International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2019): 7.583

Tissue Engineering: The Future of Most End Stage Organ Diseases and Tissue Loss Related Clinical Issues

Dr. Vimal Kishor Singh[1], Umang Berry[2]

[1]Associate Professor, Department of Biomedical Engineering, Amity School of Engineering and Technology, Amity University Haryana

[2]Junior Research Fellow, Department of Biomedical Engineering, Amity School of Engineering and Technology, Amity University Haryana

Corresponding author
@ Dr. Vimal Kishor Singh: Tissue Engineering and Regneative Medicine Research Lab, Dept. of Biomedical Engineering, Amity school of engineering and technology, Education valley, panchgaon, Manesar, Amity University Haryana 122413
E-mail: vksingh[at]ggn.amity.edu, vim_kissor[at]yahoo.co.in

Abstract: ***The major medical problems including end-stage organ diseases and tissue losses are still waiting for the most stable alternatives to restore their functional liabilities. The organ transplantation has developed as successful methods for most of these organ failure diseases but the severe scarcity (especially in pediatric population), cost of transplantations and other post-transplantation associated risks have been a major driving force for the development of more reliable and, safe and cost-effective therapeutic measures for most of these end-stage organ failure diseases. Researchers have been investigating methods for fabrication/generation of functional living tissue/organ { tissue engineering} using various approaches such as cells seeded on highly porous synthetic biodegradable polymer scaffolds for the development of biological substitutes that may replace lost tissue function. There has been a tremendous success in the past few decades towards the principles of tissue engineering in the fabrication of a wide variety of tissues/organs and reports have been there showing both structural and visceral organs regeneration and their functional applications in clinical settings. This article focuses on the current status of tissue engineering principles and outcomes an as potential therapeutic regimes for end-stage organ disease and tissue loss.***

Keywords: Tissue engineering, organ transplantations, biomedical engineering, regenerative medicine, scaffold, biomaterials, stem, cells

1. Introduction

The major medical problem still includes end-organ disease and tissue loss which causes millions of surgeries to be performed costing billions of healthcare dollars to be spent every year for the treatment of these disorders [1] There have been tremendous advancements in the current approaches to treating these disorders including organ transplantation and reconstructive surgeries. In fact, organ transplantation is the only established treatment for most of the end-stage organ diseases that have been tremendously successful in improving and saving patients lives. However, there has been a severe scarcity of the suitable donors especially in the case of pediatric patients which imposed a drastic limitation of the procedure. This evoked the researchers to investigate selective cell transplantation based approaches that emerged as a potential alternative treatment called tissue engineering approaches [1-3]

Tissue engineering could be defined as multidisciplinary field developed to restore, maintain, or improve tissue/organ function by implying various principles of life sciences and engineering to develop a biological substitute for clinical applications [1]. The distinctive feature of tissue engineering is to use the recipient's own cell/ tissue inheriting no risk of poor biocompatibility, high biofunctionality and entirely free from severe immune rejections. These outstanding advantages made tissue engineering as an ultimate ideal medical treatment. This biomedical engineering utilized three basic tools to regenerate new tissue including "cells" (i.e. stem cells), "scaffolds", and "growth factors" (Fig.1). All these three components are not always used simultaneously. For example, generation of some bone tissue may require implementation of bone morphogenesis protein (BMP) or similarly, dermal tissue may be regenerated by placing a porous collagen sheet (scaffold) on a full-thickness skin wound and there may be no need for the cell seeding or growth factors at all. The fibroblasts can migrate from surrounding healthy skin tissue into the pores of the scaffold sheet and secrete proteins/ glycosaminoglycans that reconstruct dermal tissue while the sheet is simultaneously absorbed into the body.

