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Review Article

3D Bioprinting in Obtaining Organ on a Chip

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ABSTRACT

In accordance with the Corona virus pandemic, which caused a severe financial disaster global wide, there is a need for consistent in vitro models, which can replace human use in clinical trials. Such kind of in vitro models will be a good support in resembling the behaviour of pathogens according to the therapeutic substances. Organ on a chip (OOAC) models are one of such in vitro models. They are developed in such a way that they show biomimetic function. 3D (design, develop, dispense) bioprinting techniques have high precision in the construction of OOAC models. This review gives a detailed knowledge of novel 3D bioprinting technology and OOAC models.

Introduction

Organ on a chip (OOAC), microfluidic devices are having the capability to reach the requirement of reducing animal experiments, it is the reason this area is enormously raising in the last decade. Single OOAC and multi OOAC are the two classes of OOAC devices. To analyse a single particular tissue, single OOAC devices are structured. In order to analyse many tissues in a single platform and to permit construction of self-assembled multi tissue which shows precise biological functioning multi OOACdevices are constructed [1].

3D cell culture models such as OOAC models which were made up of different kinds of human cells have gained extreme focus. These cell cultures are used as polymers as they are having similar physiological, mechanical, and chemical features as that of in vivo tissues. Polymers considered to use in OOAC models are examined through high throughput screening which makes this 3D Bioprinting OOAC model an exclusive approach. These characteristics in OOAC models provided key to the deficiencies in traditional animal testing and 2D cell culture [2]. Therefore, it is anticipated that the use of refined OOAC models for demonstrate the biomimetic function of human cells. In comparison with conventional in vivo and in vitro models, these models permit the study of therapeutic substances rapidly with less expenses [3]. OOAC is a system that mimics the biochemical processes of a physiological organ, which can regulate crucial parameters that includes concentration gradients, shear force, cell patterning, tissue - boundaries, and tissue-organ interactions [4].

These are used in various stages of drug discovery and development that provide an understanding of human organ physiology in both normal and disease conditions. Which predict precise drug safety and efficacy of the investigational drugs in humans. This is an important system that is used to study numerous processes and mechanisms [5].

The development of OOAC models using 3D bioprinting has individual characteristics. These characteristics keep them ideal from other types of bioprinting technologies. Novel 3D bioprinting technologies developed in such a fashion to use cells as bioink and develop biological organs from them [6]. Application of polymeric membrane is the important prerequisite for the production of ideal OOACs which aids the cells in supporting and functioning of OOACs similar to the extra cellular matrix (ECM) [7]. Research in the branch of biomedical, in which, polymers were regarded as bioinks to construct OOAC systems using bioprinting technologies [8].

Techniques of 3D Bioprinting:

Bioprinting is a subfield of biofabrication that aims to create functional biomimetic constructs. To print cell-laden bioinks, various 3D bioprinting techniques were developed. Bioprinting techniques like the single-material

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technique, on the other hand, cannot generate multicomponent constructions of natural tissues. As an emerging technique, unlike single material bioprinting, multimaterial bioprinting allows the construction of heterogeneous multicellular natural tissues that can regenerate their host condition. Some models of multimaterial bioprinting are studied, and their adaptation to bioprinting is observed along with a discussion of their benefits and challenges. A brief description of multimaterial bioprinting gives rise to more possibilities for the engineering of tissues and their models, the development of personalized medicine and therapeutics [8].
No studies were published on laser-based bioprinting. Understanding how these techniques work, as well as the merits and demerits in constructing OOAC systems, aids researchers to select bioprinting techniques for OOAC systems.

Different types of 3d bio-printing:

1. Micro-extrusion-based 3D bioprinting
2. Inkjet Bioprinting
3. Stereolithography
4. Fused deposition modelling
5. Electron beam melting
6. Laser assisted bioprinting

1. Micro-extrusion-based 3D printing:

According to the computer aided design (CAD), the dispensing head can move up and down along the Z axis, as well as in the horizontal plane in the both X and Y. Robotic system which includes a bioprinter, computer hardware and software (in the form of G-code file) contains all the instructions which were given by the CAD model. The printing platform in some printers can move both upward and downward also in the Z axis, whereas the head is able to move in the X and Y axes. The fluid dispensing system works from the pressure which is generated by a solenoid-based system or by the mechanical, pneumatic piston or screw driven piston. By cooling or heating the thermal jacket that holds the syringe, can control the extrusion temperature of some printers. The major controllable parameter of printing is Extrusion. To create heterogeneous and complex structures, a micro extrusion-based system is constructed with numerous printing heads that contain various bioinks or cells. Different parameters like nozzle spacing, blowing force of bioink, nozzle position, printing kinetics, and diameter of the nozzle were taken into account while using multiple heads [9].

