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Tissue Engineering and Regenerative Medicine in Craniofacial Reconstruction and Facial Aesthetics

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Abstract

The craniofacial region is anatomically complex and is of critical functional and cosmetic importance, making reconstruction challenging. The limitations of current surgical options highlight the importance of developing new strategies to restore the form, function, and esthetics of missing or damaged soft tissue and skeletal tissue in the face and cranium. Regenerative medicine (RM) is an expanding field which combines the principles of tissue engineering (TE) and self-healing in the regeneration of cells, tissues, and organs, to restore their impaired function. RM offers many advantages over current treatments as tissue can be engineered for specific defects, using an unlimited supply of bioengineered resources, and does not require immunosuppression. In the craniofacial region, TE and RM are being increasingly used in preclinical and clinical studies to reconstruct bone, cartilage, soft tissue, nerves, and blood vessels. This review outlines the current progress that has been made toward the engineering of these tissues for craniofacial reconstruction and facial esthetics.

Keywords

Craniofacial; Facial aesthetics; Regeneration medicine; Tissue engineering

The craniofacial anatomy is highly specialized and individualized and is of critical functional and cosmetic importance but is prone to genetic and environmental insults. The head and face are commonly affected by cancer and trauma,[1,2] and of all the live births affected by a minor or major anomaly, one-third involve the head and face.[3] Around 85% of the global population is in need of craniofacial tissue at some point during their lifetime,[4] and >28,000 head and neck reconstructions are performed every year in the United States (US).[5] Craniofacial deformities can have a dramatic impact on quality of life, and adequately reconstructing the complex form, function, and esthetics of facial anatomy is challenging. The criterion standard approach is to replace missing or damaged tissue with autologous grafts. Donor bone and soft tissues, however, are in finite supply and their harvest can result in significant morbidity.[6] Allogeneic grafts from cadavers or living donors

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bring the risk of infection, inflammation, lifelong immunosuppression,[7,8] and unpredictable donor-recipient anatomical compatibility.[9] Prosthetic alloplastic materials are unable to restore the multiple complex sensory and motor functions of craniofacial structures, do not expand in growing children, and are at risk for failure and infection.[10–13] Thus, a clear need exists to develop alternative strategies to reconstruct craniofacial tissues.

Regenerative medicine (RM) is an emerging interdisciplinary field which combines the principles of cellular and molecular biology, material science, and bioengineering, to support endogenous healing and replace or regenerate cells, tissues, or organs, with restoration of impaired function. Tissue engineering (TE) is a related concept centered on the engineering and manufacturing aspects of tissue replacement; however, TE and RM are often combined and treated as a single research pursuit.[14,15] TE/RM supports natural tissue regeneration processes by using cells, natural or artificial scaffolding materials, growth factors (GFs), gene manipulation, or combinations of these elements (Fig. 1). The cells of interest, often stem or progenitor cells, are typically isolated, expanded, differentiated ex vivo, seeded onto scaffolds, then reinserted into the defected areas with the scaffolds, often in combination with tissue-specific GFs. Mesenchymal stromal cells (MSCs) are the most common cell type used because of their ethical acceptance, ease of harvesting, robust proliferative capacity, and their ability to give rise to the cells commonly required for craniofacial reconstruction, namely osteoblasts, chondroblasts, adipocytes, tenocytes, myoblasts, and stromal cells.[16,17] MSCs are mostly sourced from human bone marrow-derived stem cells (BMSCs) or adipose tissue-derived stem cells (ADSCs). Although BMSCs were described first and have been the focus of TE strategies, ADSCs are in greater abundance and can be harvested with less patient-morbidity from liposuction or fat excision procedures. Scaffold and biomimetic materials can assist cellular growth and differentiation by providing a dynamic three-dimensional [3D] framework for cellular attachment, migration, and protection. Ideally scaffolds are able to withstand the immune response and eventually undergo resorption. Synthetic biomaterials have been created and refined for different tissues. The application of GFs aims to provide the necessary stimuli to promote the activity and differentiation of stem/progenitor cells toward certain cell fates required for tissue healing. Vectors or nonchemical extracellular environmental changes, such as atmospheric pressure, can also be used to alter cellular activity.

TE/RM promises many advantages over current standards of treatment for craniofacial reconstruction; customized tissues can be created for specific defects, using an unlimited supply of bioengineered resources, enabling reconstruction without the need for immunosuppression. In craniofacial and facial esthetic surgery, numerous tissue types require repair following congenital or acquired defects. This review provides for the first time a unique synopsis of current concepts of TE/RM in craniofacial reconstruction and facial esthetic surgery. We focus on TE/RM of various types of tissues relevant to the field, including skeleton, soft tissue, adipose tissue, and neurovasculature, and provide an up-to-date report on future perspectives and challenges.

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BONE

The craniofacial skeleton provides the stable, rigid, structural framework for facial soft tissue, cartilage, and dental structures, and is a key determinant of facial esthetics.[18] Loss of craniofacial bone, owing to congenital, traumatic, or neoplastic causes, can result in significant structural and functional deformities. Bone TE has large applications within craniofacial surgery and has been extensively studied (Fig. 2).[19–21] Preclinical studies have demonstrated that both BMSCs and ADSCs are effective osteoblastic precursors and when placed into mandibular or critical-sized cranial defects, they can accelerate bone regeneration.[22–25] Additionally, MSCs modified ex vivo using bone morphogenetic protein 2 (BMP-2) and applied to the dog mandible during distraction, accelerated osteogenesis.[26] In humans, MSCs have been used to engineer bone in the jaw and cranium in clinical case series and case reports.[27–32] One randomized clinical trial (RCT, n = 30) reported that β-trical-cium phosphate (β-TCP) scaffolds seeded with BMSCs, monocytes, and macrophages promoted more bone to form in areas of maxillary sinus deficiency than did scaffolds without cells.[33] The most effective bone-forming MSC remains to be identified. Specific subpopulations of ADSCs,[23] induced pluripotent stem cells (IPSCs),[34] and genetically modified ADSCs,[35] all may have enhanced osteogenic potential and are able to promote bone formation in the craniofacial skeleton of animals. Recently, the mouse (mSSC) as well as the human skeletal stem cell (hSSC) have been identified, defined as cells with the ability for self-renewal, which give rise to bone, cartilage, and stromal tissue in vitro and in vivo.[36,37] SSCs appear to be a promising cellular candidate for future skeletal tissue engineering therapies with the unique advantage of requiring less exogenous stimulation to drive differentiation of bone and cartilage compared to MSCs and ADSCs. The bone-regenerating ability of ADSCs and BMSCs can be encouraged by GFs. The members of the transforming GF-beta (TGFβ) family, such as BMPs, fibroblast GFs (FGFs), vascular endothelial GF (VEGF), and platelet-derived GF (PDGF), have all been used for bone TE.[38] Two recombinant BMPs have been approved by the US Food and Drug Administration (FDA) for clinical use: Infuse Bone Graft, containing rhBMP-2 (Medtronic and Wyeth, Watford, UK), and Osigraft, containing rhBMP-7 (Stryker Biotech, Ontario, Canada). BMP-2 and BMP-7 are able to promote bone regeneration in the alveolar ridge and facilitate the repair of critical-sized craniofacial bone defects in humans.[39–41] GFs can be incorporated into seeded cells via molecular or genetic modification,[42] or alternatively can be combined with scaffolds by soaking or bonding. Soaking results in the quick release of GFs by passive diffusion or upon degradation of the biomaterial.[42] GFs that are encapsulated or covalently bound to scaffolds are released according to cellular demands, which may more accurately recapitulates the natural bone-healing process which occurs over several weeks.[43] Multiple GFs added in unison, or in temporal/spatial succession, may have synergistic results and further promote bone formation,[44] which remains to be defined in future studies. Platelet-rich plasma (PRP) is rich in GFs[45] which are released upon platelet activation and induce cellular differentiation, enhance healing, and promote bone regeneration.[46] PRP is gaining interest in bone TE and is being increasingly used in orthopedic surgery.[47] In the craniofacial skeleton, a PRP membrane incorporating MSCs promoted the healing of critical-sized cranial defects in both mice and rabbits,[48] as well as the healing canine mandibular defects, with evidence of improved vascularization.[49]

