ge IMA has shown it has viable potential as a bioink materials due to its suitable biocompatibility and reading tunable psychochemical properties Hyaluronic acid (HA-PEG) is another natural-synthetic hybrid polymer which has been shown to be very effective in bio-printing. Creation of artificial liver is a recent use of HA-PEG in bio-printing [13]. Lastly, a series of biodegradable Polyurethane (PU)-gelatin hybrid polymers with

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tunable mechanical properties and efficient degradation rates have been implanted in organ printing. This hybrid has the ability to print complicated structures such as a nose shaped constructs [17]. All the polymers described above have the potential to be manufactured into implantable, bioartificial organs for purposes including, but not limited to, customized organs restoration, drug screening, as well as metabolic model analysis [8].

Methodology

Cell Source

Creation of a full organ also involves a number of different types of cells to be integrated, organized in distinct and patterned ways. Compared to traditional transplants, one advantage of 3Dprinted organs is the potential to use patient-derived cells for making the new organ. However, since it may not always be possible to collect all the required types of cells, it may be necessary to collect adult stem cells or to induce Pluriopotency in the collected tissue [16].

Process of Bioprinting

The process of 3D bioprinting is based on three distinct approaches; Bio mimicry or bio mimetics, autonomous self-assembly and mini-tissue building blocks.

Bio mimicry: It is the manufacture of identical reproductions of cellular & extracellular components of tissues and organs after a detailed examination of nature itself. Since the materials used in the process have a significant influence on cell attachment, cell size, and morphology, the control of proliferation and differentiation of cells is present in the scaffold. It gives detailed understanding of microenvironment.

Autonomous self-assembly: It is the approach of replicating biological tissue by using the mechanism of embryonic tissue and organ development as guide. During this process is a scaffold-free version is formed so this approach relies on the cell as the primary driver of tissue formation, which directs the localization, functioning, and structure of the resulting tissue.

Mini–tissue building blocks: These mini tissues represent the smallest structural & functional unit of the organs, like the kidney neuron. The bio printing begins with the assembly of mini-tissues into macro-tissues based on biologically inspired organization, which is then followed by the reproduction of tissue units can self-assemble to form functional structures.

Basic 3D Bioprinting generally follows three steps

Pre-Bio Printing: It is the process of creating a model that the printer will later create and choose the materials that will be used. One of the first steps is having an organ biopsy.

Bio Printing: In the second step, the liquid mixture of cells and nutrients are placed in a printer cartridge and structural using the patient's medical scans.

Post Bio Printing: To create a stable structure from the biological material, post-bio printing process is required. If this process is not well-maintained, then the mechanical integrity and function of the 3D printed object is at risk [14].

Techniques and its Types

Inkjet printing or drop based printing

Recreating a digital image by propelling droplets of ink on paper and plastic substrates is a type of computer printing. Polymerisation is triggered by calcium particles on the substratum, which migrate into the liquefied bio ink and allow a strong gel to be formed [8]. Type of printer most widely used. This form ranges from low-cost consumer models to high cost professional machines. Currently, inkjet bioprinting can be performed on bioprinters that can are custom-designed to handle and print biological materials with high precision, speed and resolution. The advantages of inkjet printing have high resolution, concentration gradient of cells and growth factors in the construct and electronic control of drop size and ejection rate. High viscous mechanical inks cannot be used as it has weak mechanical integrity to the construct [25].

Examples

Some of the common applications of inkjet bioprinting are the regeneration of functional skin and cartilage tissues where the higher printing speed of this technique enables direct deposition of cells and biomaterials onto skin and cartilage lesions.

Besides, inkjet bioprinting also allow the deposition of primary or stem cells with uniform density onto lesions while maintaining cell viability and function.

Layered cartilage constructs have also been developed using a combination of inkjet bioprinting and electrospinning technology.

Fused deposition modeling

Fused filament fabrication, also known under the trademarked term fused deposition modeling. Sometimes, is similar in structure to an inkjet printer also called filament freeform fabrication, this uses a continuous filament of a thermoplastic material. This printer uses a printer head that is similar in structure to an inkjet printer [11]. As the heated plastic is deposited from the print head, it fuses or bonds to the layers below. As each layer cools, they harden and gradually take hold of the solid shape intended to be created as more layers are contributed to the structure. Advantages of this are reasonable pricing and this method consumes less time [19].

