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A Current Overview Of Materials And Strategies For Potential Use In Maxillofacial Tissue Regeneration

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Abstract: Tissue regeneration is rapidly evolving to treat anomalies in the entire human body. The production of biodegradable, customizable scaffolds to achieve this clinical aim is dependent on the interdisciplinary collaboration among clinicians, bioengineers and materials scientists. While bone grafts and varying reconstructive procedures have been traditionally used for maxillofacial defects, the goal of this review is to provide insight on all materials involved in the progressing utilization of the tissue engineering approach to yield successful treatment outcomes for both hard and soft tissues. *In vitro* and *in vivo* studies that have demonstrated the restoration of bone and cartilage tissue with different scaffold material types, stem cells and growth factors show promise in regenerative treatment interventions for maxillofacial defects. The repair of the temporomandibular joint (TMJ) disc and mandibular bone were discussed extensively in the report, supported by evidence of regeneration of the same tissue types in different medical capacities. Furthermore, in addition to the thorough explanation of polymeric, ceramic, and composite scaffolds, this review includes the application of biodegradable metallic scaffolds for regeneration of hard tissue. The purpose of compiling all the relevant information in this review is to lay the foundation for future investigation in materials used in scaffold synthesis in the realm of oral and maxillofacial surgery.

Keywords: Materials, Maxillofacial, Tissue regeneration, Scaffold

1. Introduction

Extraoral craniofacial tissue engineering is a blossoming field that encompasses a wide variety of stimulating materials and bioactive agents incorporated into a scaffold to restore the anatomy and functionality of an injured or defected region.¹ Scaffolds are biocompatible, biodegradable three-dimensional constructs with a unique architecture that facilitate cell adhesion, migration, proliferation and differentiation.²⁻³⁶ Various biomaterials have been recently developed to accommodate the need for scaffold or implant fabrication and their surface modification aimed at regeneration and tissue engineering of different organs.³⁶⁻⁴² Craniofacial tissue engineering scaffolds and implants

can be composed of a specific material or a blend/composite of materials that correlate to the type of tissue being reconstructed, hard (bone) or soft (cartilage) tissue.⁴³⁻⁴⁶ Important factors to take into consideration in the design and implantation of the scaffold include dimensions of the defect, cell density in the surrounding tissue, and available vasculature around the area of damage.¹ Signal-inducing growth factors and attached proteins can also mitigate mechanical property enhancement and cell-cell interaction within the complex.⁴⁷⁻⁴⁹ While the scaffold is meant to facilitate the biochemical activity that gives rise to new tissue, its rate of degradation normally is equivalent to the rate of tissue formation.⁴⁸ The applicability of this division of regenerative medicine will be discussed in the two separate types of tissue application that routinely serve as surgical sites for oral and maxillofacial surgeons: cartilage and bone.

Approximately ten million people in the United States suffer from temporomandibular joint disorders (TMD).⁵⁰ Tissue engineering applied to the temporomandibular joint (TMJ) has been a part of scientific discussion and practice for three decades. Severe complications of the TMJ disc have led to discectomies, (which is the surgical procedure to remove the TMJ disc) but functional implants are being seriously considered as an alternative approach.⁵¹ Displacement of the dysfunctional disc followed by the insertion of a cell source to manufacture neocartilage is the overall goal of current researchers in the field. Using a biocompatible scaffold seeded with cells and biological modulators can facilitate this process but the regeneration needs to be self-limiting and controlled so that ossification does not occur.⁵² With current understanding of underlying causes of TMJ pathology and its instigation of myofascial pain in the patient leading to debilitating masticatory function, recent strides have been made to create a long-term resolution. The potential to induce regeneration of the TMJ disc depends on a variety of factors, such as scaffold design and material, supplementary cells, bioactive agents, biochemical compatibility between the scaffold and surrounding environment, and the ability of the host to accept the scaffold and facilitate a natural process that equates tissue formation with safe biodegradation of the three-dimensional construct. Two decades ago, several papers were published to demonstrate the capacity for a TMJ disc-specific regenerative mechanism.⁵³⁻⁵⁵ In order to safely revitalize the natural environment of the disc, in addition to restoring its functional capabilities, the proper combination of biocompatible materials and bioactive agents needs to be employed, and a variety of these scaffold designs have been successfully tested *in vitro* and *in vivo*.^{53,56} The soft tissue of cartilage can be regenerated using natural and synthetic polymers alike.^{57,58} both classes of which will be further discussed in [Section 3](#).

Significant maxillofacial bone damage that requires tissue reconstruction may result from tumors, osteoradionecrosis, trauma, or congenital defects, and traditionally, these debilitating causes were addressed by bone grafting procedures.^{59,60} Tissue engineering strategies to restore both the functional capabilities and morphology of lost bone tissue have made great strides in the last couple decades.^{61,62} Tissue engineering can be employed for bone as well by providing permanent, biomimetic, replacement tissue systems. To reach this aim, scientists can utilize the tissue engineering model ([Fig. 1](#)). In this schematic, native tissue is first evaluated to generate design parameters.⁶³

Fig. 1. Tissue engineering model applicable to TMJ tissues. The regenerative approach is initiated by the evaluation of biomechanical, biochemical, and cellular characteristics of the native tissue to generate design parameters for tissue engineering. Afterwards, cells are incorporated into scaffolds, bioactive agents, and mechanical stimuli to make a regenerated TMJ tissue that could be implanted *in vivo*.⁶³

Two methods are notable in hard tissue engineering: *in situ* tissue engineering, which incorporates an acellular scaffold matrix into the site of tissue injury to attract local cells and osteoconductive mediators that will guide the process of regeneration, and *ex vivo* cell seeding on the scaffold, which would allow the cells to orchestrate the mechanism of bone formation.⁵⁹

2. TMJ cartilage engineering

2.1. Materials for cartilage tissue engineering

2.1.1. Collagen

Although the study of most natural polymers has been very limited in the regeneration of the cartilage disc, one stands out considerably among the rest in attempts to achieve total disc reconstruction: collagen.⁶⁴ Its ability to be broken down and used as a gel has led to its widespread use, especially because of the ease at which it can be injected as a delivery system suspension into the cartilage defect, although its use as a more rigid structure is more ideal because of the need for suitable porosity to allow for cell adhesion and proliferation throughout the scaffold.^{65,66} Levingstone et al. similarly conducted an experiment to support the use of collagen in osteochondral defects, ultimately presenting evidence that collagen type 1 improved the mechanical properties of composite scaffolds for osteochondral defect repair.⁶⁷ Furthermore, Farrell et al. observed increased chondrogenic differentiation of mesenchymal stem cells in a rat model tested with a collagen-glycosaminoglycan scaffold.⁶⁸