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A variety of scaffolds act as carriers for cells and GFs. Natural biodegradable polymers made of substances, such as polysaccharides (eg, chitosan) or proteins (eg, collagen), are highly biocompatible but may lack significant mechanical strength and may cause an immune response. Synthetic polymers, such as poly(lactic-co-glycolic acid) (PLGA) and polymer of lactic acid (PLA) have easily controllable mechanical and physical properties[50] and, once degraded, do not obscure computed tomography (CT) scans[51]; however, they are expensive and generally have weak cell adhesive ability. Other bone TE scaffold biomaterials include bioactive ceramics, glass, hydrogels, metals, and composite scaffolds.[52] Hydrogels closely resemble the extracellular matrix but may lack mechanical strength. Bone is composed of 85% calcium phosphate; therefore, biphasic calcium phosphate bioceramics, such as hydroxyapatite (HA) and TCP, have been widely investigated for their use as bone scaffolds. These bioceramics are highly biocompatible, not immune reactive, and can be easily assessed radio-graphically. Biodegradable metals are absorbed within the physiologic environment and may have superior mechanical properties to biodegradable polymers.[50] Composite materials, composed of ≥2 biomaterials, could offer the best qualities from each material.[53] PLGA, for example, can be combined with HA to significantly enhance its osteogenic environment.[54] Advances in patient imaging and computer-assisted design (CAD) technologies have advanced the field, enabling the fabrication of complex 3D custom-fit scaffolds with optimal pore sizes to improve load-bearing strength, cellular adhesion, and the delivery of biomolecules.[55] 3D printing and electrospinning, for example, are based on CAD software and allow for the creation of scaffolds with more tightly manipulated internal morphology and gross geometry.[56,57] Electrospinning is able to create scaffolds made of nanofibers with architectural, functional, and morphologic similarities to collagen fibrils.[58] These nanofibrous scaffolds can be designed to have high porosity and high surface-to-volume ratio which enhances cellular attachment and proliferation.[59,60] Incorporation of metallic nanoparticles can increase the mechanical strength, cellular adhesion, long-term osteoblast function, collagen synthesis, alkaline phosphatase activity, and calcium deposition of bioscaffolds.[58,61]

Bone TE approaches have also been explored in dentistry. The teeth are highly specialized facial structures with important influences on facial esthetics. Recent systematic reviews of preclinical studies have highlighted the success of bone TE strategies to regenerate oral peri-implant bone,[62] alveolar bone,[19] and periodontal bone.[63] In humans, a clinical case series showed the benefits of bone TE for the reconstruction of oral peri-implant defects,[64] and a systematic review of clinical trials reported the effectiveness of bone TE for alveolar bone regeneration.[20,21] Another question which is important to address is whether bone TE/RM may have clinical efficacy in patients whose regenerative capacity is impaired by infection or irradiation. Delivery of BMP-2 in a collagen sponge helped to reconstruct calvarial bone in irradiated[65] or infected wounds in rabbits.[66] Dermal fibroblasts transduced ex vivo to express BMP-7 were able to promote the regeneration of calvarial bone in the defects of mice subjected to therapeutic doses of radiation.[67] These studies suggest TE/RM strategies have value in these complex clinical scenarios. To summarize, preclinical and early clinical studies demonstrate an enormous potential of TE/RM in craniofacial bone repair. There are, however, large variations in study methodology with regards to the nature of cells, biomaterial scaffolds, and type/dimensions of defects used. Future work must identify the

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biomaterials, cell, and GFs with most clinical effectiveness for certain clinical situations, in more standardized, preclinical, and clinical studies.[68]

CARTILAGE

The cartilage of the craniofacial skeleton is found in the nose, ears, pharynx, eyelids, and joints. Cartilaginous tissue has a limited ability for spontaneous repair because of its avascular, aneural, and almyphatic nature, as well as the low mitotic activity of chondrocytes. Cartilaginous deficiencies can therefore result in dramatic deformities. Existing therapies for cartilage repair are limited and surgical reconstruction of the craniofacial cartilage, including the external ear, are arguably some of the most challenging reconstructive operations because of the complex patient-specific 3D architecture. Cartilage-based TE has potentially vast application in craniofacial reconstructive surgery (Fig. 3). Implantation of autologous chondrocytes can regenerate extracranial articular cartilage in humans in extracranial regions,[69,70] and the FDA has approved autologous chondrocyte implantation/transplantation (ACI/ACT) for the clinical treatment of joints.[71–74] However, the progress made in the orthopedic field will need be duplicated in the craniofacial region, given that its cartilage is mostly subcutaneous, exposed to different physical forces, and is present in a highly antigenic environment with frequent immunological responses, including phagocytosis.[75] Initial preclinical and clinical studies have been promising; bovine articular chondrocytes seeded into 3D polyglycolic acid-(PGA)-PLA templates constructed in the form of a human ear and transplanted into the dorsum of 10 athymic mice produced lasting cartilage, both morphologically and histologically, after 12 weeks of implantation.[76] Using the same model, poly(L-lactic acid-ε-caprolactone) (PCL) copolymer scaffolds molded into human ear shapes and seeded with articular chondrocytes supported the development and maintenance of cartilage in a human ear shape over 40 weeks.[77] Additionally, human septal chondrocytes, expanded ex vivo in culture with TGFβ, FGFs, and PDGF and resuspended in alignate polymer structures maintained the size, shape, and viability, with histological, biochemical, and biomechanical features of nasal septum up to 60 days post implantation in the dorsum of athymic mice.[38] In a clinical series of 4 patients with microtia, a 2-stage ACI approach was used. Autologous chondrocytes were harvested from the underdeveloped ear, expanded first in vitro and then in a subcutaneous pocket in the patient's abdomen for 6 months, before they were explanted and hand-sculpted into an ear framework used for auricular reconstruction. Five years following auricular reconstruction, the ear had retained its form.[78] Nasal alar lobe defects of 5 patients were repaired using autologous chondrocytes harvested from nasal septal cartilage biopsies, expanded ex vivo, seeded onto fibrous collagen scaffolds, and cultured with autologous serum onto collagen type I and III membranes for 4 weeks. Engineered cartilage grafts were shaped intraoperatively and successfully implanted in regions where tumors had been excised under paramedian forehead or nasolabial flaps.[79] Another clinical trial used autologous nasal chondrocytes to reconstruct the nasal alar of 11 patients with nasal alar valve collapse. Nasal cartilage was harvested in small strips, disaggregated, centrifuged, and resuspended in autologous PRP. This fibrin gel was placed into the external nasal valve collapse defects and, at 12 months following surgery, formed persistent cartilage with the appearance of an augmented nasal dorsum without obvious contraction and deformation.[80]

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Despite these promising studies, ACI/ACT therapies are limited by the paucity of donor chondrocytes, the morbidity associated with their harvesting, and the slow proliferation capacity of harvested chondrocytes. MSCs and perichondrocyte cartilage progenitor cells[81] are gaining use in cartilage-engineering strategies. They are multipotent and have high replicative abilities, so fewer cells are required at harvest. Synovium-derived MSCs[82,83] may have a superior capacity for chondrogenesis.[84,85] MSCs, however, have the potential to form unstable cartilage with reduced mechanical stiffness and are prone to fibroblast dedifferentiation or hypertrophy in vitro and in vivo.[70,86] Additionally, chondrogenically induced BMSCs tend to lose their chondrogenic ability with passage, resulting in ectopic ossification upon subcutaneous transplantation.[87,88] Co-transplant of chondrocytes and MSCs can overcome the limitations of using each cell individually.[89,90] Human microtia chondrocytes and BMSCs seeded onto a human ear-shaped PGA scaffold in a ratio of 1:3, grown for 1 week in vitro, and then transplanted subcutaneously into nude mice, resulted in the formation of de novo cartilage 12 weeks after transplant, and maintained the delicate cartilaginous structure with proper elasticity of the cartilaginous tissue. This suggests the chondrocytes had a stable chondroinductive effect on the BMSCs.[91] In a second study, human ADSCs and auricular chondrocytes from microtia specimens and were co-grafted into a nude mouse in a 3:7 ratio, and after 8 weeks formed cartilaginous tissue with translucent appearance and good elasticity with cartilage-specific ECM components, including collagen type II, glycosaminoglycans (GAGs), aggrecan, and elastic fibres.[92] An alternative approach in future investigations may be to exploit the capacity of the aforementioned mSSC[36] to both self-renew and differentiate into cartilage and bone.

