Stem cell-based regenerative prosthodontics: A new era in prosthodontics.

Nandakishore Ghoshal[1], Arnab Pradhan[1], Samiran Das[2], Jayanta Bhattacharyya[3], Soumitra Ghosh[2], Soumadip Niyogi[4]

[1]Post graduate student, Dept. of Prosthodontics and Crown & Bridge, Guru Nanak Institute of Dental Sciences and Research, Panihati, Kolkata.
[2]Professor, Dept. of Prosthodontics and Crown & Bridge, Guru Nanak Institute of Dental Sciences and Research, Panihati, Kolkata.
[3]Principal and Head, Dept. of Prosthodontics and Crown & Bridge, Guru Nanak Institute of Dental Sciences and Research, Panihati, Kolkata.
[4]Senior Lecturer, Dept. of Prosthodontics and Crown & Bridge, Guru Nanak Institute of Dental Sciences and Research, Panihati, Kolkata.

Abstract
The ultimate goal for tissue engineering and regenerative medicine is to develop therapies to rejuvenate lost or damaged tissue using engineered or regenerated products derived from either donor or autologous cells. Cell-based therapies are widely used in the field of regenerative medicine. Stem cells are undifferentiated or partially differentiated biological cells found in multicellular organisms that can differentiate into specialized cells. Two types of stem cells are present in humans. These are the embryonic and the adult stem cells. Embryonic stem cells are isolated from inner cell mass blastocytes, and adult stem cells are found in various tissues. The dental pulp stem cells are the pluripotent mesenchymal stem cells (MSC), which are the most commonly used. However, bone marrow-derived mesenchymal stem cells are another commonly used cell type in stem cell-based regenerative prosthodontics. They help to rebuild the bone structure of the defects of craniofacial region, particularly the maxilla and mandible. Stem cell therapy is the new horizon in the field of regenerative dentistry.

Keywords: Stem cell, embryonic stem cell, adult stem cell, regenerative prosthodontics.

Address of correspondence: Dr. Nandakishore Ghoshal, Address: RC Road, Panihati, North 24 Parganas, Kolkata-700114
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Introduction

Every cell has a specific job and is shaped to do that job perfectly. A muscle cell is a muscle cell and only a muscle cell, a nerve cell will always be a nerve cell, and a bone cell will only ever be a bone cell. The differentiation of each cell is pre-determined at embryo stage and then cannot be changed. However, cutting-edge research made a significant discovery for modern science. There are these beautiful cells that exists known as Stem cells. Human adult mesenchymal stem cells (MSCs) are non-hematopoietic, non-osteoblastic, adherent fibroblast-like cells with intrinsic ability of self-renewal and potential for multilineage differentiation [1] These cells can become any cell because they are not specialized. Scientists were hugely motivated by their discovery because they can be used to repair lost or damaged organs, bones, or cartilage. They could also help treat diseases by making new brain cells to treat people with Parkinson's disease, or they could be used to repair damaged immune systems or regrow lost limbs. The discovery of stem cells is enormous for modern medicine and could have a massive impact. Thereare two types of stem cells in human beings- embryonic stem cells and adult stem cells. Embryonic stemcells are unspecialized cells, those have the potential to develop into any cell. Adult stem cells are also unspecializedcells, but they can develop into many types of cells, unlike embryonic stem cells.[2] They cannot develop into every type of cell. Adult stem cells come from different pluripotent tissues such as bone marrow. In human postnatal dental tissues, five primary sources of dental stem cells (DSCs) are dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells (PDLSCs), dental follicle stem cells (DFSCs) and stem cells from apical papilla (SCAPs).[3]

The center of stem cell research attention in dentistry is the regeneration of missing oral tissues. In particular, restoring alveolar ridge height is a significant concern to prosthodontists because bone defects that arise after tooth loss usually result in further horizontal and vertical bone loss, limiting the effectiveness of dental implants and other prosthodontic treatments. Therefore, stem- cell-based regenerative technology represents a new era in prosthodontic treatment. Thus, clinicians and researchers in the prosthodontic field should understand fundamental promising aspects of stem cells and the implications of stem cell technologies in the future of dentistry.[4]