Pressure-assisted bioprinting (PAB)

Pressure –assisted bioprinting is based on the extrusion of biomaterials out of the nozzle of the printer in order to fabricate a 3d biological structure. The speed of the printers remain low, and it provides bout 40-80% cell viability. The use of pressure-assisted bioprinting allows room temperature processing and direct incorporation of homogenous cells onto the substrate .Some of the common biomaterials used in this method include hydrogels, cells and proteins and ceramic material solutions, collagen & chitosan, etc.

Examples

Pressure-based bioprinting has been used in the printing of cells and organs with functional activity.

The technique has been used to produce human mesenchymal cells, endothelial cells and osteogenic progenitors.

Besides, the method can also be used to obtain multicellular bioprinted constructs with retention of heterogeneous cell organization in various mammalian bodies.

The mesenchymal cell constructs obtained via pressure-based bioprinting can then b differentiated into other cells that can retain activity in vivo.

Sterolithographic 3D printing

It's the mechanism by which a special 3D printing tool called a Sterolithograph system (SLS) transforms liquid plastic into solid objects. This organ printing method uses spatially controlled light or laser to create a 2D pattern in the bio ink reservoir through selective photopolymerisation [17]. It can produce parts with very high dimensional accuracy and with intricate details. Its parts have a very smooth surface finish, making them ideal for visual prototypes [6]. Sterilithography (STL) is a freeform, nozzle free technique used to produce the 3d structure of biological & non-biological materials. The speed of this method is very fast (about 40,000mm/s) with cell viability of more than 90%.

Examples

This technique has been used in several ways to produce tissues and organs of different animals, including humans.

Besides, the technique was tested upon DNA materials, but the use of UV light has chances of affecting the DNA structure. However, a custom light source can be prepared to use with DNA molecules.

Laser-assisted bioprinting (LAB)

This method of depositing biomaterials onto a surface by using a laser as a source of energy. Traditionally, this technique was limited to transferring metals, but it has since been modified to be applied to biological materials like cells, DNA, and peptides. The biomaterials to be used in this method includes a hydrogel, culture media cells, proteins and ceramic materials. The speed of the bio printers is medium and the method retains about 95% of cell viability.

Examples

Laser-assisted bioprinting has been used to produce a cellularized skin constructs with relevant cell densities in a layered tissue construct.

Cells of the human dermal fibroblasts, pulmonary artery endothelial cells, and breast cancer cells can be produced via laser-assisted bio printing.

This approach can achieve high precision rates (although not as high as the stereo lithography).

Sacrificial writing into functional tissues (SWIFT)

It is a multistep bio manufacturing process that involves creating organ building blocks composed of hundreds of thousands of induced pluripotent stem cells and then rapidly 3D printing vasculature into those building blocks [1].

Example

It is a technique that is used to create vasculature using existing 3D printing technologies like extrusion.

Additive manufacturing (AM)

Over the last decade, biomaterial additive manufacturing (AM) has evolved from a tool for quick prototyping in research and development to a viable method for producing patient-specific medical equipment. The ability to accurately manage structure and material qualities in three dimensions and adjust them to specific anatomical and physiological parameters is critical to this. Customized polyetherketoneketone bone plates for the healing of major cranial deformities and polycaprolactone bioresorbable tracheal splints for pediatric applications are among the first-in-human uses [26]. The enabling three-dimensional (3D) printing technologies are primarily based on selective laser sintering of metal, ceramic, or thermoplastic microparticles; fused deposition modeling of thermoplastics; or photopolymerization of photosensitive polymer resins, and have enormous growth potential for surgical and medical devices and tissue repair scaffolds. These methods, on the other hand, are limited in their capacity to 3D print highly soft materials like elastomers, gels, and hydrogels, which are essential components of many medical devices and are necessary for most future tissue engineering and regenerative medicine applications. Biological hydrogels made up of polysaccharides and/or proteins, in particular, are difficult to 3D print because they must be gelled in place during the production process and then maintained to avoid collapsing or deforming under their own weight [29]. Although many AM techniques require support materials, it is especially difficult for these soft biological hydrogels, where the elastic modulus is less than 100 kPa and a narrow range of thermal, mechanical, and chemical conditions must be met to avoid damage to the materials and potentially integrated cells [27].

