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Advances in Tissue Engineering and Implications for Oral and Maxillofacial Reconstruction

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Abstract

Background: Reconstructive surgery in the oral and maxillofacial region poses many challenges due to the complexity of the facial skeleton and the presence of composite defects involving soft tissue, bone and nerve defects.

Methods: Current methods of reconstruction include autologous grafting techniques with local or regional rotational flaps or microvascular free flaps, allografts, xenografts and prosthetic devices.

Results: Tissue engineering therapies utilizing stem cells provide promise for enhancing the current reconstructive options.

Conclusions: This article is a review on tissue engineering strategies applicable to specialists who treat oral and maxillofacial defects.

Practical implications: We review advancements in hard tissue regeneration for dental rehabilitation, soft tissue engineering, nerve regeneration and innovative strategies for reconstruction of major defects.

Keywords

Stem cells; oral and maxillofacial surgery; tissue engineering; nerve regeneration; organoids; reconstructive surgery

The goal for reconstructive surgery is the restoration of form, function and aesthetics. Dental and medical specialties are faced with many challenges when considering reconstruction of maxillofacial defects due to congenital deformities, trauma and benign or malignant pathology. The maxillofacial area plays a significant role in how patients define themselves and how they relate to others. Their facial appearance is an integral part of their identity, and their ability to display emotion, converse and eat are all controlled by the complex anatomic

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features in the facial skeleton. This article highlights current practices in soft and hard tissue reconstruction in the maxillofacial region and discusses advances in tissue regeneration research that have significant implications for the future of reconstructive surgery.

Many factors must be considered when deciding on the reconstructive method, including the size of the defect, the types of tissue missing, the vascular pattern present, the availability of tissue for transfer and patient and surgeon preference.[1] The current gold standard for small hard tissue defects involves nonvascularized autologous tissue transfers. Autologous block bone grafts can be harvested from the iliac crest or from intraoral sites including the mandibular ramus or symphysis.[2] Small soft tissue defects can be reconstructed with local rotational flaps. For large soft tissue or composite (both soft and hard tissue) defects, vascularized grafts (i.e., free tissue transfer) are utilized with predictable success. A large study on reconstruction with microvascular free flaps demonstrated a 95% success rate.[3] As for nerve tissue reconstruction for motor or sensory defects, autologous nerve grafts have traditionally been considered the standard of care. However, advancements in microneurosurgery have created additional surgical options including allografts, xenografts or a combination of multiple grafting modalities. Finally, there are nonsurgical restorative options for major soft and hard tissue defects, such as prosthetic devices. FIGURE 1 provides an overview of the different reconstructive options currently available for hard and soft tissue defects.

Autologous tissue transfer is unfortunately associated with multiple disadvantages. Vascularized free flap transfer is often complicated by scarring, poor color and size matching and longer surgical time.[4] A second surgical site leads to donor site morbidity such as pain and neurosensory disturbances as well as longer surgical procedures and recovery time.[2] Free flap transfers are also restricted due to limited availability of competent donor sites.[5] Because most grafts lack adequate innervation, there is also often loss of motor function and sensation.[6]

Tissue engineering is defined as “an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain or improve tissue function.”[7] Tissue engineering is an attractive alternative to the current surgical options discussed previously and relies on stem cell research. Stem cells are capable of self-renewal and differentiation to a more specialized cell type. They can be classified into three different groups based on this differentiation potential. Totipotent stem cells are able to form an entire embryo, including the extraembryonic tissues. Pluripotent stem cells can differentiate into any of the three germ cell layers (endoderm, mesoderm, ectoderm). A special type of pluripotent stem cell is “induced” pluripotent stem cells (iPSC) that can be generated directly from adult cells. Unipotent or progenitor stem cells are limited to one defined cell type.[8]

Possible applications of tissue engineering in oral and maxillofacial surgery include hard tissue regeneration for dental rehabilitation, soft tissue engineering, nerve regeneration and the reconstruction of major defects, with the possibility of eventual organoid fabrication and utilization (FIGURE 2). We will discuss some of the challenges and advances in tissue engineering for each of these categories. The purpose of this article is to provide a succinct

overview of several recent advances in tissue engineering in oral maxillofacial surgery for dentists across multiple specialties.

