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## STEM CELLS IN ORAL AND MAXILLOFACIAL SURGERY: CURRENT CONCEPTS AND RECENT ADVANCES

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### ABSTRACT

Stem cells are characterized by self-renewal and the capacity to differentiate into specialized cell types, making them important candidates for tissue engineering and regenerative medicine. This narrative review summarizes the classification, sources, biological characteristics, storage and transport considerations, marker-based characterization, scaffold systems, safety considerations, and applications of stem cells in oral and maxillofacial surgery. Embryonic, adult, and induced pluripotent stem cells are considered, with particular attention to mesenchymal stem cells derived from bone marrow, adipose tissue, dental pulp, periodontal ligament, apical papilla, dental follicle, and exfoliated deciduous teeth. The reviewed literature describes experimental and early clinical applications in dentin and pulp regeneration, periodontal regeneration, craniofacial bone repair, soft-tissue reconstruction, and tissue-engineered tooth and temporomandibular joint constructs. Stem cell-based regeneration commonly relies on coordinated interactions among cells, scaffolds, growth factors, and the extracellular microenvironment. Important translational challenges include immunological compatibility, tumorigenicity, controlled differentiation, quality control, standardization, scalability, regulatory requirements, and cost. Current developments in biomimetic scaffolds, three-dimensional bioprinting, gene editing, and precision approaches may further expand regenerative applications. However, the source literature also emphasizes the need for continued experimental and clinical investigation before widespread clinical implementation in oral and maxillofacial surgery.

**Keywords:** Stem Cells; Mesenchymal Stem Cells; Dental Stem Cells; Tissue Engineering; Regenerative Medicine; Oral and Maxillofacial Surgery

### 1 INTRODUCTION

Stem cells are a distinct population of cells characterized by the ability to self-renew while retaining an undifferentiated state and by their capacity to differentiate into one or more specialized cell types. These properties provide the biological basis for their investigation in tissue repair and regeneration. In oral and maxillofacial surgery, regenerative strategies are particularly relevant because the region contains anatomically complex tissues involved in facial expression, speech, mastication, swallowing, and aesthetics [1,2].

Conventional reconstruction of oral and craniofacial defects may involve grafts, tissue transfer, implants, or other biomaterials. These approaches can be associated with limitations such as donor-site morbidity, scarring, infection, graft resorption, and incomplete restoration of the original structure. Stem-cell-based tissue engineering attempts to address these limitations by combining regenerative cells with biomimetic scaffolds and biological signals to promote formation of functional tissues [36].

The regenerative concept is not based on the stem cell alone. Successful tissue engineering requires an appropriate cell source, a supportive extracellular environment, suitable scaffolding, and signals that regulate proliferation, migration, differentiation, vascularization, and tissue integration. The literature summarized in the source document therefore encompasses stem cell biology, cell sourcing, culture and quality control, scaffold design, safety, and applications throughout the oral and maxillofacial region [18,50].

The objective of this review is to summarize the available literature presented in the source document concerning stem cell classification and biology, major oral and maxillofacial stem cell sources, tissue-engineering principles, clinical and experimental applications, safety considerations, and future challenges.

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## 2 MATERIALS AND METHODS

This manuscript is a narrative review based on the literature compiled in the supplied source document, which contains background material, summaries of relevant studies and reviews, and a 50-item reference list. The source document was reorganized into the structure requested for a Review Article by the International Journal of Science and Research Archive (IJSRA).

No new laboratory, animal, or human-subject experiment was performed for this manuscript. The supplied material did not report a formal systematic-review protocol, database search strategy, predefined eligibility criteria, risk-of-bias assessment, or meta-analysis; therefore, these elements have not been invented or presented as having been performed. The discussion is consequently a narrative synthesis of the material and references contained in the source document.

For journal preparation, terminology and major concepts were retained from the supplied material while repetitive passages were consolidated. References were retained in numerical Vancouver order as provided in the source document; the authors should verify bibliographic details against the original publications before submission.

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## 3 RESULTS AND DISCUSSION

### 3.1 Stem cell properties and classification

Two fundamental properties define a stem cell: self-renewal and potency. Self-renewal is the capacity to undergo repeated cell divisions while maintaining an undifferentiated state. The source document relates this property to the Hayflick limit, describing approximately 40–60 population doublings for many somatic cell strains before senescence [3]. Potency refers to the capacity to differentiate into specialized cell types [1].

Stem cells may be classified according to developmental potential as totipotent, pluripotent, multipotent, oligopotent, or unipotent. Totipotent cells have the broadest potential and can contribute to embryonic and extra-embryonic structures. Pluripotent cells can form derivatives of the three germ layers but do not normally form extra-embryonic structures. Multipotent cells generate multiple cell types within a more restricted lineage, whereas oligopotent cells have a narrower range and unipotent cells generate a single principal cell type while retaining self-renewal [1,2].

Based on origin, the principal categories discussed in the source document are embryonic stem cells (ESCs), adult stem cells, and induced pluripotent stem cells (iPSCs). Adult stem cells include hematopoietic stem cells and mesenchymal stem cells (MSCs). The distinction between developmental potency and tissue source is important because the biological potential, ethical considerations, immunological characteristics, and translational risks differ between cell populations.

### 3.2 Embryonic, adult and induced pluripotent stem cells

Embryonic stem cells are derived from the inner cell mass of the blastocyst and can differentiate into derivatives of the three germ layers. Their broad differentiation potential has made them important in developmental biology and regenerative medicine research. However, the source material identifies ethical concerns, immune rejection, and the possibility of tumor formation as important limitations to clinical use [5–7].

Adult stem cells are obtained from tissues such as bone marrow, adipose tissue, dental pulp and other adult or perinatal sources. The source document describes adult stem cells as relatively accessible and not associated with the same ethical concerns as embryonic sources. Mesenchymal stem cells are particularly relevant to oral and maxillofacial tissue

engineering because many craniofacial tissues have mesenchymal contributions and MSCs can participate in osteogenic, chondrogenic and adipogenic differentiation [9,14,17].

Induced pluripotent stem cells are generated by reprogramming differentiated somatic cells toward a pluripotent state. The major turning point described in the source material was the demonstration by Takahashi and Yamanaka that defined transcription factors could reprogram adult fibroblasts into pluripotent cells [8]. iPSCs provide a potential route toward patient-specific regenerative approaches, although the source document emphasizes the continuing need to control genomic stability, differentiation and tumorigenic risk.

**Table 1: General classification of stem cells according to developmental potential. The table summarizes concepts described in the supplied source document [1,2].**

| Stem cell category | Principal characteristic                     | Examples/sources            | Relevance                                      |
|--------------------|----------------------------------------------|-----------------------------|------------------------------------------------|
| Totipotent         | Broadest developmental potential             | Zygote                      | Embryonic and extra-embryonic development      |
| Pluripotent        | Three germ layers                            | ESCs, iPSCs                 | Regenerative medicine research                 |
| Multipotent        | Multiple related cell types                  | HSCs, MSCs                  | Tissue-specific regeneration                   |
| Oligopotent        | Limited lineage potential                    | Myeloid progenitors         | Restricted tissue differentiation              |
| Unipotent          | Single principal cell type with self-renewal | Tissue-specific progenitors | Regenerative potential within a single lineage |

### 3.3 Sources of stem cells relevant to oral and maxillofacial surgery

The principal sources identified for oral and maxillofacial regenerative applications are bone marrow, adipose tissue, and tissues of the oral and maxillofacial region [1]. Bone marrow contains hematopoietic and mesenchymal stem cell populations. It can provide a relatively high stem cell yield and a broad differentiation capacity, although harvesting from the sternum or iliac crest may require an invasive procedure and may be associated with postoperative discomfort [5].

Adipose-derived stem cells (ADSCs) can be obtained from lipectomy or liposuction aspirates. The source document describes adipose tissue as abundant and readily accessible, with cells capable of multilineage differentiation [9]. These properties have supported investigation of ADSCs for craniofacial bone and soft-tissue reconstruction.

Dental and oral tissues provide several mesenchymal stem/progenitor cell populations. The major populations described are dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), stem cells from the apical papilla (SCAP), and dental follicle precursor cells (DFPCs) [10–14]. These cells are particularly attractive because their tissues of origin are directly associated with the structures targeted for dental and craniofacial regeneration.

### 3.4 Dental stem cell populations

DPSCs were isolated from human dental pulp and demonstrated clonogenicity and multilineage differentiation potential. Experimental work summarized in the source document indicates that DPSCs can differentiate toward odontoblast-like and osteogenic phenotypes and can contribute to dentin and bone regeneration [10,20,21]. Third molars are identified as a useful source because they can be obtained during routine dental procedures and the cells can be expanded and cryopreserved.

SHED are derived from exfoliated deciduous teeth. The source material describes them as highly proliferative, immature, multipotent cells and reports experimental evidence for enhanced wound healing [11,35]. Their accessibility during natural exfoliation provides a potential source for regenerative research.

PDLSCs are derived from the periodontal ligament and have demonstrated the capacity to generate cells associated with periodontal tissues, including cementum- and bone-forming phenotypes. Experimental studies summarized in the source document describe periodontal regeneration using PDLSCs with scaffolds and cell sheets, supporting their investigation for reconstruction of the periodontium [25–29,47,48].

SCAP are isolated from the apical papilla of immature permanent teeth and are described as an important source of odontoblast-like cells. Their reported high proliferative capacity and potential for odontogenic differentiation make them relevant to root development and regenerative endodontic strategies [12].

Dental follicle cells can differentiate toward cementoblast, osteoblast and periodontal ligament phenotypes. The source document describes their isolation from the dental follicle, particularly around third molars, and their potential to participate in root and periodontal tissue formation [13].

**Table 2: Major stem cell sources discussed in the supplied literature and their reported regenerative applications [9–14,17,23–35].**

| Cell source | Origin                           | Reported potential                                               | Potential application                          |
|-------------|----------------------------------|------------------------------------------------------------------|------------------------------------------------|
| DPSCs       | Dental pulp                      | Odontoblast-like cells, osteogenic and chondrogenic potential    | Dentin, pulp and bone regeneration             |
| SHED        | Exfoliated deciduous teeth       | High proliferation and multipotency                              | Wound and dental tissue regeneration           |
| PDLSCs      | Periodontal ligament             | Periodontal, cementum and osteogenic differentiation             | Periodontal regeneration                       |
| SCAP        | Apical papilla of immature teeth | Odontogenic, neuron-like and adipogenic differentiation in vitro | Root/apical regeneration                       |
| DFPCs/DFCs  | Dental follicle                  | Cementoblast, osteoblast and PDL differentiation                 | Periodontal and tooth/root engineering         |
| BMSCs       | Bone marrow                      | Mesenchymal differentiation and osteogenesis                     | Craniofacial bone and periodontal regeneration |
| ADSCs       | Adipose tissue                   | Multilineage differentiation mesenchymal                         | Bone and soft-tissue reconstruction            |

### 3.5 Stem cell biology, culture and directed differentiation

Stem cell behavior is influenced by both intrinsic genetic mechanisms and extrinsic signals from the surrounding microenvironment. During embryogenesis, pluripotent cells differentiate through germ-layer specification and progressively restricted developmental pathways. The source document emphasizes that physical cell-cell interactions, extracellular signals, growth factors and intracellular gene-regulatory mechanisms all influence cell fate.

For therapeutic use, stem cells must be expanded and, where necessary, directed toward an appropriate lineage. Directed differentiation attempts to reproduce developmental signaling conditions in a controlled environment. Signaling pathways discussed in the source include fibroblast growth factors, Wnt signaling, transforming growth factor- $\beta$  and bone morphogenetic proteins. The relative concentration, timing and duration of signaling can influence the lineage generated [38–43].

The source document also emphasizes that undifferentiated pluripotent cells require careful control because inappropriate differentiation can compromise therapeutic outcomes and may contribute to teratoma formation. For large-scale culture, feeder-free and animal-component-free systems are described as preferable, with xeno-free systems helping to reduce risks associated with animal-derived products [44–50].

### 3.6 Stem cell storage, characterization and quality control

The source material describes collection and transport of stem-cell-containing tissue in a suitable culture medium using a screw-top vial, with delivery to the processing and storage facility within 40 hours. Laboratory processing may include trypsinization and passaging to establish cell colonies, followed by exposure to inductive signals and growth factors to direct differentiation.

Before administration, cultured cells require characterization. Markers listed in the source document include Oct4, Nanog, SSEA4, TRA-1-60 and TRA-1-81. An endotoxin test is also described as necessary to identify microbial contamination. These steps form part of the broader requirement for quality-controlled cell products in regenerative medicine [44].

Scaffolds provide a physical framework for cells and can be natural or synthetic, biodegradable or non-biodegradable. Materials described in the source document include polylactic acid, polyglycolic acid, polyethylene terephthalate, polypropylene fumarate, hydroxyapatite/tricalcium phosphate, fibrin, alginate and collagen [18,50]. Scaffold properties such as physical structure, chemical composition, mechanical behavior, degradation and cell adhesion can influence cell survival and differentiation.

### **3.7 Safety and immunological considerations**

Safety is a central consideration in translation of stem cell therapies. The source document reports generally favorable safety observations in the reviewed dental surgical literature but also emphasizes that immune responses remain incompletely understood. Inflammatory mediators, host recognition of implanted cells, cell survival and altered function may influence treatment outcomes.

Allogeneic transplantation may produce greater immunological concerns because cells originate from another individual. MSCs have immunomodulatory properties, but these effects may vary according to cell source, delivery route and host-related factors. The source document notes that excessive or prolonged inflammation may interfere with tissue regeneration and could contribute to tissue damage, fibrosis or graft failure.

Tumorigenicity is particularly important for pluripotent stem cells. The source material identifies uncontrolled proliferation, residual undifferentiated cells, oncogene-related effects and genomic instability as potential concerns in iPSC-based approaches. Therefore, controlled differentiation, genetic and phenotypic characterization, and long-term monitoring remain important components of safe clinical translation.

### **3.8 Efficacy and quality of regenerated bone**

The reviewed material describes stem-cell-based approaches as capable of promoting bone formation and improving the structural characteristics of regenerated tissue. Regenerated bone has been described as relatively compact and vascularized in experimental settings, which is relevant to implant stability and long-term integration.

The source document attributes part of this regenerative effect to paracrine activity, whereby stem cells release signaling molecules that influence osteogenesis and angiogenesis. Vascularization is particularly important because adequate blood supply supports tissue viability and healing. These observations have stimulated interest in combining cells with biomaterials and adjunctive biological signals for larger or more complex defects [15–18].

Nevertheless, the quality and quantity of regenerated tissue are dependent on cell source, delivery method, scaffold properties, defect characteristics and the surrounding biological environment. The source material therefore supports continued optimization rather than assuming that stem-cell therapy uniformly replaces conventional grafting.

### **3.9 Dentin and pulp regeneration**

Dentin and pulp regeneration represents one of the most developed dental applications discussed in the source document. Experimental studies have demonstrated formation of tubular dentin using dental pulp stem cells combined with hydroxyapatite/tricalcium phosphate scaffolds. Other experimental work has examined the use of recombinant human BMP-2 with pulp stem cells to stimulate reparative dentin formation [19–22].

Regenerative approaches are particularly relevant to immature permanent teeth because conventional root canal treatment may interrupt further maturation and leave a structurally compromised tooth. The source document describes regenerative endodontic concepts involving conservative instrumentation, disinfection and sealing, with the objective of preserving or harnessing endogenous stem-cell populations. Stem cells harvested from dental pulp have also been investigated as a potential source for pulp regeneration.

### **3.10 Periodontal regeneration**

Periodontal regeneration aims to restore the coordinated architecture of cementum, periodontal ligament and alveolar bone rather than merely repairing a single component. BMSCs have been investigated for periodontal defect regeneration, with experimental studies demonstrating formation of periodontal tissues [23]. Clinical and experimental approaches have also combined MSCs with platelet-rich plasma, scaffolds, cell sheets and other biomaterials.

PDLSCs have received particular attention because of their intrinsic relationship to periodontal tissues. Experimental studies summarized in the source document describe regeneration of cementum, periodontal ligament and alveolar bone using PDLSCs in animal models and scaffold-based systems [25–29]. Cell-sheet approaches and three-dimensional biomaterials have been explored to improve cell delivery and organization.

The source document also describes periodontal tissue engineering around titanium implants using autologous bone marrow-derived stem cells and scaffolds. These findings indicate potential applications not only for natural periodontal structures but also for peri-implant tissue regeneration, although the translational evidence remains dependent on experimental models.

### **3.11 Craniofacial bone and soft-tissue reconstruction**

Large craniofacial defects may result from trauma, tumor resection, cystic disease or congenital abnormalities. Conventional reconstruction may require grafts or tissue transfer and can be associated with donor-site morbidity and incomplete restoration of complex anatomy. Stem-cell-based strategies seek to combine regenerative cells with scaffolds and growth signals to reconstruct tissue in a more biologically integrated manner [31,36].

A case report summarized in the source document describes the use of autologous adipose-derived stem cells with iliac crest bone graft and fibrin glue for a large traumatic calvarial defect in a child. The reported follow-up demonstrated new bone formation and restoration of calvarial continuity [32]. As a single case report, this observation supports feasibility but does not establish comparative clinical efficacy.

Soft-tissue reconstruction has also been explored using MSC-derived adipogenic cells in predefined scaffold shapes. Experimental work has demonstrated that adipogenic cells derived from adult MSCs can be incorporated into hydrogel-based constructs, suggesting a potential strategy for soft-tissue augmentation and reconstruction [33].

Dental pulp-derived stem cells combined with collagen sponge scaffolds have been investigated for mandibular bone defects. Scaffold-free microspheres have also been studied as a means of delivering larger numbers of viable osteogenic cells while maintaining structural integrity [31,34]. SHED have additionally demonstrated wound-healing effects in experimental models [35].

### **3.12 Tissue engineering of teeth and temporomandibular structures**

Whole-tooth regeneration requires coordinated epithelial-mesenchymal interactions, appropriate stem or progenitor cells, inductive signals and a supportive scaffold. The source document identifies three essential components of tooth regeneration: inductive morphogens, stem cells and scaffolds. A proposed sequence involves harvesting and expanding adult stem cells, seeding them into a scaffold, providing spatially controlled molecular signals and confirming gene expression appropriate for odontogenesis.

Experimental studies have generated tooth-like structures using tooth-bud cells and biodegradable scaffolds. The source document also describes work using porcine tooth-bud cells and PGA or PLGA-based scaffolds to generate tooth or tooth-bone constructs [40–43]. However, clinical translation remains challenging because of tissue complexity, control of crown morphology, eruption, color, vascularization, innervation and predictable integration.

Craniofacial tissue engineering has also extended to anatomically shaped structures such as the mandibular condyle. Adult MSCs combined with biomimetic scaffolds and bioreactor systems have been used experimentally to generate condyle-shaped constructs [37–39]. These approaches illustrate the potential of combining stem cells with imaging, scaffold design and controlled bioreactor environments.

### **3.13 Scaffolds, three-dimensional printing and bioengineering**

Scaffold-cell interaction is a major determinant of tissue-engineering performance. Scaffold architecture influences cell attachment, migration, proliferation, differentiation and extracellular-matrix deposition. The source literature emphasizes that physical, chemical, mechanical and biological properties must be considered together when designing constructs for oral and craniofacial reconstruction [50].

Three-dimensional printing and bioprinting provide methods for placing cells and biomaterials in predefined spatial arrangements. The source document describes multiphase periodontal scaffolds designed to reproduce the spatial organization of cementum/dentin, periodontal ligament and alveolar bone. Region-specific delivery of bioactive molecules can be used to provide different signals to different parts of a single construct.

Three-dimensional bioprinting has also been studied using adipose-derived stem cells, with experimental evidence of cell viability and osteogenic differentiation in printed constructs. Such technologies may help address the geometric complexity of craniofacial structures; however, producing durable, vascularized and fully functional tissues remains a major translational challenge.

### 3.14 Manufacturing standards and regulatory considerations

Clinical translation requires reproducible manufacturing and quality-control systems. The source document identifies Good Manufacturing Practice principles associated with regulatory agencies such as the European Medicines Agency and the US Food and Drug Administration. Earlier culture systems frequently used animal-derived components, which can introduce concerns related to animal antigens or pathogens. Xeno-free and standardized culture systems have therefore been developed to improve safety and reproducibility [44–50].

Important quality attributes include cell identity, purity, viability, genetic stability, differentiation potential, absence of microbial contamination and consistency between production batches. Standardization becomes increasingly important as cell-based therapies move from laboratory-scale experiments toward larger clinical applications.

### 3.15 Challenges and future directions

Several barriers must be addressed before stem cell therapy can be routinely incorporated into oral and maxillofacial surgery. These include incomplete understanding of stem cell mechanisms, variability in differentiation efficiency, difficulty in scaling cell production, immune rejection, uncontrolled proliferation, tumorigenicity, regulatory requirements and treatment cost.

The source document identifies the microenvironment as a critical determinant of regenerative success. Cells must receive appropriate spatial, temporal and biochemical signals to generate organized tissues. Future strategies may therefore depend on integrated systems combining stem cells, biomimetic scaffolds, growth factors, gene-based approaches, immunomodulation and controlled mechanical environments.

Precision medicine and gene-editing technologies may allow more individualized regenerative strategies. Three-dimensional printing and bioprinting may permit fabrication of patient-specific constructs, while in situ tissue engineering seeks to stimulate endogenous regenerative mechanisms within the defect. These approaches remain developing fields and require rigorous evaluation of long-term safety, reproducibility and functional outcomes.

The source document also highlights the importance of interdisciplinary collaboration among stem cell biologists, molecular biologists, geneticists, material scientists, engineers and oral and maxillofacial clinicians. Such collaboration is likely to be necessary to address the biological, mechanical and anatomical complexity of craniofacial regeneration.

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## 4 CONCLUSION

Stem cells provide a biologically based approach to regeneration of oral and maxillofacial tissues because of their capacity for self-renewal, differentiation and interaction with the tissue microenvironment. Bone marrow, adipose tissue and dental tissues provide important sources, with DPSCs, SHED, PDLSCs, SCAP and dental follicle-derived cells receiving particular attention for dental and craniofacial applications. Experimental and early clinical evidence summarized in the source document supports investigation of stem-cell-based strategies for dentin and pulp regeneration, periodontal reconstruction, craniofacial bone repair, soft-tissue augmentation and engineered craniofacial structures.

The clinical translation of these approaches remains constrained by the need for predictable differentiation, adequate vascularization, immunological compatibility, tumorigenic risk control, standardized manufacturing and long-term safety data. Continued research integrating stem cells with biomimetic scaffolds, growth factors, three-dimensional bioengineering and controlled manufacturing systems may improve the reproducibility and functional quality of regenerated tissues. The available evidence supports continued investigation while recognizing that many complex regenerative applications remain experimental.

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## STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

### *Disclosure of conflict of interest*

The authors declare no conflicts of interest regarding this manuscript.

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