The GFs most intensively studied for their molecular control of chondrogensis of MSCs and proliferation of chondrocytes include the BMPs, Wnts, and FGFs.[93,94] Combined BMP-2 and TGFβ1 can induce MSC chondrogenesis in pellet culture.[95] Dexamethasone also induces the chondrogenic differentiation of BMSCs.[96] GF receptor expression is thought to dynamically change during chondrogenesis and temporal control in administration of chondrogenic factors may be required to improve cell growth, matrix deposition, and the phenotype of the cartilage formation.[97,98] Similar natural and synthetic materials used for bone have been explored in cartilage TE. Natural materials include agarose, alginate, hyaluronic acid, gelatin, fibrin glue, collagen derivatives, and acellular cartilage matrix, but these may have inferior mechanical strength, disease transfer, and antigenicity, and be prone to rapid and variable host-related degradation. Of the synthetic polymers polyhydroxyacids, such as PLLA, PGA, and PCL have been well studied and are easily extruded into fibrous or open-lattice sponges. One study comparing these 3 polymers found all promoted cartilage formation, but the PCL template yielded neocartilage with the best gross architecture akin to a human ear.[75] PEG-based hydrogels are also able to promote chondrogenesis[99–101] and are biomaterials already approved by the US FDA.

The temporomandibular joint (TMJ) is a synovial joint which can be damaged by tumors, trauma, and degenerative joint disorders including rheumatoid arthritis, osteoarthritis, and ankylosis.[102] TMJ dysfunction can cause pain, problems with speech, swallowing, and mastication, and facial asymmetry. Unlike the hyaline cartilage of the knee joints, the articular surfaces of the TMJ mandibles are covered by fibrocartilage.[103,104] Additionally, regeneration of the TMJ articular surface requires an adequate bone-cartilage interphase.

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[105–107] This can be achieved by seeding both osteoblasts and chondrocytes into scaffolds that are able to fulfill the biological and mechanical requirements for the regeneration of cartilage and bone. The scaffolds can also be shaped fit the unique TMJ environment. In a preclinical study, bovine osteoblasts and chondrocytes were seeded onto a scaffold composed of PGA and PLA formed in the shape of a human mandible condyle. The scaffold was implanted into subcutaneous pockets of athymic mice, and after 12 weeks, there was evidence of trabecular bone and hyaline cartilage on the articular surface.[108] Alternatively, scaffolds can be seeded with mesenchymal progenitor cells or differentiated MSCs, as MSCs have the ability to differentiate into both bone and cartilage depending on cues in their cellular microenvironment such as matrix stiffness.[109] In one preclinical study, chondrogenic and osteogenic differentiated BMSCs were encapsulated into a bilayered osteochondral PEG-based construct that had been carved into a human mandibular condyle shape. After 8 weeks of transplantation into the dorsum of immunodeficient mice, the construct had formed de novo mandibular condyles with areas of both cartilage and bone.[99] Chondrogenic differentiated MSCs have also been directly injected into the intra-articular space of the TMJ in a rabbit model of TMJ osteoarthritis, where they were reported to integrate into the mandible and form both subchondral cancellous bone, cartilage, and synovial membrane 4 weeks post-transplantation. Interestingly, the cartilage repair was better in rabbits transplanted with differentiated, compared to non-differentiated, MSCs.[110] Developing an injectable approach for cartilage regeneration of the TMJ could satisfy a patient's desire for minimally invasive surgery, but this requires substance that is viscous or semisolid to be injected, and once injected to maintain a desired shape or form without diffusion.[111] BMSCs have also been modified using NEL-like molecule 1 (NELL-1—a GF thought to target cells toward an osteochondral lineage) seeded onto a PLGA composite and transplanted into large condylar defects in goat mandibles. This rapidly regenerated both bone and cartilage tissue.[112] Low-intensity pulsing ultrasound can stimulate stem cell growth and differentiation, and demonstrates enhanced formation of bone and cartilage tissue and their integration in rabbit mandibular condyles.[113] In humans, HA/collagen blocks have been successfully used in TMJ ankylosis with PRP to regenerate a new functioning condyles in a case series (n = 19) of children and adolescents.[114] This is a promising initial finding but longer-term clinical studies in a larger cohort of patients are required. In conclusion, the use of cartilage TE in the craniofacial region is expanding, but there are unique challenges to overcome before the more widespread use of engineered cartilage is possible for reconstruction of the nose, ears, and TMJ.

SKIN

The skin is an important tissue in the craniofacial region. In addition to its barrier functions it provides the insertion for facial muscle which is important in communication. Given the face is the most exposed part of the body, the facial skin is frequently damaged in traumatic, congenital, and neoplastic processes. Disruption of the epithelial contiguity impairs the skin's barrier, pigmentary, thermoregulatory, mechanical, and cosmetic functions.[115] Wounds that penetrate beyond the epidermis in adult mammals heal by scarring, forming tissue that is of inferior functional quality to that of normal skin.[115] Skin was one of the first

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tissues to be successfully engineered and FDA-approved, and there are currently a number of skin substitutes available for clinical use (Fig. 4).

The first skin substitutes were biodegradable porous matrices that emulated the dermis and functioned as templates for dermal regeneration. Typically, these matrices are placed on the wound bed, and promote healing by increasing adherence and proliferation of regenerative cells, and by acting as a vehicle for drug delivery. After sufficient integration and vascularization, the matrices are covered with autografts.[116] Natural and synthetic biomaterials can be used for dermal matrices. Natural polymers include polysaccharides (eg, chitosan), proteoglycans, proteins (eg, collagen). These materials are biocompatible and biodegradable with similar composition to the ECM.[117,118] Integra was the first commercially available skin substitute. It is made of cross-linked collagen and chondroitin-6-sulfate, with a silicon sheet attached to one side which functions as a temporary epidermal layer.[119] Integra is primarily used for treating deep burn wounds. It is able to facilitate dermal regeneration while preventing wound contraction, which results in improved wound healing, function, and appearance.[120] Natural polymers, however, have variable degradation rates, limited ability to be modified, and can cause immunogenic reactions.[121] Decellularized-derived matrices are made by removing cells and keeping the protein component. They preserve native skin architecture, have low immunogenicity, and reduce the risk of disease transmission.[119,122] Alloderm is a skin substitute made from decellularized donor skin used both for wound repair and reconstructive surgery. In the craniofacial region, it has been used to reconstruct the eyelid. Alloderm is sufficiently rigid to act as a replacement for the tarsus and also behaves as a scaffold promoting the regrowth of the conjunctiva on its surface.[122] Synthetic polymers may be absorbable, such as PLA, PLGA, PGA, PCL, PEG, or nonabsorbable, such as polyurethane, nylon, polytetrafluoroethylene (PTFE), and polyethylene terephthalate. Synthetic polymers are cheaper, more homogeneus, bypass the immunogenic effects, and can easily be manipulated to exhibit controlled GF release or antimicrobial effects.[123–126] Synthetic polymers have been shown to accelerate wound closure in diabetic patients.[127] Nanomaterials are extremely versatile with regards to fabrication and design methodology permitting the modification and customization of material properties to suit the wound repair environment.[128] Of the numerous matrix materials, it is difficult to identify which materials would be best for widespread clinical translation.