Types of stem cells (Figure 1)**: -**

Embryonic stem cells: Embryonic stem cells are derived from the inner cell mass of the blastocyst containing 50 to 150 cells. They differentiate into cells of all three germ layers:ectoderm, endoderm, and mesoderm. More than 200 of any particular adult cell type can be produced upon given appropriate and necessary stimulation. They do not have any contribution to the extra-embryonic membrane or placenta. They have the disadvantage of increased tumorigenesis potential, making their use less favorable.[5,6]

Adult stem cells: They are also called somatic or postnatal stem cells that exist throughout the body after embryonic development and are also found inside different tissues. They are multipotent. They are usually derived from bone marrow, umbilical cord, amniotic fluid, brain tissue, liver, pancreas, cornea, dental pulp, and adipose tissue. These cells are commonly used in current-day practice because immune rejection and teratoma formation are rare with adult stem cells.[7]

Mesenchymal stem cells: These cells are also called mesenchymal stromal cells, another type of adult stem cells. They are multipotent and are derived from bone marrow, skin, oral and maxillofacial structures, and adipose tissue. These cells can be used autologously without concern for immune rejection. They can be isolated from patients who need the treatment.[5,6]

Adipose-derived stem cells: These cells are extracted via liposuction, lipectomy, or lipoaspiration and are subsequently isolated.[8] They are abundant and accessible easily and are multipotent with a broad lineage after differentiation.[9]

Umbilical cord-derived stem cells: These are adult stem cells, and they are derived from the umbilical cord blood. [8]

Amniotic fluid-derived stem cells: These cells are isolated either at the time of delivery or duringa procedure of amniocentesis for genetic screening during gestation.

Bone marrow-derived mesenchymal stem cells (BMSC): These are adult stem cells found in the bone marrow and originate from the embryonic mesoderm. They are widely used now days in clinical practice dueto their multipotency. BMSC can form cementum, PDL, and alveolar bone in-vivo after implantation into periodontal defects. Thus, they provide an alternative source of MSC for treating periodontal diseases. [10, 11]

Induced pluripotent stem cells: Induced pluripotent stem cells (iPSC) is an emerging concept in which 3–4 genes found in the stem cells are transferred to the donor cells using appropriate vectors. These cells resemble to embryonic stem cells in their potential to divide. The stem cells thus derived by culturing will have properties almost like embryonic stem cells4 This path-breaking discovery may have a significant role in future stem cell therapy.[6]

Dental pulp-derived stem cells (DPSC): Most common source of dental tissue-derived stem cells. They have the potential to differentiate into osteogenic, odontogenic, myogenic, adipogenic, and neurogenic components both in-vitro and in-vivo as well. They can also produce pulp-dentin complex in-vivo. [13, 14]

Stem cells from human exfoliated deciduous teeth (SHED): These stem cells are derived from exfoliated teeth and exhibited more proliferative differentiation than dental pulp-derived stem cells. They have the potential to differentiate into neurogenic, adipogenic, odontogenic components and are used for tissue regeneration involving orofacial bony structures. They contain MSC markers such as STRO-1 and CD 146 andneuronal and glial markers such as Nestin and β III Tubulin, which can produce bone and dentin in-vivo. [13]

Periodontal ligament stem cells (PDLSC): These stem cells are derived from separated periodontal ligaments of third molars in humans. They specially contain progenitors for self-renewal of oral structures like cementum and bone. They are differentiated into adipogenic, chondrogenic, and osteogenic components in-vitro and cementum and periodontal ligament in-vivo. They contain MSC markers also such as STRO-1, Muc 18, CD 44, and CD 146. [15]

Dental follicle stem cells (DFSC): These stem cells are derived from the follicle surrounding human third molars. They are pluripotent and composed of ectomesenchyme and contain Notch1, STRO-1, and Nestin markers. They can differentiate into osteoblasts, adipocytes, and neuroblasts in-vitro and periodontal ligament in-vivo. [16]

Stem Cells from Apical Part of Papilla (SCAP): These cells are derived from the apical part of a developing tooth and have high proliferation, migration, and regeneration capabilities. They contain both fibroblast-like and odontoblast-like cells and also contain MSC markers such as STRO-1,CD 24, CD 44, and CD 146. They have the potential to differentiate into the pulp-dentin complexin vivo. [15]

