



## Review article

## Advanced Hydrogel systems for mandibular reconstruction



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## ABSTRACT

Mandibular defect becomes a prevalent maxillofacial disease resulting in mandibular dysfunctions and huge psychological burdens to the patients. Considering the routine presence of oral contaminations and aesthetic restoration of facial structures, the current clinical treatments are however limited, incapable to reconstruct the structural integrity and regeneration, spurring the need for cost-effective mandibular tissue engineering. Hydrogel systems possess great merit for mandibular reconstruction with precise involvement of cells and bioactive factors. In this review, current clinical treatments and distinct mode(s) of mandible formation and pathological resorption are summarized, followed by a review of hydrogel-related mandibular tissue engineering, and an update on the advanced fabrication of hydrogels with improved mechanical property, antibacterial ability, injectable form, and 3D bioprinted hydrogel constructs. The exploration of advanced hydrogel systems will lay down a solid foundation for a bright future with more biocompatible, effective, and personalized treatment in mandibular reconstruction.

## 1. Introduction

Mandibular surgery is commonly performed due to tumor (squamous cell carcinoma and osteogenic sarcomas) ablation, traumatic insult, and osteonecrosis (osteoradionecrosis, medication-related osteonecrosis) debridement [1,2]. Acute and chronic osteomyelitis, temporomandibular joint instability, delayed healing, and disfunction are major clinical challenges. The patients may also suffer from such surgical treatment with both psychological and socioeconomic burdens.

The main target of mandibular reconstruction is to restore essential functions, including chewing, phonation, breathing, and normal bone metabolism [3]. Aesthetic restoration is highly desirable [4]. Autologous bone transplantation is the choice of surgical treatment in clinical practice [5]. Free flap transplantation is frequently used in mandibular reconstruction, especially for continuity defect resulting in a loss of mandibular unity. However, the donor site morbidity and the limited resource are the major challenges [6,7], leading to a surge of

investigations on the development of bioactive materials as alternatives.

Hydrogel systems exhibit high biocompatibility, controllable degradability, and easy modification to support minimally invasive surgery, with no need for later implant removal surgery [8]. Besides, they are an excellent choice for imitating the extracellular matrix (ECM) and encapsulating various stem cells and bioactive factors, to fill the defect zone and promote bone formation [9]. These advantages make hydrogel systems meet the special demands in mandibular reconstruction. Additional challenges in mandibular reconstruction include the frequent exposure to the oral bacterial environment and aesthetic concerns of facial reconstruction, highlighting the importance of R&D of the advanced hydrogels with antibacterial, injectable and 3D programmable properties [10–12]. To date, due to the complexity of mandibular reconstruction, there is few published reviews in the literature elaborating potential of hydrogels on mandibular reconstruction. So, in the present review work, we updated the current research and emerging strategies on hydrogel systems developed for mandibular

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reconstruction, aiming to inspire more promising research and clinical translation in complex maxillofacial reconstruction.

## 2. Clinical challenges and drawbacks of the current treatments for mandibular defect

### 2.1. Causative factors

The mandibular defect is defined as the lower jaw with the loss of a portion of the bone with or without damaging facial bone and accessories [13]. Congenital malformations [14], tumors [15], trauma [16], inflammation [17], and medication-related osteonecrosis [18] can all cause mandibular defects (Fig. 1). Additionally, frequent exposure to various disease-inducing agents (cigarettes, drugs, and carbohydrates) increases the probability of periodontal diseases and oral cancers, affecting the cell functions and aggravating the inflammation reaction to destroy the alveolar bone even extended to the mandible [19,20].

The main causes of mandibular defects are congenital malformations and acquired complications [21]. In the past few decades, mandibular deformities were thought to be common among individuals with specific genetic backgrounds, presenting with the mandibular defect or underdeveloped at birth [22]. Now, the etiologies of the mandibular defects have become more diverse. For example, resection of benign odontogenic tumors and comminution caused by trauma also often results in mandibular defects. Malignant tumor ablation, radiation-induced osteonecrosis, and medication/bisphosphonate (BPs) related osteonecrosis of the jaw (MRONJ/BRONJ) are also main causes in recent years [23].

Of note, MRONJ is a progressive disease of the mandible in which the necrotic bone extends beyond the region of alveolar bone, resulting in pathologic fracture, extra-oral fistula, and osteolysis involving the inferior border of the mandible [24]. In the USA 0.1% of osteoporotic

patients treated with oral BPs and 0.8%–1.2% of patients with multiple myeloma and bone metastases treated with intravenous BPs suffer from the MRONJ [25]. In the late stage of MRONJ, segmental resection is the only method to remove the necrotic bone, resulting in a postoperative defect. Similarly, mandibulectomy is also applied in malignant jaw tumors or bone metastases [26]. Such mandible losses more than 10%, it fails to heal spontaneously [27].

### 2.2. Unsatisfactory outcome of current clinical therapies

At present, bone transplantation, metallic devices, and distraction osteogenesis have been used to fill or repair the mandibular defect in clinical practice. Among them, the fibula-free flap (FFF) transplantation is the gold standard for mandibular reconstruction [28]. The history of current clinical therapies in mandibular reconstruction is presented in Table 1.

The strengths and weaknesses of current clinical approaches are summarized in Fig. 2. The clinical treatments are limited considering the infection with the presence of bacterial contamination and the donor site morbidity. Reconstruction plates demonstrate an infection rate ranging from 7 to 13% [29]. After mandibular distraction osteogenesis, a 12.2% risk of infection related to the distraction device is reported. The patients of 30.5% and 40% suffer from hyperalgesia and neuropraxia, respectively [30]. Besides, the use of metallic devices and distractors for mandible fixation and regeneration inevitably involves multiple invasive operations and extensive presurgical modeling, thus increasing the morbidity and negative aesthetic effects associated with repeated procedures and poor biocompatibility [31].

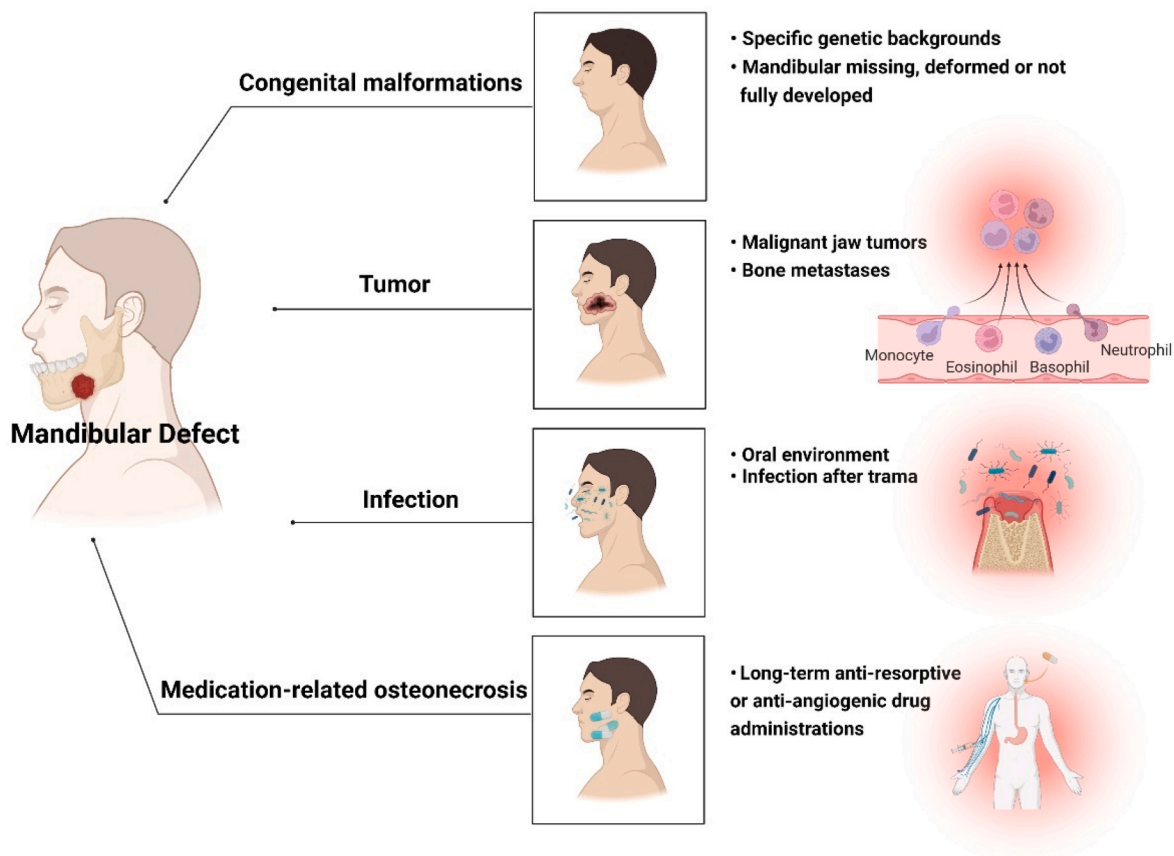


Fig. 1. Causative factors resulting in mandibular defects.

**Table 1**  
History of current clinical therapies in mandibular reconstruction.

Clinical Therapies	Years	Key Events or Representative Publications	Outcomes
Autologous and allogeneic bone transplantation	1949	Review paper of free bone grafts taken from tibia, rib, and iliac crest for mandibular reconstruction [32]	–
	1979	A report on the use of iliac crest free flap with micro-vessels	The superiority of the deep circumflex iliac vessels [33]
	1979–1997	A report of 178 mandibular reconstruction cases using microvascular-free flaps	Donor site selection strategies: ilium, fibula, or scapula (lateral bony defect), fibula (anterior bony defect) [34]
	1981	Combined homologous mandible and autologous bone and bone marrow	Failure in patients who have previous radiation therapy [35]
	1989	The fibula-free flap (FFF) transplantation has become the gold standard	All osteotomies healed primarily in 12 patients [36].
	2009	Non-vascularized bone grafts	Suitable for the condition that the defect is truly lateral and only an extraoral approach. 86% of patients with a successful initial reconstruction [37]
	Metallic devices	1909	Silver wire [38]
1953		A stainless-steel mesh prosthesis for mandibular replacement	Successful rate of 67/102 patients, failure in patients associated with histories of previous irradiation, extensive resections, and the loss of distant skin flaps [39]
1990s		Titanium (Ti) and titanium alloys [40]	71% successful rate. Plate loss occurred in large lateral defects, and pre- or postoperative radiotherapy [41]
2000		Titanium mesh wrapping cancellous bone grafts	Exposure of the titanium mesh is 7/16 in maxillary and 16/29 in mandible. The success of the bone grafting procedure was 97.72% [42]
2010s		Magnesium (Mg)-based Materials [43]	Mg screw was able to distribute the stress to the condyle and ramus region compared to polylactic acid polymer group [44]
2016		Finite element simulation and 3D printing technology prefabricated titanium meshes [45]	21 patients, insufficient bone formation (5 cases), postoperative infection (2 patients), Ti-mesh tray fracture in 2 patients
2022		Patient-specific 3D-printed miniplates for free flap fixation	High accuracy of reconstruction (3.64 ± 1.18 mm), Osseous

**Table 1 (continued)**

Clinical Therapies	Years	Key Events or Representative Publications	Outcomes
Distraction osteogenesis	1992	First applied distraction osteogenesis to the mandibular deformities' reconstruction	union occurred in all intersegmental gaps [46] Mandibular bone lengthening ranged from 18 to 24 mm [47]
	1996	A report of 5 cases of distraction osteogenesis in maxillofacial surgery	5 patients, premature consolidation (2 cases), significant relapse (1 case) [48]
	1997	Case report on a patient received trifocal distraction osteogenesis in oral floor cancer	Infection developed; Free bone transplants were needed for complete continuity [49]
	2000	Combination of mandibular distraction osteogenesis with electrical stimulation (10 μA)	Significant increase in bone mineral density [50]
	2011	Electrical stimulation on mandibular distraction osteogenesis conducted in clinical trials	10 patients, 16 distraction sites, and direct current electrical stimulation promoted bone healing [51]

### 3. Unique mode of bone formation and resorption in the mandible

#### 3.1. Bone formation in the mandible

The metabolism and turnover rate of the jaw is considered the most active in the skeletal system due to occlusal mechanical stimulation and odontogenic inflammation. The remodeling rate of the cortical bone of the mandible is 10–20 times higher than the cortex of the human iliac crest in humans [52]. The bone turnover in the adult dog's maxilla and mandible are approximately three- and six-fold higher (19–37%/year) than that of the femoral site (6.4%/year), respectively [53]. Within the mandible, the bone turnover rate of the alveolar bone is the highest. Besides, any bone damage caused by strenuous chewing and surgical intervention can accelerate the turnover rate of the jaw [52]. Researchers have detected the fluorescent-labeled BPs and found that alveolar bone was the most susceptible to the drugs as maximum fluorescence intensity was found at the mandible (Fig. 3A) [54].

Mesenchymal stem cells (MSCs) derived from the jaw exhibit unique osteogenic potentials. Mandibular bone marrow MSCs (m-BMSCs) originate from the neural crest of the neuroectoderm (Fig. 3B), which differs from appendicular bones in terms of developmental origin, mode of bone formation, and pathological bone resorption [55]. Endochondral ossification stimulates the process of long bone formation generated from the mesoderm, while craniofacial bones are formed primarily by intramembranous ossification. It has been reported that gradual-distraction mandibles exhibited direct intramembranous ossification, while fracture mandibles appeared with a degree of endochondral ossification [56].

Compared with tibial bone marrow MSCs (t-BMSCs), m-BMSCs possess stronger proliferative activity [57], exhibit higher expression of pluripotency markers, and hold stronger osteogenic differentiation potential [58]. In pathologic conditions such as ovariectomized and malnourished rodent models, the mandible loses much less bone than

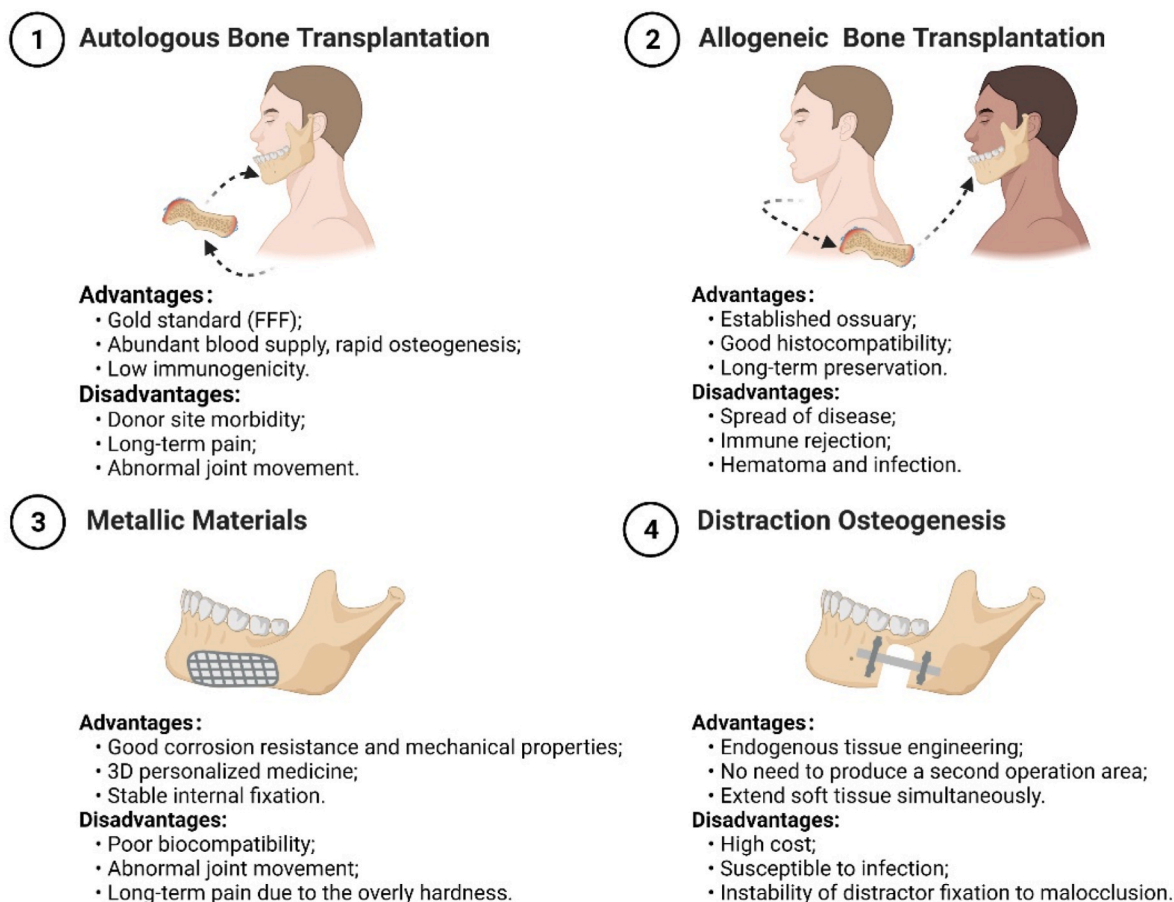


Fig. 2. Strengths and weaknesses of current clinical approaches applied in mandibular reconstruction.

the proximal tibia [59]. Microarray analysis has been used to identify 404 highly abundant genes m-BMSCs and t-BMSCs of pigs, 48 genes of them are differentially expressed for at least 1.5 times between two cell types [60], including higher expression of cranial neural crest-related genes such as BMP-4. m-BMSCs have a phenotypic profile that makes them advantageous for craniofacial bone regeneration.

Based on clinical observation, alveolar cleft repair from mandibular bone grafts yields better results than iliac grafts, mainly due to less graft resorption [61]. Interestingly, a research study tested whether skeletal stem cells from different lineages (neural crest-originated and mesoderm-originated) were functionally interchangeable by grafting neural crest-originated cells into tibia defects and mesoderm-derived cells into mandibular defects, respectively [62]. Surprisingly, the placement of NC-derived periosteum into the tibia injury site resulted in a robust intramembranous bone formation. However, the tibial periosteum failed to new bone formation and underwent an endochondral ossification with fibrotic-like “scar” tissues forming in the mandibular defect site (Fig. 3C) [62]. These differences guide the seed cell selection for the regeneration and reconstruction of site-specific bone defects.

### 3.2. Bone resorption in the mandible

The mandible possesses a special bone resorption process, owing to the different matrix composition between maxillofacial bones and long bones. The mandible has greater Type I collagen content, a lower number of mature crosslinks, and a lower extent of lysine hydroxylation (posttranslational modifications of collagen), as compared to long bones. The lysine hydroxylation is lower in the mandible (11.9%) than in both humerus (14.8%) and femur (13.7%) [64]. The differences in the number of crosslinks and the concomitant impaired degradability of

collagen may explain the observed functional heterogeneity of osteoclasts in proteases used for resorption [65,66].

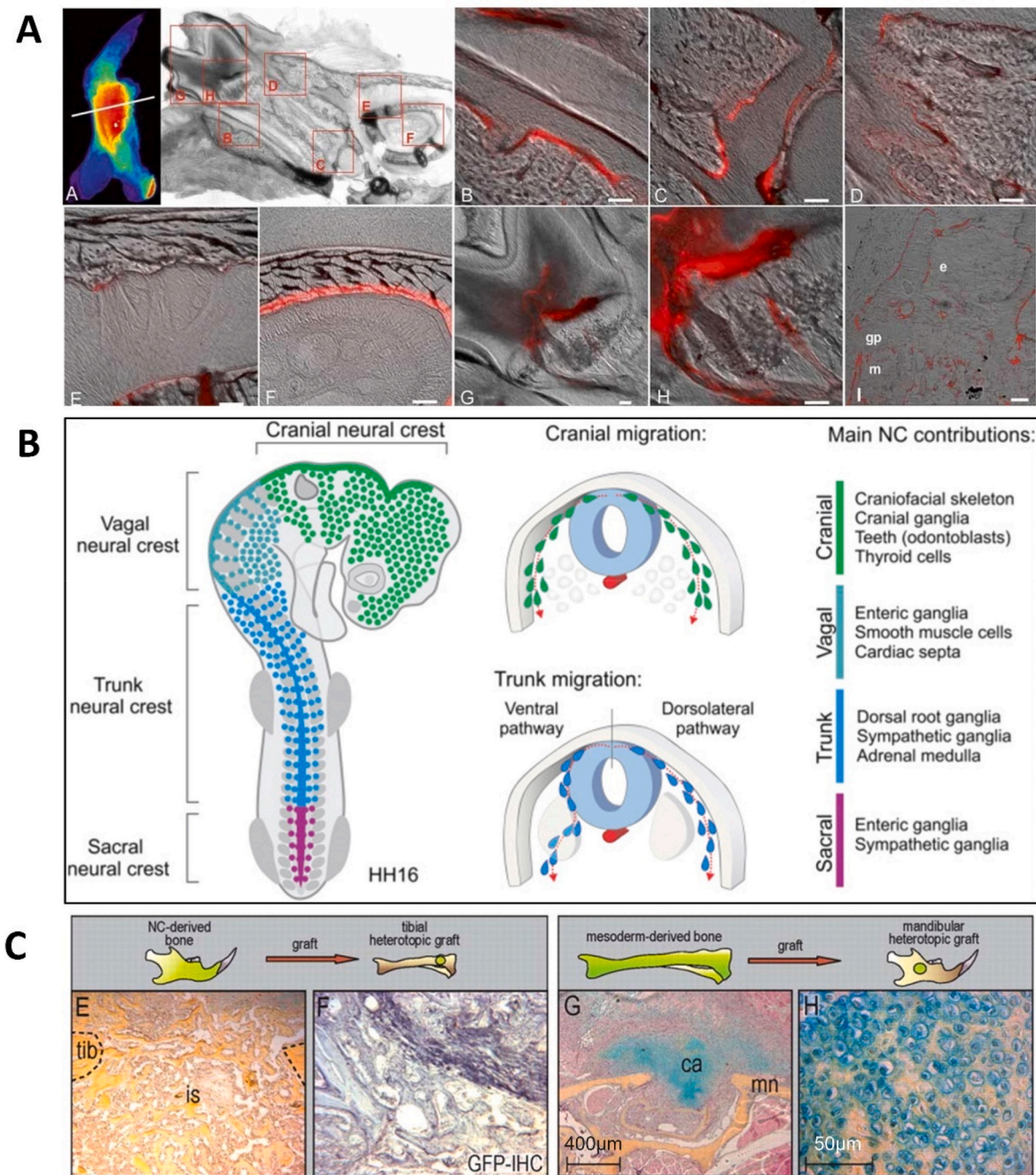
Osteoclasts from specific bone sites differentially respond to certain cytokines. Versus long bone, mandible marrow contains fewer osteoclast precursors, primarily the myeloid blasts, and showed a lower ratio of receptor activator nuclear factor kappa B ligand (RANKL) and osteoprotegerin (OPG) [67]. In contrast, maxillofacial osteoclasts are larger and contain a 25-fold higher level of tartrate-resistant acid phosphatase (TRAP) activity than those of long bones [68], which may contribute to the degradation of noncollagenous protein matrix in maxillofacial bones. Moreover, the previous studies reported that the activation of TRAP was independent of the activities of cathepsin K and L in calvarial osteoclasts (similar to mandible osteoclasts), and TRAP might partially compensate the lower cysteine proteases’ activities [68].

Besides, some antiresorptive and antiangiogenic drugs such as BPs and denosumab target osteoclasts [18], leading to the fragility of mandibular osteoclasts. It has been reported that the mandibular osteoclasts express higher anti-apoptotic genes and capture more BPs [69]. Nowadays, more and more clinical cases of mandibular defects are associated with bone resection and tumor ablation caused by osteoclast-related diseases (BRONJ, periodontitis, cherubism, and suppurative jaw osteomyelitis) [70].

## 4. Hydrogel-based mandibular tissue engineering

### 4.1. Advantages of hydrogel systems for mandibular regeneration

Hydrogel systems provide a number of advantages to meet the special demands in mandibular reconstruction [71–73], including 1) More biocompatibility and non-immunogenicity compared to the traditional



**Fig. 3. Osteogenic potential and regeneration in the mandible.** (A) The fast turnover rate in the mandible: *In-situ* fluorescence of far-red fluorescent pamidronate signal (red) labeled BPs localization in the mandible. Scale bar = 50 $\mu$ m. (Copyright © American Society for Bone and Mineral Research, Ref [54]). (B) Schematic diagram showing the location and progression of neural crest subpopulations. The cranial neural crest developed into the craniofacial skeleton (Copyright © 2018 Elsevier Inc, Ref [63]). (C) Placement of neural crest-derived periosteum into a mesoderm injury site resulted in an intramembranous bone formation. However, transplantation of the tibial periosteum initiated an endochondral ossification in the mandibular defect. GFP immunohistochemistry confirmed that the grafted cells were actively committed to the healing response (Copyright © 2022 The Company of Biologists, Ref [62]).

materials that avoid inflammatory responses; 2) Appropriate pore size and interconnected porosity supporting cell infiltration, adhesion, proliferation, and differentiation; 3) As an ideal delivery carrier of bioactive factors, antibacterial agents, and nanoparticles may enhance therapeutic effects, such as osteogenesis, angiogenesis, and anti-infection; 4) Controllable degradability, synchronizing with rapid mandible ingrowth and elimination of the second removal surgery; 5) Injectability supports minimally invasive surgery, simplifying the administration

process and meeting the purpose about aesthetic restoration of facial structures; 6) Various methods are available for improving structural stability and mechanical strength which meet the demands of load-bearing defects; 7) Easy modification suggests that it can be implanted either independently or combination. In the text below, we will describe various kinds of advanced hydrogel designs in detail and highlight their necessity and cutting-edge use in mandibular reconstruction.

#### 4.2. Hydrogel scaffolds

Hydrogels well mimic the extracellular matrix (ECM) of the natural mandible, providing the most similar environment favorable for the adhesion, propagation, and differentiation of osteoblasts, osteoclasts, and osteocytes [9]. The ideal hydrogel is highly biocompatible and nonimmunogenic, which may serve as a carrier for stem cell therapy. It can also provide a 3D network that supports the transportation of nutrients, the discharge of metabolites, and intercellular communications. Besides, the hydrogel can degrade by endogenous enzymes or hydrolysis. Capillaries, perivascular tissues, and osteoblasts can synergistically orchestrate new bones within the pores during degradation [8].

Hydrogels can be divided into two categories, natural and synthetic, according to the sources of their polymer substrates [9,73]. