ABSTRACT
Stem cells are biological cells found in multicellular organisms that can divide (through mitosis) and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. In mammals, there are two broad types of stem cells: embryonic stem cells, which are isolated from the inner cell mass of blastocysts, and adult stem cells, which are found in various tissues. Human stem cells have been isolated from the dental pulp, exfoliated deciduous teeth, the periodontal ligament, the dental follicle and the dental papilla. Stem cell markers such as STRO-1 are used for the characterization and isolation of stem cells. Stem Cell has become a booming field for research and therapeutic applications with vast areas yet to be discovered. Periodontitis, dental caries, craniofacial bone and teeth regeneration are the different areas in dental science which are yet to be studied. Various studies all over the world are going on using stem cells to cure or minimize the pain which a patient goes through diagnosis. This article provides an overview of the different types of stem cells and the different applications of stem cell in dental science.

Keywords: stem cells, bone marrow, epithelial, mesenchymal, regeneration.

INTRODUCTION
Medicine continues to move rapidly towards personalized treatment for a host of diseases, and stem cell therapy is one way to shift the move into high gear. The stem cell is the origin of life. As stated first by the great pathologist Rudolph Virchow, “All cells come from cells”. The ultimate stem cell, they can be defined as cells that can self-replicate and are able to differentiate into at least two different cell types. Both conditions must be present for a cell to be called a stem cell. Stem cells are produced from the fusion of egg and sperm cell. Stem cells have two important characteristics which make them different from other cells:

1. They are unspecialized cells that renew themselves for long time through cell division.
2. Under certain physiological conditions they can be induced to become cells with special function such as neurons.

At present, teeth lost due to any reason can only be replaced with conventional prostheses, i.e., removable prostheses, fixed dental prostheses, or implants, with prior bone augmentation if necessary. The severe bone resorption in edentulous areas makes it difficult to restore the missing teeth with dental implants or denture treatment. Therefore, progress in stem
cell biology and tissue engineering may present new options for replacing heavily damaged or lost teeth, or even individual tooth structures. The tissues and organs targeted for such regenerative medicine strategies in the dentistry include the salivary gland, tongue and craniofacial skeletal muscles, as well as the condylar cartilage of the temporomandibular joint. The promise of such treatment possibilities puts stem cells in the focus of dental research. The purpose of this systematic literature review is to present an overview of the current status of stem cell biology research in the field of dentistry and identify which methods now being developed have the potential to be used in humans in the future.

METHODS

An extensive review of literature was done which utilized most of the articles published in peer-reviewed journals relating to the subject of stem cells in dentistry. The review itself began with the search of relevant key words linked with the dental and medical profession like stem cells, mesenchymal cells, regeneration, applications in dentistry etc. in various search engines including pubmed. Reports published only in English language were included in the review. The spotlight of the present review would not only be on the basics or fundamentals of stem cells but their use in the different aspects of dentistry also included. The search also targeted different types of stem cells, their limitations, stem cell markers and how to store them. The present review noted that apart from their use in medical field, stem cells hold immense potential as a research tool in the field of dentistry for the future.

History and Source of stem cells

The term stem cell was proposed for scientific use by Russian histologist Alexander Maksimov in 1908. Research on the stem cells grew out of the work carried out by Canadian scientists (Ernest A. McCulloch and James E. Till at University of Toronto) in 1960s. The history of stem cell research had a benign, embryonic beginning in the mid1800 with the discovery that some cells could generate other cells. In the early 1900 real stem cells were discovered and it was found that some cells generate blood cells. The 1990s saw rapid expansion and success of the bone marrow program with more than 16,000 transplants to date for the treatment of immunodeficiencies and leukemia. In 1998, James Thomson isolated cells from the inner cell mass of early embryos, and developed the first embryonic stem cell line. In the same year, John Gearhart derived germ cells from cells in fetal gonadal tissues (primordial germ cells). In the year 2000, discovery of adult stem-cells in dental pulp cells, the living tissue at the centre of tooth was made. In the year 2003, stem-cells were found in baby teeth. Dr. Songtao Shi who was a pediatric dentist discovered baby tooth Stem-cells by using the deciduous teeth of his six year old daughter, he was luckily able to isolate, grow and preserve these Stem cells with regenerative ability, and he named them as SHED (Stem cells from Human Exfoliated Deciduous teeth). Stem-cells were found in periodontal ligament (2004), which holds the teeth in place in gums.

