

Recent Advances in Tissue Engineering and Regenerative Medicine

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ABSTRACT

The research in the field of tissue engineering and regenerative medicine is exponentially growing to meet the demands for organ transplantation. The advantage of tissue engineering over conventional organ transplantation is the personalized development of whole organ or a particular part of the organ. To meet these organ demands, there are various approaches of tissue engineering such as traditional approach of using scaffold to grow cells and advanced 3D printing technology. The inkjet bioprinters are used along with bio-ink for bio-fabrication of different organs. The other bio-printing techniques such as extrusion-based and laser-assisted bio-printing can also be employed based on the requirement. The extracellular matrix (ECM) materials are used as a bio-ink but are limited largely to non-vascularized organs. The decellularized extracellular matrix (dECM) bio-inks are the recent advancement in the field which can be employed to generate the vascular organs like lungs and blood vessels. Even though tissue engineering shows a promising future there are various issues to be dealt with including ethics, approval from regulatory bodies and high cost of the technology.

Introduction

Organ transplantation has been the only feasible option for millions of people around the world with organ failure, and this problem is further challenged with increasing wait list for the organ transplantation and increase in mortality rate due to organ failure [1]. The issues associated with organ transplantation are complicated by finding a suitable donor for organ transplantation and storing it for a longer period of time [2]. According to the U.S government on organ donation and transplantation report, more than 100,000 patients are in the 2019 waiting list for organ transplantation and the organ donor shortage is at its peak than ever [3].

Tissue engineering is considered as the "holy grail" in the medical field and is growing at the fast pace allowing the tailor-made organs to be an alternative and a viable solution to replace failed organs [4,5]. Tissue engineering has made the dream come to reality of having a fully functional artificially produced organ. Every year, there is exponential increase in the number of publications

in the field of tissue engineering and regenerative medicines [6,7]. Although the non-vascularized organs such as skin [4,8], urinary bladder [9], urinary tract [10], bone [11] and blood vessels [12] are commercially available, thick vascularized organs such as liver, kidney and heart are still far from reality [1,13]. Commercial applications of tissue engineering are high and versatile [14]. It will help the world not just to solve the problem of organ donor scarcity for transplantation but can also be used for research purposes, for example, to study the effect of drug toxicity on different organs [7], and to study pharmacokinetics of a drug [13,15-17]. Research to create artificially engineered organs is carried out in different research laboratories around the world and successful treatments by bio fabricated organs has been reported [18]. According to Lee et al (2013), scaffold market was 4.75 million US dollars year which is expected cross more than 10 million US dollars by 2020; whereas market for stem cell will cross 11 billion US dollars by 2020 [19]. Apart from medical applications, many researchers around the world are exploring possibilities to produce leather and meat

artificially through bio fabrication techniques [20,21]. The idea of bio fabrications is also being tested to produce microelectronics and biosensor [22].

Traditional Tissue Engineering

The idea of grafting or organ transplantation is not new. First skin grafting can be traced back to 3000 BC in India [23]. Although, the foundation of tissue engineering was laid by Dr. Ross in 1907 [24]. Dr. Ross studied nerve fiber development from embryonic tissue [25]. After four decades, in the year 1948, the first artificial kidney was made. Although it was a failure but conceived the idea of tissue engineering to produce artificial organs [17]. From early 1950s to 1960s, numerous articles were published on tissue assembly on which the present regenerative medicine and tissue engineering is established [23]. The tissue engineering can be defined as the methodology to replace the damaged tissues or organs with new tissues or working organ [26,27]. There are three ways by which it can be achieved:

- a. Damaged cells can be replaced with new cells,
- b. Injecting specific growth factors such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neutrophin-3 (NT-3) and recombinant human bone morphogenetic protein 2 (rhBMP-2) as the differentiation marker; and
- c. Growing entire organ artificially in vitro [28].

The first two methods are useful when damage is minimum, but to third method can be employed when there is need to replace larger part of organ or whole organ. The organ can be grown either as tissue scaffolds using 3D bioprinter or recolonization of decolorized organ. The major challenge in tissue engineering is to mimic the microenvironment of extracellular matrix and to arrange different cell types correctly when multiple cell types are present [29].