Freeform reversible embedding of suspended hydrogels (FRESH)

The development of a 3D bioprinting process called freeform reversible embedding of suspended hydrogels is described here (FRESH). FRESH is a highly customizable and cost-effective biological AM technology that uses a thermoreversible support bath to enable deposition of hydrogels in complex, 3D biological structures and is developed using open-source technologies [28]. FRESH's primary innovation is the deposition and embedding of the hydrogel(s) to be printed into a second hydrogel support bath, which keeps the intended structure during the print process and enhances print quality dramatically.

Extrusion Printing

It is known as a biological medium being dispensed through an automated robotic system. A computer-controlled system provides bio ink during bio printing, resulting in accurate deposition of cells encapsulated in cylindrical filaments arranged in custom 3D structure. Nozzles are 400microns wider in diameter filament [6]. It can produce continuous filament1X produce the meniscus in 30 minutes that too one filament at a time. This method has an advantage of ability to print with high cell densities. However the more viscous the bio ink, the higher the induced shear-stress during printing, resulting in higher cell apoptotic [13].This bioprinting technology is used in various academic institutions for tissue & organ research. The flexibility of the process & material availability makes the extrusion based 3D bioprinting, the most used technique to produce pharmaceutical dosage forms.

Examples:

The extrusion-based 3dbioprinting method has been widely used in various biomedical sectors ranging from the pharmaceutical industry to research sectors.

The technology is commonly used for single tissue applications, and to manufacture scaffolds that mimic tissue interfaces.

The technology is capable of producing models that mimic soft tissues and bone structures which provide an opportunity for possible implants.

Types of Printers

Growing organ is chemically mixed with specific tissues and blood cells, both physically and bio. It makes reproduction of certain organs more difficult. So this problem gave ways to different types of 3D printers and they are as follows, Inkjet Printer, Multi-nozzle printer, Hybrid printer, Electrospinning, Drop-on-demand.

These printers are used in the methods described previously. Each printer requires different materials and has its own advantages and limitations.

Findings and Interventions

Impacts

The printing of organs for medical applications is still under development. Thus, the long term impacts of organ printing have yet to be determined. Researchers hope that organ printing could decrease the organ transplant shortage. There is currently a shortage of available organs of death all over the world [11] For example, leading causes of death in the United States, is alone nearly one third of death each year in United States that could be delayed or prevented with organ transplants. Currently the only organ that was 3D bio-printed and successfully transplanted the bladder was made out of the tissue of the host's bladder [9].Researchers also suggested that the opportunity to customize organs for the recipients is a possible positive effect of 3D printed organs. Developments requiring the use of host cells of an organ recipient for the synthesis of organs reduce the risk of organ rejection into human is bladder [16]. Furthermore, the ability to print models of human organs to test the safety and effectiveness of new drugs further decreases the need for animal trails. Researchers at Harvard University determine that drug safety can be accurately tested on smaller tissues models of lungs [7]. Organovo, which designed one of the initial commercial bio-printers in 2009, showed that biodegradable models of 3D tissue can be used for research and development of new drugs, including those for cancer treatment [8]. An additional impact of organ printing includes the ability to create tissue models quickly and thus increase productivity.

Challenges

One of the challenges of 3D printed organs is recreating the vasculature required to keep organs alive. Designing a correct vasculature is necessary for the transport of nutrients, oxygen and waste. Blood vessels, especially capillaries are difficult due to the small diameter. Progress has been made in this area at Rice University, where researchers designed a 3D printer to make vessels in bio-compatible hydrogels and designed a model of lungs that can oxygenate blood. However, accompanied with this technique is the challenge of replicating the other minute details of organs [17].