2.1.2. Gelatin

Gelatin, another natural polymer, is derived from the denaturation of collagen and is favorable because of its hydrophilicity and cross-linking ability.⁶⁹ Kuo and Wang⁷⁰ exhibited *in vitro* chondrogenic differentiation with a scaffold composed of gelatin and chitosan while Xia et al.⁷¹ similarly yielded positive results with the same scaffold materials *in vivo*. Gelatin, although a recently developed material for the purpose of engineering cartilage tissue, is known to promote matrix-chondrocyte interaction, leading to the necessary cellular activity to regrow the native tissue.⁷²

2.1.3. Hyaluronic acid (HAc)

Hyaluronic acid, as a polysaccharide derivative, is quite extensively used in the regeneration of cartilage. HAc hydrogels induce stem cell differentiation into chondrocytes and are powerful in cartilage matrix synthesis, as indicated by *in vitro* and *in vivo* studies alike.⁷³ Chung and Burdick, for example, demonstrated that HAc hydrogel scaffolds support chondrogenesis and gene expression that positively impacts protein synthesis required for cartilage regeneration.⁷⁴ Due to the fact that HAc is extremely abundant in synovial fluid and cartilaginous matrices, especially cartilage glycosaminoglycans (GAGs), its biocompatibility is well known to support a favorable cartilage microenvironment.⁷⁵ Yamane et al. reported that the addition of hyaluronic acid to hybrid scaffolds can also perpetuate an increase in mechanical properties of the scaffold to support cartilage tissue engineering.⁷⁶

2.1.4. Fibrin

Despite the fact that it has not been examined as vigorously as collagen, gelatin and hyaluronic acid, fibrin has additionally been researched as potential scaffold material for the culture of stem cells.⁷⁷ Willerth et al. has employed fibrin scaffolds for the culture of ES cell derived neural progenitor cells and decided the important soluble growth factor signs are expected to encourage the differentiation of such cells in neurons and oligodendrocytes.⁷⁸ Other authors have examined the behavior of mesenchymal stem cells seeded inside of fibrin clots and treated with growth factors for utilization in engineering bone.^{79,80} Furthermore, fibrin-based scaffolds seeded with mesenchymal stem cells have likewise been employed for engineering cartilage.^{81,82} Liu et al. has ascertained the suitability of fibrin scaffolds for encouraging vasculature formation from mouse ES cells.⁸³ They proposed an assortment of stem cell lines could be cultured inside of fibrin scaffolds for various tissue engineering applications.

2.1.5. Silk

The characteristics of silk make it appealing for engineering bone and ligament tissue and a broad study has been carried out utilizing 3D silk scaffolds in conjunction with mesenchymal stem cells for tissue regeneration applications.⁷⁷ Particularly, Meinel et al. have effectively created such strategies.⁸⁴ They have revealed that human mesenchymal stem cells combined with silk scaffolds can be employed to engineer bone. Also, this study ascertained that the stream conditions around the scaffold in addition to the characteristics of the scaffold impacted the rate of calcium deposition, which is a vital thought for bone tissue engineering. Another study investigated the use of silk scaffolds modified to contain RGD (arginine-glycine-aspartic acid) peptide sequences for the culture of human mesenchymal stem cells and cleared that the aforementioned scaffolds were suitable for supplanting bone due to slow scaffold degradation.⁸⁵ Other works have explored the role of pore size to determine its impact on the stem cell's behavior seeded inside silk scaffolds.^{86,87}

2.1.6. Agarose

Agarose, which is extracted from red algae and seaweed, comprises of a galactose-based backbone and is usually employed as a medium for cell culture in the form of agar. One of the alluring characteristics of agarose is that its stiffness can be changed, taking into consideration tuning of the mechanical characteristics of the scaffold.⁷⁷ Agarose scaffolds have been evaluated in combination with stem cells in an assortment of tissue applications,

including cartilage, cardiac, and nervous tissue. A collection of studies has shown the appropriateness of agarose scaffolds for elevating stem cells to differentiate into chondrocytes.⁸⁸⁻⁹⁰ The different stem cell types utilized in these works contained human mesenchymal stem cells, bovine mesenchymal stem cells and adipose-derived stem cells. Another research study affirmed that primate ES cells cultured inside of agarose scaffolds would form aggregates and differentiate into cardiomyocytes that would pound for up to one month.⁹¹ Other works have revealed that both mouse and primate ES cells can differentiate into dopaminergic neurons when encapsulated inside of agarose microcapsules.^{92,93} This technique could be utilized as a potential treatment for Parkinson's disease. In general, agarose scaffolds provide an adaptable platform for bone regeneration.

2.1.7. Polylactic acid (PLGA)

Poly-L-lactic-co-glycolic acid (PLGA) is a synthetic polymer that has great structural versatility and mechanical properties that can be manipulated—a feature that is indeed favorable in cartilage tissue regeneration. Uematsu et al. constructed a novel PLGA scaffold for the investigation of cartilage tissue regeneration and found that the polymer supported the infiltration and differentiation of MSCs *in vivo*.⁹⁴ PLGA is also approved by the FDA for medical applications, which has been undoubtedly rare for synthetic materials.⁹⁵ Conventional PLGA, nevertheless, does not match collagen's structural compatibility to the native cartilage tissue of the TMJ disc and only sub optimally induces the functionality of chondrocytes and other cells in the native tissue, according to Kay et al.⁹⁶ In an experiment conducted by Fan et al., they demonstrated that the addition of another polymer or two in order to produce a hybrid scaffold would ultimately sustain chondrogenesis and limit the degree of degeneration.⁹⁵

2.1.8. Poly vinyl alcohol (PVA)

Poly vinyl alcohol (PVA) is a biodegradable and biocompatible polymer that has been implemented in the repair of cartilagenous defects because of its notable water content and hydrophilic behavior, in addition to its elastic and compressive properties.⁹⁷ Tadavarthy et al. demonstrated the biocompatibility of a PVA implant with the development of an Ivalon embolic material. The water content of PVA gels that measured 80%–90% by weight were implanted intramuscularly or subcutaneously into a rabbit for cartilage repair.⁹⁸ One of the first uses of PVA for articular cartilage replacement was reported by Bray and Merrill in the early 1970s.⁹⁹ There are many other studies that demonstrated the use of PVA in articular cartilage repair.¹⁰⁰⁻¹⁰² PVA hydrogel can be prepared with different polymer concentration and number of cycle tested to have tensile

strength in the cartilage range of 1–17 MPa¹⁰³ and Elastic modulus varying from 0.0012 and 0.85 MPa.¹⁰⁴ Furthermore, due to the fact that PVA has a low rate of degradation, its mechanical properties can be preserved, while still retaining a chondrogenic phenotype, as a scaffold for enough time until the neocartilage tissue is restored.¹⁰⁵

