

Stem Cell-based Regenerative Therapy in Dentistry: A Review

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ABSTRACT

Stem cells are various cell types that possess the special capability to self-renew and differentiate into multiple cell lineages. In recent decades, they have been investigated and employed for repair and regenerative therapies. In recent years, researchers have dedicated efforts to uncover the function of stem cells in addressing various illnesses. Stem cells have the ability to self-replicate and differentiate into various somatic cells. They would likewise hold a unique role in the future across different clinical areas. Consequently, identifying safe and inexpensive methods to acquire these cells is a primary goal of research. Jaw, facial, and oral tissues are abundant sources of stem cells, which are more easily obtainable than other types of stem cells. The wider use of stem cell-based procedures in dentistry could revolutionize the daily practices and methods that clinicians employ when treating patients. Nearly every area of dentistry could gain from these recent discoveries.

Keywords: Craniofacial regeneration, Pulp stem cells, Stem cells, Tooth repair.

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INTRODUCTION

A stem cell is a distinctive type of cell with a unique ability to self-renew and an extraordinary potential to transform into various cell types within the body. They serve as a repair mechanism for the body, theoretically capable of dividing indefinitely to replenish other cells as long as the individual or animal remains alive. When a stem cell divides, each resulting cell can either stay as a stem cell or differentiate into another cell type with a specific function, such as a muscle cell, a brain cell, or a red blood cell.¹ However, most cells in the body, like cardiac or skin cells, are dedicated to performing a particular function, whereas stem cells are undifferentiated until they receive a signal to evolve into specialized cells. The potential uses of stem cells include replacing and repairing tissues and organs.² Regeneration of oral and maxillofacial structures can be achieved through stem cell therapy. Which has recently gained popularity (Table 1).

BASIC CONSIDERATION

Definition

Stem cells are undifferentiated cells that can replicate endlessly and have the capability to transform into specific mature cells with specialized roles.³ These relatively unspecialized cells maintain their ability to divide and multiply throughout postnatal life, supplying progenitor cells that can evolve into specialized cells.⁴

Properties of Stem Cells^{4,5}

Stem cells possess a unique capability to divide and replace themselves over a prolonged period.

Stem cells are unspecialized: The significance of their unspecialized nature is important. This indicates that stem cells do not possess the particular components needed for specialized functions within the body. Although a stem cell does not have a specific role, it has the potential to change into a specialized cell capable of performing these functions.

Stem cells can give rise to specialized cells: The ability of stem cells to produce specialized cells is crucial; throughout

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this differentiation process, unspecialized stem cells give rise to specialized cells.

CLASSIFICATION OF STEM CELLS^{4–7}

Various categories of stem cells are commonly evaluated for their possible applications in research and medicine. They can be categorized based on:

Differentiate into different cell types:

- Totipotent cells
- Pluripotent cells
- Multipotent cells
- Oligopotent cells
- Unipotent cells

How Stem Cells Work⁴

They can perform three important functions:

- Plasticity.
- Homing.
- Engraftment.
- Plasticity: The ability to transform into various cell types. Adult stem cells that are specific to a particular tissue can produce a diverse range of cell types from other tissues under certain conditions, even spanning different germ layers. This process

Table 1: Classification of stem cells

Totipotent cells	It has the capability to produce any type of human cells, including those of the brain, liver, blood, or heart. It can also lead to the development of a fully functional organism.
Pluripotent cells	“Pluri” comes from the Latin plures, which translates to several or numerous. Therefore, pluripotent cells possess the ability to develop into any cell type.
Multipotent cells	These cells are indeed true stem cells, but they can only differentiate into a restricted variety of cell types; for instance, the bone marrow hosts multipotent stem cells that generate all blood cell types but not other cell categories.
Oligopotent cells	The capacity to develop into a limited number of cell types. Illustrations of this include adult lymphoid or myeloid stem cells.
Unipotent stem cell	A unipotent stem cell is defined as a cell that has the capability to differentiate exclusively into one specific lineage.