Licensed Under Creative Commons Attribution CC BY

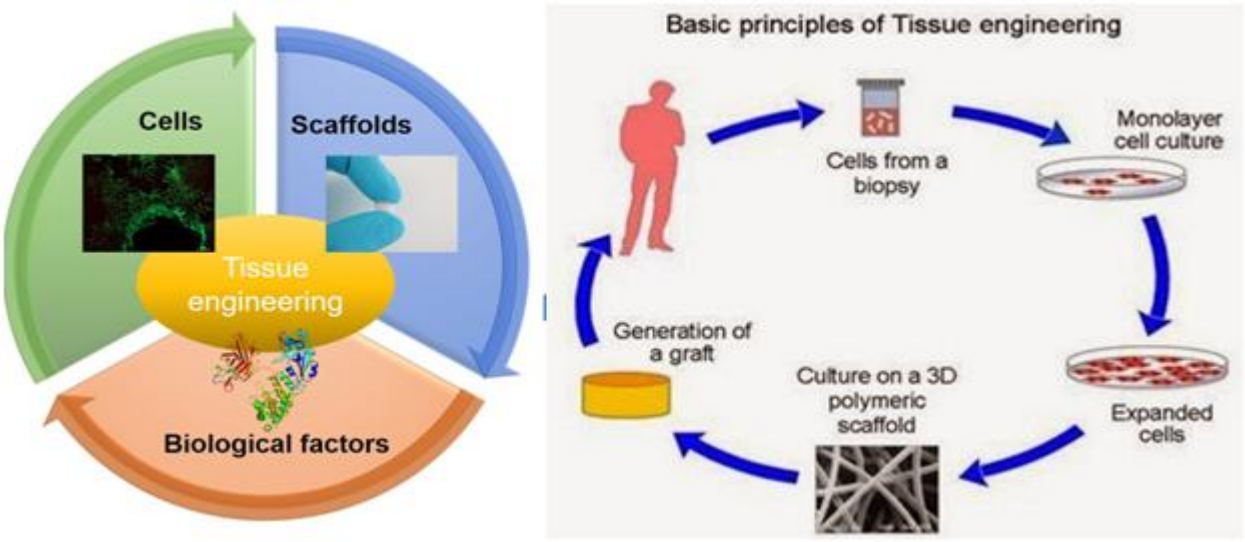

Figure 1: (a) Schematic representation of the three basic components of Tissue engineering based approaches (b) different steps involved in the tissue engineering based clinical implantation (*Obtained from Scaffolds for Tissue Engineering | Characteristics and Basic Functions of Scaffolds | Applications of Scaffolds*)

2. Most Common Examples of Tissue Engineering in Clinics

2.1 Bone Tissue Engineering

Bone is a highly specialized organ formed with organic-inorganic substituent classified as nano-composite and micro-composite tissues. Bone's functions include mineral deposition to regulate calcium and phosphate levels and also secrete hormones for phosphate and glucose homeostasis. This organ can perform true regeneration (absence of fibrotic scar tissue while healing) [4]. Loss of skeletal tissue can lead to bone structure deformation and injuries. The usage of stem cells and interactive scaffolds with several biological elements to build an ideal strategy for bone regeneration [5]. Synthetic and organic biomaterials are being used as bone substitutes. Also the use of 3D scaffolds for tissue growth has improved the healing regenerative process. Additive manufacturing technique is utilized to design complex 3D structures. Regeneration of vascular supply plays an important role in curing large defects. Mesenchymal stem cells are noted for their capability to stabilize vascularization. Endothelial cells and mesenchymal stem cells are used to design vascular networks [5]

Table 1: FDA approved bone tissue engineering products

Products	Manufacturer	Procedure	Principle
Carticel83	Genzyme Biosurgery	Knee cartilage is repaired	uses autologous chondrocytes and grows them in a biodegradable matrix
OP-1	Stryker Biotech	alternativeto patients' own bone in recalcitrant long bone non unions where an autograft is unfeasible	