2.2. Stem cells

Stem cell use in scaffold design and implantation is beneficial for TMJ disc regeneration as a result of multipotent differentiation into the fibrocartilage that composes the joint.¹⁰⁶ Extracting stem cells from the synovial capsule surrounding the joint holds promise for generating neocartilage. Bone marrow mesenchymal stem cells (BMSCs) also stimulated a higher rate of cell growth and division; its disadvantage is that the replaced tissue that the BMSCs generate is prone to endochondral ossification.¹⁰⁶ Moreover, adipose stem cells (ASCs) are advantageous in a low oxygen environment, which is the setting immediately following implantation of the scaffold. ASCs, upon differentiation, replicate the extracellular matrix environment and its components, including the various types of collagen.¹⁰⁷ The multilineage differentiation and abundant sources of adult mesenchymal stem cells make them the very suitable cell types in the regeneration of cartilage, among other tissues.¹⁰⁸

The source of the stem cells can be utilized in the maxillofacial regeneration has been given as follow:

1. Bone marrow
2. Adipose tissue
3. Stem cells from oral and maxillofacial area¹⁰⁹

2.2.1. Bone marrow

Bone marrow stem cells (BMSCs) can be reaped from sternum or iliac crest. It is made of both hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). The larger part of oro-maxillofacial structures is formed from mesenchymal cells. The upside of bone marrow is that it has a bigger volume of stem cells and can be differentiated into a wide assortment of cells. Isolation of BMSCs can be conducted only under general anesthesia with conceivable post-operative pain.¹⁰⁹

2.2.2. Adipose tissue

These stem cells can be extracted from the lipectomy or liposuction aspirate. Adipose derived stem cells (ADSCs) include a group of pluripotent mesenchymal stem cells that display multilineage differentiation.¹¹⁰ An advantage of adipose tissue is that it is easily obtainable and is plentiful in the human body.¹⁰⁹

2.2.3. Stem cells from the oro-maxillofacial area

Stem cells from the oral and maxillofacial complex overwhelmingly contains mesenchymal stem cells. In this region, different types of dental stem cells were isolated and examined.^{109,111} They contain:

(i)Dental Pulp Stem Cells (DPSCs)

DPSCs were the first tooth-derived stem cells characterized by Gronthos et al. in 2000, and they are mesenchymal inside dental pulp.¹¹² DPSCs are known to differentiate into various kinds of cells and tissues, such as osteoblasts, adipocyte-like cells, smooth muscle cells, neurons, dentin and a dentin-pulp-like complex.¹¹³ They were additionally revealed to have chondrogenic potential *in vitro*. Their multipotency, proliferation rate, availability, and cell number have exhibited to be more noteworthy than those of BMSCs. Generally, DPSCs are more appropriate than BMSCs for mineralized tissue regeneration.¹¹⁴

(ii) Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs)

SHEDs were identified to be cells of higher proliferation rate, with increased population doublings, immature multipotent clonogenic cells isolated from deciduous teeth that can differentiate into several cell types.¹¹⁵ SHEDs are progenitor cells isolated from the pulp remnant of exfoliated deciduous teeth. It is worth mentioning that they display a higher proliferation rate with enhanced population doublings, immature multipotent clonogenic cells isolated from deciduous teeth that can differentiate into numerous cell types.^{109,111,115} Osteoblasts, odontoblasts, adipocytes, and neural cells have been reported to differentiate from SHEDs.¹¹³

(iii)Periodontal Ligament Stem Cells (PDLSCs)

Although periodontal ligaments are known to be of neural crest cell origin, PDLSCs show stem cell characteristics similar to MSCs.¹¹³ Additionally, PDLSCs residing in the perivascular wall have general characteristics in phenotype, cell morphology and differentiation potentials.¹¹⁶ Immunomodulatory ability is another component that allows them to resemble BMSCs to some degree.¹¹⁷ PDLSCs can differentiate into osteoblasts,

cementoblasts, adipocytes, and chondrocytes, and they were described to form periodontal ligaments and cementum-like tissue *in vivo*.¹¹¹

(iv) Stem Cells from Apical Papilla (SCAPs)

SCAPs are cells isolated from the root apex of a newly formed tooth, which is thought to be connected to root formation.¹¹⁸ They introduce the features of MSCs and can differentiate into chondrocytes, adipocytes, osteoblasts and neurons under suitable states.¹¹⁹

(v) Dental Follicle Progenitor Cells (DFPCs)

DFPCs are stem cells obtained from dental follicles encompassing a tooth germ in early tooth formation phases.¹²⁰ The dental follicle is an ectomesenchymal cell condensation and harbors heterogeneous population of cells, including those within the periodontium. They are similarly known to differentiate into osteoblasts, chondrocytes, adipocytes and neuronal cells.^{113,121}

Since DPSCs are the most concentrated on in the literature, we will focus mostly on the utilization of DPSCs in this section.

In a clinical research study, biocomplexes fabricated from DPSCs and collagen sponges were employed in human mandible repair and showed excellent results.¹¹¹ In conjunction with other scaffolds, DPSCs have been cleared to have osteogenic differentiation ability.¹²²⁻¹²⁴ The topography of the scaffolds was described to assume an important role in clinical regeneration.¹²⁵

With regard to alveolar bone defects, Liu et al. proclaimed that DPSCs expressing bone morphogenic protein 2 (BMP-2) experience prior mineralization and produce a more noteworthy amount of bone in a rabbit model.¹²⁶ Preceding this perception, proof with respect to the impact of BMP-2 on the osteoinducibility of DPSCs was reported by several authors.¹²⁷⁻¹²⁹ Platelet rich plasma has also been examined in the same context.^{62,63,111,130,131}

The role of DPSCs in bone regeneration around dental implants was, as of late, studied,¹³¹ and a comparable study was done with BMSCs; periosteal cells displayed that DPSCs describe the most astounding osteogenic potential as a source for tissue-engineered bone around titanium implants.¹³² Furthermore, a late report recommended that immobilization of DPSCs in alginate hydrogels results in increased osteogenic potential contrasted with control cells cultured in routine stem cell media.¹³³

Osseous regeneration employing PDLSCs has been evaluated by multiple studies. For example, Chadipiralla et al. thought about the *in vitro* proliferation and calcium deposition of PDLSCs with SHEDs through retinoic acid treatment with insulin and demonstrated that PDLSCs display unrivaled characteristics.¹³⁴

Osteogenic differentiation of DPSCs has happened in conjunction with other material substrates.¹³⁵ In the Mangano et al. study, the DPSCs were cultured *in vitro* on different titanium surfaces and differentiated into osteoblasts, leading to synthesized bone on laser-sintered surfaces.¹²⁴ Lately, Akkouch et al. found that DPSCs had been pre-differentiated into osteoblast-like cells and seeded onto collagen–hydroxyapatite–poly(l-lactide-*co*- ϵ -caprolactone) composite scaffolds.¹²² They concluded that the composite scaffold encourages adhesion, proliferation and differentiation of the osteoblast-like cells, with ECM mineralization happening all throughout the scaffold. Kanafi et al. examined the possibility of immobilizing DPSCs within alginate microspheres and evaluated the *in vitro* osteogenic differentiation potential. Increased mineralization, protein secretion and an upregulated osteo-related gene profile came about because of immobilization and, curiously, immobilization activated osteogenic differentiation of DPSCs without the utilization of induction variables in the media.¹³³

2.3. Growth factors

Growth factors are highly potent and serve as a popular bioactive agent in scaffold delivery. Basic fibroblast growth factor (bFGF) is extremely useful for cell proliferation and production of collagen. GAG synthesis is significantly stimulated by bFGF and platelet derived growth factor (PDGF) as well.¹³⁶ Delivering a combination of two growth factors produces a more reconstructive effect than a single growth factor alone. Together, their cooperation contributes to the repair of the disc. Moreover, IGF-1 and bFGF synergistically aid in the biosynthesis of disc cells.¹³⁷ The growth factors induce cell proliferation but fail to synthesize the matrix of the TMJ disc.¹⁰⁷ The purpose of using growth factors essentially is to upregulate, at a biochemical level, the proliferation of fibroblasts and chondrocytes that will, in turn, give rise to the regeneration of hyaline cartilage, extracellular matrix components, glycosaminoglycans, and other tissues that compose and surround the temporomandibular joint cartilage.¹³⁸ It is well supported in the literature that IGF-1 is dominant in its effect to repair cartilage by stimulating chondrogenesis *in vitro* and *in vivo*, while also increasing the GAG fraction of the construct.^{139,140} Additionally, Blunk et al. specified that although PDGF is known to have an anabolic effect in cartilage protein synthesis and expression, more notably in cartilage explants, their experimental findings did not conclude that it was consistently favorable for cartilage tissue regeneration due to

its role in decreasing the scaffold growth rate. They lastly demonstrated that the application of TGF- β also induced ECM deposition and an increase in the total fraction of collagen in the cartilage engineering construct.¹⁴¹

Addition of growth factors into scaffolds might be refined in various routes, each of which presents distinctive characteristics. Immersion of a scaffold in growth factor-containing solution results in a loose connection with the structural material, and, in this manner, it encourages a snappy release of the craved stimulatory molecules. Alternately, growth factors might be added to and even covalently connected to the scaffold microstructure for augmented release. Cells adjusted to express and secrete osteoinductive growth factors may likewise be seeded in the scaffold, accomplishing a comparable impact.^{142,143} The fundamental cell adjustments ordinarily include gene therapy accomplished either by viral or nonviral transduction. Viral transduction is the best method of gene transfer and is commonly conducted utilizing retroviruses, adenoviruses, or adeno-associated viruses.^{144,145} Gene transfer can also be carried out through direct uptake of gene-including plasmids from solution or as a conjugate with a nucleus-bound biomolecule.^{142,145}

Issues with growth factor-loaded scaffolds are mostly associated with inconsistent release profiles. The release of growth factor is regularly managed by passive diffusion or degradation rate and does not fittingly parallel the rate of bone regeneration and healing.^{142,143} It has been demonstrated that covalent linkage of the growth factor to the scaffold may be sluggish and boost its release profile to more firmly surmised cellular requests.¹⁴⁶ For instance, covalently linked VEGF in a fibrin scaffold results in a more firmly controlled release and, in this way, a more sorted out vascularization in contrast with the scaffold with unlinked VEGF.¹⁴⁷ One peril inborn in covalently linked growth factors is changing mechanical, osteoconductive, or other characteristics of the scaffold material. However, it has been employed in animal models to effectively repair mandibular, zygomatic, and calvarial bone defects.^{142,148}

In spite of such auspicious clinical accomplishments of growth factors for tissue regeneration, debates still hound their clinical employment for tissue regeneration of the oral and maxillofacial region. The greatest debate deals with the oncogenic capability of growth factors. Numerous tumors containing malignancies in the oral and maxillofacial region have, as of now, been demonstrated to over-express the previously stated growth factors such as TGF- β , BMPs, *etc.*, which are undoubtedly valuable for tissue regeneration when expressed in sufficient quantity. For the clinical trial of growth factors, supraphysiological doses are needed for compelling tissue regeneration in addition to

enhancing the demise of tumor development. Lamentably, the optimum concentration and suitable planning for administering growth factors are not completely settled, which might be essential for fruitful clinical results without tumorigenic side effects. Biologically, growth factors more often react to each other in an exceptionally sensitive and modern way, trading criticisms from the responding cells and tissues. Thus, growth factors frequently have biphasic features contingent upon the condition of the tissue. For instance, startling deferred tissue regeneration might occur because of the upregulation of a growth factor inhibitor when an exogenous growth factor is in excess for the tissue condition. By stabilizing the appropriate dose of growth factors and the timing of their release, more studies are expected to comprehend the exact mechanisms of the falls of growth factors when the defected tissue is repaired. Furthermore, a solitary dose of exogenous protein is surely understood not to affect a biological response satisfactorily in traded off tissue conditions^{1,2}. As examined by Ripamonti et al., there is much to examine regarding growth-signaling molecules in tissue, including contrasts among animal and human models. Along these lines, blind confidence in utilizing growth factors for target tissue regeneration ought to be dodged, and more meticulous contemplations ought to consequently be supported before utilizing growth factors.

3. Mandible bone regeneration

3.1. Materials for mandible regeneration

3.1.1. Bioceramics

3.1.1.1. Calcium phosphates

Calcium phosphates are main components for dental, craniofacial and orthopedic treatments because of their similarity to bone composition, which can encourage the production of a useful functional interface.^{149,150} One category of calcium phosphates, known as calcium phosphate cements, including dicalcium phosphate anhydrous and tetracalcium phosphate, was indicated to be a suitable choice for dental and craniofacial applications.^{149,151} Calcium phosphate cement implants would be dependent on initial loading by temporary dentures and need to be resistant to flexure for periodontal bone treatments, mandibular and maxillary ridge augmentation. Furthermore, significant regeneration of the mandible and maxilla after trauma would benefit from calcium phosphate cement with optimal mechanical properties and rapid bioactivity, owing to cultured stem cells.¹⁵² Hydroxyapatite (HA), a common calcium phosphate, has been utilized for maxillofacial tissue engineering.¹⁵³ In a research study, HA-based (n-

HA/polyamide (PA)) scaffolds that had been produced using CAD/CAM models based on CT data were implanted into a mandibular condyle defect. The patients eventually obtained a jaw contour and appearance with the suitable temporomandibular joint function.¹⁵⁴ In another report, HA porous scaffolds with 30 MPa compressive strength were implanted into mandibular defects, and these scaffolds were produced with two channel geometries, including orthogonal and radial shapes, with the channel size of 444 and 366 μm and porosities of 44% and 38%, respectively (Fig. 2).¹⁵⁵ As it can be observed in Fig. 3, four defect sites were produced in each hemi-mandible. Three defects on each side were filled with HA scaffolds, and the last one was left as the control group. The results of this study indicated that although normal regeneration of bone tissue was found at 5 and 9 weeks in both designs, at 9 weeks, the average bone ingrowth increased to 45,721 and 23,728% in the orthogonal and radial designs, respectively confirming that it is possible to control the morphology of the regenerated bone tissue inside HA scaffolds through the design.¹⁵⁵

Fig. 2. (a) The locations of the defects in inferior posterior border of minipig mandible for implantation of sintered (b) radial (left) and orthogonal (right) design of HA scaffolds. The scale bar is 2 cm.¹⁵⁵

Fig. 3. (a) Bone regeneration through the pores of orthogonal design after 9 weeks. (b) Cross section of HA scaffold in low (b) and high (c) magnifications showing the regenerated bone structure. The location of tissue sections for imaging has been shown in right diagram.¹⁵⁵

In the control group (Fig. 4), although new bone formation increased gradually, woven bone and fibrous tissue were more frequently observed. Considering the obtained results, the authors concluded that porous nHA/PA composite promoted bone formation over the extension of the defect and offers interesting potential for maxillofacial reconstructive procedures in load-free areas.¹⁵⁶

Fig. 4. Surgery images from nHA/PA implants after 4, 12 and 24 weeks. Left side includes the samples and right side is a blank control. Arrows show the defect area.¹⁵⁶

3.1.1.2. Bioactive glass

Bioactive glasses (BaG) possess exceptional bioactivity, ability to deliver cells, and adjustable degradability.¹⁵⁷ The aforementioned properties made BaG a potential scaffold material for tissue engineering.¹⁵⁷⁻¹⁶⁰ BaG is reported to be able to induce more bone synthesis compared to other bioactive ceramics. *In vitro* research studies show that their osteogenic behavior is mainly owing to their dissolution products stimulating osteoprogenitor cells at the genetic level. The osteoconductivity mechanism is due to the deposition of a hydroxycarbonate apatite (HCA) layer on the surface of the BaG.¹⁶¹ Several classes of BaG have been recently introduced, including the conventional silicates, such as

BaG 45S5, phosphate-based glasses, and borate-based glasses. The BaG 45S5 has been employed in over a million patients to treat bone defects in the jaw and different orthopedic sites.¹⁵⁷ Its main marketing accomplishment is an active repair agent in toothpaste, under the name NovaMin. Clinical trials indicate that the dentifrice can mineralize tiny holes in dentine, reducing tooth sensitivity. BaG 45S5 has proven to be very stable into tooth extraction sites for treatment the tooth roots and providing a stable ridge for dentures. A 5-year research study indicated improvements over HA tooth root implants.¹⁵⁷ Since dentists, surgeons and engineers desire a material that can fill in defects easily, particles have a preferable morphology for this purpose. The first particulate BaG 45S5 product with a particle size range of 90–710 μm was PerioGlas as a synthetic bone graft for the repair of defects in the jaw that result from periodontal disease. It can be utilized to stimulate hard tissue regeneration in the jaw, so the bone quality becomes enough for anchoring titanium implants. PerioGlas is now sold in over 35 countries. For infra-bony defects between the roots of molars, clinical examinations confirmed that its regenerative behavior was increased with laser therapy after surgical treatment.¹⁶² The product has also been utilized with polymeric membranes for guided tissue regeneration.¹⁶³

The BaG research program in Finland caused the commercialization of S53P4 particulates known as BonAlive, which has received European approval to serve as a bone graft substitute in 2006. While the mandible has been basically composed of dense cortical bone that can be grafted, the maxilla consists of porous cancellous bone that resorbs quickly in periodontitis and is thus harder to graft. Treatment is typically maxillary sinus floor lifting, whereas bone grows partly into the sinus defect. In comparison to an autograft, a combination of BaG particles with autologous bone allowed the implantation of titanium dental implants in the maxilla and presented faster bone treatment with thicker trabeculae.¹⁶⁴ Clinical trials indicate that the BaG 45S5 particles adhere to the dentine, relieving the pain for longer periods.¹⁶⁵ Although, BaG particles have been popular in bone defect treatments, new components are necessary for porous scaffold production and regulatory approval.¹⁵⁷

3.1.2. Polymers

Natural scaffolds including chitosan, collagen, and hyaluronic acid have proven to be bioactive and, thus, appropriate for bone creation both *in vitro* and *in vivo*.¹⁶⁶ However, a main drawback is the lack of mechanical stability. Synthetic polymers for example poly lactic acid (PLA), poly glycolic acid (PGA), polylactic-*co*-glycolic acid (PLGA), poly methyl methacrylate (PMMA) and polycaprolactone (PCL) have been introduced as alternatives

with structural integrity. The aforementioned polymers display potential for osteoblastic differentiation and bone tissue development and are normally employed for oral and maxillofacial tissue applications.¹⁶⁶

The first generation of barrier function materials was non-resorbable, with expanded polytetrafluoroethylene (ePTFE) membranes becoming the most commonly used.¹⁶⁷⁻¹⁶⁹

Since 1982, when guided bone regeneration (GBR) method was first established, the e-PTFE membrane has been considered a gold standard for barrier function materials.^{170,171} Certainly, this non-resorbable material has all the characteristics for the GBR method, such as biocompatibility, covering the defect and coagulum stabilization;¹⁷² however, e-PTFE membranes have certain cutoff points, such as the need of a second surgical operation to evacuate them and the likelihood of bacteria infection.¹⁷³⁻¹⁷⁶ Actually, ePTFE-membrane exposure to the oral cavity dependably brought about a failure of the treatment.

Seibert and Nymann employed e-PTFE non-resorbable membranes to enhance the alveolar crest; after 55–90 days, the bone completely topped off the defect.¹⁷⁷ Urban et al. utilized e-PTFE membranes associated with autogenous grafts for implant insertions and demonstrated that implants placed were osseointegrated, and along these lines, the vertical GBR method is both protected and unsurprising.¹⁷¹

Other than avoiding a second surgery, resorbable membranes are likewise invaluable due to the boost in soft tissue healing and a lower bacterial contamination risk because of reduced exposure from the degrading membrane.¹⁷⁷ Notwithstanding the necessities expressed beforehand, there are further properties that these barrier membranes must satisfy: biocompatible degradation products that don't meddle with bone regeneration, a suitable degradation profile to synchronize with new tissue growth, and adequate mechanical and physical characteristics to carry out the barrier function and permit *in vivo* utilization.^{167,178}

Among the widely recognized bioresorbable membranes are synthetic polyesters (poly(lactic acid), poly(glycolic acid), and poly(caprolactone) and their copolymers)^{167,179-182} and tissue-derived collagen^{167,183-187} Polyester membranes show biocompatibility and have a high level of customization, with degradation rates and mechanical characteristics that can be balanced in view of polymer composition and concentration.^{167,188,189} As a natural component of the extracellular matrix, collagen is biocompatible and cell adhesive.

