

## Stem cells: Sources, and regenerative therapies in dental research and practice

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### Abstract

Stem cells are considered to be among the principle scientific breakthroughs of the twentieth century for the future of medicine, and considered to be an important weapon to fight against diseases, particularly those that have resisted the efforts of science for a long time. Human dental tissues have limited potentials to regenerate but the discovery of dental stem cells have developed new and surprising scenario in regenerative dentistry. Stem cell treatments are one example of the

possibility using adult cells sourced from patients' own bodies' means that it can be expected that in the near future such treatments may become routine at dental practices. The hope is that it will become possible to regenerate bone and dental tissues including the periodontal ligament, dental pulp and enamel, and that the creation of new teeth may also become feasible. In view of this possibility of achieving restoration with regenerative medicine, it can be considered that a new era of dentistry is beginning. Thus the aim of this review is to give dental professionals a brief overview of different stem cells sources and the latest findings and their implications for improving oral health and treating certain conditions of the human mouth and face.

**Key words:** Stem cells; Regeneration; Dental research

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**Core tip:** Stem cells are considered to be among the principle scientific breakthroughs of the 20<sup>th</sup> century. Human dental tissue has limited potentials to regenerate but the discovery of dental stem cells have developed new and surprising scenario in regenerative dentistry. The hope is that it will become possible to regenerate bone and dental tissues and that the creation of new teeth may become feasible. Thus our review gives dental professionals a brief overview of different stem cells sources and the latest findings and their implications for improving oral health and treating certain conditions of the human mouth and face.

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## INTRODUCTION

Stem cell therapies could lead to novel cures and palliative treatments. Stem cell research has clinical implications considering cell repair, replacement or regeneration to improve organ function. Thus future studies will require the collaboration of researchers from different specialties, including stem cell biology, material science, and of course, basic and clinical dentistry.

The loss of hard or soft dental tissue not only harms the patient psychologically, but also causes atrophy of the tooth supporting tissues. Regeneration may define as restoring a deficient part by complete regeneration of its architecture and function. Dramatic tooth extraction, sever periodontitis, implant dehiscence defects, tumor, or congenital anomalies may lead to alveolar bone deficiencies<sup>[1]</sup>. Alveolar bone defect regeneration techniques have many advances using minimally morbid techniques enhanced the success and patient acceptance<sup>[2,3]</sup>. Successful regeneration techniques of the craniofacial bone deficiencies, are used to optimize therapeutic approaches to bone regeneration<sup>[4]</sup>.

Autogenous bone graft remains the preferred reconstructive method but have some limitations such as increased operative time for bone graft harvesting, donor site morbidity, graft resorption, and limited availability. Various types of bone graft have become available to overcome these limitations<sup>[5,6]</sup>. There have been recent interest in the development of new grafting materials using allogeneic, xenogeneic and synthetic bioimplants for reconstructive bony procedures, and have been used as alternative for autogenous bone grafts<sup>[7-9]</sup>. A new combination of protein therapy, gene therapy and cell therapy and tissue engineering had been successfully developed and considered to be a more efficient and safer therapeutic system for bone and soft tissue regeneration<sup>[10]</sup>.

Stem cells are nonspecific cells with powerful self-regeneration properties and they are capable of organizing other cell types in the body. They are also play an important role as those undifferentiated cells have precursor properties, capable of forming many different cell types and have the property of unlimited self-renewal. Within dentistry, the hope is to regenerate both bone and dental tissues, including the periodontal ligament, dental pulp and enamel, so that new teeth could even be created, even in the presence of caries, pulpitis and periapical diseases, which are the primary causes of tooth loss<sup>[11]</sup>.

"Stem cells" are precursor cells that can give rise to multiple tissue types. Totipotent stem cells are cells that can give rise to a fully functional organism as well as to every cell type of the body. *Pluripotent* stem cells are capable of giving rise to virtually any tissue type, but not to a functioning organism. Multipotent stem cells are more differentiated cells that can give rise only to a limited number of tissues. For example, a specific type of multipotent stem cell called a mesenchymal stem cell

has been shown to produce bone, muscle, cartilage, fat, and other connective tissues<sup>[12,13]</sup>.