Table 2: Source of stem cells^{3,8,9}

Embryonic stem cells	Embryonic stem cells originate from embryos during a stage of development prior to the typical implantation in the uterus. They hold the promise of supplying an endless source of tissue for transplant therapies aimed at addressing various degenerative diseases.
Embryonic germ cells	Embryonic germ cells are pluripotent stem cells that originate from primordial germ cells, which are the precursors to the gametes (sperm and eggs) found in adults.
Adult stem cells	Somatic cells, which are unspecialized, are present in the specialized tissues and organs of adults. They can be obtained from either bone marrow or the peripheral system.

can be triggered by altering the growth medium while culturing stem cells *in vitro*, or by transplanting them into a different organ than the one from which they were originally derived (Table 2).

- Homing: These cells move towards the area of tissue injury.
- Engraftment: To merge with different tissues.

RESEARCH ON STEM CELLS

Stem cell biology represents a promising and evolving area within the life sciences. The ability of stem cell technology to create therapies for numerous untreatable conditions through cellular replacement or tissue engineering is well acknowledged. With this therapeutic potential in mind, both fundamental and applied research is actively encouraged by the department across various institutions, hospitals, and industries. To date, over 55 programs focused on different facets of stem cell research have been recognized and supported globally.

STEM CELL CULTURING^{10–14}

The process of growing cells outside of a living organism is known as cell culture. To achieve this, cells need to be positioned on either a natural or synthetic extracellular medium (ECM). Such materials are commonly termed scaffolds.

STEM CELL THERAPY¹⁵

In the past 30 years, numerous groundbreaking discoveries have significantly advanced our knowledge of cell and developmental biology, marking pivotal moments in our comprehension of life. The ongoing issue in transplantation medicine is the scarcity of appropriate donor organs and tissues, as well as the need for therapies that can restore or improve the function of injured tissue via cell transplantation or replacement therapy. Potential sources for cell repair encompass autologous (from oneself), allogeneic (from another of the same species), xenogeneic (from a different species), primary or immortalized cell lines, and cells derived from adult stem cells. The capacity to culture, expand and alter these cell types has either restricted or enhanced their application in particular

treatment approaches. Currently, human cell-grafting therapies have only utilized stem cells derived from allogeneic or matched donors. Although the differentiation capabilities of specific adult stem cells, such as hematopoietic stem cells and mesenchymal stem cells (MSC), are well characterized *in vivo* or *in vitro*, the capacity for transdifferentiation in many adult stem cells continues to be a matter of controversy, largely due to different culture conditions and the potential impact of contamination or cell fusion events. Despite these limitations, it is anticipated that research on human stem cells (both embryonic and adult) could provide significant benefits for millions who are afflicted by various persistent human diseases.

Applications in Dentistry

Tooth repair and regeneration: A significant benefit of using teeth for stem cell extraction is that the postnatal root, which has a high concentration of dental stem cells, develops in a way that makes the cells involved in root formation resemble embryonic cells more closely than those from other sources of dental stem cells. Cell types that exhibit stem cell-like characteristics comprise:

- Cells from the pulp of both shed children’s teeth and adult teeth.
- The periodontal ligament (PDL) connects the tooth root to the bone.
- And from the surrounding tissue (dental follicle) of the unerupted tooth.^{16,17}

All these cells have a shared origin, from neural crest cells.

Pulp stem cells (DPSC)—In instances of significant tooth damage that penetrates both enamel and dentin and impacts the pulp, these cells trigger a restricted natural healing mechanism that leads to the formation of new odontoblasts, which generate dentin to mend the injury.^{17,18}

- Stem cells obtained from naturally lost human primary teeth—Stem cells extracted from the pulp of naturally shed primary teeth in humans support bone development, produce dentin, and transform into various non-dental mesenchymal cell types *in vitro*.^{19–22}

- Stem cells derived from the PDL—The PDL holds groups of progenitor cells. Recent research has discovered a stem cell population in human periodontal ligament (PDLSC) capable of differentiating into mesenchymal cell lineages, producing cementoblast-like cells, adipocytes, and collagen-rich connective tissue both *in vitro* and *in vivo*.^{6,23,24}
- Human third molars as a source of stem cells—Third molars initiate their development after birth, usually during childhood at approximately 5–6 years of age, and their calcification commences between 7 and 10 years of age. By the ages of 18–25 years, the roots of the third molars have finished their development. Due to the ongoing development of their roots, these molars serve as an important source of dental stem cells, including DPSC, PDL cells, and stem cells from the apical papilla (SCAP) cells.
- Stem cells of the root apical papilla—The root apical papilla can be found at the ends of developing tooth roots. The apical papilla tissue is only found during the formation of the root before the tooth comes into the oral cavity. Stem cells derived from the apical papilla (SCAP) are capable of differentiating into odontoblasts and adipocytes. These cells show CD24+ expression, which decreases as odontogenic differentiation takes place *in vitro*, in line with an increase in alkaline phosphatase levels.²⁴
- Dental follicle stem cells—Dental follicle cells develop into PDL fibroblasts, which play a crucial role in creating PDL through collagen synthesis and interaction with fibers on the surfaces of nearby bone.
- Muscle tissue regeneration—Satellite cells, which are the native stem cells found in muscle tissue, are crucial for muscle growth and development. The initial investigation shows how dentin-derived stem cells (DPSCs) can be transformed into cardiac muscle cells through an *in vitro* co-culture with neonatal cardiac muscle cells. However, in this culture setting, DPSCs did not show any expression of myogenic markers. Studies indicate that DNA methylation might influence the regulation of skeletal muscle myogenic differentiation.^{25–29}
- Bone regeneration: Inflammation acts as the initial phase in the bone healing process. After the inflammatory phase, endogenous stem cells are drawn from nearby and distant sources to the injury location, where they transform into chondrocytes or osteoblasts. Osteoblasts execute intramembranous ossification by directly depositing bone, whereas chondrocytes are responsible for endochondral ossification. A particular type of stem cell obtained from human dental pulp Odontogenic Human Dental Pulp Stem Cells (ODHPSCs) exhibits the ability to form bone-like tissue *in vivo*, indicating osteogenic potential. Periodontal ligament stem cells usually form cementum/PDL-like structures when placed under the skin. The insertion of human PDLSCs into periodontal injuries in immunocompromised mice results in the formation of trabecular bone adjacent to the PDL, indicating their possible role in the regeneration of alveolar bone.^{30,31}
- Craniofacial regeneration: The restoration and renewal of craniofacial structures remain challenging for healthcare professionals and biomedical engineers.^{32,33} Restoration of craniofacial tissues that are pathologically impaired is frequently necessary due to tumors, injuries, or congenital defects. The procedures for regenerating craniofacial tissue are often quite intricate due to the inherent complexity of the craniofacial area, which includes bone, cartilage, soft tissue, and neurovascular

bundles. For example, there are various surgical techniques employed to repair injured craniofacial bones. Autologous bone grafts are regarded as the gold standard in bone regenerative treatments. In combination with allogenic bone grafts, this category of bone graft material accounts for over 90% of the grafts conducted. Nonetheless, these grafting techniques possess various drawbacks, such as hematomas, complications at the donor site, inflammation, infection, and significant expenses.^{33,34} Craniofacial tissue regeneration employs MSCs, which are versatile cells able to differentiate into various lineages.

Stem cells refer to a group of undifferentiated biological cells capable of transforming into specialized cells and undergoing mitosis to produce new cells. They were initially found in organisms with multiple cells. To rehabilitate a specific tissue or organ, it is crucial to comprehend the conclusion of the developmental process of the specific structure and then create it. Ernest A. McCulloch and James E. until the 1960s, the University of Toronto was pioneering in the area of stem cell research. The body's tissue repair process occurs with the assistance of pluripotent embryonic stem cells. Subsequently, these cells can develop into multipotent cells of different origins, such as epithelial, mesenchymal, and various tissue-specific stem cells.³⁵ When stem cells engage with one another, they result in the development of new tissue or organs. The pluripotent embryonic stem cells diminish in vitality. Over time, the specialized multipotent adult stem cells become embedded deep within the tissues and assist in the fix as necessary.³⁶ In 2003, Dr. Songtao Shi identified dental pulp stem cells by using the deciduous teeth of his daughter and he referred to them as stem cells derived from human shed deciduous teeth.³⁷ Huang et al. mentioned that dental stem cells derived from specialized tissue are isolated for their strong abilities to differentiate into dental-related cells. Nonetheless, they possess the capacity to generate different cell lineages that resemble, yet are distinct in potency from that of bone marrow mesenchymal stromal cells (BMMSCs). Recognizing non-embryonic sources of cells exhibiting similar characteristics to tooth germ cells and creating Techniques in culture that can enhance cells retaining the ability to form teeth are presently the primary focus. This is complicated further by the reality that dental growth requires the collaboration of 2 types of cells: Epithelial and mesenchymal. The epithelium of the teeth is accountable for the initiation of odontogenic capability. When combined with non-odontogenic mesenchyme, dental epithelium from pre-bud phases can stimulate tooth formation, as long as the mesenchymal cells have stem cell-like traits similar to neural crest cells.^{18,38} Owing to the complex architecture of the periodontium (consisting of hard and soft tissues), its complete regeneration continues to be a challenge. All existing regenerative methods like allografts autologous bone grafts and alloplastic materials have limitations and cannot be used in every clinical scenario. As a result, a cell-mediated bone regeneration approach may serve as a potential treatment option.³⁹ Recently, PDLSCs have been identified as diverse stem cell groups from the PDL of removed human third molars. These PDLSCs form adherent clonogenic clusters resembling fibroblasts that can differentiate into adipocytes, osteoblasts, and cementoblast-like cells in laboratory conditions, along with cementum and PDL-like structures in living organisms. Periodontal ligament stem cells present a variety of cementoblast and osteoblast indicators along with the BMSSC-related markers,

STRO-1, along with CD146 antigens, are also found on dental pulp stem cells.⁴⁰ Utilizing MSCs for craniofacial tissue regeneration offers a beneficial different treatment option.^{28,41,42} Mesenchymal stem cells are multipotent cells that can differentiate into various lineages. Differentiation influenced by the existence of inductive signals from the microenvironment issues of incomplete dental regeneration.^{43,44} Mesenchymal stem cells are found in a broad range of postnatal tissue types and have been effectively extracted from various orofacial fabrics. Orofacial-derived MSCs have shown superior growth characteristics compared to bone marrow. Research is focused on mesenchymal stem cells to validate their ability for self-renewal and their potential to develop into different lineages BMMSCs.^{44–46} Consequently, dental MSCs might be more effective at differentiating into craniofacial tissues, rendering them attractive for craniofacial uses. During bone development, MSCs aggregate into mesenchymal condensations, which is similar to tooth formation but absent epithelial invagination. Bone formation through intramembranous and endochondral processes. Production represents the two types of bone development. The mesenchymal aggregations undergo chondrogenesis followed by ossification to produce cartilage and bone in endochondral bone advancement.⁴⁷ Bone possesses the natural capability to regenerate during an individual's lifetime. The damaged bone tissue can be effectively repaired by nearby cells in the majority of bone injuries (fractures) (such as chondroblasts, osteoblasts, endothelial cells, and fibroblasts). When the fractures are so serious self-repair is impossible. To repair them (including major bone defects resulting from trauma, infection, tumor removal, and skeletal anomalies), a sufficient quantity of stem cells is essential for successful bone restoration. Oral MSCs seem to be outstanding candidates for bone regeneration. Both oral and non-oral MSCs can transform into chondroblasts and osteoblasts when provided with suitable inductive conditions *in vitro*.^{48,49} Certain research teams have also concentrated on the muscle- and tendon-generating characteristics of oral stem cells.⁴⁰ Yamada et al.⁵⁰ were the first to report that DPSCs can develop into cells resembling cardiomyocytes, when co-grown, with neonatal rat cardiomyocytes for approximately 4 weeks *in vitro*. Graziano et al.⁵¹ showed that DPSCs successfully differentiated into muscle cells producing dystrophin in muscles paralyzed by cardiotoxin in a mouse model, which carries significance for the research and management of muscular dystrophy.

REFERENCES

- Fortier LA. Stem cells, classifications, controversies and clinical applications. *Vet Surg* 2005;34:415–423. DOI: 10.1111/j.1532-950X.2005.00063.x.
- Bluteau G, Luder HU, De Bari C, et al. Stem cells for tooth engineering. *Eur Cell Mater* 2008;16:1–9. DOI: 10.22203/ecm.v016a01.
- Anna M Wobus. *Stem cells –2nd edn India*; 2008. Springer-Verlag, national academic digital library Ethiopia. Available from: <http://10.6.20.12:80/handle/123456789/38871>.
- Poliwoda S, Noor N, Downs E, et al. Stem cells: A comprehensive review of origins and emerging clinical roles in medical practice. *Orthop Rev (Pavia)* 2022;14(3):37498. DOI: 10.52965/001c.37498.
- Hans R. Schöler et al. *The Potential of stem cells: An inventory. Human biotechnology as social challenge 2007*. [ISBN:9781315252933 book: Human biotechnology as social challenge 2007].
- Mitalipov S, Wolf D. Totipotency, pluripotency and nuclear reprogramming. *Adv Biochem Eng Biotechnol* 2009;114:185–199. PMID: 19343304.
- Understanding stem cells: An over view of the science and issues from national academics 2008. PMID: 19343304.
- Bishop AE, Buttery LDK, Polak JM. Embryonic stem cells. *J Pathol* 2002;197(4):417–565. DOI: 10.1002/path.1154
- Kiessling AA, Anderson SC. *Human Embryonic Stem Cells*, 2nd edition. New York: Elsevier; 2010. pp. 26–28.
- van der Sanden B, Dhobb M, Berger F, et al. Optimizing stem cell culture. *J Cell Biochem* 2010;111(4):801–807. DOI: 10.1002/jcb.22847.
- Stem cell basics. Available from: http://en.wikipedia.org/wiki/stem_cells; 2005.
- Kirschstein R, Skirrboll L: Stem cells: Scientific progress and future research directions. [<https://mpapi.bjcancer.org/>] [CreateSpace Independent Publishing Platform (2013-01-17), E1]
- Marshak DR, Gardner RT, Gottlieb D. *Stem Cell Biology*. New York: Cold Spring Harbor Laboratory Press; 2009.
- Morrison SJ, White PM, Zock C, et al. Prospective identification, isolation by flow cytometry. *Cell* 1999;96:737–749. DOI: 10.1016/S0092-8674(00)80583-8.
- Wobus AM, Boheler KR. Embryonic stem cells. Prospects for developmental biology and cell therapy. *Physiol Rev* 2005;85:635–678. DOI: 10.1152/physrev.00054.2003.
- Saini R, Saini S, Sharma S. Therapeutics of stem cells in periodontal regeneration. *J Nat Sci Biol Med* 2011;2(1):38. DOI: 10.4103/0976-9668.82316.
- The human embryonic stem cell and the human embryonic. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK223690/>.
- Volponi AA, Pang Y, Sharpe PT. Stem cell-based biological tooth repair and regeneration. *Trends Cell Biol* 2010;20(12):715–722. DOI: 10.1016/j.tcb.2010.09.012.
- Smith AJ, Lesot H. Induction and regulation of crown dentinogenesis: Embryonic events as a template for dental tissue repair? *Crit Rev Oral Biol Med* 2001;12(5):425–437. DOI: 10.1177/10454411010120050501.
- Yu J, He H, Tang C, et al. Differentiation potential of STRO-1+dental pulp stem cells changes during cell passaging. *BMC Cell Biol* 2010;11(1):32. DOI: 10.1186/1471-2121-11-32.
- Yalvac ME, Rizvanov AA, Kilic E, et al. Potential role of dental stem cells in the cellular therapy of cerebral ischemia. *Curr Pharm Des* 2009;15(33):3908–3916. DOI: 10.2174/138161209789649439.
- Sakai VT, Zhang Z, Dong Z, et al. SHED differentiates into functional odontoblasts and endothelium. *J Dent Res* 2010;89(8):791–796. DOI: 10.1177/0022034510368647.
- Cordeiro MM, Dong Z, Kaneko T, et al. Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth. *J Endod* 2008;34(8):962–969. DOI: 10.1016/j.joen.2008.04.009.
- Wang J, Wang X, Sun Z, et al. Stem cells from human-exfoliated deciduous teeth can differentiate into dopaminergic neuron-like cells. *Stem cells Dev* 2010;19(9):1375–1383. DOI: 10.1089/scd.2009.0258.
- Nakamura S, Yamada Y, Katagiri W, et al. Stem cell proliferation pathways comparison between human exfoliated deciduous teeth and dental pulp stem cells by gene expression profile from promising dental pulp. *J Endod* 2009;35(11):1536–1542. DOI: 10.1016/j.joen.2009.07.024.
- Gault P, Black A, Romette JL, et al. Tissue-engineered ligament: Implant constructs for replacement. *J Clin Periodontol* 2010;37(8):750–758. DOI: 10.1111/j.1600-051X.2010.01588.x.
- Handa K, Saito M, Tsunoda A, et al. Progenitor cells from dental follicle are able to form cementum matrix *in vivo*. *Connect Tissue Res* 2002;43(2-3):406–408. DOI: 10.1080/03008200290001023.
- Lin NH, Gronthos S, Bartold PM. Stem cells and periodontal regeneration. *Aust Dent J* 2008;53(2):108–121. DOI: 10.1111/j.1834-7819.2008.00019.x.
- Armiñán A, Gandía C, Bartual M, et al. Cardiac differentiation is driven by NKX2.5 and GATA4 nuclear translocation in tissue-specific mesenchymal stem cells. *Stem Cells Dev* 2009;18(6):907–918. DOI: 10.1089/scd.2008.0292.

30. Yang R, Chen M, Lee CH, et al. Clones of ectopic stem cells in the regeneration of muscle defects in vivo. *PLoS One* 2010;5(10):e13547. DOI: 10.1371/journal.pone.0013547.
31. Knight MN, Hankenson KD. Mesenchymal stem cells in bone regeneration. *Adv Wound Care* 2013;2(6):306–316. DOI: 10.1089/wound.2012.0420.
32. Huang GJ, Gronthos S, Shi S. Mesenchymal stem cells derived from dental tissues vs. those from other sources: Their biology and role in regenerative medicine. *J Dent Res* 2009;88(9):792–806. DOI: 10.1177/0022034509340867.
33. Seo BM, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *The Lancet* 2004;364(9429):149–155. DOI: 10.1016/S0140-6736(04)16627-0.
34. Sachlos E, Czernuszka JT. Making tissue engineering scaffolds work. Review on the application of solid freeform fabrication technology to the production of tissue engineering scaffold. *Eur Cell Mater* 2003;5:29–39. DOI: 10.22203/ecm.v005a03.
35. Sachlos E, Czernuszka JT. Making tissue engineering scaffolds work. Review: The application of solid freeform fabrication technology to the production of tissue engineering scaffolds. *Eur Cell Mater* 2003;5(29):39–40. Available from: <https://pubmed.ncbi.nlm.nih.gov/14562270/>.
36. Ansari S, Seagroves JT, Chen C, et al. Dental and orofacial mesenchymal stem cells in craniofacial regeneration: The prosthodontist's point of view. *The Journal of prosthetic dentistry* 2017;118(4):455–461. Available from: <https://pubmed.ncbi.nlm.nih.gov/28385446/>.
37. Yann Picand D. Stem cell: Definition of stem cell and synonyms of stem cell (English). Available from: http://dictionary.sensagent.com/Stem%20cell/en-en/#cite_note-77 [Last accessed July, 2020].
38. Egusa H, Sonoyama W, Nishimura M, et al. Stem cells in dentistry—part I: Stem cell sources. *J Prosthodont Res* 2012;56(3):151–165. DOI: 10.1016/j.jpor.2012.06.001.
39. Friedlander LT, Cullinan MP, Love RM. Dental stem cells and their role in apexogenesis and apexification. *Int Endod J* 2009;42:955–962. DOI: 10.1111/j.1365-2591.2009.01622.x.
40. Duailibi MT, Duailibi SE, Young CS, et al. Bioengineered teeth from cultured rat tooth bud cells. *J Dent Res* 2004;83(7):523–538. DOI: 10.1177/154405910408300703.
41. Langer R, Vacanti JP. Tissue engineering. *Science* 1993;260(5110):920–926. DOI: 10.1126/science.8493529.
42. Yu J, Vodyanik MA, Smuga-Otto K, et al. Induced pluripotent stem cell lines derived from human somatic cells. *Science* 2007;318(5858):1917–1920. DOI: 10.1126/science.1151526.
43. Salinas CN, Anseth KS. Mesenchymal stem cells for craniofacial tissue Regeneration. *J Dent Res* 2009;88:681–692. DOI: 10.1177/0022034509341553.
44. Saltz A, Kandalam U. Mesenchymal stem cells and alginate microcarriers for craniofacial bone tissue engineering: A review. *J Biomed Mater Res A* 2016;104:1276–1284. DOI: 10.1002/jbm.a.35647.
45. Mao JJ, Giannobile WV, Helms JA, et al. Craniofacial tissue engineering by stem cells. *J Dent Res* 2006;85:966–979. DOI: 10.1177/15440591060850110.
46. Zhang L, Feng G, Wei X, et al. The effects of mesenchymal stem cells in craniofacial tissue engineering. *Curr Stem Cell Res Ther* 2014;9:280–289. DOI: 10.2174/1574888x09666140213204202.
47. Sonoyama W, Liu Y, Fang D, et al. Mesenchymal stem cell-mediated functional tooth regeneration in swine. *PLoS One* 2006;1:70–79. DOI: 10.1371/journal.pone.0000079.
48. Tomar GB, Srivastava RK, Gupta N, et al. Human gingiva-derived mesenchymal stem cells are superior to bone marrow-derived mesenchymal stem cells for cell therapy in regenerative medicine. *Biochem Biophys Res Commun* 2010;393:377–383. DOI: 10.1016/J.BBRC.2010.01.126.
49. Armiñán A, Gandía C, Bartual M, et al. Cardiac differentiation is driven by NKX2.5 and GATA4 nuclear translocation in tissue-specific mesenchymal stem cells. *Stem Cells Dev* 2009;18(6):907–918. DOI: 10.1089/scd.2008.0292.
50. Yamada Y, Ito K, Nakamura S, et al. Promising cell-based therapy for bone regeneration using stem cells from deciduous teeth, dental pulp, and bone marrow. *Cell Transpl* 2011;20(7):1003–1013. DOI: 10.3727/096368910X539128.
51. Graziano A, d'Aquino R, Laino G, et al. Dental pulp stem cells: A promising tool for bone regeneration. *Stem Cell Rev* 2008;4(1):21–26. DOI: 10.1007/s12015-008-9013-5.