Growing cells in a scaffold is a traditional method of tissue engineering [30,31]. In this method, cells are seeded in the scaffold, which are usually porous and allowed to mature in the bioreactor [32]. The scaffold mimics the extracellular matrix of the cells. Extracellular matrix (ECM) is very important for the cell as it allows the cells to interact, provides nutrients and supplies oxygen [33]. Scaffold is typically made of either synthetic or natural polymers to provide the structural design and property of the organs [14,26,34]. Though this methodology is successful, but it has some shortcomings as well. This is not suitable for vascularized organs, as the cells in these organs are situated over the 200 μ m of vascular structure [35,36]. Blood vessels help in transfer of nutrient and oxygen which pose a major threat to the cell differentiation and maturation [37]. The second problem is when the cells are seeded in the scaffold, at times they do not adhere to the scaffold. Finally, synthetic grafts are prone to bacterial infections and thrombin formations [35].

Advances in Tissue Engineering

In 1985, 3D printing technology was patented. Three years later, Kelbe et al (1988) published a paper on 3D positioning of the cells, or "Conscribing" [38]. Initially, 3D printing was used for printing of the scaffold and cells were seeded in it. Shortcomings of the scaffold-based technology have motivated researchers to find other strategies [39]. The need of organs for transplant has not been fulfilled by organ donations and therefore need to regenerate organs through tissue engineering is gaining popularity. Tissue engineering has the ability to revolutionize the medical field with the bio fabricated organs and tissues [28,40]. In 1995, 3D printing technology and regenerative medicine converged together and gave rise to new era of 3D organ printing. Bio fabrication is defined as the process of using living cells, biomaterials, extracellular matrices and molecules to generate complex living as well as non-living biological products [24]. 3D printing provides more mechanical stability and nutrition diffusion than that of scaffold and applying 3D printing technology, tissues of different shapes and sizes can be fabricated [39,41].

In 2003, Inkjet bioprinter was introduced [42]. Bio-inkjet printer is similar to that of the desktop printer but in the cartridge, it consists of bioink [42]. Bioinks are the ECM materials such as fibrin, hormones and growth factors that are printed as layers and cells are deposited in it [43]. It also requires a computer-aided software for deposition of the cells. Bioprinting technology involves three processes: Preprocess, process and post process. In the preprocessing step, blueprint of the organ and tissue is designed with the help of computer [44]. After designing, processing takes place. Bioprinter prints layers of cells over ECM. In the last step, bioreactor is used for tissue maturation and differentiation. The main challenges in 3D bioprinting are lack of growth factors needed for the cell differentiation [45], production of the branched vascular network [29] where new blood vessels are grown with having same structure and biological function [46], and scarcity of the technical aspect of bioprinting process such as material and resolution of bioprinting [29]. 3D printing technology provides more cell to cell interactions and it closely mimic the indigenous microenvironment for tissue growth [47]. After two-decades, Organovo launched the first commercial bioprinter in the market [48]. Due to its expectation of usefulness in the field of organ transplantation and drug studies, many companies have launched commercial bioprinters, and Stryker had invested around 400 million US dollars in 2016 [49].

Apart from bio-inkjet there are other two bio-printing techniques such as extrusion-based bio-printing and laser-assisted bio-printing [50]. The extrusion-based bio-printing is simple technique with high cell density as compare to other bio-printing with few limitations like time consuming and less resolution [51]. The laser-assisted bio-printing is a technique with high resolution and accuracy, where the bio-printing is assisted with the help of laser beam aided with the computer aided design (CAD) [52].

Parallely, decellularization process was considered as one of the primary ways to produce artificial organs. The main idea is to decellularize the organ and repopulate with the host stem cells. Though the small organs such as skin [53], heart valve [54] and vascular patches [55], cartilage [56] have been decellularized earlier, the first decellularization of whole organ was done.

