Applications of Tissue Engineering in Oral Medicine

Suganya[1], Maria Priscilla David[2]

ABSTRACT

Tissue engineering is an interdisciplinary field of study, which employs the principles of engineering and life science to develop the biological components, which need to be healed or improved. Furthermore, this field is based on three fundamental principles, namely: (I) the cells, responsible for synthesis of the new tissue matrix; (II) growth factors that promote and facilitate cell function; and (III) scaffolds that act as an extracellular matrix, allowing cell differentiation, proliferation and biosynthesis. In Dentistry, there is need for regenerative therapies that would be capable of recovering the function of tissues lost due to oral, maxillofacial and dental pathologies of traumatic, inflammatory and neoplastic origin and diseases of endodontic, periodontal, among others. Hence this article aims to present an overview of applications of tissue engineering in oral medicine.

Keywords: Tissue Engineering, Oral Medicine

INTRODUCTION:

Tissue engineering is an interdisciplinary field that applies the principles and methods of bioengineering, material science, and life sciences toward the assembly of biologic substitutes that will restore, maintain, and improve tissue functions following damage either by disease or traumatic processes. Tissue engineering comprises three major components of biologic tissues, that is, adult stem cells, growth factors, and extracellular matrix scaffolds.[2] The term "tissue engineering" was coined in 1987. Langer and Vacanti worked extensively together to develop polymer biodegradable scaffolds, where they were able to tailor the physical and chemical properties. Hence functional tissue equivalents were generated using biocompatible, biodegradable polymer scaffolds seeded with practical cells.

CURRENT APPROACHES TO TISSUE ENGINEERING ARE:

(1) Substitutive approaches (ex vivo) are essentially whole organ replacement.
(2) Histioconductive approaches (ex vivo) involve the replacement of missing or damaged parts of an organ tissue with ex-vivo constructs.
(3) Histioinductive approaches facilitate self-repair and may involve gene therapy using DNA delivery via plasmid vectors or growth factors.

CRITERIA FOR TISSUE ENGINEERING

1) An adequate number of cells must be produced to fill the defect.
2) Cells must adopt appropriate three-dimensional structural support/scaffold and produce ECM.
3) Produced cells must be structurally and mechanically compliant with the native cell.
4) Cells must successfully be able to integrate with native cells and overcome the risk of immunological rejection.

TRIAD OF TISSUE ENGINEERING

It involves the combination of three pillars: Cells, Scaffolds, and Signaling molecules.

I. Cell

The source of cells utilized in tissue engineering can be autologous (from the patient), allogenic (from a human donor but not immunologically identical), or xenogenic (from a different species donor), mature (non- stem) cells, adult stem cells or somatic stem cells, embryonic stem cells and totipotent stem cell or zygotes.

Cell source for progenitor cells

1. Periodontal ligament – derived cells: It has multipotential characteristics and the cells are regarded as useful sources for the regeneration of periodontal tissues containing bone, cementum, and periodontal ligament.
2. Periodontal ligament – derived mesenchymal stromal cells: It possess multipotency, clonogenic ability, high proliferation and the expression of the putative stem cell marker STRO-1, as well as the perivascular cell marker CD146.
3. Periosteal cells: The cultured periosteum has the capacity to differentiate into an osteoblastic lineage and expresses periodontal tissue related genes.
4. Gingival epithelium and fibroblast: Gingival epithelial sheets derived from human gingival tissues have been developed and applied clinically as a treatment for chronic desquamative gingivitis.
5. Bone marrow- derived mesenchymal stem cells: It has the ability to extensively proliferate and is capable of guided differentiation into multiple cell types, establishing a provocative cell source for potential tissue engineering. It also demonstrated that auto transplantation of bone marrow derived mesenchymal stem cells induced periodontal regeneration.

[1]Mds Post Graduate Student, Oral Medicine and Radiology, M R Ambedkar Dental College and Hospital, [2]Professor and Head of Department, Oral Medicine and Radiology, M R Ambedkar Dental College and Hospital, Bengaluru, Karnataka, India

Corresponding author: Suganya, #154/2, 4th Cross, Rashad Nagar Arabic College Post Nagawara, Bangalore -560045, Karnataka, India

How to cite this article: Suganya, David MP. Applications of tissue engineering in oral medicine. International Journal of Contemporary Medical Research 2022;9(4):D1-D6.