Despite the fact that collagen is not innately mechanically stable, it can be changed *via* different means of crosslinking.¹⁷⁸ Poly(ethylene glycol) (PEG) is otherwise a biodegradable and biocompatible polymer. Since numerous oral and maxillofacial defects are uniquely shaped, an injectable material is alluring, such as a PEG-based *in situ* forming gel for GBR that exhibited adequacy in a clinical trial.¹⁹⁰⁻¹⁹² Poly-DTE-carbonate has displayed promising characteristics, such as low immunological response and high ability to incite bone regeneration.^{170,192}

A number of works on resorbable membranes have been performed to examine the conditions associated with various experimental and human models. Specifically, Gottlow (1984) demonstrated that a biological space impelled right bone regeneration, while without this space the membrane caved in and thus traded off bone regeneration.^{170,193}

Hyder et al. and Kodama et al. stated that the inflammatory infiltrate incited by synthetic membranes was lower than heterologous animal membranes.^{194,195} Robert and Frank displayed that, changing the polymer concentration, the membranes persist for about 4 months.¹⁹⁶ Laurel et al. cleared a period of resorption between 6 and 12 months, but the hydrolyses of the membrane led to little inflammation.¹⁹⁷

A final note encompassing polymeric scaffolds for bone tissue engineering is that single polymer-derived scaffolds are not significantly applicable to maxillofacial bone tissue regeneration strategies; therefore, this paper will more heavily focus on the diverse composites used to make a substantial impact in hard tissue growth.

3.1.3. Polymer Matrix Composites (PMC)

Polymer matrix composite materials have been extensively used for the regeneration of bone. A primary reason for combining polymers and ceramics in hybrid composites is to integrate the advantages of each class of materials into one, making an optimal blend with suitable mechanical strength, osteoconductivity and biodegradability for effective bone tissue formation.¹⁹⁸⁻²⁰⁴ One such example is PLLA / HA, and it has been utilized successfully as an osteochondral construct for mandible bone engineering by the porcine chondrocytes delivery in the polymer layer and fibroblasts transduced with adenovirus driving the expression of bone morphogenetic proteins.²⁰⁵ In a pilot *in vivo* study, eight dogs were used for a model of the mandibular condyle that had been produced by rapid prototyping of PGA/PLA scaffold that was then seeded with bone mesenchymal stem cells. While research studies have explored the appropriateness of different kinds of materials in making the CAD/CAM scaffolds, histological evaluations focusing on bone

mesenchymal stem cells seeding in scaffolds have confirmed that PGA/PLA is one of the best available choices for the new bone regeneration.²⁰⁶ Xu et al.,²⁰⁶ have introduced a technique for production of PGA/PLA mandibular condyle porous scaffolds for bone regeneration that confirms outstanding morphological modification and accuracy. Moreover, synthetic biodegradable polymers such as PGA/PLA can be freely adjusted to the shape of a defect. Zhou et al.²⁰⁷ indicated that physiological healing of articular cartilage defects and the corresponding subchondral bone is possible *via* autologous bone mesenchymal stem cells and PGA/PLA polymers. This study confirms that PGA/PLA has appropriate cytocompatibility due to the bone mesenchymal stem cells dispersed in PGA/PLA scaffold.²⁰⁶

Post-operative analysis is common in most circumstances of *in vivo* testing of scaffold implantation and subsequent hard tissue engineering because it is necessary to carry out histological evaluation to evaluate both the effectiveness of the scaffold in tissue repair and to monitor the site for any adverse reactions from the host in response to the scaffold. In another *in vivo* research study, a 2 cm incision was created in the lower edge of the mandible body of adult New Zealand white rabbits and was filled with porous nano-hydroxyapatite/polyamide composite (nHA/PA). After the surgery, no necrosis, inflammation or postoperative complication was seen in any animal, and the bone defects were healing well. At 1 month, macroscopic inspections indicated that the scaffold was stable in the defects and the amount of callus creation was significant enough that nearly 70% of the implant surface was covered. According to the results of macroscopic, radiographic, histological and histomorphometric examinations that were carried out up to 6 months postoperatively, the defects were entirely occupied by neo-bone with density similar to the host bone.¹⁵⁶

Chitosan has been a potent material in the rampant use of wound-healing agents in maxillofacial and periodontal regeneration as well. Its osteoinductivity was supported by confirmative mineralization of hard tissue following the extraction of third molars.²⁰⁸ Chemical mediators, in fact, are so effectively enhanced by the addition of chitosan that the number of osteogenic colonies drastically increases in patients with chronic bone defects, such as periodontitis.²⁰⁹ Zhou et al. prepared two types of scaffolds composed of different PMCs by way of homogenization and radiation crosslinking.²¹⁰ Results showed that both scaffolds demonstrated remarkable biocompatibility and biodegradation following *in vivo* implantation in the mandible of beagle dogs, and osteogenesis occurred at the outer edges of the scaffolds initially before moving inward toward the center, with gelatin/CM-chitosan/ β -TCP quantifiably containing a higher volumetric density than gelatin/CM-chitosan composite.²¹¹

3.1.4. Ceramic Matrix Composites (CMC)

While PMCs are more flexible and more easily maneuverable than ceramic matrix composites for filling the shape of an irregular bone defect, CMCs have a distinct advantage in increasing the mechanical strength of the construct to withstand load-bearing applications, especially the compression of the jaw.²¹² However, it is more difficult to implant the scaffold because of its brittle nature; therefore, fitting the scaffold into the shape of the defect is a challenge for surgeons and could result in increased time of surgery as well as surrounding tissue damage.^{213,214} Xu et al., furthermore, demonstrated that while CMC scaffolds are durable and strong enough to withstand immense compressive force, the addition of a polymer, such as chitosan, can induce macropore formation for bone ingrowth and can also lead to a synergistic hardening and an overall superior fracture resistance.²¹⁵

A strong example of inorganic CMC scaffolds include cements composed of calcium phosphate (CaP's) and typically either hydroxyapatite, β -tricalcium phosphate (β -TCP), or bioactive glass.²¹⁶ CaP's, in particular, have demonstrated that doping scaffolds with other inorganic materials not only stabilize certain factors, such as mechanical strength and dissolution rates.²¹⁷⁻²¹⁹ Similarly, the addition of oxides to β -TCP scaffolds may result in 150% increase in compressive strength and approximately 90% rise in cell viability.²¹⁷ Furthermore, Biphasic hydroxyapatite (HA)/TCP was investigated by Cavagna et al. in 109 orthopedic spinal fusion patients, showing the compound's promise in load-bearing bone tissue engineering applications.²²⁰ Ashuri et al. also experimentally demonstrated that a novel HA/bioactive glass scaffold exhibited optimal mechanical strength with 20 wt.% bioactive glass, but it eventually decreased over time following immersion in simulated body fluid (SBF).⁵ Although CMC scaffolds have their own distinct advantages applicable to craniomaxillofacial regeneration, as noted above, the literature appears to support the claim that PMCs are more widely applicable to these applications in medicine and provide scientists and clinicians with a greater sense of optimism moving forward in the field.

3.1.5. Metals

Biodegradable metals (BMs) are anticipated to corrode gradually *in vivo*, with a suitable host reaction evoked by released corrosion products, then wholly break down after satisfying the purpose of assisting with tissue recuperation without implant deposits [221]. Among BM frameworks, Mg-based BMs, which now have several applications reported in past clinical trial results, are viewed as effective material types for potential application in treating maxillofacial bone defects.^{22,221}

Mg is mostly applied in bone tissue regeneration, it is an important element in the human body, and its presence is useful to bone growth and strength.²²²⁻²²⁷ It is a cofactor for several enzymes and serves as a stabilizer of DNA and RNA structures.²²⁸ Additionally, Mg is that the fourth most copious ion in the human body, further indicating its biocompatibility.^{229,230} In extracellular liquid, the level of Mg reaches somewhere around 0.7 and 1.05 mmol/L, and its homeostasis is kept up by the digestive tract and kidneys.^{222,223} The frequency of hyper-Mg is uncommon because of the effective excretion of the element in urine.^{222,229}

Mg is osteoconductive and a bone growth stimulator material, as proposed by numerous studies. A remarkable increment of bone deposition has been seen in Mg-based implants compared to some polymeric scaffolds, such as PLA.²³¹⁻²⁴⁰ The erosion layer around Mg inserts has been discovered to contain calcium phosphates, which seemingly makes it in direct contact with the encompassing bone.²³¹ Xu et al. demonstrated new bone formation around Mg-Mn-Zn implants in their *in vivo* application in rats.²⁴¹ Witte et al. revealed that three months after the operation, open porous Mg scaffolds inserted in rabbits were mostly degraded, foreign body giant cells phagocytizing the remaining corrosion products were rarely found, and no osteolytic changes were discovered around the insertion site.²⁴² It has been demonstrated that porous Mg has better degradation characteristics, including lower pH change, slower hydrogen development, and slower decrement of compressive strength in simulated body fluid (SBF) soaking tests.²⁴³ Zreiqat et al. revealed an enhancing bone cell adhesion on Mg-doped alumina, as communicated by an increased level of $\alpha 5\beta 1$ integrin receptor and collagen extracellular matrix protein.²⁴⁴ Two studies using Mg-doped apatites or collagen materials displayed strong biocompatibility on bone cell adhesion and tissue growth.^{245,246}

Mg and its alloys are extremely lightweight metals, having density going from 1.74 to 2.0 g/cm³, which is less than that of Ti alloys (4.4–4.5 g/cm³) and is near that of native bone (1.8–2.1 g/cm³).²²⁴ They have an extensive variety of elongation and tensile strength properties from 3% to 21.8% and from 86.8 to 280 MPa, respectively. Mg has a more prominent toughness contrasted with that of bioceramics, and its elastic modulus (41–45 GPa) is closer to that of native bone contrasted with other metals. This property could assume a crucial role in avoiding the stress shielding effect. Mg also has preferable ductility over synthetic hydroxyapatite and a higher strength than existing biodegradable polymers.²⁴⁷ The elastic modulus of pure Mg is nearer to that of cortical and cancellous bones, which is an unrivaled component for bone scaffolds, further indicating their vast potential for load-bearing maxillofacial bone regeneration. Mechanical characteristics of Mg could be further enhanced by alloying and thermo-mechanical methods. The addition of

alloying elements, such as silver, silicon, zinc, tin, zirconium and indium, could boost both the strength and elongation of Mg alloys.²⁴⁸ Moreover, some fabrication procedures, such as hot extruding, hot rolling, and equal-channel angular pressing (ECAP) could likewise improve the strength of Mg alloys, and at times, these processes can further enhance ductility.²⁴⁸⁻²⁵⁰

Random cellular Mg could be produced through powder or chip sintering (conventional, spark plasma and laser assisted), low pressure casting, or removable spacer techniques. These production methods create a random cell framework, wide distributions of cell size, and morphology, giving rise to unpredictable material characteristics over the range of 100 μm .^{225,251} Processes that could be employed to produce Mg with a topologically ordered open cell framework include the space holder technique, solid free-form process, replication, leaching technique, electrodeposition, and vapor deposition. Fig. 5 displays an example of porous Mg scaffolds fabricated by two different methods.²²⁵

Fig. 5. Porous Mg scaffolds: (a) fabricated by laser-assisted mechanical perforation method;²⁸³ (b, c) produced by solid free-form fabrication technique.²⁸⁴

3.2. Stem cells

The incorporation of mesenchymal stem cells (MSCs) in bone regeneration scaffolds has revolutionized the role of tissue engineering in medicine and dentistry. Their osteogenic capacity has demonstrated osteoprogenitor differentiation, osteoblast proliferation, and matrix deposition *in vitro* and *in vivo*.²⁵²⁻²⁵⁴ MSCs also display diversity in clinical applications *via* proven acceleration in repair of femoral, craniomaxillofacial, and spinal defects, especially in animal models.²⁵⁵⁻²⁵⁷ These cells also heavily increase the osteoinductive potential of scaffold biomaterials by promoting osteogenic factor activity, and they influence the surrounding microenvironment with pressure cues that are favorable for mineral deposition and bone formation, in addition to angiogenesis of the

implant for increased blood flow and nutrient diffusion to the newly formed tissue.²⁵⁸⁻²⁶⁰ Mauney et al. mention that although efforts to conduct *ex vivo* expansion limit the differentiation potential of MSCs, the addition of certain growth factors, such as FGF-2, ultimately assist in retaining these properties.²⁶¹ Because of the previous body of work committed to utilizing the enormous potential of these stem cells, their mention in this paper is beneficial to potential approaches in load-bearing mandible regeneration scaffolds.

3.3. Growth factors

Similar to its uses in cartilage regeneration, growth factors play a vital role in bone reconstruction due to their ability to elicit cellular responses and direct ligand-receptor binding that can positively impact osteogenic activity.²⁶² Transforming growth factor- β (TGF- β) has been used for many decades for not only osteoblast differentiation but also the activity of mesenchymal cells and production of ECM.²⁶³ Because of its popularity and widespread use in animal models over the years, TGF- β is an ideal growth factor candidate for regenerative therapy in the craniomaxillofacial complex.^{264,265} Another highly noteworthy growth factor is bone morphogenetic protein (BMP). They are the most widely studied osteogenic agents for bone synthesis in large defects.^{266,267} With over 30 isoforms, the BMP family is effective in both the embryonic phase and adulthood and is unlimited in its availability in the recombinant form.²⁶⁸ Intraoral and craniofacial bone repair has been investigated with recombinant human BMP (rhBMP), but human clinical trials are still limited.²⁶⁶ Other growth factors, such as insulin-like growth factor (IGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), have also been employed and studied as potent molecules for bone defects.²⁶⁹

4. Newest progress in maxillofacial tissue regeneration

Two decades ago, Sachs et al. developed a novel method of tissue fabrication in 3-dimensional bioprinting.²⁷⁰ This rapid prototyping technique serves as an efficient way to design and manufacture reproducible, commercializable, and cost-efficient scaffolds in high volumes.²⁷¹ While the type of material printed a few decades ago was limited to metals and ceramics, polymers and composites have recently been used to optimize mechanical properties or bioactivity in addition to maintaining scaffold biocompatibility.²⁷²⁻²⁷⁴

Three-dimensional bioprinting can be manipulated with different biomaterials or varying manufacturing techniques, such as extrusion and laser-assisted sintering. Gross

macroanatomical structures can be designed by CAD data and the internal geometry can similarly be regulated by changing scaffold strand width and porosity.²⁷⁵

Bone tissue development by three-dimensional printing does not only necessitate mimicry of the original bone architecture but stable functionality as well. It is essential that the printed vascularized bone scaffolds integrate into the native tissue by allowing for nutrient diffusion and cell migration while maintaining homeostatic angiogenesis.²⁷⁶ Depending on the type of biomaterial employed, the temperature can be varied in the bioprinting method to incorporate bioactive agents and drugs.²⁷⁷

In vivo bone substitutes fabricated by 3-D printing have been tested and reported in the literature with a common underlying goal of optimizing the mechanical properties, such as compressive strength, to match those of the cranium. Orthotopic examples of *in vivo* implantation have been noted in rabbits and dogs, and although craniofacial implants did yield some degree of calvarial regeneration in rabbits, the samples differed in regenerative consistency due to differences in blood supply patterns in the region.^{278,279} Klammert et al. experimented with craniofacial ceramic implants in dogs, as noted above, and observed the degradation of secondary phosphate phases.²⁷⁹ These two studies demonstrate that a multitude of factors play a role in optimal scaffold fabrication. Wang et al. even modified bioceramic scaffolds by filling it with a phage nanofibers to form a virus-activated matrix, which was also seeded with MSCs, and successful bone synthesis was seen as a result of osteoprogenitor differentiation, increased endothelial cell activity and stimulated angiogenesis.²⁸⁰ These positive *in vivo* results show promise in the future of regenerative medicine as clinicians and research scientists work together in order to produce the most ideal scaffold for human craniofacial defect repair.

In a recent 2016 study by Kang et al., it was proven that craniofacial reconstruction, specifically biofabrication of the ear and mandible, can be achieved by means of the 3D printing process.²⁸¹ Varying concentrations of the hydrogel composite were tested for optimal cell delivery and viability as well as suitable mechanical properties. The design of their ear construct was planned intricately, maneuvering the printing process in a way that oriented synthetic PCL in certain layers and the cell-laden hydrogel in others to confer an ideal mechanical stability to the structure and fabricate microchannels that allow for the passage of nutrients and oxygen. Their handling methods of mandibular and calvarial defects differed in that they assessed that mandibular defects are arbitrary and so, dispensing paths of the composite hydrogel need to be determined with a CAD-based motion program. With regard to calvarial defects, which typically result from injury or trauma, they took the mandibular test one step further by conducting *in vivo* trials in rats

with the 3D printed bone sample and observed the sample exhibited vascularized bone growth in the central portion and periphery alike (Figs. 6 and 7).²⁸¹

Fig. 6. Integrated tissue organ printer (ITOP) system. (a) The ITOP system consists of three main units: (i) 3-axis stage/controller, (ii) dispensing module containing multi-cartridge and pneumatic pressure controller and (iii) a closed acrylic chamber with temperature controller and humidifier. (b) Illustration of basic patterning of 3D architecture containing multiple cell-laden hydrogels and supporting polycaprolactone polymer. (c) CAD/CAM process for automated printing of 3D shape imitating target tissue/organ. A 3D CAD model yielded from medical image data produces a visualized motion program, which contains details for XYZ stage movements and actuating pneumatic pressure to generate 3D printing operations.²⁸¹

Fig. 7. Mandible bone reconstruction. (a) 3D CAD model identified a mandible bony defect from human CT image data. (b) Visualized motion program was developed to construct a 3D architecture of the mandible bone defect utilizing CAM software. Lines of green, blue and red colors show the dispensing

paths of PCL, Pluronic F-127 and cell-laden hydrogel, respectively. (c) 3D printing process utilizing the integrated organ printing system. The image displays patterning of a layer of the construct. (d) Image of the 3D printed mandible bone defect construct, which was cultured in osteogenic medium for 28 days. (e) Osteogenic differentiation of hAFSCs in the printed construct was demonstrated by Alizarin Red S staining, designating calcium deposition.²⁸¹

Wang et al. also expanded on the previous work of experts in the field of regenerative medicine by introducing anti-inflammation functionality with the incorporation of Atsttrin, which suppresses TNF- α signaling, into an alginate/nano-hydroxyapatite scaffold.²⁸² The pro-inflammatory factor was known to stagnate the process of tissue regeneration by interfering with osteoblastic differentiation. By adding Atsttrin to the scaffold, superior osteogenesis was observed in mouse calvarial defects compared to the control and other experimental groups. Wang et al. ascertained that not only can 3D printed scaffolds yield calvarial bone regeneration *in vivo* but the incorporation of bioactive agents can undoubtedly have a stimulatory effect on the repair of defected tissue.²⁸²

5. Conclusions

Over the last decade or so, the significant rise in hard and soft tissue engineering applications has drawn the attention of experts in the fields of medicine, dentistry, bioengineering, and materials science. Great strides have been made to improve on previous results to replenish large numbers of cells and bioactive agents that ultimately give rise to newly formed tissue. Scaffold-based regeneration with the use of an abundant variety of biomaterials, in addition to stem cell and growth factor use, has proven to efficaciously restore the microanatomy and functionality of bone and cartilage tissue both *in vitro* and *in vivo*, and these results are surely paving the way for future clinical trials that are patient-specific and cost effective.

Studies of tissue engineering methods in the realm of oral and maxillofacial surgery have demonstrated that different scaffolds, polymeric, ceramic or composite, can be employed in load-bearing applications in the craniomaxillofacial complex. Their potency in revitalizing bone and cartilage in not only this region but also the entire human body provide promise and vast potential in future widespread incorporation in the defects of different maxillofacial tissues. Moreover, the expanding field of materials science is allowing bioengineers and clinicians to manufacture scaffolds of varying materials and composites that are ultimately proving to be effective in the regeneration of bone and cartilage. The evidence provided by this interdisciplinary, therapeutic approach that has

the potential to target maxillofacial anomalies provides the medical community with enthusiasm to advance the treatment of patients in a safe and effective fashion.

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