In the year 2008. This was achieved by completely removing cells from the organ. Decellularization is done by three processes. (i) Chemical or enzymatic approach. (ii) Mechanical approach and (iii) Combination approach. In the first approach surfactants and acids are used to remove the host cells. Sometimes enzymes such as DNase are used to assist the reaction. While chemicals deteriorate the cell, enzymes are used to degrade the DNA of the cell. Chemical methods are effective in removing the cells, but it also destroys the signal protein which are important for biochemical pathways. Hence in order to protect the biochemical property mechanical approach is exploited. In this approach, cells are destroyed using temperature and pressure. But mechanical methods are not effective in destroying the host genetic which leads to tissue rejection. Both chemical and mechanical methods have its own advantages and disadvantages. Therefore, in order to improve the effectiveness of the process both the methods are combined [57]. In the recolonization process stem cells are seeded and allowed to grow in bioreactor [58-62].

Production of vascularized organ decellularize organs gave hope to reach the reality of producing functional organ. Many decellularized vascular rich organs such as liver [63], kidney [64], lungs [65] and urethra [66] were synthesized in the later years. A 3-year-old child was treated with engineered trachea in 2010. Within a couple of years, more research was conducted on decellularized methods. It is shown that when the decellularized

organ was introduced into the body, it grows by 57% [67]. The first decellularized whole heart was produced in the year 2008 [68]. This was performed in rat and transplanted successfully. Decellularized kidney was produced from rhesus monkey and repopulated with other cells. Adult lung tissue is yet another example with limited regeneration capacity. Petersen et al (2010) harvested lung tissue from adult Fischer 344 rat, removed cellular components, retained the scaffold of extracellular matrix that retains the hierarchical branching structures of airways and vasculature, seeded endothelial cells and transplanted these cells into rat. Their findings suggested implanted cells with functional for gas exchange activity and repopulation of acellular matrix is a feasible approach to produce engineered lung [69]. These and other studies have attracted interest of many scientists because of less immunogenicity observed with the decellularization technology. In the process of decellularization, all the materials responsible for immunogenicity are removed, thus immunogenicity is greatly reduced. The other reason is whole organs can be produced by this methodology. Unlike organ printing, where only sheet or miniature of organs are possible. ECM is intact in this methodology which helps in nutrient transport and signal transduction. Shortcoming of this technology is availability of the organs. So far, the decellularized organs have been obtained from either cadaver or animals. Decellularization also reduce the tensile property [70]. A good example of its success story comes from successful trachea transplantation in a 10-year-old boy [59]. Two patients were treated with decellularized human extracellular matrix scaffold who were suffering from non-Hodgkin lymphoma and hemophagocytic lymphohistiocytosis, post chemotherapy they had ovarian failure, they conceived after successful small invasive transplantation of ovarian tissue which was cryopreserved with the dECM scaffold [71-81] (Tables 1 & 2) (Figure 1).

Table 1: Timeline for the milestone in Tissue engineering.

Year	Achievement	Reference
1907	Dr. Harrison Ross first observed living developing nerve fiber	[25]
1948	First artificial Kidney was synthesized	[13]
1988	3D positioning of cells	[38]
1993	Term "Tissue engineering" was defined	[72]
1994	Bio-fabrication	[73]
1997	Commercially available skin	[18]
2002	Commercially available bone	[74]
2003	Patent for bio-printer	[75]
2008	Decellularized organ	[68]
2010	10-year-old child saved	[59]
2015	Development of soft tissue	[76]
2019	Development of new stereolithographic process for multi-vascular networks	[77]

Table 2: Difference between Scaffold, Decellularization, Scaffold free and dECM bioink [5,39,78-81].

Parameters	Scaffold	Decellularization	Scaffold free	dECM bioink
Immunogenicity	High	Minimum	Minimum	Low
Mechanical stability	High	Very low	High	High
Infection, calcium deposition and thrombin	High	Low	Yes	Low
Mimicking the microenvironment	Very low	High	Low	Provides the specific ECM
Availability	High	Less organ donors	High	Still in research stage
Vascular organ	No	Yes	No	No
Custom made	Yes	Not possible	Possible	Possible
Success Rate	For non-vascular organs	Vascularized organs made	Small organoids are produced	For synthesis of soft tissue and whole organs
Cost	Low	Moderate	Low	High