The effectiveness of stem cells can be attributed to many factors such as: Stem cells can be expanded *ex vivo*, thus a small number of them can be sufficient to heal large defects or to treat diseases. Stem cells in the presence of vasculature may elaborate and organize tissues *in vivo*. Also they may play an important role in regulating local and systemic immune reactions of the host favoring tissue regeneration.

## STEM CELL TYPES AND SOURCES

Stem cells have important criteria of self-renewable and the ability to differentiate into at least two different types of cell. Types of stem cells are determined based on their source and differ in regard to the types of cells into which they differentiate<sup>[14,15]</sup>.

Embryonic stem cells, they are pluripotent cells that can differentiate into any other type of cell<sup>[14]</sup>.

Adult stem cells, also called somatic stem cells, lack the potency of their embryonic counterparts, but have been used successfully to treat diseases. They can be harvested from an individual and, be used to regenerate tissue by autologous or allogeneic transplant<sup>[14]</sup>.

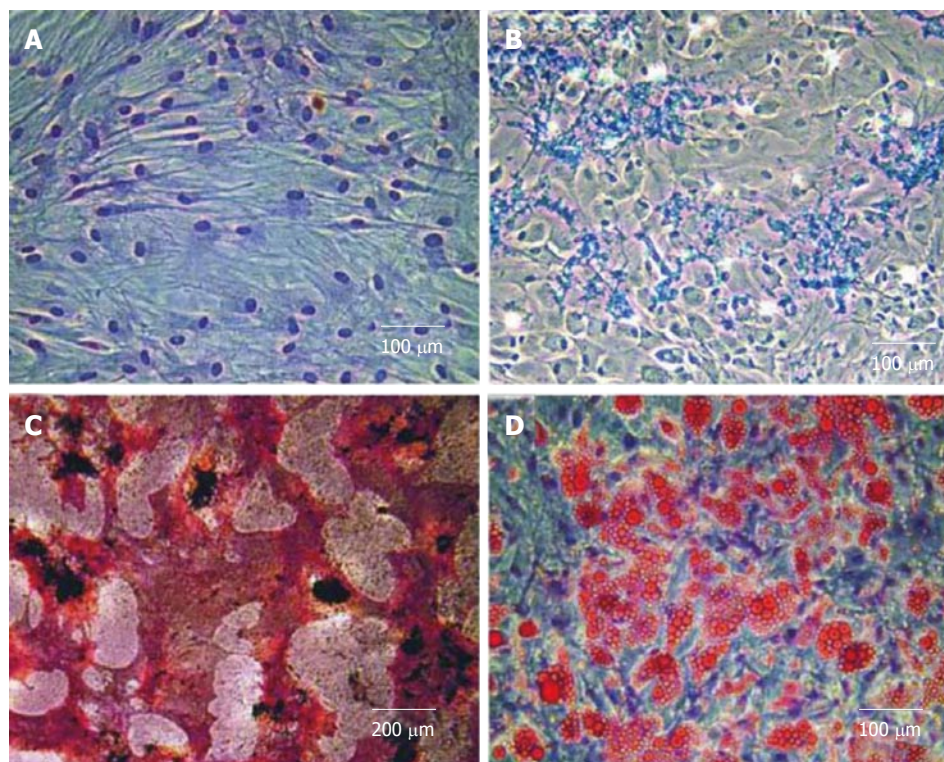
Induced pluripotent stem cells - adult stem cells having the potential to serve as the source of a large number of autologous stem cells, but the main drawbacks are their capacity for proliferation and concomitant potential for carcinogenicity<sup>[16]</sup>.

Bone marrow-derived mesenchymal stem cells can self-replicate and have been differentiated into osteoblasts, chondrocytes, myoblasts, adipocytes and other cell types. MSCs are often viewed as a yardstick of adult stem cells (Figure 1)<sup>[17]</sup>.

Adipose-derived stem cells (AS) are typically isolated from lipectomy or liposuction aspirates. AS have been differentiated into adipocytes, chondrocytes, myocytes, neuronal and osteoblast lineages. They have many advantages over other adult stem cell populations, as adipose tissue is available in large number and become easily accessible<sup>[18]</sup>.

