International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Exploring the Promise of Stem Cell Therapy: A Review of Sources, Classification, and Potential Medical Applications

Shah Kinjal[1], Virani Rhut[2], Usman Ifzah[3]

[1]Former Assistant Professor at Department of Pedodontics and Preventive Dentistry, Manubhai Patel Dental College, Vadodara, Gujarat, India.

[2]Former Assistant Professor at Department of Preventive dentistry, Manubhai Patel Dental College, Vadodara, Gujarat, India.

[3]Private Practitioner at Dr Manzoor Orodental Speciality, Srinagar, Jammu Kashmir, India

Abstract: ***In recent years, stem cell therapy has become a very promising and advanced scientific research topic. The development of treatment methods has evoked great expectations. This paper is a review focused on the discovery of different stem cells and the potential therapies based on these cells. Stem cells are classified mainly by their source into three basic types: Embryonic, umbilical, and adult stem cells. Each differs in its plasticity and could thus potentially be used for different medical purposes. Stem cell therapy is emerging as a potentially revolutionary new way to treat disease and injury, with wide - ranging medical benefits. Given the fact that there are populations of stem cells that reproducibly reform bone and its marrow, cementum, dentin, and perhaps even periodontal ligament, it is possible to envision the complete restoration of the hard tissues in the oral cavity using the patient's cells, thereby avoiding issues of histocompatibility. Nevertheless, stem cell therapy, a prologue to an era of medical discovery of cell - based therapies that will one day restore function to those whose lives are now challenged every day, is still at the beginning of the road.***

Keywords: Stem cells, Adult stem cells, Embryonic stem cells, Umbilical stem cells, Hematopoietic stem cells, Pluripotent stem cells, Differentiation, Leukemia Inhibiting factor (LIF), Dental follicle progenitor cells (DFPC), Stem cells from exfoliated deciduous teeth (SHED), Periodontal ligament stem cells (PDLCs), Stem cells therapy.

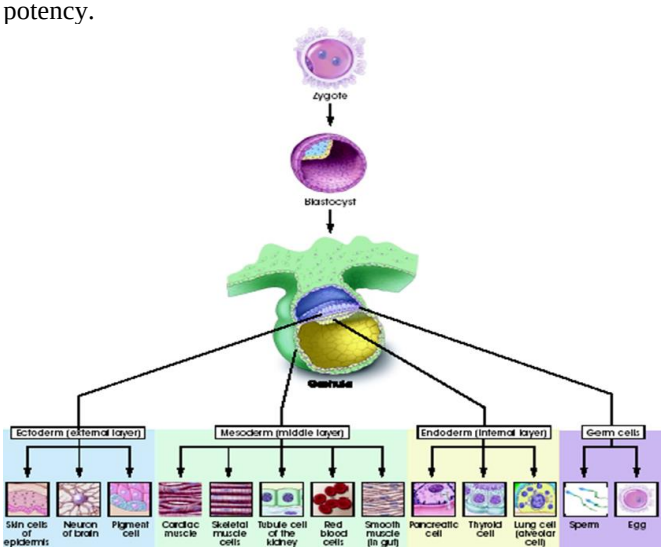
1. Introduction

Science is the fuel for the engine of technology. Scientific discoveries from cellular, developmental and molecular biology have truly revolutionized our collective understanding of biological processes, human genetic variations, continuity of evolution, etiology, and pathogenesis of innumerable human diseases and disorders. Improved understanding of disease processes and methods to prevent and cure them has led to an increased life span of the human being which has led to the shift of paradigm from the replacement of the lost or injured tissues to the regeneration of the same. This has given life to a new age of Tissue Engineering.1

Tissue engineering is a science based on fundamental principles that involve the identification of appropriate cells, the development of conductive scaffolds, and the understanding of the morphogenic signals required to induce cells to regenerate a tissue or organ. Stem cells are the key elements for Tissue Engineering. Stem cell research provides knowledge of regenerating healthy cells, tissues, and organs from a single cell.1

Dentists can use stem cells to regenerate lost or damaged dental and periodontal structures. The discovery of dental stem cells and recent advances in cellular and molecular biology have led to the development of novel therapeutic strategies that aim at the regeneration of oral tissues that were injured by diseases or trauma.