Hard Tissue Engineering

The restoration of bony defects continues to remain a challenge in dental rehabilitation. While autogenous grafts have been shown to be successful in repairing some of these defects, the associated donor site morbidity has encouraged research into other more innovative options. Some studies have demonstrated improved clinical outcomes with the use of stem cells and tissue engineering. Bone marrow derived mesenchymal stem cells (BMDSCs) and adipose derived mesenchymal stem cells (ADSCs) have been shown to induce improved bone formation in animal and human models when compared to no treatment or acellular management strategies.[5] Rickert et al. utilized a split-mouth design to compare implant stability in maxillary sinuses augmented with Bio-Oss treated with mesenchymal stem cells to Bio-Oss treated with autogenous bone. The authors found mesenchymal stem cells induced bone comparable to that of autogenous bone.[9] Osteocel, which contains mesenchymal stem cells seeded on demineralized freeze-dried bone allograft, has been used for sinus grafting and implant site development.

A systematic review by Al-Moraissi et al. reported no significant increase in bone formation between tissue-engineered bone using mesenchymal stem cells and conventional bone grafts at three to four months, but a statistically significant increase in bone in the tissue-engineered bone group at six months. Additionally, there was no difference found in residual graft particles, connective tissue, bone gained or implant failure rate.[10]

Stem cells also hold promise for implant therapies and peri-implant defects. A study on the efficacy of adipose-derived stem cell-impregnated scaffolds in dogs demonstrated a significant increase in bone regeneration in peri-implant marginal gaps when used at the time of implant placement.[11] In a clinical trial of 11 patients using BMDSCs combined with biphasic calcium phosphate granules for horizontal ridge augmentation, there were significant increases in alveolar width and volume sufficient for the placement of implants in all patients.[12] However, studies by Rickert et al. reported decreased implant survival compared to autologous grafting techniques with survival rates of 91% and 100%, respectively, within the first 12 months.[13] Furthermore, a systematic review of the literature of stem cell use in maxillary sinus augmentation by Niño-Sandoval et al. showed that stem cells, when compared to other graft types, did not lead to a significant difference in multiple outcome measures including implant survival rate, bone height, marginal bone loss following implant placement or new bone formation.[14]

Alveolar clefts are another type of hard tissue defect that could benefit from stem cell therapy. Alveolar clefts are formed when there is improper fusion of the maxillary prominences during the fifth and sixth weeks of gestation.[15] Tissue engineering may eventually offer an alternative to autologous bone grafts to limit morbidity associated with the donor surgical site. Preclinical studies in animal models provided promising results regarding the use of stem cells to augment bone formation across alveolar clefts.[16] Zhang et al. showed that mesenchymal stem cells combined with a beta-tricalcium phosphate scaffold

were as effective in bone generation as autologous bone in a dog model and allowed for adequate bony support for orthodontic movement.[17]

While clinical trials are lacking, many case reports have demonstrated efficacy of stem cells in bone formation in alveolar clefts in humans.[16] The incorporation of mesenchymal stem cells not only improved bone formation but also allowed for tooth eruption in multiple case studies.[18,19] Further studies confirmed the usefulness of stem cells in improving alveolar cleft defects to allow for orthodontic tooth movement.[20,21] While most studies have not provided long-term follow-up, Chai et al. showed that bone formed utilizing BMDSCs and demineralized bone matrix was maintained for up to three years.[22] Although many of the studies using stem cells for the regeneration of bone in alveolar clefts have been promising, one randomized control trial in patients with horizontal alveolar bone deficiencies demonstrated that stem cells had limited efficacy in larger alveolar defects.[2]

While artificial transplant materials such as hydroxyapatite or beta-tricalcium phosphate are another alternative to autografts, their use has been limited due to mixed clinical outcomes, especially in studies involving orthodontic movement.[23] A study in dog models demonstrated significantly improved bone formation when stem cells were added to carbonated hydroxyapatite (CAP) versus CAP alone with improved radio-opacity in the experimental sites. They also demonstrated significantly greater numbers of capillary vessels on the experimental side, implying that stem cells may also improve vascularity in the newly formed bone, posing a promising adjunct to artificial transplant materials.[24]

While the current literature shows much promise for the use of stem cells as an alternative therapy for bone augmentation and improvement of hard tissue defects, there are major variations in reports of their success rates. Additionally, autologous grafts still demonstrate superiority compared to stem cell-engineered grafts, although this finding varies from study to study.[25] There is a need for further studies and optimization of stem cell protocols and therapies before they become a widely used treatment in dental rehabilitation and alveolar clefts.