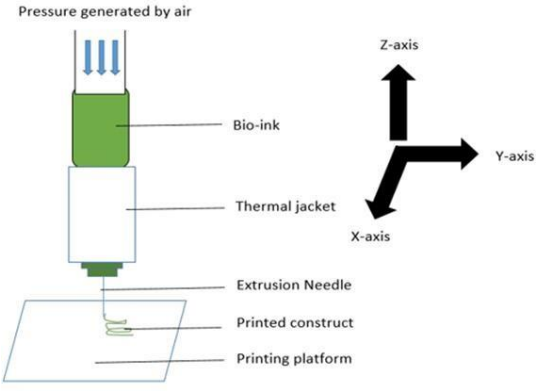
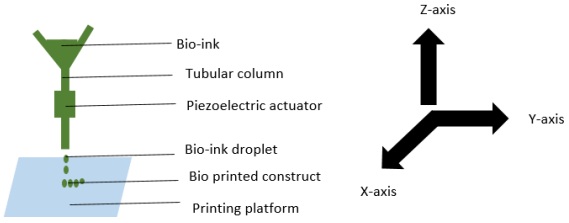


Figure 1: Micro-extrusion-based 3D-Bioprinting

2. Inkjet Bioprinting:

To fabricate a 3D construct in inkjet bioprinting, bioink which is formed as droplets through the process of vaporization and gets dispensed through an extruder (which was controlled by means of an actuator) onto a platform in a layer-by-layer fashion. The mode of the actuator can be piezoelectric or can be thermal. For fabrication of OOAC, the extruder can move in all 3 (X, Y, Z) axes according to the CAD design. In some printers, the bioink extruder remains immobile while the printing platform will be in a movable state in all X, Y, and Z axes.

The droplet size of the bioink which was determined by the modality of the actuator is the main parameter that can be controlled in inkjet printing. An inkjet bioprinter with its high resolution of 30m, enables to fabricate of OOAC with sizes of hundred microns or less than a hundred microns. Furthermore, constructions done by inkjet bioprinter, can provide a great level of cell viability. In comparison to other bioprinting techniques, the inkjet bioprinter's shape fidelity of vertical constructions is lower and this type of bioprinter is suitable only for the bioinks which are having low viscosity like 0.1 pas. Using a droplet-based printing method a defined droplet volume of bioink (suspension form of cells) can be extruded onto a predetermined site of OOAC. When the bioink passes through the printing nozzle using different apparatus like electric heating nozzle, magnetic fields, piezoelectric actuators, and acoustic actuators, microbubble



formation occurs which results to form bioink droplet.

Figure 2: Inkjet Bio printing

3. Stereolithography:

The main principle of stereolithography is photo polymerization. Different materials like polymers, composites, cells, hydrogels, and ceramics can be employed in this technique. These innovative techniques aid in the fabrication of individual patient specific models for implant fabrication which are mould assisted. Also, this technique supports complex surgeries and hearing aids can be constructed using this type of bioprinter [11].

To form a solid layer in this stereolithography technique, a UV laser polymerizes light sensitive resin containing cells. Then, the build layer shifts down in the Z direction, and the process is again repeated to form another layer. This is continued till the construction is completed. To move the printer in X, Y axes, a projector array, and electronic micro mirror devices are used. The resin which is sensitive to light is made up of polymerizable biocompatible oligomers and a photo initiator. The position of the Ultraviolet (UV) laser focus and its intensity are the two main controllable parameters in this stereolithography technique.

In the process of polymerization, UV, IR (infrared), or visible light are usually used. To solidify the structures in reservoirs which are made up of cells, photo initiators, and bioinks, laser pulses are used. Using all these parameters, solidified 3D layers are piled to construct a 3D biological structure which is nothing but an OOAC system [12].