2.2 Vascular Tissue Engineering

Blood vessels form an intricate design, supplying oxygen and nutrients to tissues with a maximum distance of 200µm. Tissues such as skin, cornea, cartilage can achieve this from vessels at a greater distance, by the process of diffusion, which is not possible in other tissues. There arises the need for the formation of blood vessels along with tissues for regenerative purposes. [8] Different bioengineering approaches such as spatial micropatterning, sacrificial materials, tissue decellularization, and 3D bioprinting enable the generation of more precisely controllable neovessel formation as compared to angiogenic cell therapy and growth factor treatment. [7] Good scaffold design using biodgradable and biocompatible biomaterials are key components. Materials such as polyphosphazenes, polyurethanes, aliphatic polyester elastomers, polylactones, tyrosine derived polycarbonates and many more are being used. There are several fabrication methods used to form 3D constructs which must promote optimal growth, differentiation, cell attachment and proper function. [7] Addition of angiogenic growth factors in scaffolds increases the potential for the formation of vascular networks. Two of the best used strategies are controlled release of growth factors and immobilization of these growth factors to promote angiogenesis. Hydrogels are used for that purpose due to their biocompatibility and tunable release profiles using chemical- or photo-crosslinking. But, there is a chance of abnormal cell behavior after immobilizing the growth factors causing detrimental consequences such as damage to bioactive functional groups [6-7] Sacrificial materials can be physically removed or chemically dissolved, which results in the formation of desired architecture made of non-sacrificial element. Sacrificial component can also be formed using additive processes such as 3D bioprinting. For example, Carbohydrate glass was transformed into 3D filament network present within various gels like agarose, alginate, fibrin and matrigel gels, and PEG hydrogels. Though this strategy shows promising results, incomplete removal of sacrificial materialcould prove toxic to the cells as well as host. [7]

Licensed Under Creative Commons Attribution CC BY

Micropatterning strategies have high spatial precision which can assist in incorporating tissue engineered constructs with micro- and nano-scale details. Currently, the best method used is decellularized tissue constructs which are capable of closely mimicking in vivo tissue architecture and vascular network organization, but antigenicity caused from xenogenic tissues is yet to be solved. 3D bioprinting the next most successful future strategy because of high reproducibility, precison of design, architectural control and low cost. [7]

2.3 Cartilage Tissue Engineering

Cartilage is an anural, alymphatic and avascular tissue which has a very limited capability of regeneration due to less number of chondrocytes. One of the major cause of ailment isdegeneration either caused by accidents or disorders like osteoarthritis. [9-10] .Cartilage tissue engineering deals with these issues by either seeding single cells (chondrocytes) in biodegradable scaffolds or they are incorporated on the scaffolds to promote tissue repair. For such procedure to be successful, it demands for highly coordinated interactions between cells, growth factors, materials,and their mechanical factors [11]. There are several challenges that need to be dealt with, such as biocompatibility, One of the leading causes of death is Heart Failure which results due to improper function of cardiomyocytes. Currently, cell therapies such as isolated cell suspension injection, biomaterial injection (with cells or without cells or growth factors) are approached. Several natural biomaterials are studied for the microenvironment's improvement of myocardial infarction. Synthetic biomaterials with better tensile strength are also used. Microencapsulation, integration of nanoparticles and hydrogels for the delivery of growth factors to infarcted site come under drug delivery procedures. Although, myocardial cell therapy is still a subject under investigation, various techniques have been employed as a part of cardiac tissue engineering. [12]

2.4 Pancreas tissue engineering

One of the major diseases affecting the organ is pancreatitis which can be acute or chronic. Surgery is a very rare option and only includes removal of damaged part of the pancreas. [13] Also, Diabetes type-1 is caused due to destruction of β-cells which are produced by the endocrine compartment of the pancreas. Glucose levels can be controlled by transplantation of islets of Langerhans but is not effective enough. Though regeneration and transplantation of islet cells is progressive but there are several problems related to availability of cells and their longer survival rates. [12]