Soft Tissue Engineering

Innovations in tissue engineering have produced the ability to create different tissue types such as skin, mucosa, bone and cartilage.[26] Autologous-engineered skin substitute grafts have been used widely in burn victims, especially in those patients who have limited healthy skin sites for autologous grafting.[27] However, skin is a complex structure composed of epidermis, dermis, vascular plexus, melanocytes and hair follicles. Currently, no engineered substrates can truly replicate this complexity.[28] Comparatively, oral mucosal equivalents have also been fabricated using tissue engineering. Izumi et al. reported enhanced maturation of the submucosal layer and vascular ingrowth using a tissue-engineered oral mucosa construct in patients with premalignant or cancerous lesions when compared to AlloDerm alone.[29]

Soft tissue constructs composed of different tissue types have remained more elusive. Mucocutaneous human tissue constructs have been fabricated to replicate tissues with a

mucocutaneous junction, such as the vermilion of the lip.[30] Kim et al. further developed a mucocutaneous construct in vitro that was then grafted over the latissimus dorsi muscle in rats in an attempt to create a prelaminated musculocutaneous flap for lip reconstruction. This served to develop a mature trilaminar flap that could then be harvested and placed into the defect site.[26] These constructs hold promise for the ability to restore complex soft tissue defects with better function and aesthetics than current options allow.

Tissue engineering has also been evaluated for its possible therapeutic effects in gingival defects. The utilization of stem cell therapy may help overcome limitations of free gingival and connective tissue grafts, such as donor site morbidity and limited tissue for grafting.[31] One study of five patients with missing keratinized mucosa or mucogingival defects showed a gain of keratinized gingival width, but no significant change in probing depths.[32] A systematic review by Gaubys et al. reported that stem cell therapy had the ability to enhance periodontal ligament and cementum regeneration.[33] A more recent study evaluated the ability of a stem cell impregnated membrane to improve gingival recession when compared to membrane alone; however, the differences in gingival recession and keratinized gingiva remained nonsignificant between the treatment groups. The only significant finding was improved root coverage in the stem cell impregnated membrane group.[34]

Although soft tissue engineering modalities hold potential for regeneration and reconstruction of soft tissue defects in the oral and maxillofacial region, clinical studies focused on soft tissue engineering are limited when compared to the literature on hard tissue engineering. Well-designed clinical trials are needed to develop efficacious and viable treatment options that utilize stem cell therapies.

Nerve Regeneration

Dysfunction of the trigeminal or facial nerve following injury or disease of the maxillofacial region is significantly distressing and debilitating for patients. It can lead to paresthesia or dysesthesia, dysgeusia, paralysis of the muscles of facial expression, inability to chew and maintain lip and cheek competence and altered speech patterns. In cases of trigeminal nerve injury, the inferior alveolar nerve is most frequently affected, followed by the lingual and infraorbital nerves.[35] Initial treatment options for trigeminal nerve injury without indications for immediate surgical intervention are often pharmacological, using medications such as NSAIDs or antiepileptic drugs like gabapentin or carbamazepine. Other options such as local and regional anesthesia have also been used. Low-level laser therapy has also demonstrated efficacy, but the effect is decreased with time from injury.[36,37]

Microneurosurgical repair with end to-end anastomosis or grafting procedures are explored in circumstances where nonsurgical options are ineffective. However, neurorrhaphy can be challenging in cases of inferior alveolar nerve injury due to a limited ability to advance the nerve across a gap without tension. Grafting procedures include the use of both allogenic or autologous nerve grafts.[38] One commercial decellularized allogenic nerve graft is available, which is heavily marketed among surgical specialists who perform sensory or motor nerve repair. Studies using allogenic nerve graft show some success in the repair of nerve defects and reinnervation of distal targets with the allograft comparable to that seen with autografts.