In the early stages of Stem cell research, bone marrow was the sole source. Since then a number of other sources have been found to contain Stem cells.

- Bone marrow: Stem cell usually comes from the long bones. The best sources are pelvic bones, femur and sheen bone.
- Umbilical cord blood: Stem-cells are obtained from the umbilical cord blood, which are collected just after the birth of the baby.
- Embryonic cells: are obtained from the blastocyst phase of the embryo. Cells are highly efficient in producing newer types of cells.
- Placental Stem-cells: provide almost all the life supports to keep a baby alive. After birth it has been found to give rise to more number of Stem cells as compared to embryonic Stem-cells.
Stem Cells Of Oro-Dental Region

- Menstrual Stem-cells: have an extraordinary improvement over the umbilical cord blood cells. They have a rapid growth rate.
- Dental Stem-cells: are cells obtained from the pulp of deciduous or wisdom teeth. This has been found to produce bones, cartilage, and muscle cells if cultured.
- Stem cells are also present in natal teeth, mesiodense or supernumerary teeth.

Classification of Stem cells\textsuperscript{14,15}:

1. According to their plasticity
   a) Totipotent: Each cell can develop into a new individual.
   b) Pluripotent: Cells can form any (>200) cell types.
   c) Multipotent: Cells differentiated but can form a number of other tissues.
   d) Oligopotent: Differentiate into five types of blood cells (monocytes, macrophages, eosinophils, neutrophils and erythrocytes).
   e) Quadripotent: Differentiate into four types of cells (cartilage cells, fat cells, stromal cells and bone-forming cells).
   f) Tripotent: Differentiate into three types of cells (2 types of astrocytes and oligodendrocytes).
   g) Bipotent: Differentiate into two types of cells (B cells and macrophages).
   h) Unipotent: Differentiate into single type of cell (mast cells).
   i) Nullipotent: No cell division and are terminally differentiated like red blood cells.

2. According to the growth stage
   a) Embryonic stem cells: Embryonic stemcells (ES) are derived from embryos that develop from eggs fertilized in-vitro in fertilization clinics donated for research purpose with informed consent of the donors. The embryos from which human embryonic stem cells are derived are four to five days old and in “blastocyst stage”. Inspite of various advantages, they have certain disadvantages\textsuperscript{16,17} like: it is hard to control its growth, ethically controversial to use human embryos and may be rejected by the immune system of the human body. In addition to the ethical issues, the tissue engineering applications of ES cells are limited because the cells are allogenic and thus may be immunologically incompatible between donors and recipients.
   b) Adult stem cells: An adult stem cell is an undifferentiated cell found among differentiated cells in a tissue or organ; it can renew itself, and can differentiate to yield the major specialized cell types of the tissue or organ. The primary role of the adult stem cell is to maintain and repair the tissues in which they are primarily found. They are also known as somatic stem cells or postnatal stem cells. They are mostly multipotent cells. Advantages of these types of cells include: immune to immunological attack, partly specialized and flexible in nature as they may form other type of tissues. Disadvantages include: scarce and vanishing in nature as they don’t live long and they are very rare\textsuperscript{17,18}. These cells are believed to reside in a specific area of each tissue, i.e., a “stem cell niche”. Many type of adult stem cells reside in mesenchymal tissues, and these cells are referred to as mesenchymal stem cells or mutipotent mesenchymal stromal cells (MSCs).

- Mesenchymal stem cells (MSCs)

MSCs are among the most promising adult stem cells for clinical applications. They were originally found in the bone marrow, but now they have also been isolated from many other adult tissues, including skin, adipose tissue and various dental tissues\textsuperscript{19,21}. In 2006, the International Society for Cellular Therapy
(ISCT) termed MSCs as mesenchymal stromal cells and proposed certain criteria to define such cells as MSCs must be adherent to tissue-culture-treated plastic when maintained in standard culture conditions, MSCs must express certain specific surface molecules and they must be able to differentiate to osteoblasts, adipocytes and chondroblasts in vitro.