Oral mucosa-derived stem cells: They may either be oral epithelial stem cells or gingival stem cells. The oral epithelial stem cells generally are unipotent and develop only into epithelial cells in-vivo. They develop a well stratified oral mucosal graft when used ex-vivo. They are used for grafting procedures involving oral structures. Gingival stem cells are also multipotent. They have reprogramming capabilities, are more abundant, are easy to isolate, and have a rapid ex-vivo proliferation that makes their use clinically viable. [17]

Human dental epithelial stem cells (hDESC): They are derived either from third molars or the epithelial sheaths that disintegrate into the rest of Malasez. They express different epithelial stem cell markers such as p75, E-CAM, and Bmi-1 along with embryonic stem cell markers like Nanog andOct-4. [15]

Periosteum-derived stem cells: Human periosteum-derived stem cells are also multipotent with odontogenic, chondrogenic, adipogenic, and myogenic potential in-vitro and in-vivo as well. They produce cortical bone and are therefore used to regenerate significant congenital or surgical defects in the orofacial region. [17]

Salivary gland-derived stem cells: Cells derived from the salivary gland can differentiate into duct cells andacinar cells in-vitro and retain the capacity to produce both mucin and amylase as well. Therefore, they can be used to rehabilitate patients with reduced salivary gland function following irradiation.

It is really an arduous job to isolate the cells exists since the harvested cells contain the parenchymal, stromal, and blood vessel cells. [17]

Dental stem cell therapy:

Dental stem cell therapy aims to restore the anatomy and function of damaged or lost tissue through regeneration. Goals of regenerative dentistry include continuation of root formation, regeneration of pulpal tissues, reconstruction of the periodontium, aiding in transplantation and replantation, root bio-engineering, and engineering of the pulp-dentin complex. In order to obtain stem cells, an appropriate process of collection, isolation, culture, and replication has to be established. SHED is banked stem cells. [18]

Collection and isolation of dental stem cells:

The prime source of stem cells such as a tooth with a vital pulp with optimum blood supply,follicle, periodontal ligament, apical tissue, etc., are immediately taken to the culture lab in a transport medium after tooth extraction or exfoliation. As these cells have obvious characteristics and a single tooth can have multiple tooth tissues to obtain from stem cells, these tissues are isolated in the cell culture lab in a sterile environment. From the dental tissues, stem cells can be collected by enzymatic or mechanical dissociation. After enzymatic and mechanical dissociation, stem cells are put in a culture medium for growing on plastic flasks or dishes.[19](Figure.2)

Application in Prosthodontics:

Tooth regeneration/ Bio-engineered tooth: The regeneration of adult teeth will be possible with the help of bioengineering. This can be a substitute for dental implants. Tooth regeneration requires epithelial-mesenchymal exchanges. It includes the reciprocal exchange of signals between the two germ layers, which leads to form inimitable terminal phenotypes with their supporting cells. Inductive morphogens, stem cells, and scaffolds are generally the critical elements in tooth regeneration. [20]

Tooth regeneration involves the following steps:

At first, the adult stem cells are harvested and spread out. An optimized environment for growth is created by seeding the stem cells as scaffolds.Targeted soluble molecular signals are provided to the cells. For odontogenesis purpose, the gene expression profile is confirmed by the cells.

Periodontal regeneration: Regeneration of periodontal tissue always shows challenges because it includes soft and hard tissues. Allografts, autologous bone grafts, or alloplastic materials of contemporary techniques have definite restrictions. They are not suitable for all clinical conditions. Therefore, the therapeutic alternative is a cell-mediated bone regeneration technique. Kawaguchiet al. and Hasegawa et al. stated that periodontal ligament cells cultured in-vitro were effectively reimplanted into periodontal defects in animals to countersign periodontal regeneration. Resultant studies by them proposed a parallel approach in humans. These studies presented specific evidence that stem cells regenerate tissue as complex as the periodontium.[21] (Figure.3). In this modern era, implants have outmatched fixed and removable partial dentures for replacing missing teeth and to restore the functions. Still, problems exist with the implants because of lacking the periodontal ligament. Inflammation around the implants may lead to bone loss than does the inflammation around the natural tooth, having periodontal ligament. This can be solved if implants with PDL are developed and this can be achieved bythe concept of **Ligaplants,** which is the combination of bio-engineered ligament tissue with implant biomaterial.

Craniofacial Regeneration: Dental-derived mesenchymal stem cells are encapsulated in a suitable scaffold-like alginate hydrogel. These cells are subjected to molecular signaling. This cell therapy is used in craniofacial tissue augmentation. Clinical and laboratory analyses of treatment sites demonstrated that cell therapy accelerated the regenerative response of applied sites. [22, 23] (Figure.4)

Regeneration of Alveolar bone: Mesenchymal condensation by segregation of mesenchymal stem cells is seen in the development of bone. This includes both intramembranous and endochondral bone formation mechanisms. During adulthood, bone possesses the intrinsic potential for regeneration throughout life. In most bone injuries (fractures), the damaged bone tissue can be functionally regenerated by the local multipotent cells (including chondroblasts, osteoblasts, endotheliocytes, and fibroblasts). When the fractures are serious (such as comminuted fractures, infection, tumor resection, and skeletal abnormalities) enough that self-healing in not enough to repair, an adequate supply of stem cells (such as bone marrow stem cells) is required for optimum bone regeneration. So, the adequate quantity of stem cells is the prime to regenerate efficient bone. [24] Oral mesenchymal stem cells exhibited better potential for bone regeneration [25]. (Figure.5)

Chair side cellular grafting approach [26]: - In 2006, Smiler and Soltan first reported a technique for chair-side cellular graft preparation with the utilization of freshly aspirated bone marrow from the iliac crest that was mixed with a resorbable matrix, and they also showed bone marrow aspirate that was transplanted with biocompatible scaffolds or allograft bone blocks could successfully regenerate bone.

Thereafter, cellular grafting approaches using the mononuclear fraction obtained from processed fresh marrow have been well documented till date. This method has been developed as a system is known as ‘‘Bone Marrow Aspirate Concentrate (BMAC)’’. The mononuclear fraction consists of two principal lineages of stem cells; the first one is responsible for hematopoiesis and another regarded as an MSC population. The chair-side preparation of MSCs and combination with BBM (bovine bone mineral, Bio-Oss) particles have been shown to form lamellar bone and provide a reliable base for implants.

Application of stem cells in implant dentistry: Dental implants are quickly gaining popularity as a means of partial or full mouth tooth reconstruction. Approximately 3-4 million implants are placed every year worldwide, and 60% of the implant sites deficit of enough height and width of the residual alveolar ridge due to resorption following tooth loss. The lack of adequate alveolar bone height is a severe impediment to dental implant placement. The aim is to develop new dental implant systems consisting of biomaterial scaffolds, in conjunction with bone-inducing agents and dental implants, which have the capacity to guide vertical bone regeneration. In a study by Nicole Y. C. Yu et al. on rats to check the efficacies of various dental implant systems, the most significant formation of new bone was observed in those animals that received biomaterial scaffolds (polymer or ceramic composite scaffold) in addition to the osteogenic factor BMP-2. Combining bone-inducing growth factors with a biomaterial scaffold is a promising procedure to improve osseointegration around dental implants. In another experiment, they reported that on applying a protein directly on to implant, they could achieve thatthese proteins could direct endogenous stem cells to become bone-forming cells. This led to a complete regeneration of lost tissue. [27] (Fig-6)

Mandible condyle regeneration: Injury to the temporomandibular joint disc or condyle (condylar osteochondral defect) arising from trauma or arthritis can result in lifelong pain and disturbed masticatory performance for patients. Tissue regeneration technique on these defects can hold the potential to affect the quality of life of these patients.

In a goat jaw model, the combination of cartilage tissue engineering using cartilage-derived progenitor cells carried in a hydrogel and distraction osteogenesis was successfully utilized to reconstruct condylar osteochondral defects. [28]

A human anatomically shaped mandibular condyle was successfully engineered from chondrogenically and osteogenically induced rat BMSCs encapsulated in a biocompatible polymer applied in the defect region. Mesenchymal stem/stromal cells (MSCs) were isolated from femoral and tibial bone marrows of adult rats and they were exposed separately to either chondrogenic or osteogenic supplemented culture medium. MSC derived chondrogenic and osteogenic progenitor cells were encapsulated in PEGDA hydrogel into a negative mold of an adult human cadaver mandibular condyle in two stratified and yet integrated layers. The photopolymerized osteochondral construct was implanted into the dorsum of immunodeficient mice for up to 12 weeks [29]. After 4 weeks of in vivo implantation process, de novo formation of the tissue-engineered mandibular condyles, which retained the macroscopic shape and dimensions of the cadaver mandibular condyle.

Current treatments and future challenges:-Current and expected future prosthodontic treatments for alveolar bone resorption and tooth loss. Current regenerative prosthodontic treatments are associated with difficulty in maintenance of the grafted bone height and volume. Future solutions to the challenges encountered may include a wise application of a dense cellular layer of BMSCs and induced pluripotent stem (iPSC) derived bioengineered bone to achieve vertical alveolar bone augmentation without postoperative bone loss. Bio-hybrid implants and bioengineered teeth are also expected to be providing alternatives to current osseointegrated implants. Purified BMSCs and iPSCs are expected to be emerging cell sources that enrich the scope of next-generation regenerative prosthodontics. (Fig-8)

Conclusion: Stem cell-mediated tissue regeneration presents an immense opportunity for the entire medical field. It helps to the regenerate the damaged tissues, aids in tissue grafting, or induces bone reconstruction if grafting is not feasible. Oral epithelial and mesenchymal stem cells have an excellent regenerative ability that can be applied in prosthodontics. The oral stem cells show their capability to repair the teeth, periodontal tissue, craniofacial tissues, alveolar bone,etc.

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Figures and Legends

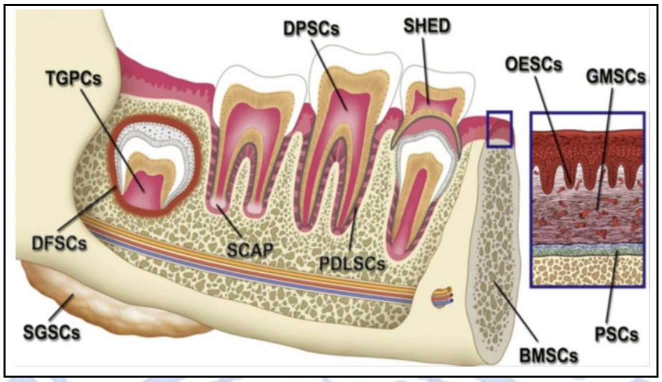

Fig 1:- Sources of adult stem cells in the maxillofacial region- BMSCs: bone marrow-derived MSCs from mandible; DPSCs: Dental pulp derived stem cells; SHED: stem cells of human exfoliated deciduous teeth; PDLSCs: periodontal ligament stem cells; DFSCs: dental follicle stem cells; TGPCs: tooth germ progenitor stem cells; SCAP: stem cells from the apical papilla; OESCs: oral epithelial progenitor/stem cells; GMSCs: gingiva-derived MSCs, PSCs: periosteum-derived stem

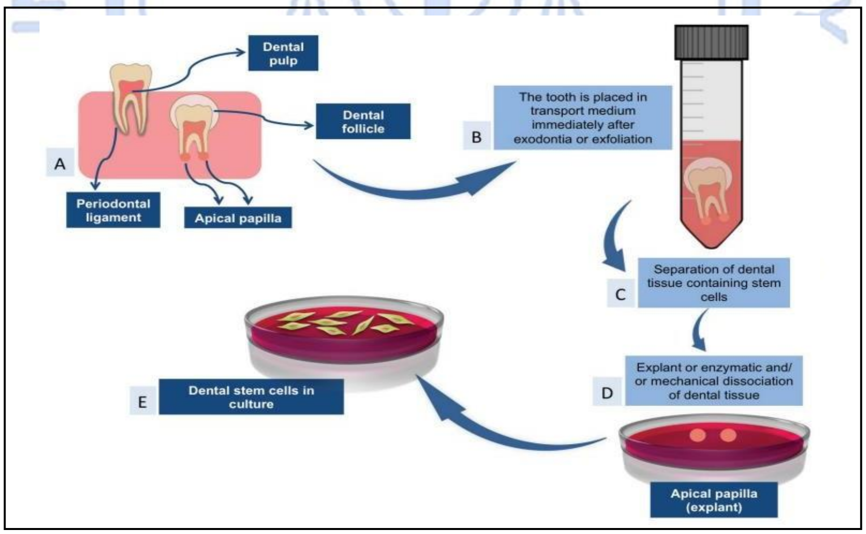

Fig-2: Collection and Isolation of stem cells

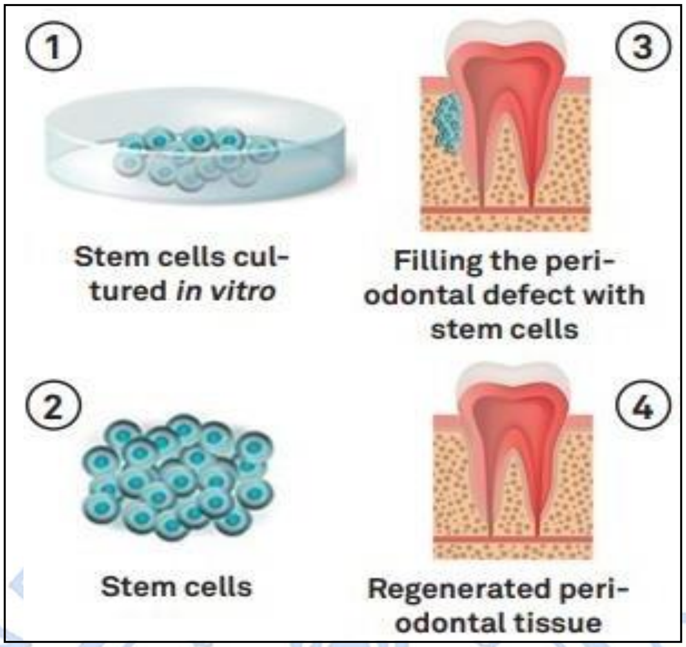

Fig-3: Periodontal Regeneration procedure

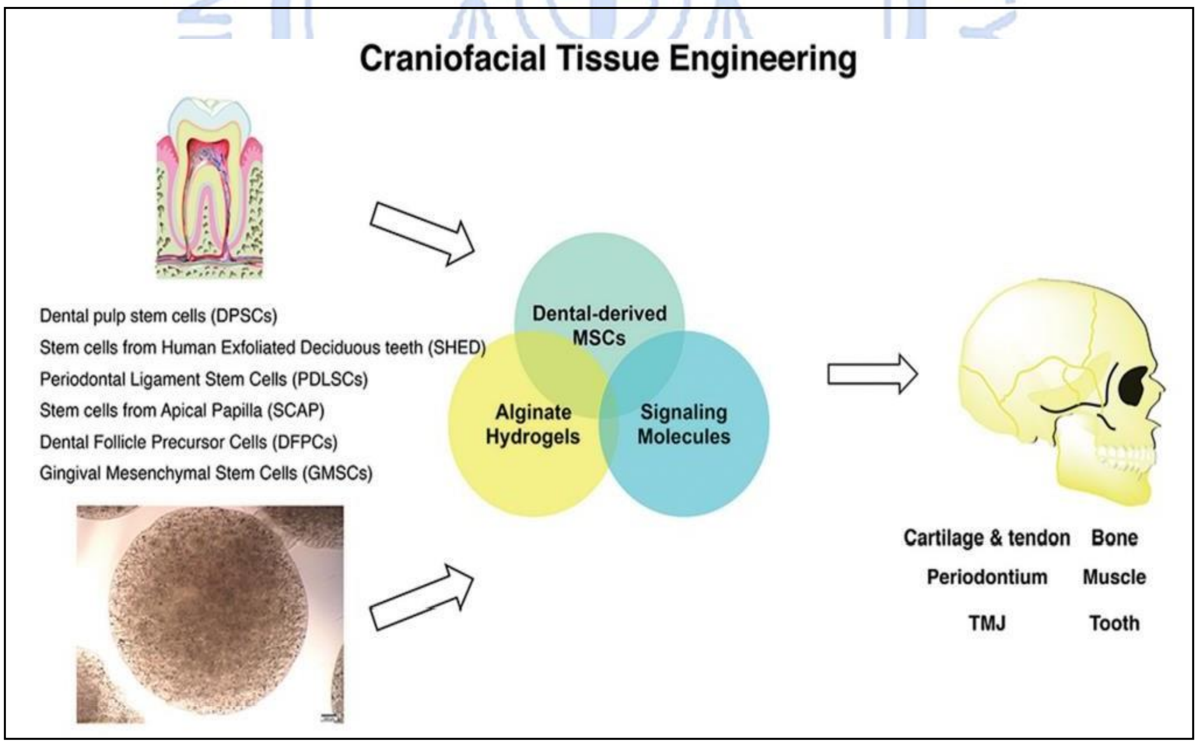

Fig-4: Craniofacial Regeneration process

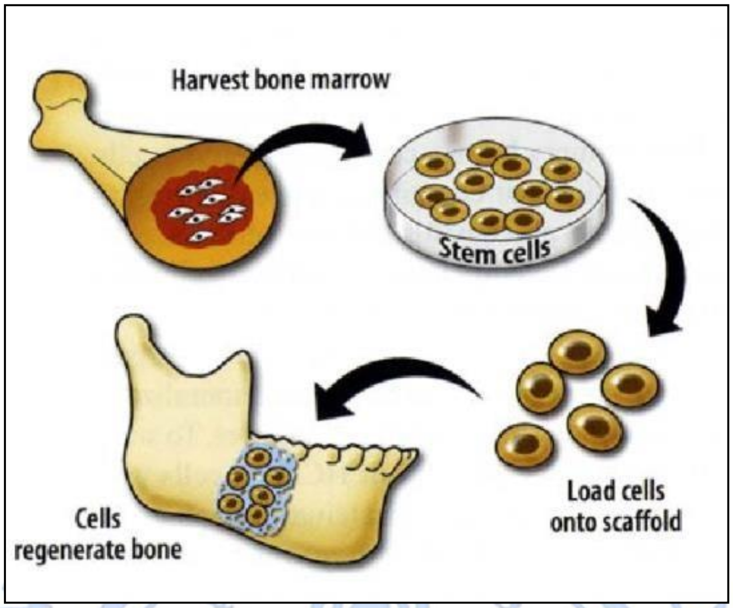

Fig-5: Regeneration of alveolar bone

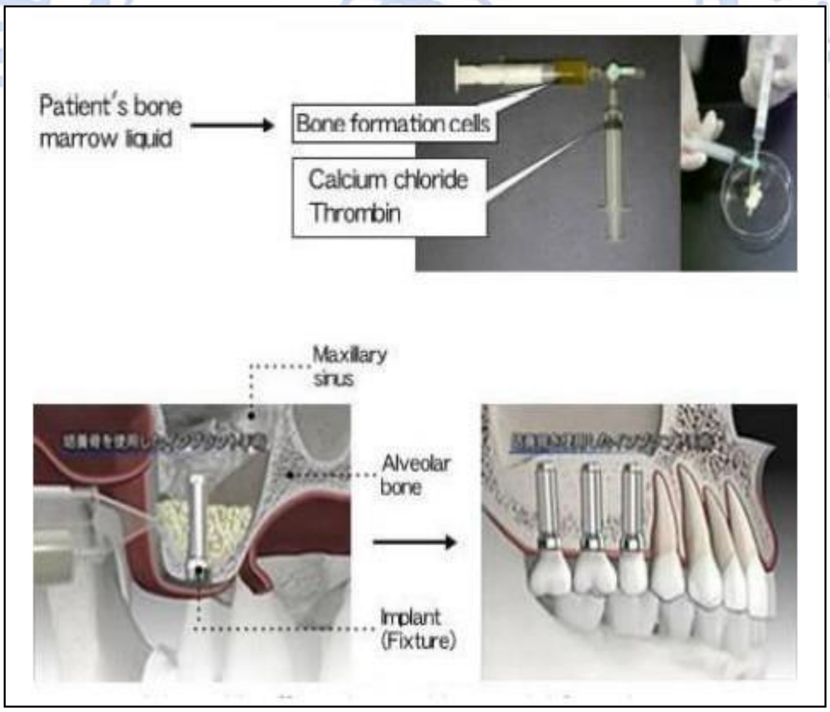

Fig-6: Application of stem cells in implant dentistry

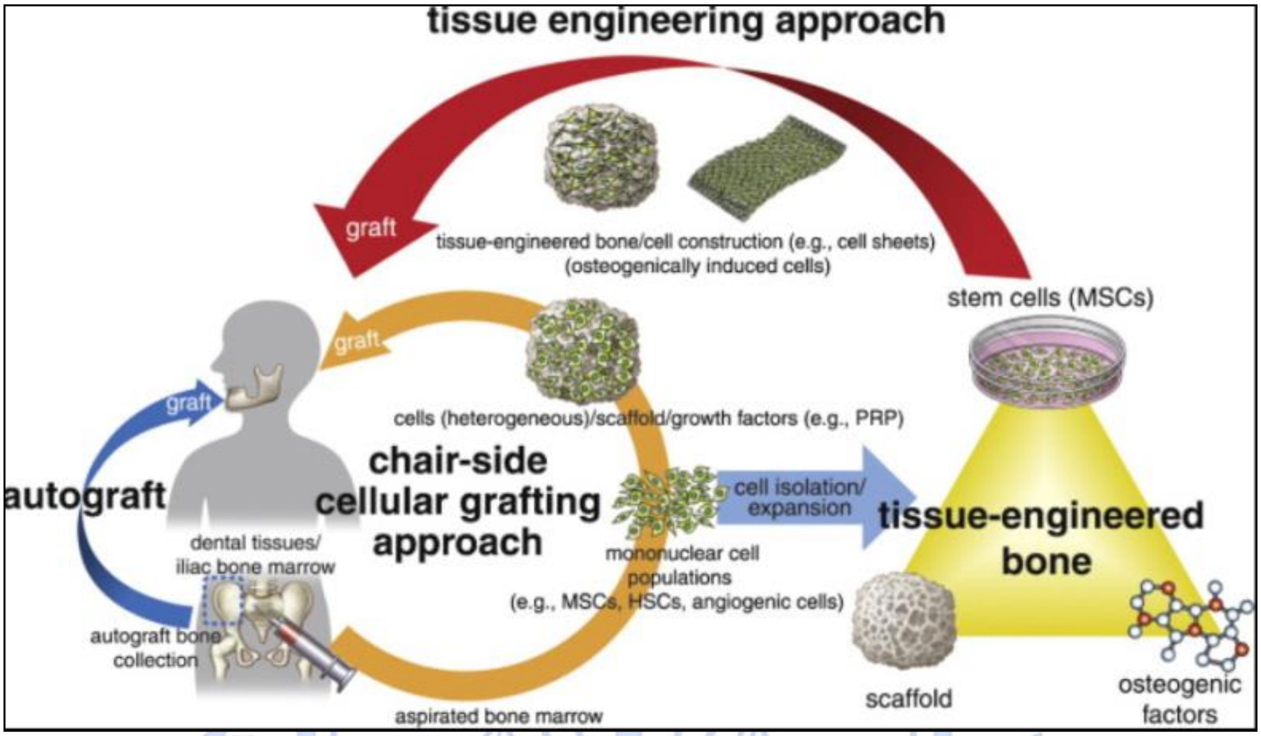

Fig- 7 Schematic diagram describing the recent clinical approaches to stem-cell-based bone augmentation. The chair-side cellular grafting approach (orange arrow) utilizes patient-derived freshly processed bone marrow (mononuclear cell population), which consists of mesenchymal stem/stromal cells (MSCs), hematopoietic stem cells (HSCs), and angiogenic cells, mixed with a scaffold and special growth factors like platelet-rich plasma (PRP), as a grafting material. The tissue engineering approach (red arrow) utilizes the MSCs, which are isolated from freshly aspirated bone marrow and expanded *in vitro*. The MSCs are further cultured with osteogenic factors rich medium and provide a scaffold to generate an osteogenic construct (tissue-engineered bone) or cell sheets as a grafting material.

Autograft bone augmentation (blue arrow) uses autologous bone collected from the illium