But the effect is diminished in longer gaps when utilization of an allograft would be most beneficial.[39,40]

Cell-based therapies pose a promising alternative treatment option that would minimize some of the disadvantages associated with autologous nerve grafts, such as donor site morbidity, neuroma formation and limited length of available grafts.[39] Bone marrow-derived mesenchymal stem cells can differentiate into myelinating cells and support nerve fiber regeneration.[41] ADSCs have also been shown to physically engraft and myelinate regenerating axons and are comparable to BMDSC in in vivo studies.[42]

BMDSCs can be induced to express neural stem cell markers. Studies utilizing pre-differentiated stem cell transplantation showed they accelerated regeneration of transected axons and achieved improved myelination that was comparable to the results observed after Schwann cell transplantation.[43,44] However, contrasting studies showed primary Schwann cells were significantly better than BMDSCs and ADSC-loaded conduits at promoting distal stump sprouting.[42]

De Carvalho Raimundo et al. demonstrated improved whisker movement and eyelid closure in rats following nerve injury with a 5 mm gap when stem cells were injected into the polyethylene conduit connecting the two segments. The study also demonstrated improved nerve fiber area and myelin sheath thickness in the stem cell groups.[45] Another study by Choi et al. compared the effectiveness of nerve repair in a 15 mm defect in rabbits between a vein conduit with BMDSCs to a vein conduit alone. The vein conduit filled with BMDSCs demonstrated superiority in axon formation, the number of nerve fibers generated and the diameter of the nerve fibers.[46]

Stem cells also play a role through other supporting measures for nerve regeneration. They can secrete a variety of growth factors, such as nerve growth factor, brain-derived neurotrophic factor, vascular endothelial growth factor and glial cell-derived neurotrophic factors, that act as neurotrophic molecules to help provide a beneficial microenvironment for neural cell survival and neurogenesis. Additionally, they synthesize myelin proteins that serve to enhance myelination and function of the regenerated nerves.[47]

While many of the current in vitro and in vivo studies provide promising results for the use of tissue engineering in nerve regeneration, few clinical trials have been conducted.

Reconstruction of Major Defects

Microvascular reconstruction of large defects in the oral and maxillofacial regions is the current standard of care for restoration of form and function, as it provides the most predictable results. It allows for the regeneration of both hard and soft tissue and carries its own blood supply, which is crucial in defects where a sufficiently vascularized tissue envelope may not be feasible due to lack of adequate healthy tissue, such as in traumatic or oncologic defects. Despite the improvements osteocutaneous flaps provide, donor site morbidity, limited tissue availability and compromised aesthetics due to mismatch in tissue color and dimension prove to be challenging (FIGURE 3).

Tissue engineering may provide an alternative for the repair of these large defects. However, there are significant challenges that need to be addressed before this becomes a viable treatment option. Large tissue-engineered constructs created in vitro have a limited vascular supply that is unable to support the constructs and prevents their utilization in clinical settings.[48] One method to overcome this problem is the use of in vivo bioreactors composed of nondegradable custom-shaped chambers filled with either osteoconductive or osteoinductive materials. Allowing the graft to mature in vivo generates a tissue-engineered vascularized graft that can then be harvested and transferred with a vascular pedicle for reconstruction (FIGURE 2).[49]

Kasper et al. summarized the case reports of five different prefabricated vascularized free flap approaches in patients. While all the reports demonstrated bone formation within the in vivo bioreactor chambers, two out of five of the constructs failed or required significant revisions.[49] Cheng et al. designed a prefabricated bone graft that was transferred to a mandible that had deficient bony dimensions for implant placement following fibula free flap. The transferred tissue was able to maintain dental implants at 16 months, although the patient eventually died of hepatocellular carcinoma before the implants could be restored.[50]

Two other case reports described restoration of large mandibular defects (angle-to-angle and parasymphysis-to-retromolar region) that were restored using tissue-engineered constructs utilizing in vivo bioreactors. The first study by Orringer et al. in 1990 created a mandibular-shaped polyurethane tray packed with autograft from the iliac crest combined with human bone morphogenetic protein (BMP). The prefabricated graft was used to restore the mandible and lower lip.[51] In the second case report, Warnke et al. used a titanium mesh scaffold filled with mineral bone blocks coated with BMP and augmented with bone marrow aspirate from the iliac crest. The graft was implanted into the latissimus dorsi muscle for seven weeks, then harvested with a vascular pedicle containing the thoracodorsal artery and vein and transplanted to the area of defect. The case report only described up until postoperative week four at which time the patient recovered some masticatory ability, even though he remained edentulous at that time.[52]

These studies lead to questions about the possible fabrication of organoids for the maxillofacial region. Organoids are “self-organizing 3D structures grown from stem cells that mimic the in vivo architecture and multilineage differentiation of the original tissue in mammals.”[53] Various studies have demonstrated that organoids can be produced from multiple different types of stem cells including embryonic, adult and patient-derived pluripotent stem cells. It is theorized that these organoids could be utilized for cancer research, drug screening and eventually reconstruction.[54] However, at this time none have been transplanted into patients. Furthermore, while there are lingual and salivary gland organoids, there are no mandibular or bony organoid constructs.[55,56]