(i) Bone marrow-derived MSCs (BMSCs)

Adult bone marrow contains rare multipotent progenitor cells that are generally termed BMSCs. According to the source, they are further classified into two types:

• BMSCs from the iliac crest

The stem cells most commonly used to date for bone regeneration in dental patients are BMSCs from the iliac crest. However, this source has certain disadvantages such as: age-related decline in the osteogenic potential of BMSCs and limited in-vitro expansion capability with decreasing potential of differentiation.

• BMSCs from orofacial bone

Orofacial bone-derived BMSCs (maxilla and mandible) can be obtained not only from younger patients but also from relatively aged individuals. BMSCs derived from orofacial bones have higher proliferation and osteogenic differentiation capacity as compared to BMSCs derived from iliac crest. However, the total volume obtained from orofacial bone is less than that obtained from iliac crest. So, a safe and reliable expansion method should be followed when orofacial BMSCs are used for clinical trials.

(ii) Dental tissue-derived stem cells

To date, two types of adult stem cells have been found in dental tissues, i.e., epithelial stem cells and MSC-like cells. Till date, no information is available for dental epithelial stem cells in humans. To date, several MSC sources have been identified in the dental tissues and have been characterized below:

• Gronthos and colleagues in 2000, isolated stem cells from human dental pulp, calling them DPSCs (Dental pulp stem cells). DPSCs can differentiate to odontoblasts, which makes them the most promising candidate for dentin-pulp complex regeneration.

• DPSCs, harvested from deciduous teeth, were named stem cells from Human Exfoliated Deciduous Teeth (SHED). SHED along with DPSCs have the specific ability to regenerate the dentin-pulp complex when transplanted into immunocompromised mice. In addition, SHED can specifically induce the formation of a bone-like matrix with a lamellar structure by recruiting host cells. This distinct property of SHED for bone formation may be explained by the nature of deciduous teeth, whose root resorption is accompanied by new bone formation surrounding the root.

• A new class of dental stem cells was isolated from the dental papilla of wisdom teeth i.e stem cells from apical papilla (SCAP). SCAPs have a greater capacity for dentin regeneration than DPSCs because the dental papilla contains a higher number of adult stem cells compared to mature dental pulp. Also importantly, SCAP are easily accessible since they can be isolated from human third molars.

• The periodontal ligament, which connects the alveolar bone to the root cementum and suspends the tooth in its alveolus, contains stem cells (PDLSCs) which have the potential to form periodontal structures such as cementum, ligament and alveolar bone. Characteristics of PDLSCs may depend on the harvest location because PDLSCs from the alveolar bone regeneration compared with PDLSCs from the root surface.

• The dental follicle, which is a dental sac that contains the developing tooth and differentiates into the periodontal ligament, contains dental follicle stem cells (DFSCs) with the ability to regenerate periodontal
tissues.

(iii) Oral mucusa-derived stem cells
To date, two different types of human adult cells have been identified in the oral mucosa. One is the oral epithelial progenitor/stem cells, which are a subpopulation of small oral keratinocytes. Other stem cells in the oral mucosa have been identified in the lamina propria of the gingival known as human gingival-derived MSCs (GMSCs). GMSCs proliferate faster than BMSCs, display a stable morphology and do not lose MSC characteristics with extended passaging.31

(iv) Periosteum-derived stem/progenitor cells
Stem cells obtained from periosteum are capable of differentiating into osteoblasts, adipocytes and chondrocytes. In-vivo potential of periosteum cells to form bone is higher than that of ilium-derived BMSCs and alveolar bone cells.

(v) Salivary gland-derived stem cells.
Patients suffering from head and neck cancer who receive radiotherapy suffer from an irreversible impairment of salivary gland function. Therefore, stem cells in the adult salivary gland are expected to be useful for autologous transplantation therapy in the context of tissue engineered-salivary glands or direct cell therapy.