It is difficult to replicate the entangled networks of airways, blood vessels, and bile duct and complex geometry of organs. Additional challenges include designing clinical trials to test the long-term viability and biocompatibility of synthetic organs [13]. While many developments have been made in the field of organ printing more research must be conducted.

Applications

Tissue engineering

This is one of the most prominent applications of 3D printing. It enables the fabrication of complex tissues and organs that can replace failed or lost tissues. Nevertheless, a wide variety of tissues have been successfully bioprinted while maintaining mechanical integrity and functioning. Some common examples of tissues that have been bioprinted for various purposes:

a. Skin

Skin tissue fabrication is achieved by a no. of tissue engineering approaches.

Tissue engineering can be done to produce substitutes like an autologous split-thickness skin graft, allografts, acellular dermal substitutes and cellularized graft like commercial products.

Bioprinting of skin tissue can be done using an eight channel valve-based bioprinter where a 13 –layer tissue is constructed using collagen hydrogel.

The biomaterial used for the process might differ but the most common cells used as keratinocytes and fibroblasts.

Besides, skin with infections or diseases can be used as biomaterials for bioprinting to study the pathophysiology of the distance.

b. Bone and cartilage

Bone & cartilage fabrication is the most mature use of bioprinting as the composition of such hard tissues is uncomplicated and is mostly composed of inorganic elements.

Even though other techniques like gas foaming , salt leaching , freeze-drying have been employed to produce such hard tissues,3D bioprinting produces the most accurate structures.

Thermal inkject bioprinter is used to fabricate polymethacrylate scaffolds from bone –marrow-derived human mesenchymal stem cells.

The cells are coprinted with nanoparticles of bioactive glass to control the spatial placement of cells.

In cartilage tissue engineering, a printable bio ink is prepared as a combination of nanofibrillated cellulose and alginate with human chondryoctes.

c. Blood vessels

Bioprinting of vascular networks is essential as the fabrication of tissues and organs depend on vascularization to provide oxygen and media to the bioprinted constructs.

The bioprinted technology used for the production of bio printed vascular networks includes extrusion and laser-assisted bioprinting technique.

During bioprinting, hydrogen gas including sodium alginates and chitosan are bioprinted directly in tubular form with encapsulated cells.

The tubular structures thus formed have improved metabolic transportation and cellular viability.

d. Liver tissue

Bioprinting of liver tissue is comparatively less prevalent as the cells of the liver have strong ability.

However, there is a limitation of healthy donors, and the regeneration period for such liver is long.

The bio ink used for this purpose include cells like primary hepatocytes and stem –cell-derived hepatocytes.

3d printing technology can provide the exact size and shape of the liver, which is suitable for the patient.

Bioprinting produces canoliculi that are linked together by the collagen matrix to form larger structures.

Drug development/screening

Drug discovery requires time-consuming and costly processes that demand substantial financial investment and workforce .Thus the development of technique to improve the ability to predict the efficacy and toxicity of newly developed drugs earlier in the drug discovery process helps in reducing the time and money required. Biopriting can fabricate 3d tissue models that resemble that of native tissue and are capable of high throughout assays. Most commonly, liver and tumor tissues are the primary focus to create tissue models for pharmaceuticals [24]. Besides, depending on the target cells of developed drugs, the tissue models of such cells can be prepared and tested. Initially, tissue constructs of epithelial cells are prepared as these cells form the living through which the drug diffuses into the blood stream.

Based on the studies on such constructs, the path of drugs and their action on the target cells can be assumed. Similarly, bioprinted can be used s an alternate way for the development of prescription drugs. The drugs can even be customized for each patient by preparing appropriate doses of drug print by using a set of biochemical inks. 3D printed composite pills containing multiple drugs with unique release rates can e used instead of taking multiple pills throughout the day.

Toxicology screening

Toxicology screening or testing is the process of identifying potential adverse effects of chemicals on individuals or to the environment. Chemicals might include compounds like pharmaceutical ingredients, cosmetic ingredients, household, and industrial chemicals

Studies evaluating the toxicity of some chemicals might requires a large number of human subjects with diverse metabolism, which might seem unethical. Some studies can be performed on animals, but animal might not predict human responses to an accurate or reliable manner. Instead, the use of 3d bioprinting can provide a highly –automated and advanced technology that mimic the structure and function of human tissues [23].

Testing of cosmetic ingredients on human-relevant skin tissue models has been performed for a long time. These tests study skin absorption, skin irritation, skin corrosion, and skin sensitization on models mimicking human tissue structures.

Tissue model for cancer research

2D tumor models have been used in cancer research for a long time, but those do not represent for a long time, but those do not represent the physiologically relevant environment as the 2Dmodels lack cell-cell interactions. However, 3dbioprinting allows the recapitulation of the cancer micro environment so as to study cancer pathogenesis and metastasis accurately [22]. Multiple cell types can be simultaneously bioprinted to form multicellular structures in a reproducible manner with a spatially medicated micro environment and controlled cell density and cell-cell distance. Bio printing of HeLa cells can be done in a gelatin-alginate composite hydrogel so as to study cell aggregation. These tissues can be used to study the progression of cancer and the changes in tissue structure and function with the progression [20]. Besides, tissue models can also used to study the efficiency of treatment methods against various carcinogens.

Organ donation

Currently, the sole method for treatment for those in organ failure is to await a transplant from a living or recently decreased donor. In United States alone, there are over 100,000 patients on the organ transplant list waiting for donor organs to become available. Patients on the donor list can wait days, weeks, months, or even years for a suitable organ to become available [3]. The average wait time for some common organ transplants are as follows: four months for a heart or lung, eleven months for a liver, two years for a pancreas, and five years for a kidney. An organ is deemed suitable for a patient based on the type of blood, comparable body size between donor and recipient, severity of medical condition of the patient, the length of time the patient has been waiting for an organ, patient availability, and the proximity of the patient to the donor organs. 3D organ printing has the patient to remove both these issues, if organs could be printed as soon as there is need, there would be no shortage [5].

Physician and surgical training

3D printing's surgical use has grown from the printing of surgical instruments to the development of patient-specific tools for complete joint replacement, dental effects, and hearing aids [7]. For patients and surgeons, technologies may be provided for in the field of organ printing. The functionality of the organ is not needed for these cases and is used as proof-of -concept. Such model organs offer innovation to develop surgical procedures, train new surgeons and push towards different treatments for patients [10].

Organ-on-chip printing technology can also be combined with microfluidic technology. The researchers are able to create a body-on-chip by combining 3D printed organs includes liver, back, lung, and kidney-on-chip [6].The organs-on-chip are printed or assembled separately, and then incorporated together. Using this platform drug toxicity studies are performed at high throughout, lowering the cost and increasing the drug discovery pipe line efficiency [3]. 3D printed techniques have been used for the overall goal of manufacturing a product in a variety of industries. At the other hand, organ printing is a new technology, using biological components to establish therapeutic applications for organ transplants [2]. Due to the increased interest this field, the regulation and ethical consideration are in desperate need to be established. Specifically, there can be legal complications from pre-clinical transition for this treatment method [3].

Conclusion

3D bioprinting has the robust potential to easily manufacture tissue/organ structures; however, it requires more improvements in different fields, such as bioinks, marketing of 3D printed goods and so on [11]. This approach will promote the creation of more complex 3D structures unique to patients for urgent medical needs. It has numerous advantages, such as flexibility in design, printing modes, cell line use, biodegradation control, and mechanical properties, etc [21]. This analysis addressed the different selection criteria for the bioinks and their properties. The production of the ideal bio ink is still ongoing and thanks to major contributions from around the world [16]. This technology may in future be used for commercial applications. Even though cell laden biomaterial bio inks are highly used, Extra Cellular Matrix – based bio inks, Decellularized bio inks, cell aggregates or spheroids are also showing promising results towards the development of functional tissues or organs using 3D bio printing technology [17]. Apart from the bio inks, it is also considered that the development of advanced bio printers. Mind blowing innovations come almost every day to medicine and healthcare, Hope our paper is one of them with its own unique features [19].

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