While the development of prefabricated flaps and organoids presents exciting possibilities for the future of reconstructive and regenerative medicine, there is still significant preclinical research to be performed before we could even begin to plan clinical trials. Organoids could represent an alternative to the in vivo bioreactor approach, but there are still few applications for the oral and maxillofacial surgeon. Ultimately, the goal is to produce viable constructs

for large multitissue maxillofacial defects that would abolish the need for vascularized free flaps altogether.

Conclusions

Despite the promise that stem cell therapy holds, it is not without limitations. Tissue engineering still requires the harvesting of autologous bone cells, which has associated donor site morbidity; however, the collection procedures are less invasive and traumatic than autograft harvesting.[14,47] Obtaining stem cells may or may not require general anesthesia or sedation, depending on the selected site for cell collection.

Prefabricated flaps also still require multiple staged procedures for the implantation of the construct and eventual transfer. Additionally, because the grafts utilizing an in vivo bioreactor are buried beneath the skin as they mature, they are not visible for observation and rely on alternative modalities such as Doppler ultrasound to monitor their maturation.[26] Currently, stem cell therapies are inefficient, as they require culturing and expansion, especially in grafts requiring vascularity and perfusion.[6] This extended treatment timeline is impractical in patients who have large oncologic defects, as they will need to be reconstructed with a reliable vascularized graft prior to adjuvant radiation and chemotherapy.

There is also concern for tumorigenic potential of stem cells because they share many characteristics with cancer cells.[17] Both have long life spans with abilities to self-renew and replicate for long periods of time.[57] For example, in one study of a rat model with sciatic nerve injury transplanted with neural stem cells, 25% developed large neuroblastoma-like tumors.[58] The degree of differentiation of the stem cell may play an important role in determining the true risk of malignant transformation.[57]

Tissue engineering using stem cell therapies represents an innovative step forward in regenerative medicine. As we continue to search for ideal methods to restore form, function and aesthetics in the maxillofacial region, there is much hope that these treatment modalities will provide viable alternatives to the current restorative options. Currently, there are limited publications regarding the utilization of tissue engineering in patients, especially for complex soft tissue constructs. Furthermore, there are many variations in protocols used with no consensus on the optimal harvesting and isolation techniques.[14] There are also few studies evaluating long-term stability of tissue-engineered constructs.[16] These limitations highlight the importance of focused and thoughtful research in tissue engineering to optimize and standardize protocols before stem cells can be used routinely in clinical practice.

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C.E. CREDIT QUESTIONS

November 2021 Continuing Education Worksheet

This worksheet provides readers an opportunity to review C.E. questions for the article “Advances in Tissue Engineering and Implications for Oral and Maxillofacial Reconstruction” before taking the C.E. test online. You must first be registered at cdapresents360.com. To take the test online, please click here. This activity counts as 1.0 of Core C.E.

1. Which of the following is not associated with autologous tissue transfer?:

- **a.** Multiple options for competent donor sites
- **b.** Poor color and size matching of vascularized free flap
- **c.** Pain and neurosensory disturbances at donor site
- **d.** Longer recovery time

2. Which of the following stem cells classifications is able to form an entire embryo?

- **a.** Pluripotent
- **b.** Totipotent
- **c.** Unipotent or progenitor
- **d.** An induced pluripotent (iPSC)

3. A literature review of stem cell use in maxillary sinus augmentation, when compared to other graft types, showed that stem cell grafts were comparable in which of the following areas?

- **a.** Implant survival rate
- **b.** Bone height
- **c.** New bone formation
- **d.** All of the above

4. Stem cells show promise for supporting nerve regeneration because of their ability to do which of the following (mark all that apply)?

- **a.** Secrete nerve growth factor
- **b.** Secrete vascular endothelial growth factor
- **c.** Regenerate transected axons
- **d.** Synthesize myelin proteins

5. Organoids are “self-organizing 3D structures grown from stem cells that mimic the in vivo architecture and multi-lineage differentiation of the original tissue in mammals.” Which of the following statements about organoids is incorrect?

a. They can be produced from multiple different types of stem cells.

b. They are currently being utilized for cancer research.

c. There are salivary gland organoids.

d. There are not yet bony organoids.

6. True or False:

A promising method for overcoming the lack of vascularity of large, in vitro-created tissue-engineered constructs is to instead allow the tissue to mature in vivo bioreactors filled with bone conductive or inductive materials.

7. Preliminary results from stem cells studies used for alveolar cleft repair show promise for which of the following (mark all that apply)?

a. Augmenting bone formation across alveolar clefts

b. Improving the vascularity of newly formed bone

c. Superiority to autologous grafts

d. All of the above

8. Which stem cells have been shown to physically engraft and myelinate regenerating axons?

a. Adipose-derived mesenchymal stem cells

b. Bone-derived mesenchymal stem cells

c. Nerve-derived mesenchymal stem cells

9. Cell therapies pose a promising alternative treatment option that may minimize which of the disadvantages associated with autologous nerve grafts (mark all that apply)?

a. Donor site morbidity

b. Neuroma formation

c. Limited length of available grafts

d. None of the above

10. True or False

Though reviews are mixed, autologous grafts still demonstrate superiority compared to stem cell-engineered grafts. Hence, there is a need for further studies and optimization of stem cell protocols and therapies before they become a widely used treatment in dental rehabilitation and alveolar clefts.

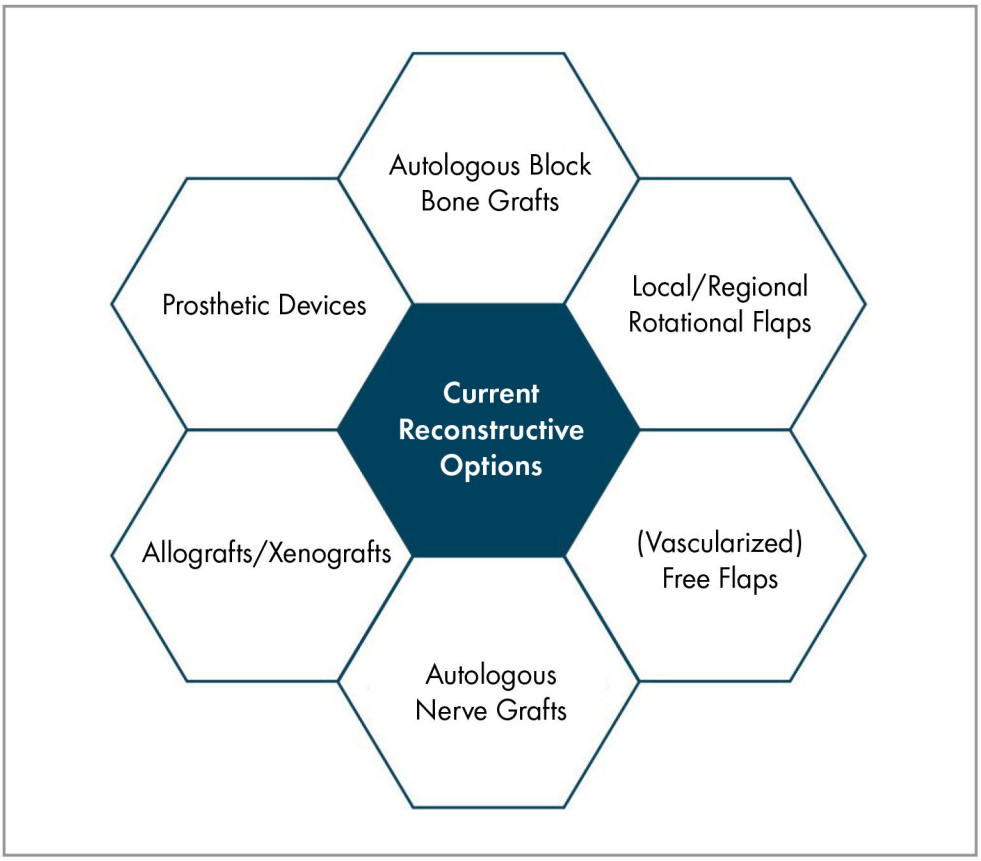


FIGURE 1.
Schematic summarizing current options for reconstructive treatment modalities.

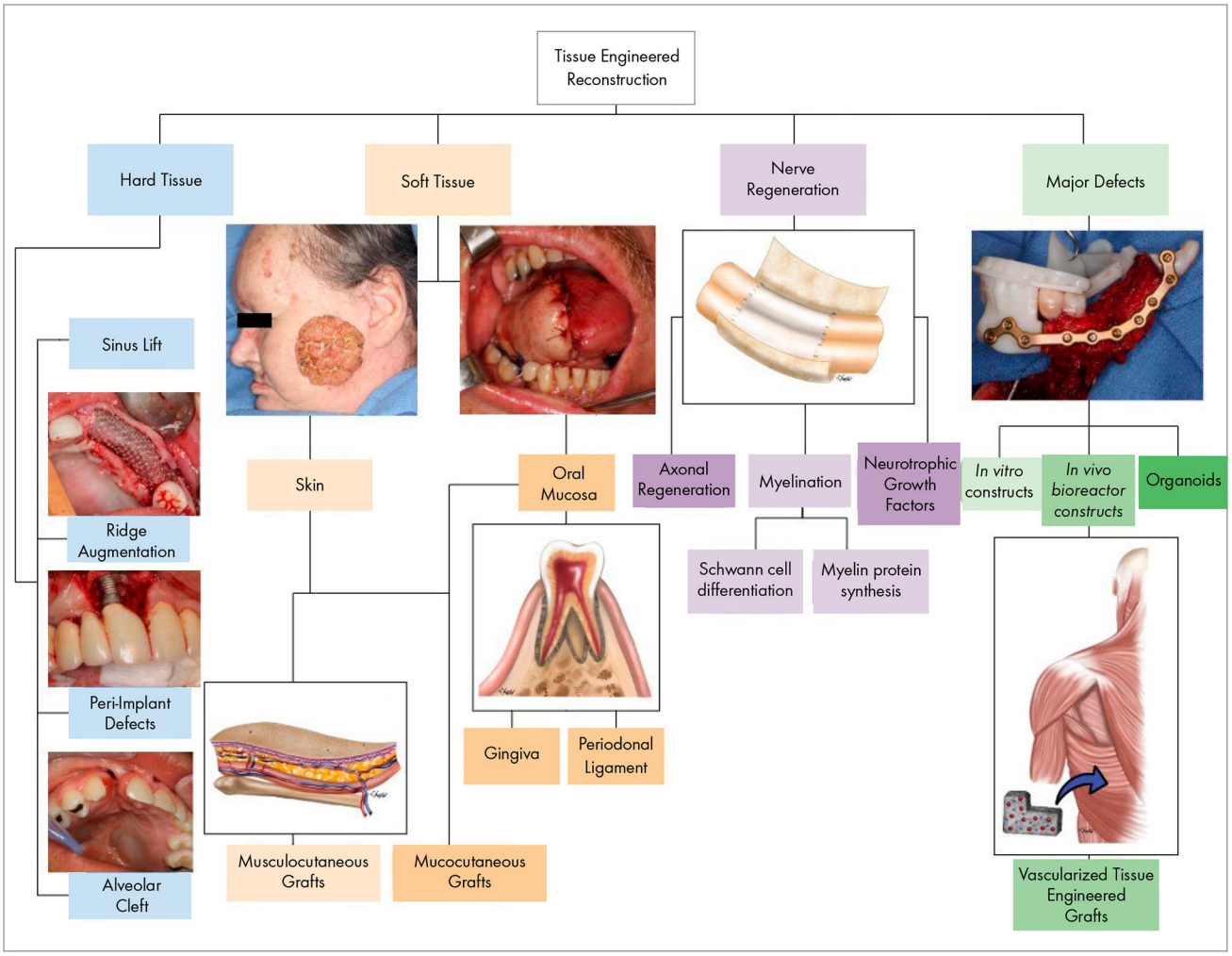
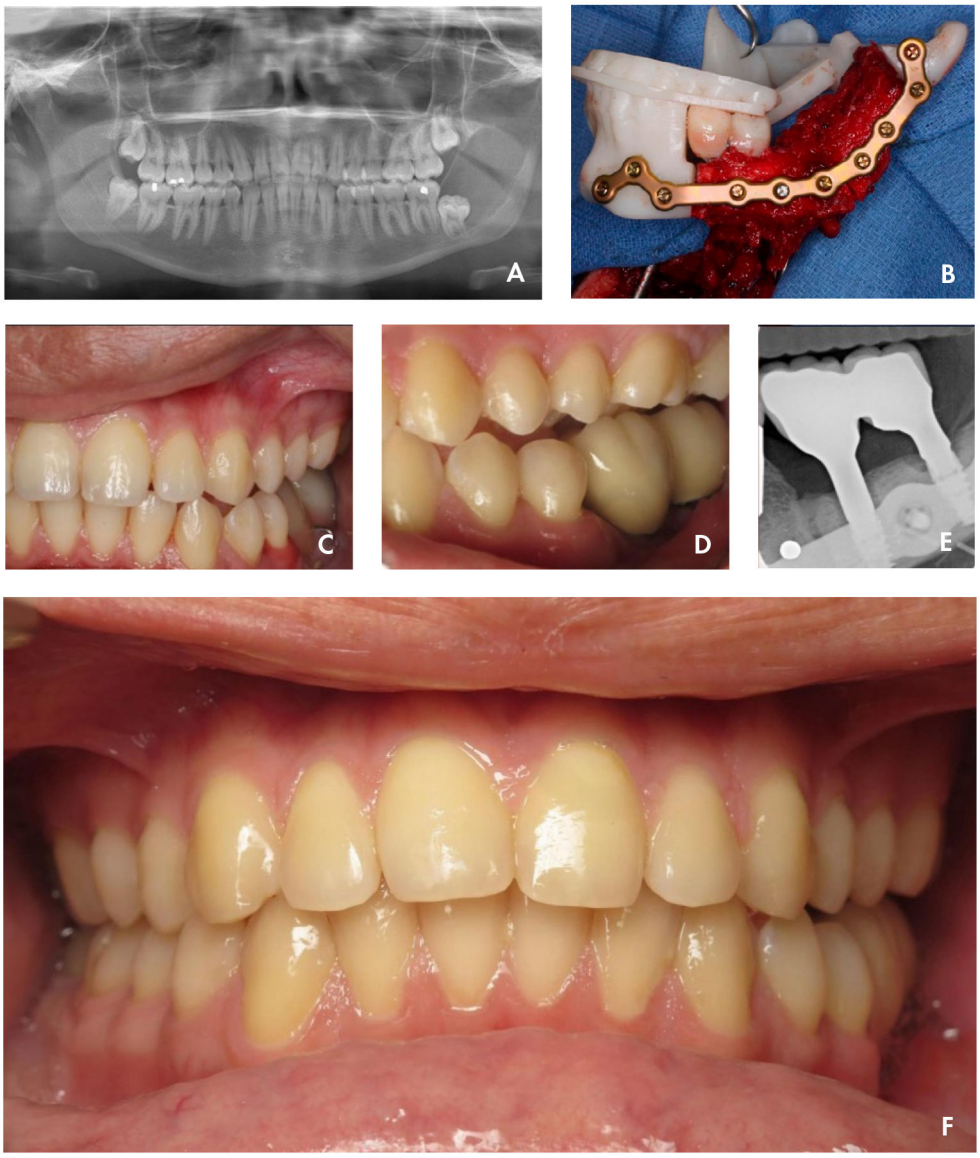


FIGURE 2.

Diagram demonstrating potential areas for utilization of stem cell therapies including hard and soft tissue engineering, nerve regeneration and reconstruction of major defects using bioreactors and eventual organoids.



FIGURES 3.

The panoramic radiograph is of a patient with ameloblastoma of the left posterior mandible (**3A**). The patient is treated with the "Jaw in a Day" technique, in which the patient undergoes a mandibulectomy (here, with osteotomies through tooth No. 19 anteriorly and the sigmoid notch posteriorly to achieve clear tumor margins), with fibula microvascular free flap reconstruction, where dental implants are also placed in the fibula and a prosthesis is cemented to the dental implants (**3B**). This entire fibula, implant and prosthesis construct (shown in this picture, while still connected by the vascular pedicle in the leg) is transferred to the mandible defect and microvascular surgery is performed to connect the fibula pedicle with an artery and vein in the patient's neck. This technique allows for immediate reconstruction of hard and soft tissue defects and missing teeth in one surgery, efficiently restoring the patient's form and function after tumor ablation. The picture shows the immediate postoperative occlusion after microvascular reconstruction (**3C**), the final

implant-supported restorations (**3D**), (**E**) final periapical radiograph (**3E**) and final frontal occlusion(**3F**). This case was performed by Dr. Chi T. Viet (microvascular surgery), Dr. Alan Herford (tumor resection) and Dr. Jui Min Su (prosthodontics) at Loma Linda University.