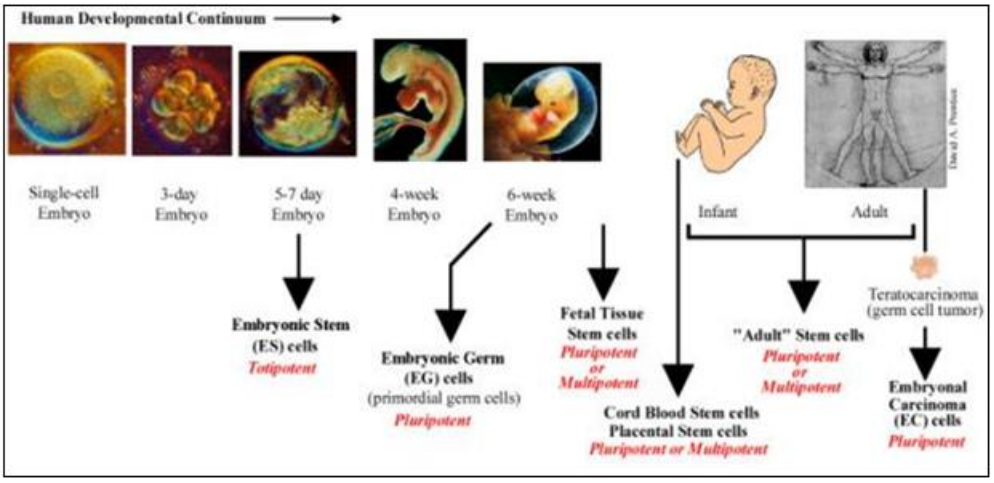
Stem cells are "generic" cells that have two special properties: self - renewal: the ability to divide itself into exact copies numerous times, without changing into specific cell types of potency, the ability to divide themselves into cells that will form specific cell types that will build special tissues in the body (heart, brain, blood).2 A stem cell is defined as a cell that can continuously produce unaltered daughter cells and can generate cells with different and more restricted properties. Stem cells can divide either symmetrically (allowing the increase in stem cell number) or asymmetrically.3 There are various qualities of stem cells as their ability to divide and renew themselves, being unspecialized cells, can give rise to specialized cells and to replicate in unlimited numbers without losing their total potency.



Divisions of stem cells

Stem cells can be classified as per their extent to which they can differentiate into Multipotent stem cells are only able to become a certain type of cell, such as a blood cell. Pluripotent stem cells can become almost any cell in the adult body. However, they lack the ability to become the placental or supporting tissue cells needed for development in the human uterus. Totipotent stem cells can become any cell in the human body. Unipotent stem cells are descendants of a multipotent stem cell and can give rise to a single cell type. Stem cells may be derived from several sources and research is currently ongoing for the therapeutic use of stem cells from all sources.[4, 5] The isolation and extraction of stem cells allow them to be categorized as:

- Embryonic stem cells: They are extracted from embryos and can give rise to virtually any specialized cell in the human body.
- Cord blood stem cells: This source of stem cells is derived from cord blood and has enormous potential in treating disease.
- Adult stem cells: These are present in adult tissues such as the bone marrow, brain, and blood but are limited in potential relative to embryonic stem cells.
- Fetal stem cells: Stem cells are collected from aborted fetal tissue, the pre - natal diagnostic tissue. Fetal stem cells can be mesenchymal and hematopoietic cells.
- The Extraembryonic tissue also considered as one of the sources of cultivating stem cells, such as Wharton's jelly is the connective tissue surrounding the umbilical vessels and includes the perivascular, inter - vascular, and sub - amnion regions and Amniotic fluid has emerged as a major source of putative pluripotent stem cells that avoid many of the problems associated with embryonic stem cells (ES) such as their non - suitability for autologous use, their capacity for tumor formation and the ethical concerns they raise. Placenta is a fetomaternal organ involved in maintaining fetal tolerance and allows nutrient uptake and gas exchange with the mother, but also contains a high number of progenitor stem cells.
- Stem cells from the oral and maxillofacial region: These types of stem cells predominantly contain mesenchymal stem cells. They include
- Dental Pulp Stem Cells (DPSCs)
- Stem Cells from Exfoliated Deciduous Teeth (SHED)
- Periodontal Ligament Stem Cells (PDLSCs)
- Stem Cells from Apical Papilla (SCAP)
- Dental Follicle Progenitor Stem Cells (DFPSCs)



Classification of stem cells

A. Embryonic Stem Cells as a Source [6, 7]

An Embryonic Stem Cell (ESC) is defined as cells derived from embryos that develop from eggs that have been fertilized in vitro and then donated for research purposes with the informed consent of the donors. The embryos from which human embryonic stem cells are derived are typically four or five days old and are a hollow microscopic ball of cells called the blastocyst. The blastocyst includes three structures: the trophoblast, which is the layer of cells that surrounds the blastocyst; the blastocoel, which is the hollow cavity inside the blastocyst; and the inner cell mass, which is a group of approximately 30 cells at one end of the blastocoel. There is another category of stem cells as ESC, is cord blood stem cells and fetal stem cells.