Subsequent approaches to skin TE focused on developing keratinocyte culture techniques to produce live cultured skin products. Traditionally, keratinocytes were cultured into epidermal autografts (CEA) or seeded onto natural or synthetic dermal scaffolds.[129,130] Epicel is an example of a cultured autologous epidermis first produced in 1988. Without a dermal layer, these scaffolds are thin, fragile, and lack elasticity, suppleness, and tensile strength. Epicel and epidermal constructs are used for major burns wherein very little autologous viable skin remains. Dermoepidermal skin substitutes (DESS), containing both epidermal and dermal layers, were subsequently developed. In addition, the inclusion of fibroblasts in dermal substitutes was found to improve wound healing.[131,132] Autologous skin cells are used where possible but several weeks are required before skin biopsy cells are sufficiently expanded for grafting.[119] Commercial skin substitutes such as Apligraf and Dermagraft, therefore, use allogenic epidermal and dermal cells and can be immediately

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applied to injured skin.[133] Dermagraft consists of allogeneic neonatal dermal fibroblasts cultured on a polyglactin mesh. As the mesh degrades, the cells produce de novo ECM matrix proteins.[119] Apligraf consists of neonatal foreskin fibroblasts and keratinocytes cultured to form dermal and epidermal layers.[119] The fibroblasts are first mixed with type 1 collagen to form a strong network of cells and matrix proteins, and the keratinocytes are then seeded onto the construct and form stratified layers. Dermagraft and Apligraf are ultimately rejected but before rejection can help heal the cutaneous layers.[134,135] "Minced micrografting" is a new approach where a small full-thickness skin sections are removed from the patient, minced, mixed with hydrogel, and applied onto the wound. It is cheap, simple, and effective in grafting large wounds with little donor skin amounts.[136]

A number of GF families are integral to endogenous wound healing and may promote healing if applied at specific time points during injury. Topical application of epidermal GF (EGF) in a double-blind clinical trial (n = 12) accelerated the epidermal regeneration of skin graft donor sites.[137] A double-blind RCT (n = 118) found that topical application of PDGF safely and effectively stimulated healing of chronic full-thickness diabetic ulcers.[138] FGF accelerated the healing of chronic wounds in 2 RCTs (n = 58, n = 50 respectively).[139,140] Stromal cell-derived factor 1[141] and TGFβ[142] have shown beneficial effects in animal studies and results remain to be translated to humans. Topical factors must be able to withstand degradation by the wound's proteolytic environment.[143] The method by which to deliver GF to achieve maximum therapeutic effect remains to be determined.[128]

The skin substitutes in current clinical use have established milestones in the treatment of skin disorders,[116,144] and address the primary therapeutic concern which is rapid recovery of the skin's barrier function to diminish water loss and prevent infection. However, these substitutes are not routinely used because of their high cost, limited effectiveness, and the inability to fully recreate the functions and aesthetics of skin.[145] Long-term success is limited by the absence of self-renewing stem/progenitor cells.[146] A number of animal studies have demonstrated the benefit of the topical application of ADSCs[147–151] and BMSCs[152–155] on healing wounds. A small number of clinical studies have shown that autologous BMSCs help to heal chronic wounds.[156–159] Two randomized studies found that intramuscular injection of BMSCs into the limbs containing chronic ulcers, in addition to the topical application of cultured autologous BMSCs on the ulcers, decreased wound size (n = 41, n = 24, respectively).[157,160] Autologous ADSCs, topically applied to wounds resulting from radiation injuries, using an artificial dermis and supplemented with FGF, helped to heal the chronic wounds (n = 10).[161] ADSCs differentiated into adipocytes and injected into depressed scars resulted in long-term restoration of volume (n = 17).[162] ADSCs may also promote skin rejuvenation and the repair of atrophic and photo-damaged skin, perhaps through the secretion of cytokines and GFs that stimulate dermal fibroblasts to synthesize collagen, a process that decreases in skin aging.[163] Subcutaneous injection of ADSCs in hairless aged mice increased dermal thickness and collagen density,[162] increased angiogenesis, and reduced UVB-irradiated induced wrinkles.[164,165] In one clinical study, autologous lipoaspirate composed of around 25% ADSCs was injected intradermally into the photo-aged skin of a patient, and improvement was noted in skin texture and wrinkles at 2 months with increase in dermal thickness detected with ultrasound.[163] These initial clinical studies are promising but are few in number and limited by sample size and long-

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term follow-up.[166] They remain to be validated in larger studies conducted with more patients.

Another limitation of currently available skin substitutes is their inability to carry out the functions of normal skin owing to missing dermal appendages.[115,116] The sweat and sebaceous glands, hair follicles, adipose tissue, Langerhans cells, and neurovasculature are responsible for thermoregulation, insulation, sensation, ultraviolet protection, and the esthetic appearance of skin. Inclusion of progenitor cells may facilitate generation of dermal components. Hair follicle cells are skin progenitor cells able to reconstitute all components of the cutaneous epithelium,[167] and facilitate re-epithelialization as well as the formation of sebaceous glands and hair follicles following cutaneous wounding.[168–173] Application of hair follicle cells to wounds in animal studies reduces time for closure and forms skin with cycling hair follicles.[169,174,175] A preliminary clinical study (n = 10) demonstrated that inclusion of hair follicles in skin grafts reduces the wound size in chronic leg wounds with evidence of increased re-epithelialization and vascularization on histology at 18 weeks.[176] An RCT (n = 12) demonstrated that implantation of skin grafts containing scalp hair follicles reduced wound size of chronic wounds compared to non-hairy skin grafts and formed hair-bearing skin.[177] No clinical studies have attempted to reconstitute scalp hair, and this remains a subject of future investigation. Hair follicles are also able to guide nerve migration both in vitro and in vivo and their inclusion in skin grafts enhances the innervation of tissue-engineered skin.[178] Full restoration of sensation in engineered skin, however, has not yet been demonstrated. To form pigmented skin, keratinocytes, fibroblasts, and melanocytes were co-transplanted subcutaneously into mice and rats and were demonstrated to successfully form pigmented skin with functioning melanocytes several months after surgery.[179–181] Current skin substitutes neglect the subdermal fat layer which results in skin with reduced mobility and more noticeable contour defects. Multilayered skin substitute have been made in vitro by co-culturing preadipocytes and keratinocytes,[182] or by simply growing ADSCs, which are able to generate 3-layered skin composites with epidermal, dermal, and hypodermal elements by a self-assembly process.[183] Gene therapy is another possible way to augment the regeneration potential of skin cells, and gene-targeted epidermal cells showed long-term regenerative capacity when grafted into immunodeficient mice.[184] Many of these preclinical studies, however, remain experimental,[185] and although skin TE has undergone substantial development, there remains a number of areas need to be elucidated before it is possible to engineer fully functional adult human skin, and to create skin capable of healing without scarring.