Table 2: FDA approved Pancreas tissue engineering products

Product	*Manufacturer*	*Purpose*	*Principle*
	Metabolex	Microencapsulation of insulin	Produced using thin, conforming, biocompatible coatings
	BetaGene	Detection and treatment of diabetes	Uses engineered cell lines to treat diabetties and also produce insulin in bulk
Pancre Assist System	Circe Biomedical	To treat diabetes	Consists of insulin producing islets with diskshaped covering surrounding single tubular membrane

2.5 Skin Tissue Egnieering

Skin is the biggest organ of our body and is capable of self-renewal. But deep wounds such as cuts and severe burns cannot repair themselves. Injuries deeper that 4 centimeters require grafting and tissue engineering substitutes are one of the largest followed techniques. [14] Pigment disorders such as Vitiligo are treated with special cell sprays where skin lesions are sprayed with a cell suspension consisting melanocytes. Tissue engineering approaches such as cell therapies, a cellular skin substitutes, skin constructs are some of the most effective, cost reasonable techniques. Vascularization is still a problem. [15]

Table 3: FDA approved skin tissue engineering products [22]

Product	Manufacturer	Purpose	Principle
Dermagraft69	Advanced Tissue Sciences (1998)c		Cryopreserved human fibroblast-derived dermal substitute, composed of fibroblasts, ECM, and a bioabsorbable scaffold.
TransCyte66	Advanced Tissue Sciences (1997)	Short term wound cover for burns, till new tissue forms	Dermal keratinocytes are grown on a biodegradable polymer.
Apligraf67	Organogenesis	Treats foot ulcers and diabetic leg	Dual layer skin similar to human skin is formed using human skin cells
EpiDex68	Modex Therapeutics	Treats chronic skin ulcers	Uses hair follicle stem cells
Integra		Used for dressing	Acellular, two-layered, first is a synthetic epidermis layer and the second one is made of collagen fibers
Epicel	Genzyme Biosurgery (based on research by Howard Green)	Permanent burn wound treatment	autologous skin graft
Alloderm71	LifeCell	Third degree burns,	cell-seeded allogenic skin replacement , human dermal collagen seeded with allogenic fibroblasts.
Xenoderm	LifeCell	Burn wound replacement	Consists of porcine dermis