(vi) Adipose tissue-derived stem cells (ASCs)
Adipose-derived MSCs can be readily harvested via lipectomy from areas such as chin, upper arms, abdomen, hips, buttocks and thighs and exhibit robust osteogenesis and are thus expected to be an alternative source of MSCs for bone regeneration in dentistry.32

(c) iPS cells: In 2006, Dr. Shinya Yamanaka discovered that normal mouse adult skin fibroblasts can be reprogrammed to an embryonic state by introducing certain genetic factors, and the resulting cells were termed induced pluripotent stem cells (iPS). These cells have been generated from various oral mesenchymal cells, such as SCAP, DPSCs and SHED, TGPCs, buccal mucosa fibroblasts, gingival fibroblasts and periodontal ligament fibroblasts. Thus, these types of cells may be used for developing missing jaw bones, periodontal tissues, salivary glands and lost teeth.

3. According to their source
   a) Autologous stem cells: cells are obtained from the same individual in whom they will be implanted.
   b) Allogenic stem cells: cells originate from a donor of the same species.
   c) Xenogenic stem cells: cells that are those isolated from individuals of another species.

POTENTIAL CLINICAL APPLICATIONS OF STEM CELLS IN DENTISTRY
As stem cells are found to have a great potential in forming various cell types, the major question which arises in our mind is what are the implications of stem cell in dentistry? The focus of stem cell research as it applies to dentistry is on facial reconstruction. “Tissue engineering” is another area which has been in boost recently. It refers to the number of ways in which the tissue lost due to trauma or disease is restored. Dental stem cells have become a feasible tool for dental tissue engineering. Tissue engineering using scaffold and cell aggregate methods has also been used to produce bioengineered teeth from dissociated cells for therapeutic applications (i.e. whole tooth replacement).

Dental tissue stem/progenitor cells are particularly useful in dentistry for the development of cell transplantation therapies, for the repair of damaged dentin and for periodontal disorders, and the stem cells are, therefore, currently the subjects of extensive research. Tooth maladies are widespread in different parts of the world. Many people suffer from periodontitis which is...
the frequent cause of tooth loss. Therapies based upon cell replacement and tissue engineering, underpinned by stem cell biology, are emerging as potentially powerful strategies in modern regenerative medicine. Dental pulps were basically extirpated from healthy permanent teeth (third molars and premolars). After splitting the teeth, the pulps were removed and cultured in basal media or osteogenic, chondrogenic and adipogenic conditions. Constructing complex structures like periodontium, which provides the functional connection between a tooth and an implant, could effectively improve modern dentistry.

Dental regenerative therapies which restore or replace defective teeth using autologous explants are being investigated using current understanding of developmental biology, stem cell biology and regenerative medicine. Recently, dental tissue stem progenitor cells, which can differentiate into dental cell lineages, have been identified in both impacted and erupted human teeth, and these cells can be used to regenerate some dental tissues. With the advent of dental stem cells, companies such as Store-A-ToothTM, 99 Hayden Avenue, Suite 200 Lexington, Massachusetts (USA), are providing services to properly preserve a child’s dental stem cells—a sort of biological insurance in anticipation of these cells becoming important as the field advances.

The property of stem cells to reach the site of injury or disease makes them suitable in cell based therapy. The two common methods of cell delivery are intravenous injection and cell encapsulation systems. In the field of dentistry, stem cell research is directed towards achieving the following: Regeneration of damaged coronal dentine and pulp, regeneration of resorbed root, cervical or apical dentin and perforations, periodontal regeneration, craniofacial defects by osteogenesis, whole tooth regeneration and treatment of oral mucosal lesions (oral submucous fibrosis, oral lichen planus, dyskeratosis congenita, premalignant lesions like leukoplakia, recurrent oral ulcers, graft versus host disease and oral cancers).

So, the potential application of using stem cells in dentistry can be summarized by:

a) **In continued root formation:** Findings of the experiment conducted on pigs suggested that root apical papilla plays a pivotal role in root formation. So stem cells from apical papilla could play an important role in continuous root formation.

b) **In pulp healing and regeneration:** Stem cells can play an important role in apexogenesis/apexification of the tooth, for e.g tooth with history of apical periodontitis with sinus tract formation where there is complete pulpal necrosis and infection and required apexification. Although Iwaya et al and Banchs and Trope described this phenomenon as ‘revascularization’, what actually occurred was physiological tissue formation and regeneration initiated by the stem cells.