II. Scaffold or supporting matrices

The major roles for supporting matrices are listed:

1. It serves as a framework, which maintains the shape of the defect.
2. It serves as a 3D anchorage for cellular adhesion, emigration, augmentation and production of extracellular matrix.
3. It serves as a barrier to restrict cellular emigration in a selective manner.
4. It potentially serves as a delivery vehicle for growth factors.

Biomaterials used as scaffolds

1. Ceramics

Natural and synthetic hydroxyapatite (HA) and beta tricalcium phosphate (TCP) are ceramics used in bone tissue engineering. They are biocompatible, osteoconductive and being protein free, they stimulate no immunological reaction.

2. Polymers

These include synthetic polyesters, such as polyglycolic acid, polylactic acid and polycaprolactone and natural polymers like collagen fibrin, albumin, hyaluronic acid, cellulose, chitosan, polyhydroxyalkanoates, alginate, agarose and polyamino acids.

III. Signaling molecules in tissue engineering:

To enhance the in vivo efficacy, incorporation of various bioactive molecules (growth factors) into scaffolding materials sustain release of bioactive molecules for longer periods of time.

1. Platelet derived growth factor:

The material released from platelets is the principal source of mitogenic activity present in serum, and is responsible for the growth of many cells in culture that are serum dependent. This activity was later localized to the alpha granules within platelets. Application of the combination of PDGF-B and IGF-I can significantly enhance the formation of periodontal attachment apparatus during early phases of wound healing following surgery.

2. Fibroblast growth factor (FGF)

It is the member of heparin binding growth factor family. FGF stimulates angiogenesis, DNA synthesis and cell replication.

3. Bone morphogenetic proteins:

BMP appears to possess a multitude of effects that promote periodontal healing. It helps undifferentiated pluripotent cells to differentiate into cartilage and bone forming cells. Along with β-FGF, it stimulates angiogenesis.

4. Insulin like growth factor:

IGF-I is known as somatomedin C and IGF-II has been called multiplication stimulating activity. IGF-I is found in substantial levels in platelets and is released during clotting along with the other growth factors. It is a potent chemotactic agent for vascular endothelial cells resulting in increased neovascularization. IGF-1 has strong effect on periodontal ligament fibroblasts mitogenesis and protein synthesis in vitro. It promotes osteogenesis and cementogenesis. IGF-II is the most abundant growth factor in the bone and it also promotes parameters of bone formation but is not as potent as IGF1.

5. Transforming growth factor-β:

TGF-β was found in highest concentration in bone and platelets. It is a strong promoter of extracellular matrix production. It selectively stimulates periodontal ligament fibroblast proliferative activity. It stimulates type I collagen, fibronectin and osteocalcin biosynthesis, as well as bone matrix deposition and chemotaxis of osteoblast.

6. Periodontal ligament derived growth factor (PDL-CTX):

This peptide is highly specific autocrine chemotactic agent for human periodontal ligament cells, which is 1000-fold more potent than many known growth factors (IGF, PDGF, TGF).