Licensed Under Creative Commons Attribution CC BY

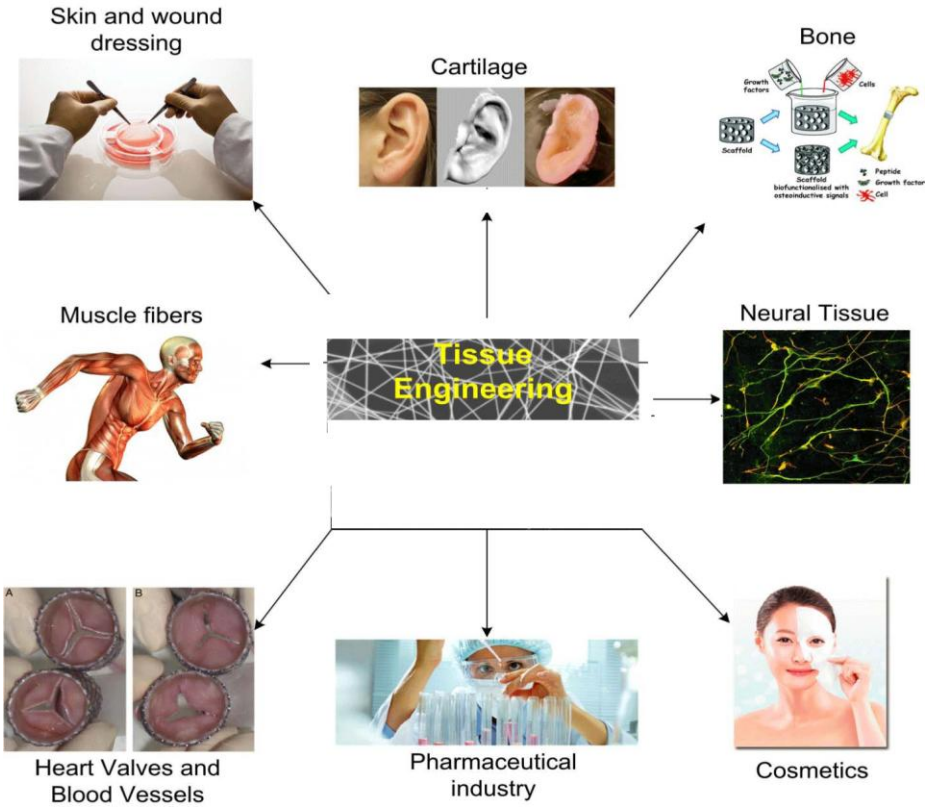

Figure 2: Various applications of tissue engineering based approaches [Figure obtained from ***Citation:*** *Hiremath N, Bhat G (2015) Melt blown Polymeric Nanofibers for Medical Applications- An Overview. Nanosci Technol 2(1): 1-9. DOI: http://dx.doi.org/10.15226*] [20]

3. Concluding Remarks

The multidisciplinary field of tissue engineering may provide enormous potential for the curing the end stage organ diseases, genetic disorders of metabolic deficiencies and tissue loss. There have been a successful clinical trial for many of these disorders by employing selective transplantation procedures. The applicability of tissue engineering principles has been well demonstrated in the fabrication of a wide variety of tissues. The various examples described above indicate the key importance of collaboration among medical practitioners (conduct implantation and evaluation), biomaterial scientist (essential for scaffold fabrication). This delicate collaboration among different fields is essential to meet the patient's expectations. Scaffolding approaches, bioprinting techniques and the plethora of other strategies are being researched upon day by day. Tissue engineering is evolving on a daily basis encouraging researchers to solve some of the most irremediable conditions. A better future with easily accessible cures and less convalescence period is a plausible hope.

4. Acknowledgment

We thank the honorable chancellor and the Honorable Vice-chancellor, respected Deputy Vice chancellor and respected Pro Vice-Chancellor and Director ASET, of the Amity University Haryana, for their kind encouragement and support.

References

[1] Langer R, Vacanti JP: Tissue engineering. Science 260:920-926, 1993
[2] Russell PS: Selective transplantation. Ann Surg 201:255-262, 1985
[3] Vacanti JP: Beyond transplantation. Arch Surg 123:545-549, 1988
[4] J. Henkel, M. A. Woodruff, D. R. Epari, R. Steck, V. Glatt, I. C. Dickinson, P. F. M.Choong, M. A. Schuetz, D. W. Hutmacher, "Bone Regeneration Based on Tissue Engineering Conceptions – A 21st Century Perspective," Bone Research, vol. 3, pp. 216-248., 2013.
[5] C. R. M. Black, . V. Goriainov, . D. Gibbs, J. Kanczler, R. S. Tare and R. O. C. Oreffo, "Bone Tissue Engineering," Current Molecular Biology Reports, vol. 1, no. 3, pp. 132-140, 2015.
[6] K. Lee, E. A. Silva and D. J. Mooney, "Growth factor delivery-based tissue engineering: general approaches and a review of recent developments," J R Soc Interface, vol. 8, no. 55, pp. 153-170, 6 February 2011.
[7] L. H. N. F. H. Joseph J. Kim, "Vascularization of Three-Dimensional Engineered Tissues for Regenerative Medicine Applications," Acta Biomater, vol. 41, pp. 17-26, 1 September 2016 .
[8] C. K. P. J. K. Esther C. Novosel, "Vascularization is the key challenge in tissue engineering," Advanced Drug Delivery Reviews, vol. 63, pp. 300-311, 2011.
[9] M. Keeney, H. J. Lai and F. Yang, "Recent progress in cartilage tissue engineering," Current Opinion in Biotechnology, vol. 22, no. 5, pp. 734-740, October 2011.

Licensed Under Creative Commons Attribution CC BY

[10] Y. Liu, G. Zhou and Y. Cao, "Recent Progress in Cartilage Tissue Engineering—Our Experience and Future Directions," Tissue Engineering, vol. 3, no. 1, pp. 28-35, 2016.
[11] K.-C. Li and Y.-C. Hu, "Cartilage tissue engineering: recent advances and perspectives from gene regulation/therapy.," Advanced Healthcae Materials, vol. 4, pp. 948-968, 2015,.
[12] C. Castells-Sal, M. A.-Ribes, T. F.-Munos, L. R.-Sancho, P. L.-Chicon, C. A.- Reverte, J. C.-Camino, A. M.-Gill, C. E. Semino, "Current Applications of Tissue Engineering in Biomedicine," J Biochip Tissue chip, vol. S2:004, 2013.
[13] L. C. Murtaugh and M. Keefe, "Regeneration and Repair of the Exocrine Pancreas," Annu Rev Physiol. 2015 Feb 10; 77: 229–249., vol. 77, pp. 229-249, 10 Feb 2015.
[14] Komal Vig, A. Chaudhari, S. Tripathi, S. Dixit, R. Sahu, S. Pillai, V. A. Dennis and S. R. Singh, "Advances in Skin Regeneration Using," International Journal of Molecular Sciences, vol. 18, p. 789, 2017.
[15] A. Oryan, M. Jalili and A. Kamali, "Tissue Engineering In Burn Wound Healing: Current Modalities and Future Directions," International clinical pathology Journal, vol. 4, no. 1, 2017
[16] A. S. Mao and D. J. Mooney, "Regenerative medicine: Current therapies and future directions," Proceedings of the National Academy of Sciences of the United States of America, vol. 112, no. 47, 2015.
[17] C. A. Vacanti, "The History of Tissue Engineering," Journal of cellular and molecular medicine, vol 10, no 3, pp 569-576, 2006.
[18] E. S.Bishop, S. Mostafa, M. Pakvasa, H. H. Luu, M. J. Lee, J. M. Wolf, G. A. Ameer, T.-C. He and R. R. Reid, "3-D bioprinting technologies in tissue engineering and regenerative medicine: Current and future trends," Genes & Diseases, vol. 4, no. 4, pp. 185-195, 2017.
[19] F. Colomboa, G. Sampognaa, G. Cocozzaa, S. Y. Guraya and . A. Forgione, "Regenerative medicine: Clinical applications and future perspectives," Journal of Microscopy and Ultrastructure, vol. 5, pp. 1-8, 2017.
[20] H. Kaul, Y. Ventikos, "On the Genealogy of Tissue Engineering and Regenraive Medicine," TISSUE ENGINEERING: Part B, vol. Volume 21, no. Number 2, 2015.
[21] H. Wobma, G. Vunjak-Novakovic,"Tissue Engineering and Regenerative Medicine 2015: A Year in Review," TISSUE ENGINEERING: Part B, vol. Volume 22, no. Number 2, 2016.
[22] J. Viola, B. Lal and O. Grad, "The Emergnce of Tissue Engineering as a Research Field," The National Science Foundation, Arlington, 2013.
[23] M. E. Gomes, M. T. Rodrigues, R. M. Domingues and R. L. Reis, "Tissue Engineering and Regenerative Medicine: New Trends and Directions—A Year in Review," TISSUE ENGINEERING: Part B, vol. 23, no. 3, 2017.
[24] T. G. Bird, W.-Y. Lu, L. Boulter, S. Gordon-Keylock, R. A. Ridgway, M. J. Williams, J. Taube, J. A. Thomas, D. Wojtacha, A. Gambardella, O. J. Sansom, J. P. Iredale and S. J. Forbes, "Bone marrow injection stimulates hepatic ductular reactions in the absence of injury via macrophage-mediated TWEAK signaling," Proceedings of the National Academy of Sciences of the United States of America, vol. 110, no. 16, 2013.

Licensed Under Creative Commons Attribution CC BY