c) **In replantation and transplantation:** Stem cells help in the ingrowth of bone and periodontal ligament (PDL) (next to the inner dentinal wall) into the canal space with arrested root formation after the replantation of avulsed maxillary incisors, suggesting a complete loss of the viability of pulp, apical papilla, and/ or HERS. Skoglund et al observed revascularization of the pulp of replanted and autotransplanted teeth with incomplete root development in dogs. In growth of new vessels occurs during the first few postoperative days. After 10 days, new vessels are formed in the apical half of the pulp, and after 30 days, in the whole pulp.

d) **Pulp/dentin tissue engineering and regeneration:** Dentin pulp tissue engineering was first tested by Mooney’s group. Bohl et al reported that culturing pulp cells grown on polyglycolic acid (PGA) in vitro resulted in high cell density tissue
similar to the native pulp. Burma et al. found that pulp cells seeded in PGA and implanted into mice produced extracellular matrix. New blood cells also penetrated the cells/PGA implants invivo 3 weeks after the implantation. After the invention of DPSCs and SHED, using these stem cells for the use of pulp/dentin tissue regeneration has drawn great interest. These findings provide new light on the possibility of generating pulp and dentin in pulpless canals.

e) **Stem cells for Bioroot engineering:** Dental implants have recently gained momentum as a preferred option for replacing missing teeth instead of bridges or removable denture. However, the fundamental pitfall is the lack of a natural structural relationship with the alveolar bone (i.e. the absence of PDL). The lack of natural contours and its structural interaction with the alveolar bone make dental implants a temporary option until a better alternative is available. This alternative may be tooth regeneration. Using animal study models, cells isolated from tooth buds can be seeded onto scaffolds and form ectopic teeth in vivo. Nakao et al recently engineered teeth ectopically followed by transplantation into an orthotopic site in the mouse jaw. From both DPSCs and SHED, tissues similar to normal dentin-pulp have been reported to be regenerated which can be later on used for regenerative endodontics. SCAP have higher proliferative rate as compared to DPSCs. They appear to be the source of primary odontoblasts that are responsible for root dentin formation, whereas DPSCs are the likely source of replacement odontoblast. Instead of forming entire tooth, even a bioroot with PDL tissue has been generated by utilizing SCAP along with PDLSCs. This bioroot is encircled with PDL tissue which has natural relationship with the surrounding bone.

f) **Whole tooth regeneration:** Whole tooth regeneration efforts largely consist of 2 approaches: one involves invivo implantation of immature tooth structure grown invitro from dental progenitor cells, while the other uses in vitro expanded, cultured dental progenitor cell populations seeded onto polymer scaffolds and implanted invivo.

Research on the fabrication of teeth from dissociated cells was first performed using tooth germ cells. When explants, seeded with porcine third impacted tooth bud cells, made of polyglycolate/poly-l-lactate (PGA/PLLA) or poly-l-lactateglycolate (PLGA), were transplanted for 20–30 weeks into omentum, bioengineered teeth were visible within the explants. The cultured molar bud cells increased in number and were also able to form bioengineered teeth. Recently, it has been reported that use of a collagen sponge scaffold formed teeth with a higher rate of success than use of biodegradable polymer. Several studies have shown that a tooth crown has been formed with different layers of enamel, dentin and pulp-like structure. Tooth regeneration involves three key elements which include:

- Inductive morphogenes
- Stem cells
- Scaffold

Steps involved in regeneration of tooth are:

1. Harvesting and expansion of adult stem cells.
2. Seeding the stem cells into scaffold which provides optimized environment.
3. Cells are instructed with targeted soluble molecular signals spatially.
4. Confirming the gene expression profile of the cells for next stage in Odontogenesis.

g) **TMJ formation:** Given that the mandibular condyle consists of two stratified layers of cartilaginous and bone tissues, MSCs were first differentiated into chondrogenic
and osteogenic cells. MSCs derived chondrogenic and osteogenic cells were encapsulated in a biocompatible hydrogel in two stratified layers molded into the shape and dimensions of an adult human mandibular condyle. Following in vivo implantation in immunodeficient mice for up to 12 weeks, the retrieved mandibular joint condyles retained the shape and dimensions of the native condyle. The chondrogenic and osteogenic portions remained in their respective layers. Lastly and most importantly, there was mutual infiltration of the cartilaginous and osseous components into each other’s territory, which resembles mandibular condyle. Therefore, the proof of principle has been established to regenerate the human-shaped TMJ condyle.