1) Cord blood stem cells [8, 9]

Stem cells found in cord blood are important precursors to a person's fully functioning immune system. They also differentiate into White blood cells, red blood cells, platelets. Umbilical cord blood is now an established source of transplantable HSCs that have a greater proliferative capacity, lower immunological reactivity, and lower risk of Graft - Versus - Host Disease (GVHD). Cord blood is also known as placental blood; following birth it is the remaining blood in the umbilical cord and placenta after the cord is cut. As a matter of routine, cord blood is usually disposed of following the baby's birth. The cord blood is, however, a valuable and promising source of stem cells. Umbilical cord blood stem cells are capable of repopulating bone following intra - bone injection of severe combined immunodeficiency mice and are used clinically as an alternative to adult bone marrow stem cells.

2) Fetal stem cells: [10, 11, 12, 13]

Stem cells are collected from aborted fetal tissue, the surplus of prenatal diagnostics tissues or tissues at delivery, subject to informed consent, institutional ethics approval, and compliance with national guidelines covering fetal tissue research. They are mainly of 2 types:

- Fetal mesenchymal stem cells (MSCs**)** - MSCs are multipotent stem cells that can differentiate towards mesoderm - derived lineages (i. e. osteogenic, adipogenic,

chondrogenic, and myogenic) and isolated from fetal tissues such as blood, liver, bone marrow, lung, and pancreas are spindle - shaped cells with the capacity to differentiate into the standard mesenchymal lineages i. e. bone, fat, and cartilage. They were first identified in the adult bone marrow where they represent 0.001 - 0.01% of total nucleated cells. Fetal tissues also contain Adherent Stromal Cells (ASC) which possess greater proliferation capacity and differentiation potential. Fetal tissues have the potential to repair damaged tissue and their immune - modulatory properties make them very useful for a wide range of regenerative medicine applications such as cell therapy and tissue engineering for hollow and solid organs.

- Fetal hematopoietic stem cells (HSCs) - HSCs are multipotent stem cells that maintain functional hematopoiesis by the generation of all hematopoietic lineages throughout fetal and adult life. They are characterized by the expression of CD34 and CD45 antigens, and the absence of markers such as CD38 and human leukocyte antigen (HLA). During ontogeny, the site of hematopoiesis is modified several times. An area along the dorsal embryonic aorta termed the Aorta - Gonad - Mesonephros (AGM) is a rich source of HSCs, which then migrate to the embryonic liver and hematopoietic tissues such as the bone marrow. HSCs are usually assayed in animal models based on their capacity to repopulate the entire hematopoietic system in conditioned recipients after transplantation.

First - trimester fetal blood contains more $CD34^+$ cells than term gestation blood. The number of circulating HSCs increases from the first trimester to peaks in the second trimester in utero, probably because of cells migrating from the fetal liver to establish hematopoiesis in the fetal bone marrow. Some HSCs remain in the umbilical cord at delivery, where they can be collected for allogenic or occasionally autologous cell transplantation. In the second trimester, $CD34^+$ cells constitute 4% of cells in the blood, 16.5%in the bone marrow, 6% in the liver, 5% in the spleen, and 1.1% in the thymus. This frequency of $CD34^+$ cells in the blood gradually diminishes during the third trimester, probably reflecting the establishment of the marrow as the primary site of hematopoiesis and the declining role of the fetal liver in that regard. The number of cells negative for CD38 within the $CD34^+$ population is also higher in early fetal blood, suggesting that these cells are more primitive and have greater potential than HSCs circulating later in ontogeny.

- **Adult Stem Cells as a Source [14, 15]**

An adult stem cell is an undifferentiated cell found among differentiated cells in a tissue or organ, can renew itself, and can differentiate to yield the major specialized cell types of the tissue or organ. The primary roles of adult stem cells in a living organism are to maintain and repair the tissue in which they are found. Some use the term somatic stem cell instead of adult stem cell. Unlike embryonic stem cells, which are defined by their origin (the inner cell mass of the blastocyst), the origin of adult stem cells in mature tissues is unknown.