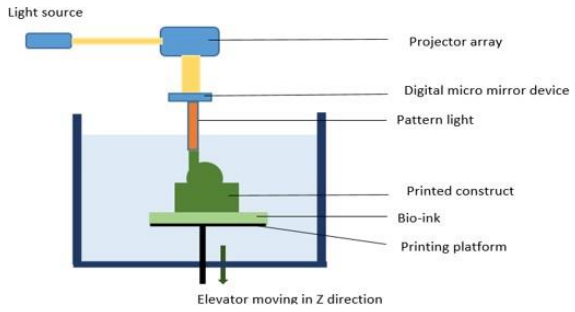


Figure 3: Stereolithography

4. Fused deposition modelling:

As the process progresses, the mixture of API, and polymer are passed through the nozzle extruder. The temperature of the nozzle is above the melting temperature of the mixture of API and polymer. This results in melting of mixture in layer by layer fashion that is solidified immediately. This model is having the ability to create complex drugs. Hence, it is most used in the research field.

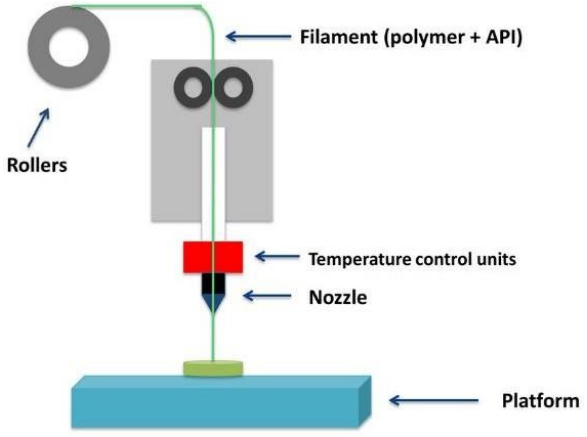


Figure 4: Fused deposition modelling

5. Electron Beam Melting Process:

The basic mechanism of electron beam melting (EBM) process is depended upon high energy beam and the metal powder. EBM works with high power in vacuum atmosphere which makes it suitable to work with various materials. Due to their good biocompatibility property this EBM is used in medical implants [13].

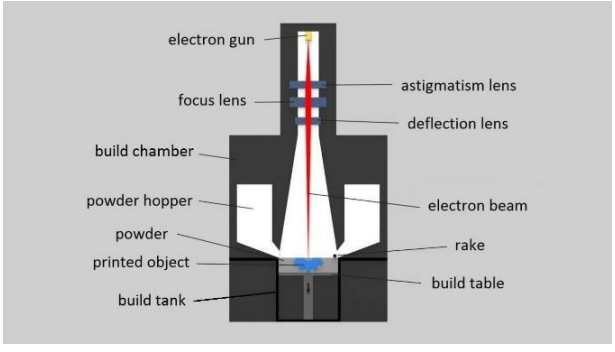


Figure 5: Electron beam melting

6. Laser assisted bioprinting:

This technique is used based on the laser as the energy. This technology consists of 3 structures: a pulsed laser source, a ribbon coated with liquid biological materials that are deposited on the metal film, and a receiving substrate. When the laser irradiates the ribbon liquid in the biological material gets evaporated the cells are transferred from the ribbon to preserve cellular adhesion and sustained growth by a receiving substrate that contains a cell culture medium [14].

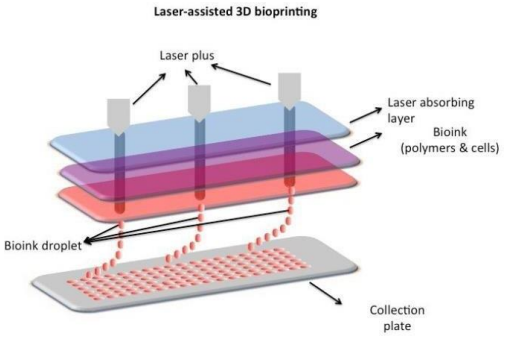


Figure 6: Laser assisted bioprinting

Polymers in 3D Bioprinting:

Repeating units of monomer units that are joined by covalent bonds results in the formation of long chained Polymers. Polymers are classified as either natural or synthetic based on their origin. To justify the biomaterial prerequisites, a polymer which is having a high degree of biosimilarity with the extracellular matrix of cells or tissues should be used. To meet the bioink criteria, Natural polymers which are abundant in plant and animal extracellular matrices are helpful [15]. Under certain physiological conditions, these polymers are compatible, degradable, and nontoxic in biological conditions and they can retain moisture in them to support the development of tissues, organs, blood vessels, lymph vessels, and nervous tissue. Most of the natural polymers are hydrophilic in nature. Synthetic polymers are manmade and are synthesized in such a way to meet required conditions that influence their properties. Synthetic polymers are more advantageous than natural polymers in the way of customizing the 3D design to attain all the needs of OOAC applications like resembling certain structures of tissues or organs. Synthetic polymers through chemical modifications allow in tailoring and modelling of biomaterial (OOAC) physical, chemical, and mechanical, surface properties.

For the construction of OOAC Polydimethylsiloxane (PDMS) is mostly used. PDMS is a polymer that is made up of silicon. It is having many ideal properties like elasticity, flexibility, transparency, the permeability of oxygen, biocompatibility, and is less expensive. PDMS has good compliance with different kinds of micro fabrication techniques like moulding and soft lithography.

As a polymer, Silicon is well suitable for different microfabrication processes, such as laser processing, etching (plasma etching or wet etching), and different methods of bonding because it has several suitable mechanical properties and is inexpensive.

The most common materials used are PDMS, polycarbonate (PC), and polyethylene terephthalate (PET). Of several materials, here we mentioned

the most important ones which are highly used in OOAC designs [14]. Several natural and synthetic polymers are used to mimic extracellular matrix properties. To get more resemblance of the extracellular matrix of biological condition, hydrogels can be combined with several technologies and can be used in OOAC applications [16].

Table1: Different types of polymers that can be used in OOAC

Type of Polymer	Substance	Merits	Demerits	Cross linking
Natural	Alginate	Easy process of gelation and stability of polymer is good	Less interaction of cells with low biodegradation	Electrolytic (Ionic bond)
	Glyco-gelatin	less antigenicity	Poor mechanical stability	Ultraviolet
	Hyaluronan	High interaction of cells	Poor mechanical stability	Ultraviolet
	Silk-fibroin	Process of degradation is slow	Less cell interaction	Physical
	Collagen	Good interaction of cells	Low mechanical properties	Temperature dependent
	Fibrinogen derivative (Fibrin)	Fast gelation	Easily clogs, less mechanical stabilities	Enzymatic
	De-cellularized extra cellular matrix	Same composition and structure of extracellular matrix	Less mechanical properties Low strength to retain its shape	Temperature dependent
	Sepharose	Easy process of gelation	Low mechanical properties and stability of polymer is less	Temperature dependent
Manmade	Polyethylene glycol (PEG)	Easy chemical modification and regeneration	Less mechanical strength and low interaction of cells	UV
	polysiloxane	Degradation is slow with suitable mechanical properties	Expensive and low interaction of cells	UV

Approaches:

3D- bio printing has three central approaches:

A. Bio-mimicry
B. Autonomous self-assembly
C. Mini tissue building blocks [17]

A. Bio-mimicry:

Biomimicry or biomimetic (originated from Greek words bios-means life and mimetic means imitate):

The process of studying nature and its system process, to solve human problems more effectively Consolidation of biomimetic components into a bio printed construct has a great impact on endogenous and exogenous cell attachment, migration, proliferation, and function are defined as biomimicry.

Materials that have a significant impact on the attachment of cells, cell shape and cell size, allowing for regulation of cell proliferation and differentiation of cells in a scaffold. Furthermore, Nano-scale characteristics like grooves, ridges, and steps have a further impact on attachment to cells, cell proliferation and assembly of cell structures. However, apart from these factors cell shape and cell differentiation of tissue engineered construct can be influenced by the 3D environment. By understanding the composition of parent tissue, which was selected to build, is constructed by 3d bioprinting using biomimicry approach [17][18].

B. Autonomous self-assembly:

Organ development at the embryo stage is very important in the formation of tissues in a biological system. This autonomous self assembly is dependent on factors such as structural and functional properties, tissue localization, and tissue composition. There is a necessity to have a thorough understanding of embryonic as well as organ development mechanisms for this approach to be successful [14].