h) Periodontal tissue regeneration: Periodontal tissue regeneration represents the ultimate goal of periodontal therapy and entails the formation of all components of the periodontium. Commonly used growth factors for PDL regeneration therapies include BMPs, platelet-derived growth factor, emdogain and recombinant amelogenin protein. The resultant improved regenerative capability could be related to increased recruitment of progenitor MSCs which subsequently differentiate to form PDL tissue. Transplanted cell seeded polyglycolic acid sheets regenerated new bone, cementum and well-oriented collagen fibers when inserted into root surface, thus providing multipotency of PDLSCs. The combined use of transplanted MSCs and added exogenous signaling molecule could accelerate the directed differentiation of MSCs invivo, providing more effective promotion of periodontal tissue regeneration.

Recently, a new tissue engineering technique, termed cell-sheet based bioengineering, has been developed and utilized successfully for tissue regeneration. In this technique, enzymatic cell digestion is not required and the cell-to-cell contact in the engineered construct thus remains intact, which should be beneficial for tissue regeneration. Additionally, ECM proteins can be used without requiring an additional scaffold.

i) Orthodontic implications: Unwanted alveolar bony defects are often created after orthodontic extractions. Repair of these defects is needed to avoid the risk of dehiscence and other periodontal insults at a later stage after the teeth have been retracted into the extraction site. Often an accidental loss of the buccal plate has occurred during extraction of a buccally placed premolar for orthodontic purposes. This type of defect can be repaired with the help of stem cells.

Alveolar bone within the maxilla and mandible is one of the most actively remodeled during orthodontic/orthopedic treatment. The proliferation and differentiation of osteoblastic and osteoclastic stem cells are important in the remodeling process being controlled by local signaling/growth factors and systemic hormones.

j) Distraction osteogenesis: This is done frequently for generating new bone in cases requiring orthognathic surgery. This is done by progressively distracting bone surfaces. It is essentially a bone remodeling procedure which included mobilization of the osteoblastic/osteoclastic cells. Hence stem cells which can regenerate bone can play active role in these procedure.

k) Salivary gland regeneration:

Regeneration of salivary glands by stem cell transplantation is an important study topic for head and neck oncology and surgery because radiotherapy unavoidably impairs salivary gland function and results in xerostomia as a side effect. Two main approaches have been applied for restoring the damaged salivary glands. One method
is to develop an artificial salivary gland using tissue engineering technologies and another method is to apply stem cells to the damaged salivary gland tissue.

1) **Tongue regeneration:** Advances in stem cell biology and tissue engineering may enable the reconstruction of the damaged or resected tongue with normal physiological function.

**DENTAL STEM CELL MARKERS**

Stem cell markers help identify, characterize, and isolate stem cells. STRO-1, a trypsin-resistant cell-surface antigen, is a commonly used dental stem cell marker for all dental MSCs. It is expressed, for example, from bone marrow mesenchymal cells. STRO-1 is one of the early surface markers of mesenchymal stem cells. Its expression diminishes gradually during cultivation of the stem cells. Another stem cell marker, Stro-4, binds to heat shock protein-90 beta of multipotent MSCs and is also suited to identifying stem cells. In addition to mesenchymal stem cell markers, immature dental pulp stem cells also express markers of embryonic stem cells, such as Oct-4, Nanog, SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81.

**STEM CELL BANKING**

Cord stem cell preservation consists of collecting the 'leftover' umbilical cord blood from the placenta and umbilical cord after the baby is delivered and the cord is cut. This blood is sent to a bank where it is processed and preserved by freezing them in liquid nitrogen at temperature of -195°C. Many clinical studies showed that unrelated cord blood transplantation is safe and is an acceptable alternative to bone marrow transplantation for many patients. However, the studies also found that, as with bone marrow transplants, patients who receive cord blood from siblings or related donors generally have higher survival rates than those who receive cord blood from unrelated donors. Collecting and preserving a baby's cord blood stem cells would be a security blanket for the baby and his family members. In fact, it is estimated that the probability of a need for cord blood stem cells arising within a family is as high as 1/1,500.