Adult stem cells have been identified in many organs and tissues. One important point to understand about adult stem cells is that there are a very small number of stem cells in each tissue. Stem cells are thought to reside in a specific area of each tissue where they may remain *quiescent (non - dividing)* for many years until they are activated by disease or tissue injury. The adult tissues reported containing stem cells include the brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, and liver. Some examples of potential treatments include replacing the dopamine - producing cells in the brains of Parkinson's patients, developing insulin - producing cells for type I diabetes, and repairing damaged heart muscle following a heart attack with cardiac muscle cells.

- **Oro- Maxillo Facial Region Stem Cells as a Source [16, 17, 18]**

The discovery of stem cells in teeth helped us to have an accessible and available source of stem cells. Using one's own stem cells for medical treatment means a much lower risk of rejection by the body and decreases the need for powerful drugs that weaken the immune system. Stem cells from teeth replicate at a faster rate and for a longer period than stem cells harvested from other tissues of the body. There are three distinct tooth groups in which patients have the opportunity to recover their stem cells. The three groups of teeth from where stem cells can be isolated are:

- **Deciduous Teeth[19]**

The healthy pulps of deciduous teeth are a rich source of viable stem cells. Stem cells isolated from healthy pulp of deciduous teeth are highly proliferative, even when the pulp is recovered in small quantities. The ideal deciduous tooth for stem cell recovery is a canine or incisor that has just started to loosen, has more than a third of the root structure left intact, and is not extracted for reasons such as infection or associations with pathology. Ideal root for stem cell extraction should have at least a resorbed root – less than 1/3rd of the remaining root.

- **Wisdom Teeth[20]**

The healthy pulp from wisdom teeth is another excellent source of viable stem cells. Whole or sectioned portions of third molars containing healthy pulp can be recovered at the time of their removal. When an impacted third molar needs to be sectioned for removal, the pulp is often exposed. Developing third molars have a larger volume of pulpal tissue than teeth that are mature with their roots completely formed. It is best to recover these teeth during the developmental stage (between 16 - 20 years of age), when the stem cells are very active in the formation of the root and supporting root structures. Third molars with healthy pulp can also be recovered later in life and are always considered a source for viable stem cells.

- **Permanent teeth[21]**

All permanent teeth with healthy pulp are potential sources of stem cells. Bicuspids needing to be removed for orthodontic indications are an example of this. Permanent teeth to avoid for stem cell therapy include endodontically treated or nonviable teeth, teeth with active infections, teeth with severe periodontal disease and excessive mobility, teeth with deep caries or large restorations, and teeth with sclerosing or calcified pulp chambers. The stem cells from within the pulp become less proliferative as individuals age increases, so it is best to recover stem cells at the earliest opportunity.

- **Dental Pulp Stem Cells (DPSs)** [22, 23]

The dentine - pulp complex displays exquisite regenerative potential in response to injury. A population of multipotent mesenchymal progenitor cells known as Dental Pulp Stem Cells with high proliferative potential for self - renewal is important to the regenerative capacity of the tissue. Pulp notch is considered to be an important signaling molecule that controls stem cell fate. It was found that 3 days following pulp capping, Notch 1 expression was increased in the pulp, whereas 1 and 3 were associated with the perivascular structures. This suggests that they are in different locations throughout the pulpal tissue and the responsiveness varies according to the location.

The DPSC niche in human dental pulp was identified by antibodies against STRO - 1, CD146, and Pericyte - Associated Antigen (3G5) and was found to be localized in the perivascular and perineural sheath regions.

- **Stem Cells from Exfoliated Deciduous Teeth (SHED)** [24]

SHED contains multipotent stem cells which are highly proliferative, clonogenic cells and can differentiate into a variety of cell types including neural cells, adipocytes, odontoblasts etc. After in vivo transplantation, SHED was found to be able to induce bone formation, generate dentine, and survive in mouse brains along with the expression of neural markers. The advantages of using SHED for various stem cell therapies including autologous stem cell transplantation and tissue engineering not only because they are accessible tissue resource, and noninvasive but also can provide enough cells for potential clinical application.

- **Periodontal Ligament Stem Cells (PDLSCs)** [25]

The periodontal ligament, which is highly fibrous and vascular tissue, has one of the highest turnover rates in the body. Many cells are present in the periodontal ligament including cementoblasts, osteoblasts, fibroblasts, myofibroblasts, endothelial cells, nerve cells, and epithelial cells. These progenitor cell populations within the periodontal ligament appear to be enriched in locations adjacent to blood vessels and exhibit some classical cytological features of stem cells, including small size, responsiveness to stimulating factors and slow cycle time. Thus, within these are groups of cells with characteristics of mesenchymal stem cells, capable of sustained renewal and tissue regeneration.