C. Mini tissues:

The mini-tissues concept is applicable to biomimicry and autonomic self-assembly 3D bio printing strategies. Mini tissues are the smaller and functional building blocks that result in the development of Organs and tissues. For instance, in the kidney, the nephron will be the smaller and more functional building block of tissue. Using the approach of mini- tissues, the created mini-tissues can be assembled as larger tissue structures using rational design and self-assembly. The two main approaches of mini-tissues are: first, with the use of in-vivo tissue design and its organisation; the second approach is tissue units with a high percentage of accuracy and resolution are designed, organised into efficient large tissue.

Building a network of branched vascular tissue is one of the examples, as in the usage of 3D bioprinting which accurately generates functional units of tissue to create an “organ on a chip”, as they are connected and maintained by a network of microfluid used in drug and vaccine selection or as in vitro disease models. A combination of the above strategies is likely to be required for imaging and design of the material to develop a 3D structure with biological features.

The main steps in the process of bioprinting are cell selection and construction of tissue by printing. Then, the constructed tissue is subjected to in vitro analysis [17].

Applications:

1. Blood brain barrier ON CHIP:

A highly selective semipermeable blood brain barrier (BBB) consists of microvascular endothelial cells (BMEC) as they are found in capillaries pericytes and endocytes in it prevents many drugs and antagonistic towards pathogens. For drug discovery and research on the brain, we use BBB on chip models as they are based upon human cells. To develop a BBB on chip we need two main criteria: A permeable membrane is used to divide blood and brain parts for synchronous sampling of blood and brain channels for analysing the control of blood and brain components. Polarity is to be maintained by brain endothelial cells as they stimulate biological functions. Here are a few examples of BBB on chip models that meet the above criteria: A Researcher modelled the BBB within using sandwiched double channel which is separated by a porous membrane. To obtain brain

endothelial cells which are arranged within the base of chip we need to arrange primary astrocytes and pericytes on the upper channel effective barrier function was indicated up to two weeks along with the validation of delivery systems across the BBB of humans. A plausible design was demonstrated by different scientists with integrated sensors which is better than the former design [8].

2. Heart ON CHIP:

It is important to have cost effective drugs for the treatment of cardiovascular diseases as it is the most common cause of death. To understand the mechanism of the heart we need 3D bioengineered OOAC of the heart as it is useful for drug testing. Cardiomyocytes are used to perform cardiac motion with a frequency of 0.6-Hz, heart beating 40-120 beats per minute whereas the flow rate, calcium ion concentration electric stimuli are related to this function. This chip should have the ability to perform contractility techniques that describe the relative ability of the heart to eject a stroke volume at a given prevailing afterload (called as arterial pressure) and preload (called as end-diastolic volume). The heart on chip model which was designed by different scientists consists of dual conducted microfabricated devices as it is useful in research and in personalized medicine [19][20].

3. Lung on CHIP:

The lung is the third tissue that has been developed for platform establishment. As most of the harmful particles can easily get enter into the lung, it is one of the important tissue to evaluate and develop a platform by using a modified micro reactor which contains a semipermeable membrane where the endothelial cells, lung fibroblasts, and lung epithelialcells where layered. The epithelial surface, which is exposed to the air liquid interface, and a stomal component represents the tissue structure form of a 3D organoid that resembles the native airway tissue. Using fluorescent probes as well as hematatory and erosion the 3 distinct cell populations in cross sectional can be viewed. This is a simple technique and can quickly initiate an organized tissue that constitute the structure of normal airway tissue. The organoid can easily monitor when it consists of transepithelial resistance (TEER), short circuit current (isc) and electrophysiological sensing. Cystic fibrosis transmembrane conductance regulator (CFTR) is an important regulator as the normal lung function depends on the genetic coding of this regulator. Upon CFTR activation as they activate the ion channels which consist in the 3D lung organoid. As ifwe administer histamine, it shows TEER levels in the organoid [21].