Dental stem cells - recently these cells have been found in various dental tissues, such as Stem Cells from Human Exfoliated Deciduous teeth<sup>[19]</sup>, dental Pulp Stem Cells<sup>[20]</sup>, Periodontal Ligament Stem Cells (PDLSCs)<sup>[21,22]</sup>, while in dental papilla of wisdom teeth Stem Cells from Apical Papilla is present<sup>[23]</sup> and researchers termed stem cell found in dental follicles of developing wisdom teeth as Dental Follicle Precursor Cells<sup>[24-26]</sup>.

There are some advantages of dental stem cells: (1) they are readily accessible and provide an easy and least invasive way to obtain them; (2) stem cell banking is a reasonable and simple alternative to harvesting stem cells<sup>[27]</sup>; (3) they show good interaction with scaffolds<sup>[28]</sup>; and (4) they have a high proliferative and multidifferentiation potential<sup>[29-31]</sup>.



**Figure 1 Mesenchymal stem cells are viewed as a yardstick of adult stem cells.** A: Human mesenchymal stem cells (MSCs) isolated from anonymous adult human bone marrow donor after culture expansion (H and E staining); B: Chondrocytes derived from human mesenchymal stem cells showing positive staining to Alcian blue. Additional molecular and genetic markers can be used to further characterize MSC-derived chondrocytes; C: Osteoblasts derived from human mesenchymal stem cells showing positive von Kossa staining for calcium deposition (black) and active alkaline phosphatase enzyme (red). Additional molecular and genetic markers can be used to further characterize MSC-derived chondrocytes; D: Adipocytes derived from human mesenchymal stem cells showing positive Oil Red-O staining of intracellular lipids. Additional molecular and genetic markers can be used to further characterize MSC-derived chondrocytes<sup>[16]</sup>.

## ROLE OF MESENCHYMAL STEM CELLS IN TISSUE REGENERATION

By chemotaxis Mesenchymal Stem Cells can migrate to tissues showing inflammation and injury in the organism<sup>[32]</sup>. They can differentiate into different cell types, able to secrete a variety of cytokines, showing anti-inflammatory activity and create an anabolic microenvironment. Moreover, they play a role in regeneration of injured tissues by various means, as they directly differentiate into tissue-specific cells and thus substitute damaged or lost cells. On the other hand, they indirectly influence tissue regeneration by secretion of soluble factors. Thirdly, they are able to modulate the inflammatory response. So, they can effectively promote vascularization, cell proliferation, differentiation and modulate an inflammatory process<sup>[33,34]</sup>.

## CHALLENGES IN STEM CELL BIOLOGY

Notable increase in the applications of craniofacial tissue engineering, among them is: (1) isolation of stem cells from several craniofacial tissues and their clinical therapeutic applications in the craniofacial structures; (2) several prototypes of the human-shaped temporomandibular joint condyle have been engineered with integrated cartilage and bone layers from a single

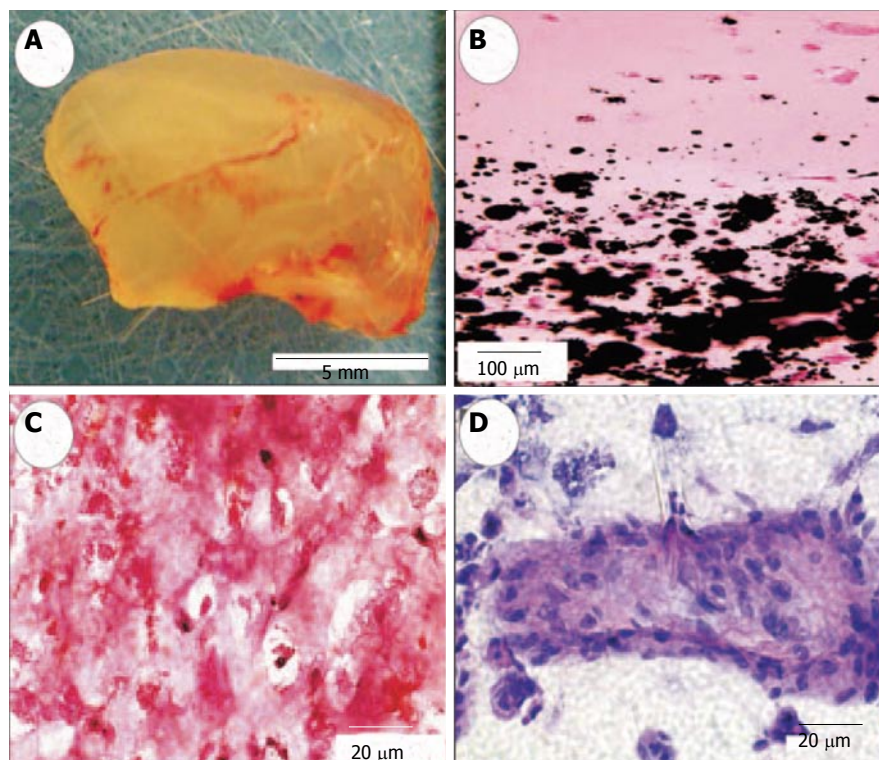
population of mesenchymal stem cells; (3) cell-based or non-cell-based tissue engineering of periodontium elements, including the periodontal ligament and cementum; (4) the application of stem cells, growth factors, and/or biomaterials in craniofacial bone engineering; and (5) adipose stem cells, with its efficient applications in facial soft and hard tissue reconstructive surgeries<sup>[35]</sup>.