- **Stem Cells from Apical Papilla (SCAP)** [26]

Stem cells of the apical papilla (SCAP) have been identified as an important population of mesenchymal stem cells (MSCs) in Regenerative Endodontics. SCAPs have the capacity to undergo osteogenic, adipogenic, chondrogenic, and neurogenic differentiation when they are cultured in the appropriate inductive media.

- **Dental follicle progenitor cells (DFPSCs)** [27, 28]

The tooth is a complex organ consisting of distinctly different hard and soft tissue areas, including enamel, dentin, cementum, and pulp. The formation of the hard tissue structures is controlled by ameloblasts, odontoblasts, cementoblasts, and cell differentiation and morphogenesis are regulated by reciprocal epithelial - mesenchymal interaction. Teeth have the specific feature of being the only organ that penetrates from the host's internal tissue, i. e., the jawbone, through the "oral integumentary layer" and into the oral cavity. Tooth roots within the jawbone are firmly anchored in the alveolar bone proper, and a thin layer of membrane, called the periodontal ligament (PDL), resides between the tooth and bone. The PDL is essential for many functions that support the tooth. During root development, cementogenesis begins during root formation. During this stage, the inner and outer enamel epithelium fuse to form the bilayer Hertwig's Epithelial Root Sheath (HERS), which then induces the differentiation of DFSCs into cementoblasts or osteoblasts. According to classical theory, DFSCs is the origin of the periodontium, including the cementum, PDL, and alveolar bone, and this developmental cascade confirms the existence of stem cells in the dental follicle.

The DF is a loose connective tissue sac derived from ectomesenchyme tissues. It surrounds the developing tooth and plays different roles during the life of a tooth. The DF is formed at the cap stage of tooth germ development by an ectomesenchymal progenitor cell population originating from cranial neural crest cells. The DF also regulates osteoclastogenesis and osteogenesis for eruption. Alternatively, under pathological conditions, the DF can proliferate into stratified squamous epithelium to generate dental cysts.

Implication in Medical Science [21, 27]

Organ Transplantation was the only treatment available that could replace the dead cells and tissues of our body, until the advent of new treatment modalities like stem cell transplant.

Disadvantages of Organ transplantation is: -

1) The risk involved during the surgery.
2) Only certain organs such as the heart, lungs, and the kidney can be transplanted, but organs such as the brain and the immune system cannot be transplanted.
3) There is always a problem of rejection; therefore, the patient must take an immunosuppressant for the rest of their life.

Stem cell transplant follows the principle of "Homing". It means that the respective stem cells do not have to be implanted into a damaged organ because they will find their way into the damaged organ. Every diseased organ can be treated by stem cell transplantation. Besides transplanting new stem cells there is another mechanism of action of stem cell transplantation - "A Direct Stimulation of Regeneration". If stem cells are properly prepared, they can be implanted without immunosuppression and thus avoid all complications caused using such medication.

- **Cerebral palsy (CP)** [28]

Cerebral palsy is the commonest cause of severe neurological disability in children. The general prevalence is 2 - 3 per 1000 live births and has slightly increased in recent years. This is due to the decreased mortality of low birth - weight infants together with an increased rate of cerebral palsy in the survivors. CP describes a group of permanent disorders of the development of movement and posture, causing activity limitations.

- **Gene therapy**[29]

The broad aims of gene and stem cell therapy are to overcome the barriers to successful human gene therapy, develop models to understand the biology of adult stem cells and discover disease mechanisms in diseases such as cancer and genetic disorders. Gene therapy remains a fairly new and experimental procedure for the treatment of disease. The potential for stem cells to be used in gene therapies is a valid one that has important ramifications for treating a range of diseases.

- **Leukemia**[28]

Leukemia is a devastating disease that can affect young and old alike. Stem cells are one traditional therapy that has been around for decades; helping sufferers to bring their cancer into remission and helping them recover from the deadly disease. To effectively treat leukemia, bone marrow transplant can help to enhance the effects of the chemotherapy and restore the patient's immune system.

With a bone marrow transplant, the patient's bone marrow stem cells get replaced with healthy ones from a suitable, matching donor. All their abnormal ones are first eliminated through chemotherapy and then the donor's bone marrow that has healthy stem cells gets transferred into the cancer patient's bloodstream which then travels to the patient's bone marrow and starts producing healthy new white blood cells to replace the cancerous ones, but this procedure is still under investigation.

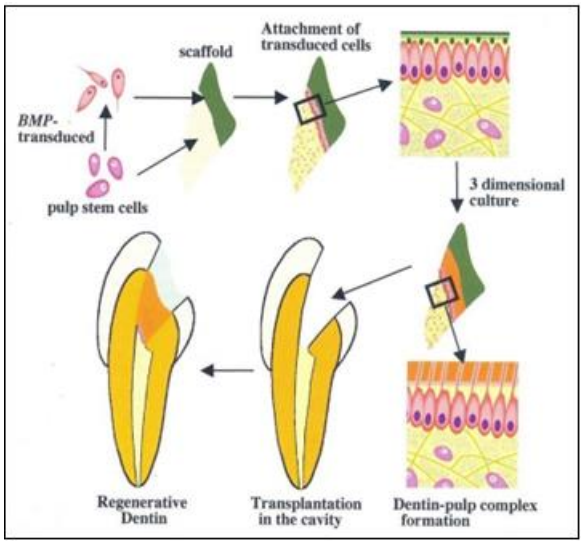
Implications in Dentistry [30, 31, 32]

- **Enamel formation**

A direct link exists between impaired Tbx1 function and enamel defects. Various findings suggest that Tbx1 is involved in the maintenance of dental epithelial stem cells that are responsible for ameloblast formation.

- **Dentine regeneration**

A population of multipotent mesenchymal progenitor cells known as dental pulp stem cells with high proliferative potential for self - renewal has been described and is important for the regeneration of the dentine. A study shows that dentine can be regenerated by combining dental pulp stem cells with recombinant human Bone Morphogenic Protein (BMP 2).



- **Cementum regeneration**

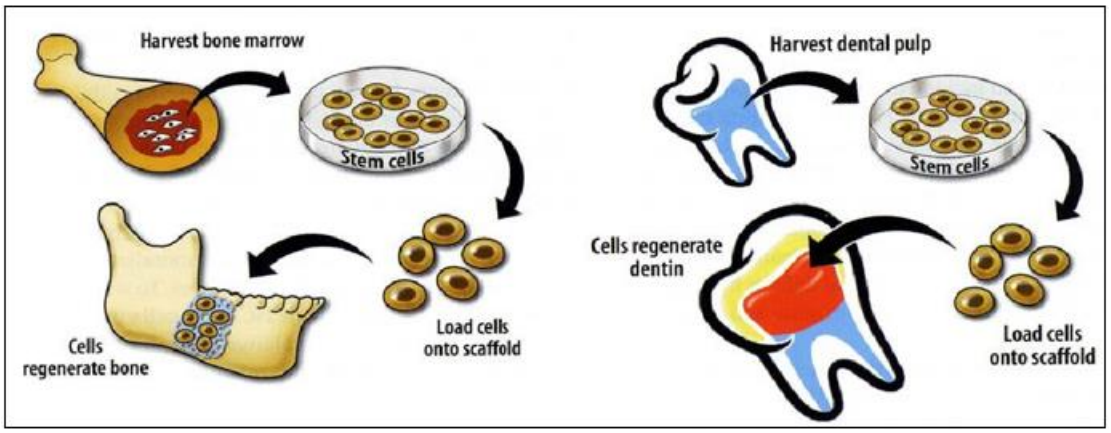
Human Cementum - Derived Cells (HCDCs) have been established from healthy teeth using a collagenase pre - treatment as had been established previously for the culture of trabecular bone cells. Thus, formed cells (HCDCs) form bone - like tissues that have osteocytes or cementocytes - like cells embedded within a mineralized matrix.

- **Cleft Lip and Palate (CLP) defects**

Cleft lip and palate, one of the most frequent congenital malformations, affects the alveolar bone in the great majority of cases, and the reconstruction of this defect still represents a challenge in the rehabilitation of these patients. One of the current most promising strategies to achieve this goal is the use of bone marrow stem cells (BMSC); however, isolation of BMSC or iliac bone is still the most used graft in the surgical repair of these patients. Therefore, in order to identify a new alternative source of stem cells with osteogenic potential without conferring morbidity to the donor, Orbicularis Oris Muscle (OOM) fragments were used which are regularly discarded during surgery repair (cheiloplasty) of CLP patients.

- **Regeneration of irradiated salivary glands**

Stem cell therapy could be utilized to prevent radiation - induced damage to the salivary gland. Bone marrow - derived stem cells (BMCs), when mobilized to the blood circulation, are able to contribute to the regeneration of acinar cells and blood vessels of irradiated mice salivary glands, resulting in increasing saliva production.