ADIPOSE TISSUE

Fat transplantation is a technique used for a variety of reconstructive procedures in the craniofacial region, including the treatment of contour and soft tissue alterations following trauma, infection, radiation therapy-related, involutional disorders such as hemifacial atrophy, or for cosmetic procedures such as lip augmentation and wrinkle therapy. Fat transplantation, however, is limited by variable resorption rates[186] and partial necrosis, which can lead to shape and volume loss with time and unreliable long-term outcomes.[187–189] Late enlargement of facial fat grafts can also occur with overall patient weight gain and requires surgical intervention. Adipose TE bypasses these issues (Fig. 5). Preclinical and

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early clinical series show that ADSCs enhance soft tissue augmentation and survival of fat grafts.[190–192] BMSC and ADSC-seeded hydrogel or collagen scaffolds promote adipogenesis and show retention of form for up to four weeks in mice.[193,194] In humans, the addition of ADSCs to aspirated fat before lipotransfer ("cell-assisted lipostransfer" or CAL) improves survival and vascularity of the adipose used to augment human breast tissue.[192,195,196] This has become a popular technique in plastic surgery. In the craniofacial region, BMSCs (n = 10)[197] and ADSCs (n = 5)[198] have been successfully used to enhance fat grafting into the face of human patients with Parry-Romberg syndrome, a condition characterized by progressive hemifacial atrophy of skin, dermis, subcutaneous fat, muscle, cartilage, and bone. Additionally, a RCT reported that ADSC grafting was effective, safe, and superior to conventional lipoinjection for facial recontouring in patients with craniofacial microsomia.[199] CAL was found to improve volume and symmetry in a patient with Parry-Romberg syndrome.[200] CAL has also been used in facial augmentation operations to recontour the faces of patients with lupus erythematosus profundus (n = 3),[201] and in face-lift procedures (n = 9).[202] CAL is effective, safe, and potentially superior to conventional lipoinjection or fat grafts. Compared to autologous fat grafts, grafts supplemented with ADSCs underwent less resorption when assessed by CT in patients with hemifacial atrophy.[198] An RCT (n = 20) comparing autologous fat grafts with CAL found patients receiving CAL required no further treatments, whereas those receiving fat grafts required multiple treatments.[203] The micro-RNA21 in ADSCs has been found to be regulated by EGF, and addition of EGF can therefore increase proliferation and inhibit the apoptosis of ADSC.[204] These preliminary studies thus suggest that ADSCs improve retention capabilities of transplanted fat in a minimally invasive therapy for facial tissue deformity. The efficacy of ADSC-based adipose TE treatments, however, remains to be evaluated for safety and efficacy in large randomized double-blind controlled trials. The FDA considers autologous ADSCs to be a "drug" because collagenase enzyme is used to separate the ADSCs from lipoaspirates, and CAL-based therapies therefore require complete regulation.[205] The 2 major limiting factors in facial CAL include lack of cell survival and vascularization.[206]

PERIPHERAL NERVES

The facial nerve is susceptible to injury during parotid tumor surgery, trauma, and petrous bone surgery, or may be congenitally absent. Facial nerve defects can lead to functional movement deficits and facial asymmetry, which can significantly affect quality of life. When primary nerve end coaptation is not possible, autografting is the criterion standard surgical reconstruction,[207] but is limited by availability of donor nerves and the morbidity associated with grafting, such as scarring, infection, and pain. Neuronal TE has been increasingly used in preliminary studies to regenerate the facial nerve (Fig. 6). The cells used in neural TE include neural stem cells (NSCs) which are able to promote nerve regeneration in animals,[208] but are difficult to isolate. Instead, BMSCs[209] and ADSCs[210] can be transdifferentiated into cells similar to Schwann cells which provide trophic, structural, and directional support to regenerating axons in the peripheral nervous system. BMSCs and ADSCs secrete trophic factors and are able to produce myelin-forming which can establish the supportive microenvironment for nerve regeneration.[211,212] ADSCs express genes that belong to the

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glial phenotype and are responsible for neuron metabolism and function,[213] and their secretome includes neurotrophic factors such as nerve GF (NGF), glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor.[214,215] A number of animal studies have used ADSCs, BMSCs, or dental pulp cells to promote regeneration of the facial nerve.[216–224] Uncultured stromal vascular cells seeded onto nerve conduits extending from the facial nerve were able to promote more nerve regeneration in rats than the nerve conduit alone.[225] Gene therapy has shown promise as a means of enhancing neural regeneration by promoting overexpression of neurotrophic factors, but durable improvements in functional outcomes and the consequences of vector-mediated gene delivery remain unknown.[226] Biomaterial scaffolds can guide axon regeneration.[227] The nerve conduits are designed as cylindrical tubes with internal channels or matrices, constituting porous walls to guide regeneration. Different material conduits (glasses, collagen, PGA) have been used,[228] and cells or bioactive agents can be incorporated. In studies on facial nerve regeneration, the GF employed basic FGF, delivered using acidic gelatin hydrogel microspheres to enhance its half-life,[229] GDNF,[216] and NGF.[222] Methods to improve delivery and bioavailability are needed.[230] Translational studies are required as considerable optimization of these therapies will be required for their potential to realize in their clinical potential.[228]

BLOOD VESSELS

Sufficient vascularization is a challenge common to all engineered tissues, except cartilage which is avascular, and becomes especially important when using 2D or 3D constructs.[231] Scaffold microarchitecture significantly influences the ability of engineered tissue to become vascularized. Scaffold pore sizes of 150 to 500 mm are recommended to support vascularization and blood vessel invasion.[232] Another option is co-transplantation of endothelial progenitor cells (EPCs) with MSCs which has shown to improve vascularization of bone and muscle. In critical-sized bone defects in animals, co-transplantation of EPCs and MSCs improved vascularization and was associated with increased release of VEGF.[233–235] Alternatively, vasculogenic and stimulatory ligands, such as VEGF and erythropoietin, can be added to synthetic scaffolds, to encourage neovascularization post-implantation.[236] In bone scaffolds, controlled release of VEGF from scaffolds can induce a more organized vasculature compared to the vasculature associated with uncontrolled VEGF release.[237] Despite these options, vascularization of large TE constructs remains a major limiting factor for organ engineering. The concept of axial vascularization may provide a promising strategy to overcome this challenge in the future. Axial vascularization of TE constructs may be provided by the principles of prelamination[238] and prefabrication.[239] Prelamination involves the implantation of a nonvascularized TE construct into a highly vascularized territory (eg, a flap) which then serves to create an axially vascularized unit suitable for free transplantation via its pedicle. Warnke et al[240] showed that axially vascularized flaps may serve as an “in vivo bioreactor” for ex vivo engineered bone constructs. For mandibular reconstruction after cancer resection, they loaded a computer-designed custom titanium mesh with HA blocks coated with recombinant human bone morphogenetic protein-7 and bone marrow-derived MSCs. Using the principle of prelamination, the construct was implanted into the patient’s latissimus dorsi muscle for a period of 7 weeks to promote

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heterotopic bone growth and vascularization from the thoracodorsal artery before successful inset into the bony defect.[240,241]

Prefabrication of TE constructs is achieved by implantation of vascular pedicles, such as arteriovenous (AV) bundles or AV loops, thus enabling the vascularization of bone or soft-tissue constructs, which then can be transplanted into distant defect areas.[242] This technique has shown promising results for mandibular reconstruction in large animal models.[243]

CHALLENGES AND LIMITATIONS

Despite the significant progress in techniques of TE/RM in recent years, there are still considerable challenges, which have to be addressed before successful translation into routine clinical applications can be achieved. Although a combination of different cell types, GFs, and scaffolds builds the foundation of many promising TE approaches, the successful vascularization of TE constructs remains a major limiting factor for TE of large volumes or whole organs. As adequate perfusion is a crucial determining factor for the development and host integration of TE constructs, the translation of TE concepts into clinical applications depends on the success of future strategies to improve vascularization.

A further limitation which remains to be systematically analyzed in future studies is the oncologic safety of the components used for tissue engineering approaches such as GFs, cell types, and scaffolds. Especially for ADSCs, which may be a potential treatment strategy for defect reconstruction following oncologic resection or irradiation, oncologic safety concerns have been raised. ADSCs used in CAL may promote tumor growth and recurrence through stimulatory paracrine actions with in vitro and in vivo animal studies suggesting a prooncologic effect of ADSCs.[244] To date, only few studies have investigated the use of ADSCs in craniofacial reconstruction of congenital anomalies[200] and long-term data on oncologic safety are not available.

Functional reconstruction of tissues or organs is a further limitation of TE/RM. Owing to missing dermal appendages like sebaceous glands, hair follicles, as well as neurovascular structures, skin substitutes are yet unable to recreate fully functional skin layers. Substantial progress is still needed in all areas of TE, to translate functional TE applications from bench to bench side.

The conclusions that can be drawn from the current literature are limited variations in study methodology regarding the nature of cells, different scaffolds, and defect characteristics. Future more standardized comparative studies are needed to identify cell types, scaffolds, and GFs with high effectiveness for certain clinical scenarios.

FUTURE PERSPECTIVES

Recent technologic advances which have been proven to be particularly valuable to the field of craniofacial reconstruction are 3D printing of biomaterials and nanotechnology.

3D printing is a rapidly emerging technology which enables the organization of a template into an appropriate 3D structure using computer-enabled printers and has the potential to

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replace more complicated processes of template fabrication in TE. In craniofacial reconstruction, the use of 3D printing for calvarial bone TE can produce porous structures with superior interconnectivity and fabricate custom templates for calvarial bone defects with specific anatomic shapes.[245] Published case series in human patients have shown high success rates with a limited number of complications despite being of high methodological bias.[246]

The use of nanomaterials such as nanoparticles, nanotubes, or nanofibers has been shown to improve mechanical properties of scaffolds, increase cellular attachment, and facilitate tissue regeneration. Several studies have shown improved biomechanical and biochemical properties of nanomaterials highlighting a great potential for TE in various tissues of the oral and maxillofacial region. With the risk of potential accumulation of nanomaterials in different organs, reliable dose-response and toxicity evaluation techniques, however, are urgently needed before routine clinical applications can be conducted.[247,248]

CONCLUSION

In craniofacial reconstruction and facial esthetic surgery current concepts of TE and RM provide strategies for reconstruction of several tissue types such as bone, cartilage, soft tissue, nerves, and blood vessels to treat congenital or acquired defects. Significant advances have been made and the results of preclinical and clinical studies are encouraging, however, differences in study methodology limit the conclusions that can be drawn and clinical translation. Early clinical success has been demonstrated with TE of bone and cartilage and experimental results for soft tissue reconstruction are promising. Larger and more systematic studies are required to determine the most effective cell types, scaffold characteristics, and delivery methods before TE and RM principles in craniofacial surgery can be brought from bench to bedside. Further advances will be possible through interdisciplinary collaboration between the fields of molecular biology, polymer chemistry, molecular genetics, materials science, robotics, and mechanical engineering.

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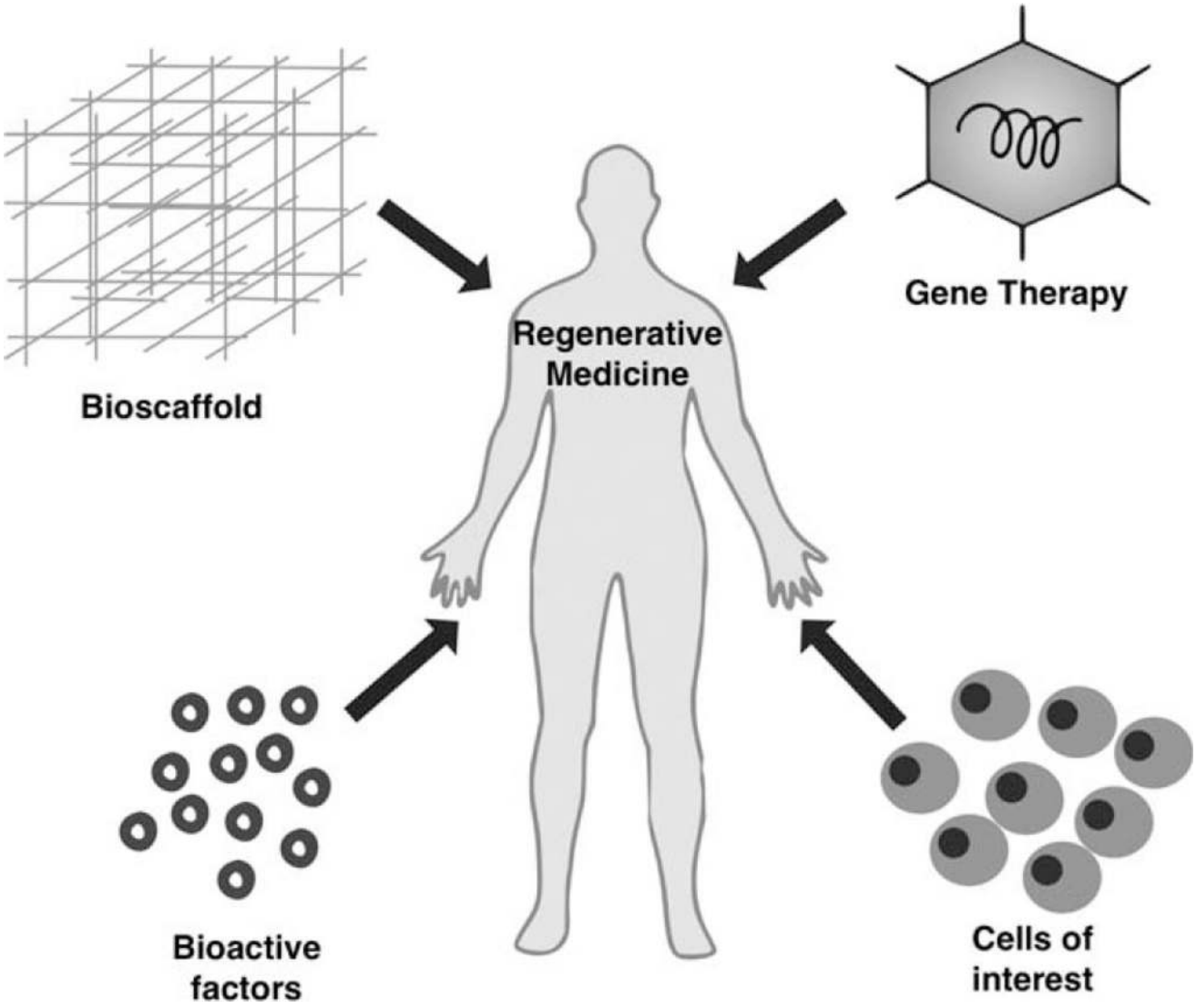

FIGURE 1.
The process of tissue engineering/regenerative medicine.

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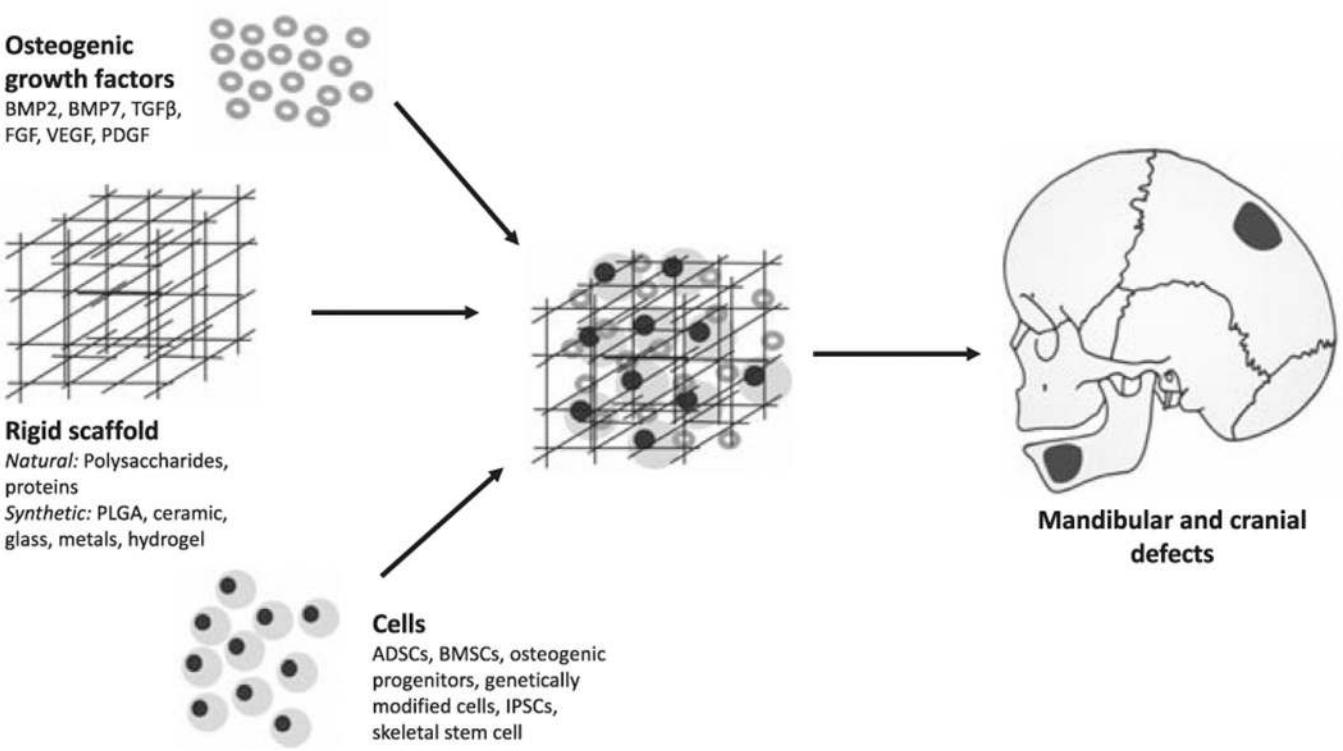

FIGURE 2.
Skeletal tissue engineering.

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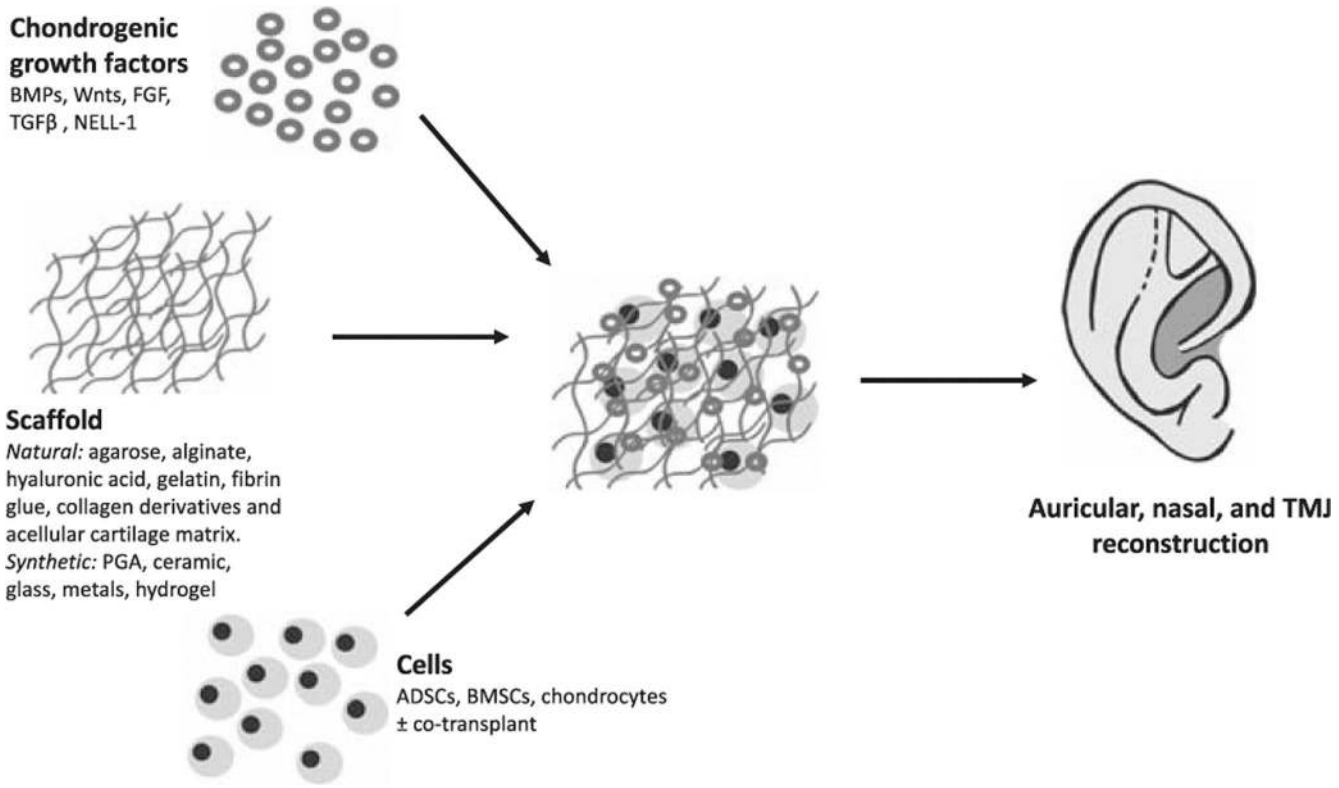

FIGURE 3.
Facial cartilage tissue engineering.

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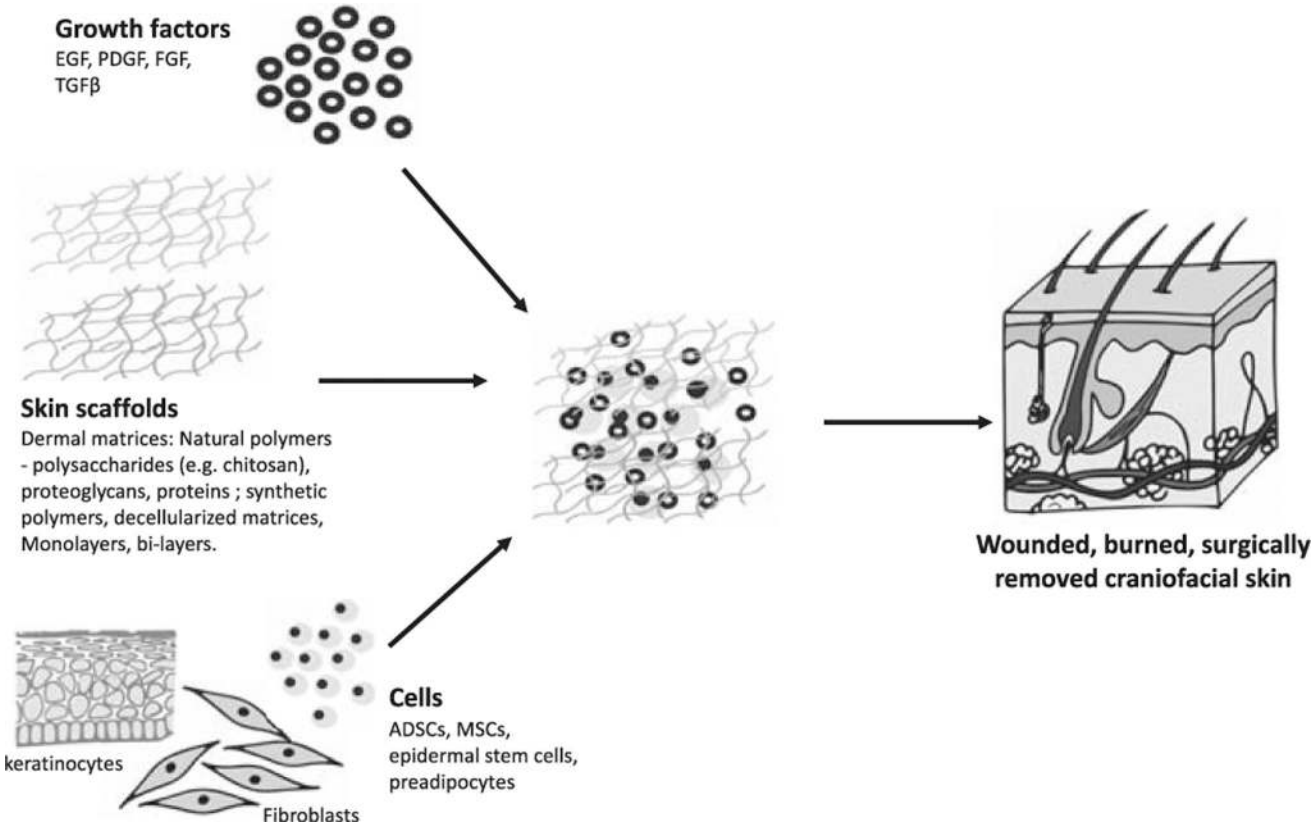

FIGURE 4.
Skin tissue engineering.

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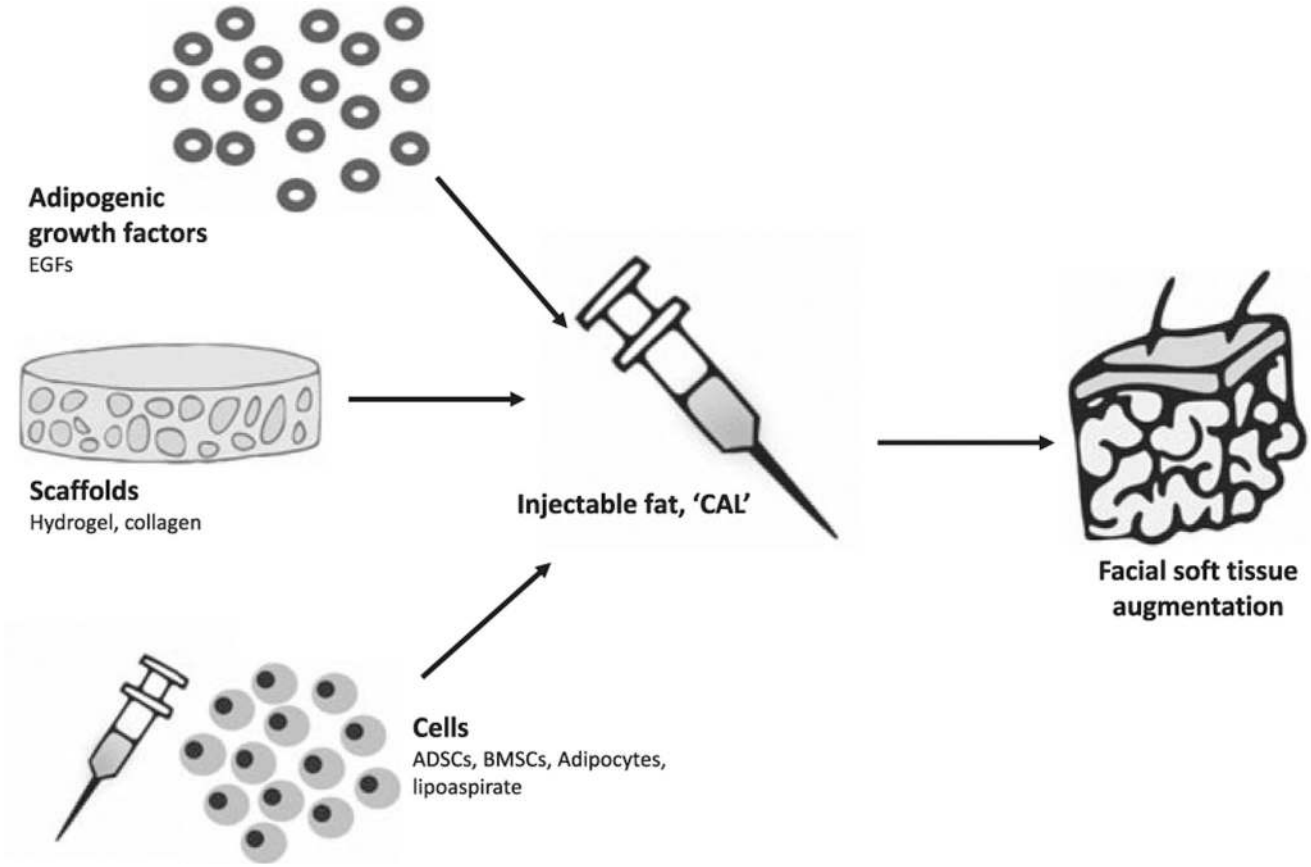

FIGURE 5.
Facial adipose tissue engineering.

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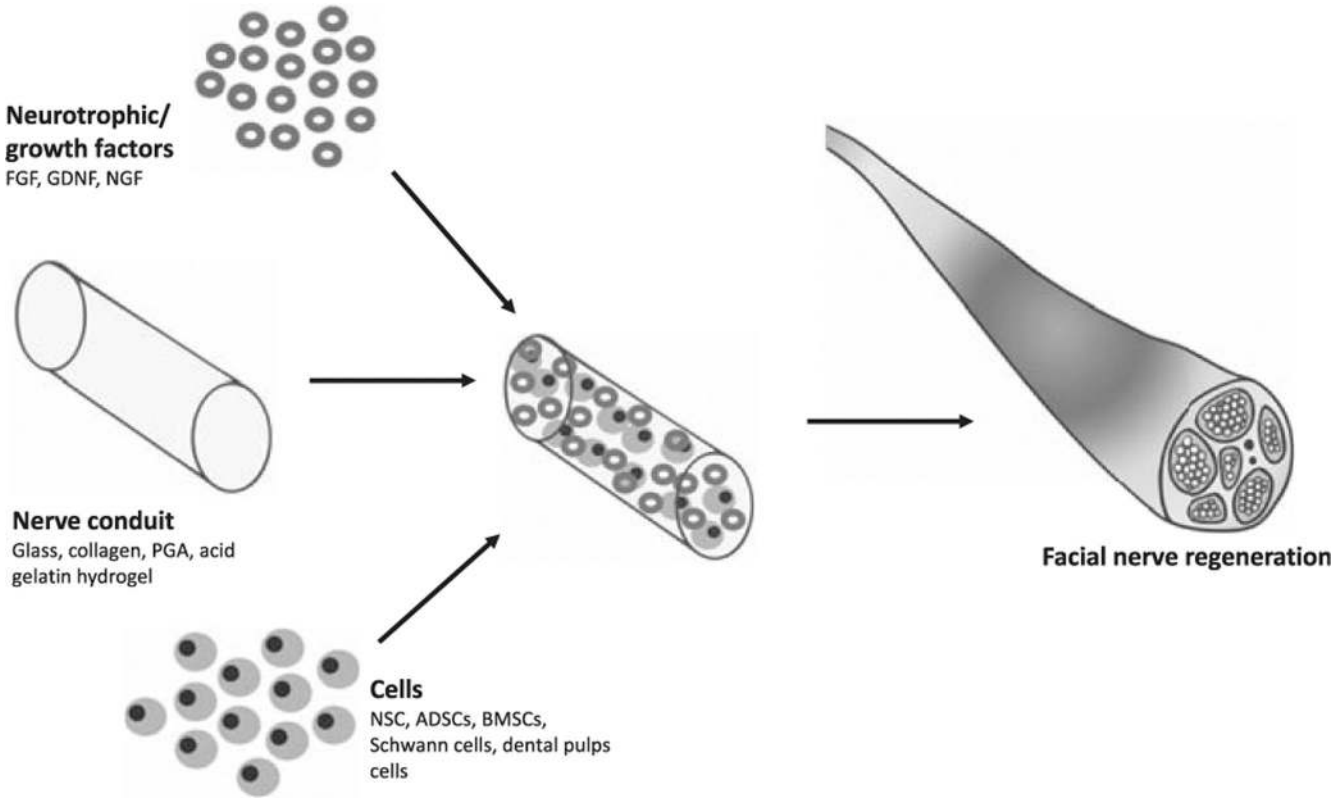

FIGURE 6.
Facial nerve tissue engineering.