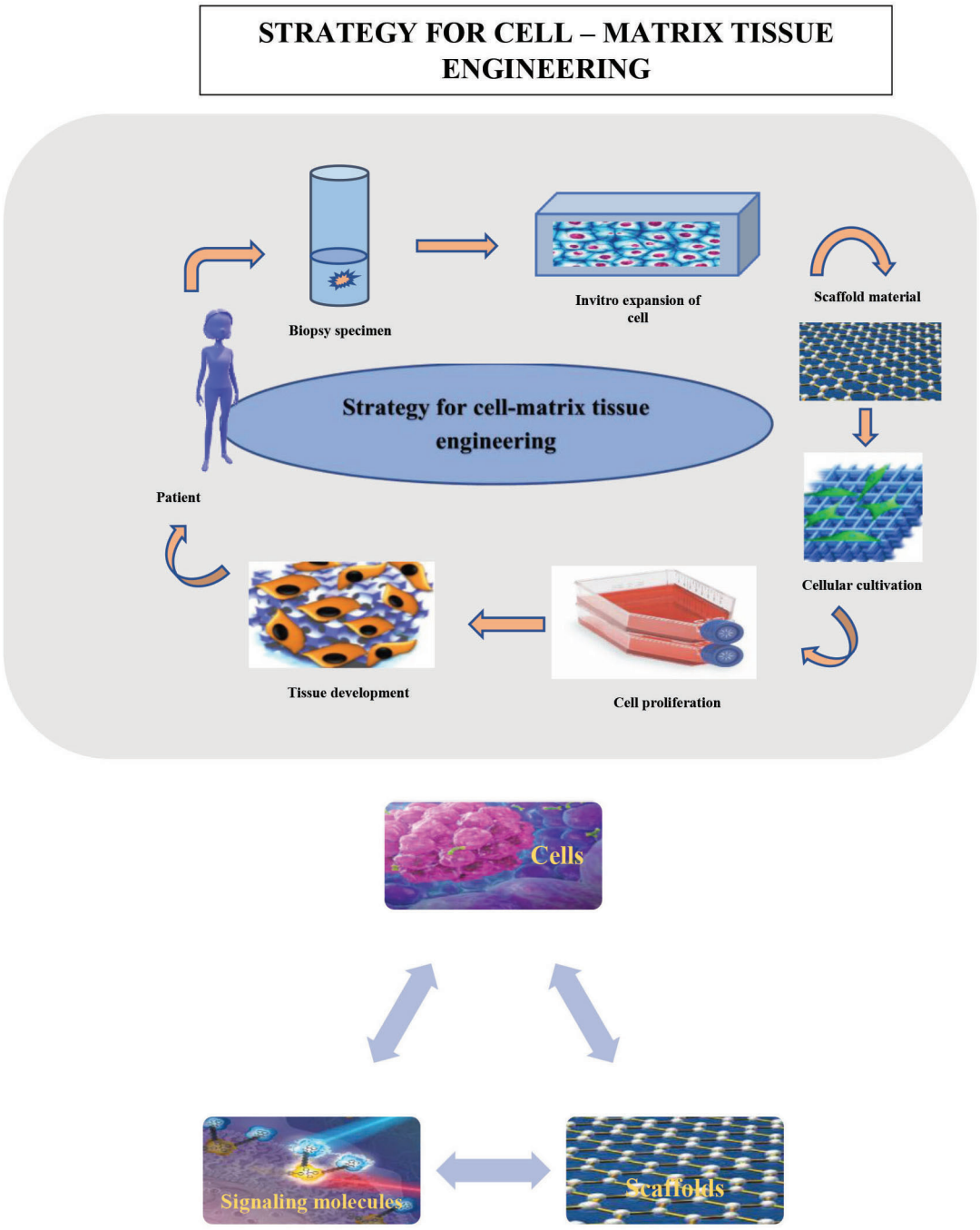
APPLICATION OF TISSUE ENGINEERING IN DENTISTRY

1. Endodontitis: The regeneration of the dentine-pulp complex, obtained with pulp capping materials e.g., calcium hydroxide, mineral trioxide aggregates, Biodentine1 has been correlated with the stimulation of differentiation of the pulp progenitor cells into odontoblast-like cells or secretion of TGF-b131 which plays a key role in angiogenesis, recruitment of progenitor cells, cell differentiation and finally mineralisation of the injured area. Dental -pulp complex regeneration has been attempted by stem cell therapy and dental tissues are a very rich source of it. In dental pulp tissue engineering, soft scaffolding, such as hydrogels can be used. Such scaffolds are in syringe type and are injectable in the root channel. One of the other probable applications of stem cells in endodontics is in apexogenesis and apexification.[2]

2. Periodontitis:

Periodontitis is a chronic inflammatory disease of periodontium, which destroys the connective tissue and bone that supports teeth. Severe and prolonged periodontal inflammation leads to loss of teeth, thereby affecting oral functions such as mastication, speech and facial esthetics. Regeneration of cementum-periodontal ligament bone interfaces and structures are very challenging and require the synergy of all cellular and molecular events involved in regeneration of these complex tissues. Guided tissue/bone regeneration membrane (GTR/GBR) utilises occlusive membranes to maintain the defective space, selectively encourage the appropriate cells to regenerate the lost tissues and support the newly formed tissues. Several synthetic polymers were used as GTR/GBR membranes which include polytetrafluoroethylene, polylactide, glycolide and polylactide/glycolide. To fabricate nanofibrous scaffolds with a wide range of properties, a combination of both synthetic and natural polymers can be employed. Platelet rich plasma has increased the proliferation, differentiation and hence odontogenic and osteogenic gene expression of human periodontal ligament and dental pulp stem cells.

APPLICATIONS OF TISSUE ENGINEERING IN ORAL MEDICINE



3. Oral and maxillofacial surgery

Platelet Rich Plasma (PRP) is an autologous concentration of human platelets in a small volume of Plasma. PRP has demonstrated efficacy in the healing of split thickness skin graft donor sites. The revascularization is quickly enhanced by the angiogenic activity of PDGF and TGFß. PRP Gel also improves the handling of particulate graft apart from enhancing the osteogenesis of sinus lift graft. Both vertical horizontal and ridge augmentation procedures benefit from PRP. It may be used over sinus lift windows, to cover sinus membrane perforations, or over dental implant fixtures. PRP treated extraction socket have shown better hemostasis, faster soft tissue flap healing, decreased post operative swelling and decreased rate of alveolar osteitis. Alveolar bone grafting demonstrated on the cleft lip and palate patients with PRP shows a good regeneration of bone to the alveolar cleft. PRP in implant surgeries has shown better alveolar bone reconstruction of the jaw prior to implant placement which leads to increased height and width and the integration of the implant which can then support a fixed dental bridge. A mixture of autologous bone platelet gel filled in the distraction gap to create a bony scaffold for distraction regenerate can been used to restore atrophic mandible during distraction osteogenesis.

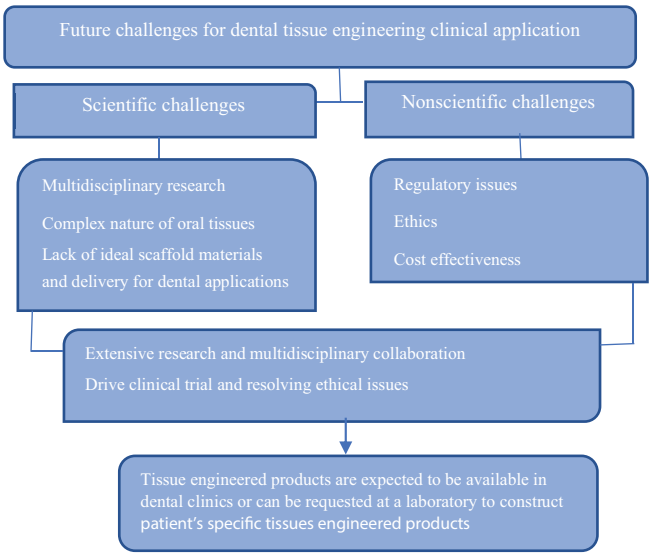


Figure-2: Major challenges

4. Tissue engineering of temporomandibular joint

TMJ is a ginglimoarthrodial synovial joint which is the most complicated tissue to treat due to limited blood supply and capacity for self-repair. The articular cartilage of TMJ has a surface layer of fibrocartilaginous and deep layer of hyaline-like hypertrophic zone with a thin intermediate proliferative zone. For regeneration of this unique cartilage, cell therapy comes first and injectable smart hydrogels could be employed to transfer cells. Cell source used in TMJ regeneration are human umbilical cord derived mesenchymal-like stem cells (HUCM) are primary costal chondrocytes (CCs). Regeneration of bone and cartilage require different competing conditions, therefore growing a biphasic osteochondral construct in vitro is very challenging. Regarding the cellular component, adipose stem cells (ADSCs) could be a potential cell source for TMJ engineering. Platelet-derived growth factor (PDGF) could be an effective for engineering of TMJ disc. PDGF within an optimal concentration of 5 ng/ml significantly increased the proliferation rate of the TMJ-disc derived cells, collagen and hyaluronic acid synthesis. It also upregulated RNA levels of type I and II collagens, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs). Basic fibroblast growth factor (bFGF), transforming growth factor-b1 (TGF-b1) and insulin-like growth factor-1 (IGF-1) have been also investigated for potential application in TMJ disc regeneration. All these growth factors induce bone marrow mesenchymal stem cell differentiation into fibroblast-like cells, which could synthesis TMJ disc matrix of GAG and type I collagen.

5. Tissue engineering of salivary glands

Losing function of salivary glands can follow adverse effect of medicines, radiotherapy, and autoimmune diseases, such as Sjogren's syndrome. Salivary glands are composed of four certain types of epithelial cells such as acini, ducts, basal, and myoepithelial and discovering a cell able to differentiate to these cells is a great challenge for tissue engineering. The progenitor epithelial cells of salivary gland could be used in tissue engineering.

6. Prosthodontics

Today, missing teeth are replaced with denture or with implant. But even these successful treatments have several shortcomings. In regeneration of whole tooth in vivo, the planted stem cells on a scaffold can be transplanted in the body and transformed to dental structures. This phenomenon calls for differentiation of several tissues such as enamel, dentin, pulp, cementum, and the formation of periodontal ligament using various messaging molecules. At present, there are numerous problems to the complete regeneration of dental structure such as identifying an appropriate source of epithelial and mesenchyme stem cells which can differentiate to all dental structures, the germination of implanted tooth, in that the dental follicle which play an important role in teeth germination is absent in these conditions and the type of connection of implanted tooth with vessels and nerves of the apical area.

7. Tissue engineering of skin and oral mucosa

Regeneration of skin and oral mucosa in patients, who lost a part of their tissues due to burn, major surgeries, or trauma is a matter of utmost significance. All FDA-certified regenerated skill products are composed of Foreskin neonatal-based cells. These cells are capable of proliferation and could be the generator of 80,000 meters of final skin product. Like skin, oral mucosa is formed of stratified squamous epithelium, which covers the lamina propria. Recently mucocutaneous construct has been engineered using mucosal and skin keratinocytes in vitro and has been claimed to be used for the repair of lips. The tissue engineered oral mucosal grafts have been reported to achieve the specific requirements for clinical procedures such as vestibuloplasty, release of tongue and pre-laminating the radial flaps.

Recent advancements in tissue engineering:

Gene therapy

Gene therapy is a process by which small DNA or RNA sequence are transferred to cells or tissues to correct a genetic defect or treat a disease. Genetic information is transferred to the target cells, which enables them to synthesize a protein of interest to treat disease. Gene transfer is accomplished through the use of viral and non-viral vector and can be introduced directly to the target site.

1. Gene therapy for Bone Repair: Bone loss occur due to several oral conditions such as periodontal disease, trauma, neoplasm, reconstructive surgery. It enhances the bone regeneration by osteoinduction via expression of growth factors, induce osteoblast differentiation, facilitate the production of osteoid matrix and utilize an osteoconductive apparatus.
2. Gene therapy for salivary gland disorders: It is used as a clinical trial for regeneration and stimulation of salivary tissues in patients with head and neck cancer, who underwent radiotherapy. Salivary glands are excellent target sites for gene transfer. It produces a large amount of proteins and the sites are easily accessible

for gene transfer with minimum invasiveness through intracannulation.

3. Gene therapy for Autoimmune disease: In Sjögren's syndrome, the destruction of glandular tissue may be isolated to salivary and lacrimal tissue or by secondary autoimmune diseases such as rheumatoid arthritis. Due to the autoimmune nature of the disease, infiltrating CD4+ cells release pro-inflammatory mediators (cytokines interleukin-2, interferon-γ, tumor necrosis factor α) as well as anti-inflammatory mediators (interleukin-4, interleukin-6, interleukin-10). The upregulation of genes coding for anti-inflammatory cytokines, therefore, has been pinpointed to offer relief for dry mouth, keratoconjunctivitis. hIL-10 immunomodulatory therapy, using a recombinant Adeno associated virus vector encoding the gene for hIL-10, has been tried successfully to treat several autoimmune diseases, including rheumatoid arthritis.
4. Management of Pain with Gene Therapy: Gene transfer may be particularly useful for managing chronic and intractable pain conditions such as trigeminal neuralgia, orofacial pain, temporomandibular disorders, migraine. A virus carrying gene for endogenous opioid, which can be injected directly to the spinal fluid adjacent to the dorsal root ganglia. Since the dorsal root ganglia acts as a pathway to higher pain centers and opioids produce morphine-like blockade of this pain pathway, results lasting for up to 3 months.
5. Gene Therapy for Orthodontic Tooth Movement: Tooth movement depends on the remodeling of alveolar bone, which is controlled by osteoclasts and osteoblasts. The molecules mediating such interactions are the receptor activator of the nuclear factor kappa B (RANK) or RANK ligand (RANKL). Osteoclastic precursors express on their surface RANK, the receptor for RANKL that binds and converts them into multinucleated giant cells. RANKL is also a ligand for Osteoprotegerin (OPG), a soluble receptor produced by osteoblasts or periodontal ligament cells and acts as a decoy receptor for RANKL, preventing RANKL-RANK binding. OPG is in competition with the RANK receptor binding to RANKL. On binding with RANKL, it inhibits osteoclastogenesis, thus jamming the process of bone resorption.
6. Gene Therapy for Head, Neck, and Oral Cancer:

Several modalities have been developed for cancer gene therapy, which includes

1. Immunogenic therapy which involves modulation of immune responses through the transfer of cytokines, immune accessory molecules, or tumor antigens.
2. Antiangiogenic therapy which involves the introduction of genes with antiangiogenic properties in a variety of tumor cells, thereby inducing apoptosis.
3. Oncolytic virus therapy, which selectively kills tumor cells but not normal cells.
4. Gene replacement therapy which involves the introduction of tumor suppressor genes, such as p53 in cancer cells.
5. Suicide gene therapy that is able to convert a prodrug into an active drug that is toxic for target cells.

MAJOR CHALLENGES

Replacing lost or damaged dental tissues can be a reality in the near future where tissue emergency products can be available for dental patients. However, there are various challenges before we reach this stage. One such major challenge is to design an appropriate capillary network to allow gas exchange, provide nutrition and remove waste from the implanted constructs.

CONCLUSION

Tissue engineering provides a new era for therapeutic medicine which is progressing very rapidly and extends to involve all tissues in our body. The future of tissue engineering in dentistry is most promising, and this new approach is expected to enable regeneration of tissues damaged by different dental and orofacial pathologies. A great deal of progress has been made in research, with the development of different materials and fabrication techniques, with the purpose of improving the properties of the materials for this field of interest. However, in spite of these advances, complete regeneration of dental tissues continues to be challenging. Therefore, dentists must be aware of these advances, help with the development of research and use new technologies in daily clinical practice, thereby providing patients with more efficient therapy, and consequently, improvement in their quality of life. Translating tissue engineering research and development into clinical practice still drives much of science and technology in this field.

REFERENCE

1. Elisa Battistella, Silvia Mele and Lia Rimondini, University of Eastern Piedmont "Amedeo Avogadro" Novara, Italy. Dental tissue engineering: a new approach to dental tissue reconstruction. Biomimetics, Learning from Nature.
2. Alizadeh E, "A review on the applications of tissue engineering in branches of dentistry, Int J Contemp Dent Med Rev, vol. 2017, Article ID: 010617, 2017.
3. K.M. Kim and G.R.D Evans, Tissue Engineering: The Future of Stem Cells, Topics in Tissue Engineering, Volume 2, 2005.
4. Ensanya Ali Abou Neel et al, Tissue engineering in dentistry. Journal of dentistry 42 (2014) 915–928.
5. Ahuja A et al: Tissue Engineering in Oral & Maxillofacial Surgery. IJMDS January 2012; 1(1).
6. Zafar et al. Oral Tissue Engineering Progress and Challenges. The Korean Tissue Engineering and Regenerative Medicine Society. Tissue Eng Regen Med 2015;12(6):387-397.
7. JS MORO et al. Tissue engineering perspectives in dentistry: review of the literature. RGO, Rev Gaúch Odontol. 2018 Out-Dez;66(4): 361-367.
8. Dr Manish Kumar et al. Tissue Engineering: Emerging Concept in Oral Maxillofacial Reconstruction-A Review Article JMSCR Volume 05 Issue 08 August 2017.

9. Priya, Tissue engineering in periodontal regeneration. IJOCR Oct - Dec 2015; Volume 3 Issue 4.
10. George Huang, Pulp/dentin tissue regeneration. Regen. Med. (2009) 4(5), 697-707.
11. Indhulekha Vimalakshan et al., Applications of gene therapy in dentistry - a review. Drug invention Today / Vol 10. Issue 6. 2018.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 25-02-2022; **Accepted:** 28-03-2022; **Published:** 30-04-2022