2. Limitations of Stem Cells[33]

- Cell differentiation factors that induce embryonic stem cells to become specific cell types are not well characterized in humans.
- Organ construction presents similar obstacles to transplantation. Embryonic stem cell - derived organs will be grown outside the human body and will therefore require some type of scaffolding during development. This has yet to be achieved with animal or human embryonic stem cells.
- Immunological rejection is a particularly important consideration for stem - cell - based therapies. Immune rejection is one of the major causes of organ transplant failure and is one of the problems, which will need to be overcome for any stem cell - based therapy to be effective.
- Stability of the genome in embryonic stem cell lines may increase as they 'age'. Almost every time a cell divides a mutation occurs, thus self - renewing embryonic stem cells will probably develop more mutations the longer they are stored.
- Cancer development could be an inadvertent side effect of embryonic stem cell therapies. The injection of undifferentiated embryonic stem cells into extra - uterine sites can result in the development of tumors called "TERATOMAS".
- Integration of embryonic stem cell - derived somatic cells into recipient tissues, and their ability to function appropriately in vivo, has not been demonstrated in animal models or humans. If such cells are unable to interact with pre existing populations, their use in cell therapies will be minimal.

3. Future of Stem Cell Research in Dentistry

Clearly, advances in adult stem cell biology have provided a great deal of impetus for the biomedical community to translate these findings into clinical application. Stem cell therapy aims to repair damaged and diseased body parts with healthy new cells provided by stem cell transplants. Diseases and disorders with no therapies or at best, partially effective ones, are the lure of the pursuit of stem cell research. Nevertheless, stem cell therapy, a prologue to an era of medical discovery of cell - based therapies that will one day restore function to those whose lives are now challenged every day, is still at the beginning of the road.

References

[1] Pera, M. F, Reubinoff B, and Trounson A. Human embryonic stem cells. J. Cell Sci.2000; 113: (1) 5 - 10.
[2] Prusa, AR, Hengstschlager M. Amniotic fluid cells and human stem cell research: a new connection. Med Sci Monit.2002; 8: 253–257.
[3] Domen J, Weissman IL. Self - renewal, differentiation or death: regulation and manipulation of hematopoietic stem cell fate. Mol Med Today.1999; 5: 201 - 08.
[4] Cherian E, Nandhini G, Kurian A - Stem cells. JP Medical Ltd, 2011.
[5] Weissman, I. L. Stem cells: units of development, units of regeneration, and units in evolution. Cell.2000; *100:* 157–68.
[6] Klimanskaya, I., Chung, Y., Becker, S., Lu, S. J. & Lanza, R. Derivation of human embryonic stem cells from single blastomeres. Nat. Protoc.2007; 2: 1963–72.
[7] Mountford, J. Human embryonic stem cells: origins, characteristics and potential for regenerative therapy. Transfus. Med.2008; 18: 1–12.
[8] Sedgley CM, Botero TM. Dental stem cells and their sources. Dent Clin North Am.2012; 56 (3): 549 - 61.
[9] O'Donoghue, K. & Fisk, N. M. Fetal stem cells. Best Pract. Res. Clin. Obstet. Gynaecol.2004; 18: 853 –75.
[10] Gucciardo, L., Lories, R., Ochsenbein - Kolble, N., Done, E., Zwijsen, A. & Deprest, J. Fetal mesenchymal stem cells: isolation, properties and potential use in perinatology and regenerative medicine. Br. J. Obstet. Gynaecol.2009; 116: 166– 72.
[11] Guillot, P. V., Gotherstrom, C., Chan, J., Kurata, H. & Fisk, N. M. Human first - trimester fetal MSC express pluripotency markers and grow faster and have longer telomeres than adult MSC. Stem Cells 2007b; 25: 646 –54.
[12] Pittenger M. F and Marshak D. R. Mesenchymal stem cells of human adult bone marrow. Marshak, D. R., Gardner, D. K., and Gottlieb, D. eds. (Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press).2001; 349–74.
[13] Ulmer Fl, Winkel A, Kohorst P, Stiesch M, Stem Cells – Prospects in Dentistry. Schweiz Monatsschr Zahnmed.2010; 120 (10).
[14] Yokoi T, Saito M, Kiyono T, Iseki S, Kosaka K, Nishida E, Tsubakimoto T, Harada H, Eto K, Noguchi T, Teranaka T. Establishment of immortalized dental follicle cells for generating periodontal ligament in vivo. Cell Tissue Res 2007; 327: 301 - 11.
[15] Hargreaves KM, Giesler T, Henry M, Wang V. Regeneration potential of the young permanent tooth: What does the future hold? J Endod 2008; 34: 551 - 56.
[16] Cordeiro MM, Dong Z, Kaneko T, Zhang Z, Miyazawa M, Shi S, et al. Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth. J Endod 2008; 34 (8): 962–9.
[17] Eslaminejad MB, Vahabi S, Shariati M. In vitro Growth and Characterization of Stem Cells from Human Dental Pulp of Deciduous Versus Permanent Teeth. Jour of Dent Tehran University of Medical Sciences 2010; 7 (4): 185 - 95.
[18] Iglesias - Linares A, Yáñez - Vico RM, Sánchez - Borrego E, Moreno - Fernández AM, Solano - Reina E, Mendoza - Mendoza A. Stem cells in current pediatric dentistry practice. Arch Oral Biol.2013; 58 (3): 227 - 38.
[19] Alastair J, Sloan J, Rachel J, Waddington. Dental pulp stem cells: what, where how? Int J Peditr dent 2009; 19: 61 - 70.
[20] Isaka J, Ohazama A, Kobayashi M, Nagashima C, Takiguchi T, Kawasaki H, Tachikawa T, Hasegawa K. Participation of periodontal ligament cells with regeneration of alveolar bone. J Periodontol.2001; 72 (3): 314 - 23.
[21] Honda MJ, Tsuchiya S, Shinohara Y, Shinmura Y, Sumita Y. Recent advance in the engineering of tooth and tooth structures using postnatal dental cells. J Dent Sci Rev 2010; 46: 54 - 66.