### **Tissue engineering of the temporomandibular joint**

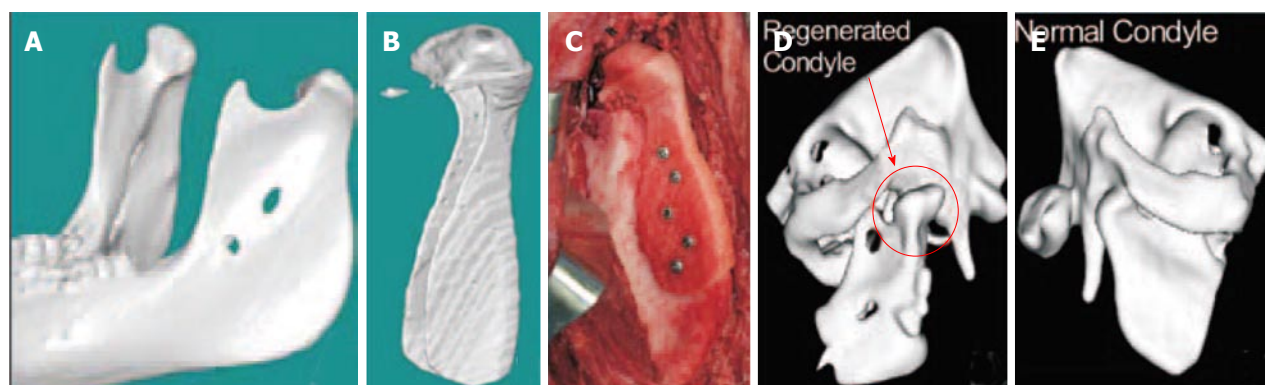
Current approaches for replacing degenerated mandibular condyles suffer from deficiencies such as donor site morbidity, immune-rejection, implant wear and tear, and pathogen transmission. So, advances in the management of temporomandibular joint degenerative diseases have been established: (1) to promote matrix synthesis and tissue maturation of stem cell-derived chondrogenic and osteogenic cells (Figure 2)<sup>[36]</sup>; (2) to enhance the mechanical properties of a tissue engineered mandibular condyle for ultimate in situ implantation into the human temporomandibular joint (Figure 3)<sup>[37]</sup>; and (3) to facilitate the remodeling potential of a tissue-engineered mandibular condyle.

### **Periodontal tissue engineering<sup>[35]</sup>**

The modulation of the exuberant host response to microbial contamination that plagues the periodontal wound is considered as the main challenge. It clarified



**Figure 2 Engineered neogenesis of human-shaped mandibular condyle from mesenchymal stem cells.** A: Harvested osteochondral construct retained the shape and dimension of the cadaver human mandibular condyle after *in vivo* implantation; B: Von Kossa-stained section showing the interface between stratified chondral and osseous layers. Multiple mineralization nodules are present in the osseous layer (lower half of the photomicrograph), but absent in the chondral layer; C: Positive safranin O staining of the chondrogenic layer indicates the synthesis of abundant glycosaminoglycans; D: H and E-stained section of the osteogenic layer showing a representative osseous island-like structure consisting of MSC-differentiated osteoblast-like cells on the surface and in the center. Reproduced with permission from Biomedical Engineering Society<sup>[36]</sup>.