4. Multi organ on CHIP:

3 types of tissue OOAC system which consist of lung, liver and heart called as multi organ on chip by using 3D extrusion bioprinting technology and also by using bioinks. Hydrogels are positioned inside the micro reactor in which the cardiac and hepatic constituents are bioprinted in a globular organoid [22]. Micro fabricated devices consist of the cells of the lung in which they were placed on the uppermost permeable membrane. In vivo main parameters like safety, efficacy and also the side effects of a drug can be monitored with the help of multi organ on chip. Upon continuous research, there has been successfully tested eye on a chip which showed a positive response towards the critical effects of the eye. As to enhance the possibilities of these modules bioprinting and microfluids together are used. Cardiac muscle tissues of the heart can be developed using 3D bioprinting which will be mostly developed by the next generation [23][24].

Benefits:

1. It is appropriate for fabricating organ-on-chip systems that include a variety of ECM and cells or tissues.
2. Bioprinting processes which are based on extrusion, are typically faster than other bioprinting processes. The technology's relative simplicity makes it simple to use for researchers of all disciplines.
3. Resin polymerization can be controlled for polymerization of selective polymers upon controlling the laser focus positioning. This achieves high resolution which is required for the development of OOAC systems.
4. Stereolithography constructs the vertical part of the OOAC system with high quality.

Limitations:

1. Micro extrusion based bioprinters have low resolution, clogging of nozzle and have less viability of cells. These all occur due to variations in types of cells that are sensitive to shear stress in different ways.
2. Process parameters optimization is dependent on different biomaterials which were used in printing.
3. When compared to other bioprinting techniques, inkjet bioprinting is suggested for bioinks with less viscosity. This printer cannot persist in its shape for a long time in vertical constructions.
4. Stereolithography, takes a long time in comparison to all other bioprinting techniques.
5. In the bioprinting technique of stereolithography, high intensity UV radiation is needed which is harmful to cell viability [2].

Challenges:

1. For the general use of OOAC, it became expensive for manufacturing and practical development currently. OOAC critics have brought into question that how precisely these novel technologies can involve and succeed in recreating micro physiological conditions.
2. In-process sample collection will result in a change in concentration of metabolites in bioink which may in turn interfere with its functioning. Hence, sensors that are more suitable are needed. The functioning of a greater number of OOAC became difficult and also results in data risks.
3. For long-term study these OOAC models are not completely reflecting the in vivo conditioning.
4. Numerous experimental solutions to conquer the limitations have been proposed. However, development is still in progress.
5. Capacity requirements for 3d printing, hot embossing, and injection moulding are inadequate. In this case, soft lithography can be used.

Surface treatment capabilities of injection Moulding are limited [23].

6. Some OOAC models are not much capable of understanding cell structures, and they develop cells with uneven distribution across the platform which will decrease the potential for clinical development.
7. 3D bioprinting is now possible to integrate cells layer by layer allowing for the heterogeneous cells to build complex hierarchical structural organization [25].

Conquer OOAC Challenges:

1. To build an accurate OOAC, sensors that are highly suitable should be used.
2. For high performance of OOACs and to mimic physiological conditions by controlling external factors, OOACs should be united with cell biology and micromachining.
3. For efficient use of OOAC the constructive components should be easy to dispose and of low cost. Expensive materials used for fabrication of OOAC should be reusable.
4. Collection of samples from OOAC should be done in a careful manner to avoid unwanted mistakes.
5. Connector size and bioink volume should be controlled for accurate results [4].

CONCLUSION:

In the process of development of OOAC, 3D bioprinting technology is having expedited speed and a high rate of precision. These printing models are suitable in medical therapies for low rejection reactions. To use these OOAC technologies in the therapeutic field, there are some challenges in the selection of bioinks, development of bacterial free conditions, biomechanics, construction of designed structures, vascular supply for developed structures, and better shelf life of bioprinted structures. Because of these considerations, bioprinting of OOAC models is still in the research phase and not used in clinical practice. Globally, most of the bioprinting technologies are experimenting with cartilage and bone cell culture engineering. On several practical experiments and breakthrough development of OOAC bioprinting models have achieved good yields in different clinical sectors. For general use, bioink connector size and media volume are reduced to employ this 3D bioprinting in OOAC. These 3D bioprinting technologies are having broader applications in research purposes in many fields of medical science, life science, materials, and engineering science. The development of the 3D bioprinting technology of OOAC replaces the use of humans in clinical trials. To achieve this main goal, still there are many efforts need to do in different disciplines of science.

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Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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