[22] Honda MJ, Imaizumin M, Tsuchiya S. Dental follicle stem cells and tissue engineering. J Oral Sci 2010; 52 (4): 541 - 52.
[23] Yokoi T, Saito M, Kiyono T, Iseki S, Kosaka K, Nishida E, Tsubakimoto T, Harada H, Eto K, Noguchi T, Teranaka T. Establishment of immortalized dental follicle cells for generating periodontal ligament in vivo. Cell Tissue Res 2007; 327: 301 - 11.
[24] Eisenberg LM, Eisenberg CA. Stem cell plasticity, cell fusion, and trans differentiation. Birth Defects Res C Embryo Today 2003; 69: 209 - 18.
[25] F u, Y. - S., Cheng, Y. - C., Lin, M. - Y. A., Cheng, H., Chu, P. - M., Chou, S. - C., Shih, Y. - H., Ko, M. - H. & Sung, S. Conversion of human umbilical cord mesenchymal stem cells in Wharton ‘s jelly to dopaminergic neurons in vitro: potential therapeutic application for Parkinsonism. Stem Cells 2006; 24: 115– 124.
[26] Fortier LA. Stem cells: classifications, controversies, and clinical applications. Vet Surg 2005; 34: 415–23.
[27] Cipriani, S., Karien G., Bonini, D., Marchina, E., Balgkouranidou, I., Caimi, L., Grassi Zucconi, G. & Barlati, S. Dental pulp stem cells – A new era in tissue engineering. J Smile dent.2009; 4 (2): 110 - 14.
[28] Atala A, Foundations of Regenerative Medicine: Clinical and Therapeutic Applications 1st edition: Elsevier - 2009
[29] Dr Ifzah, Dr Prahlad D, Dr. Subramaniam P, Dr. Shah Genetics In Pediatric Dentistry –A Review. IOSR Journal of Dental and Medical Sciences (IOSR - JDMS): e - ISSN: 2279 - 0853, p - ISSN: 2279 - 0861. Volume 15, Issue 7 Ver. I (July 2016), PP 120 - 128.
[30] Kumar S, Singh NP. Stem cells: A new paradigm. Indian Journal of Human Genetics 2006; 12 (1): 1 - 7.
[31] Iohara K, Nakashima M, Ito M, Ishikawa M, Nakasima A, Akamine A, Dentin Regeneration by Dental Pulp Stem Cell Therapy with Recombinant Human Bone Morphogenetic Protein 2 J Dent Res August 2004 83: 590 - 595.
[32] Nakashima M, Akamine A: The application of tissue engineering to regeneration of pulp and dentin in endodontics. J Endod 2005; 31 (10): 711 - 8
[33] Panno J. Stem cell research: medical applications and ethical controversy.2009.