**Figure 3 Design and engineering of minipig mandibular condyle.** A: Original computed tomography scan of minipig mandible; B: Image-based design of condyle scaffold; C: Ppolycaprolactone degradable polymer scaffold fabricated with selective laser sintering attached to the ramus; D: Regrowth of condyle following 3 months' implantation (new condyle shown in red circle); E: Comparison with normal condyle from contralateral side in Yucatan minipig<sup>[37]</sup>.

the interactions of multiple cell lineages including cementogenic cells, fibroblasts, and osteogenic cells. Regeneration of severe periodontal defects necessitates the attraction of endogenous periodontal tissue forming cells by growth factors.

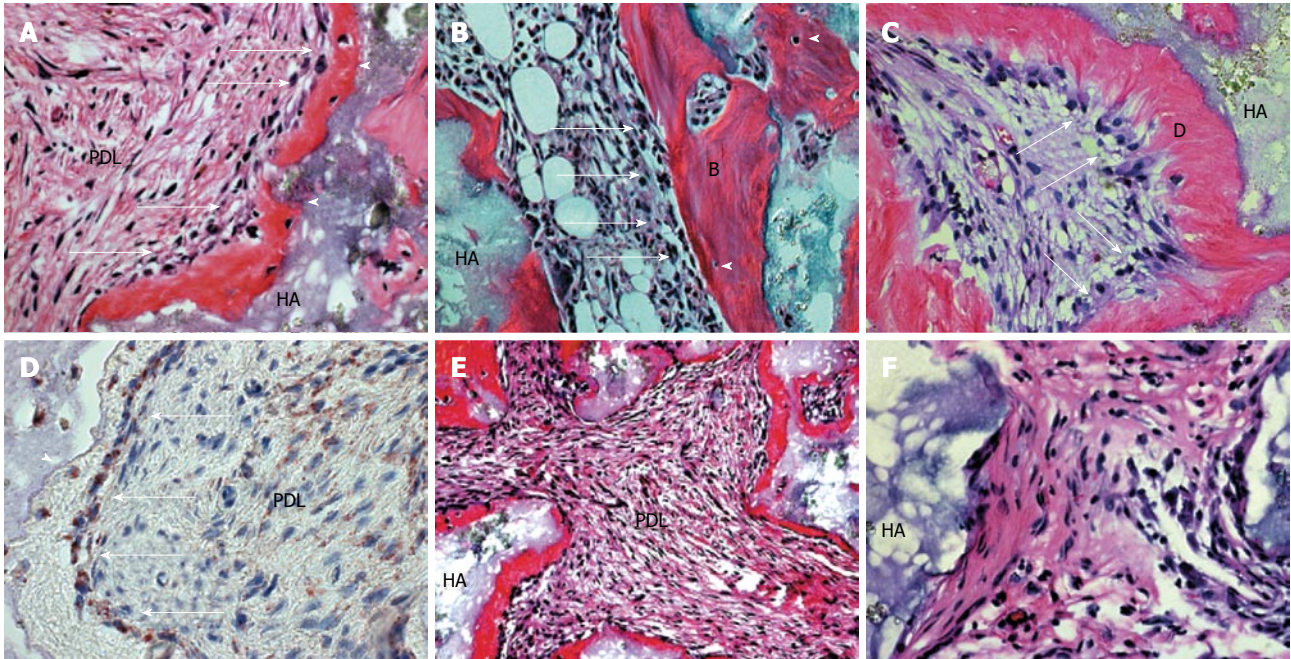
As regard the periodontal ligament (PDL) function, a recent report identified stem cells in human PDL (PDLSCs) and found that PDLSCs implanted into nude mice generated cementum/PDL-like structures that resemble the native PDL as a thin layer of cementum that interfaced with dense collagen fibers, similar to

Sharpey's fibers (Figure 4)<sup>[38,39]</sup>. Thus, the PDLSCs have the potential for forming periodontal structures, including the cementum and PDL.