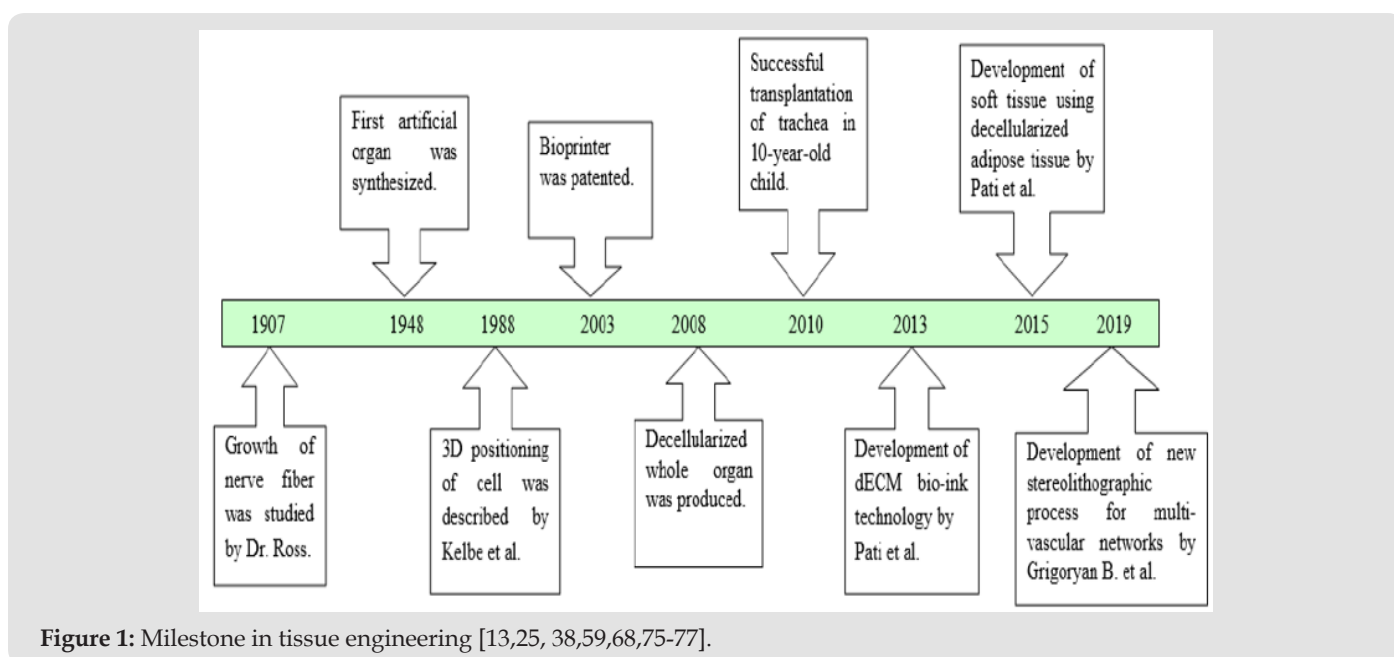


Figure 1: Milestone in tissue engineering [13,25, 38,59,68,75-77].

DECM Bio ink

In order to overcome the shortcomings of the decellularized organs and bio inkjet printing organ new technology is emerged by merging both. In this method, organs are decellularized first [82,83] and then ECM from decellularized organs is used as the bioink for the bioprinter [79]. Decellularized matrix is considered as next generation bioink [78,80]. Pati et al (2014) developed this technology and year later in 2015 they developed soft tissue using decellularized adipose tissue [83]. By this method, a layer of 400-300µm thickness is made and stacked up to 10 layers which is twice the size of the traditional printing method [76]. This technology is so far found to be useful in producing the whole organ and the mechanical property of decolorized organs was improved by hybrid technology, which uses re-absorbable polymer scaffold [84].

Future Aspect

Advances in tissue engineering research and its methodology lead to the formation of scaffold to bioprinter and then to the

decellularized organs. More research in methodologies are overcoming the shortcomings of previous ones. Improving knowledge in the biology of regeneration, development in microelectronics and 3D printing technology is helping in further overcoming the hurdles [85]. Production of commercially available organs is not the distant future anymore. FDA regulations [26], associated cost [86] and ethical issues [87,88] may delay the technology, however research trend suggests death due to organ scarcity will be reduced in foreseeable future [89].

Conflict of interest

None of the authors declares any conflicts of interest in this study.

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