Tissue banking of one's own cells may overcome immunological and ethical considerations involved in the use of allogenic cells. Dental stem cell banking, i.e., the process of storing stem cells obtained from patient's deciduous teeth and wisdom teeth, may be one of the methods to realize the potential of dental-stem-cell-based regenerative therapy. Recently, cell/tissue banks in the dental field have been planned and placed into practice in several countries, e.g., Advanced Center for Tissue Engineering Ltd., Tokyo, Japan (http://www.acte-group.com/); Teeth Bank Co., Ltd., Hiroshima, Japan (http://www.teethbank.jp/); Store-A-ToothTM, Lexington, USA (http://www.store-a-tooth.com/); BioEDEN, Austin, USA (http://www.bioeden.com/) and Stemade Biotech Pvt. Ltd., Mumbai, India (http://www.stemade.com/).

**LIMITATIONS IN THE FIELD OF STEM CELLS**

A sufficient number of cell sources currently exist including DPSCs, SHED, SCAP and PDLSCs. In contrast, human dental epithelial stem cell sources are limited for the following 2 reasons: first, dental epithelial cells undergo apoptosis after enamel formation is completed and therefore are no longer present in erupted teeth. Secondly, exvivo dental epithelial expansion can be difficult, due to the fact that it is inherently more difficult to expand epithelial cells in culture as compared to mesenchymal cells.

Successful whole-tooth regeneration requires the formation of both functional tooth crown and root structures. To date, bioengineered tooth root formation with accompanying functional PDL tissue has proved to be quite challenging, with only a few reports of success indicating that increased effort will be needed to achieve this goal. Finally, potential immune...
responses to bioengineered human dental implants have yet to be examined and remain virtually unknown at this time. Ideal tooth replacement therapies would use autologous cells harvested from the patient, thereby avoiding potential immunological rejection responses.65

Successful bone tissue engineering by cell transplantation requires sufficient number of viable cells with osteogenic potential for tissue regeneration. But several animal studies have pointed that transplanted cells die quickly or migrate out of the transplanted site. Survival of the transplanted cells require sufficient vascular supply; therefore, the cross-talk between implanted BMSCs and resident stem cells may play an important role in cell survival and subsequent bone regeneration.

Given that the fate of stem cells is influenced by their interaction with the microenvironment, understanding the key components regulating the properties of stem cells may elucidate ways to expand stem cells properly and control their differentiation precisely. The technical challenges in stem cell therapy are associated with cell manipulations, scaffold materials and delivery systems. Clinical challenges in stem cell-based periodontal therapy relate to immune rejection after administration, oncogenic properties of stem cells and functional integration of transplanted tissues into the host.

CONCLUSION
Stem-cells derived from all sources hold immense medical promises. Stem-cell therapies have virtually unlimited medical and dental applications. Stem cells have been used extensively in many medical disciplines for the repair and/or regeneration of defective tissues and organs such as bone, cartilage, heart and spinal cord. In dentistry, the identification of mesenchymal stem cell-like populations from both dental and non-dental tissues has presented exciting possibilities for the application of tissue engineering as well as gene based therapies.

The challenge for the dental professional in the anticipated era of stem cells and tissue engineering is imminent. What would be a dentist’s response when patients ask whether they can get their own stem cells if they have their wisdom teeth banked? What are the odds that tooth stem cells will grow a new tooth or be used to treat diabetes? Should I use a growth factor called PDGF or BMP2 to treat my periodontal bone defects or have a bone graft? Should my son’s baby teeth be banked for stem cells, and, if so, what are the odds that these baby teeth stem cells will cure a bone fracture he may get during a soccer game? However, the engineering of tooth substitutes is hard to scale up, costly, time-consuming and incompatible with the treatment of extensive tooth loss.

Scientific knowledge is not enough and the main challenge in stem-cell therapy is to find a compromise between the benefits to the patients, regulatory agencies, increased stem cell requirements, costs, coverage by health insurance and the role of pharmaceutical companies. Stem-cell therapy has brought in a lot of optimistic hope amongst researchers, doctors, and not to forget the patients who are the chief beneficiary of this innovation. Stem-cells regenerate hope and not all that is happening in research is hype.

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