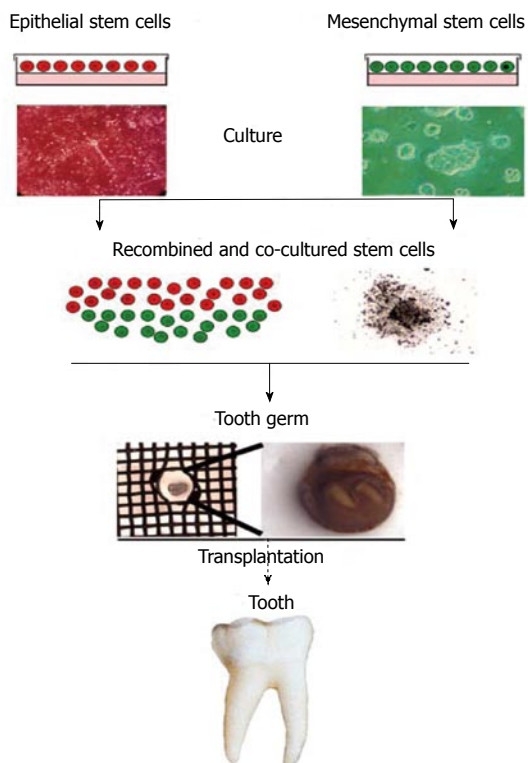
**Challenges in improving stem cell-based researches**

Tissue engineered bone with customized shape and dimensions have the potential for the biological replacement of craniofacial bones, and segmental defects in the appendicular bones.

Stem cell therapy encompasses new technologies and therapies and poses many challenges in stem cell



**Figure 4** Generation of cementum-like and PDL-like structures *in vivo* by PDLSCs. A: After 8 wk of transplantation, PDLSCs differentiated into cementoblast-like cells (arrows) that formed a cementum-like structure (C) on the surface of the hydroxyapatite tricalcium phosphate (HA) carrier; cementocyte-like cells (arrowhead) and PDL-like tissue (PDL) were also generated; B: BMSSC transplant was used as control to show the formation of a bone/marrow structure containing osteoblasts (arrows), osteocytes (arrowhead), and elements of bone (B) and haemopoietic marrow (HP); C: DPSC transplant was also used as control to show a dentin/pulp-like structure containing odontoblasts (arrows) and dentin like (D) and pulp-like (Pulp) tissue; D: Immunohistochemical staining showed that PDLSCs generated cementum-like structure (C) and differentiated into cementoblast-like cells (arrows) and cementocyte-like cells (arrowhead) that stained positive for human-specific mitochondria antibody. Part of the PDL-like tissue (PDL) also stained positive for human specific mitochondria antibody (within dashed line); E: Of 13 selected strains of single-colony derived PDLSC, only eight (61%) generated cementum/PDL-like structures *in vivo* as shown at lower magnification (approximately 20). New cementum-like structure (C) formed adjacent to the surfaces of the carrier (HA) and associated with PDL-like tissue (PDL); F: The other five strains did not generate mineralised or PDL-like tissues *in vivo*<sup>[38]</sup>.



**Figure 5** Use of stem cells for tooth formation *in vitro* and *ex vivo*. A tooth germ can be created *in vitro* after co-culture of isolated epithelial and mesenchymal stem cells. This germ could be implanted into the alveolar bone and finally develop into a fully functional tooth<sup>[40]</sup>.

research, such as: (1) biological challenges: Despite biological evidence showing that regeneration can occur in humans, complete and predictable regeneration still remains an elusive clinical goal (especially in advanced periodontal defects); (2) technical challenges: The technical challenges in stem cell therapy are associated with cell manipulations, scaffold materials and delivery systems; and (3) clinical challenges: 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.

### Stem cells for tooth engineering

Building a tooth logically requires the association/cooperation of odontogenic mesenchymal and epithelial cells. The recombination of dissociated dental epithelial and mesenchymal tissues leads to tooth formation both *in vitro* and *in vivo* (Figure 5). The bioengineered teeth have been produced in ectopic sites and with missing some essential elements such as the complete root and periodontal tissues that allow correct anchoring into the alveolar bone. Recently, a new approach has been proposed for growing teeth in the mouse mandible<sup>[40]</sup>.

## CONCLUSION

For dental applications, stem cell therapy and tissue

engineering are gold solution for bone and soft tissue regeneration and provide hope of future application in humans within the next few years. Tissue engineering modalities will provide numerous clinical dental applications, including improved treatments for intraosseous periodontal defects, enhanced maxillary and mandibular grafting procedures, perhaps more biological methods to repair teeth after carious damage and possibly even re-growing lost teeth. This review highlights the sources and the regenerative therapies in the clinical practice of dentistry in the future.

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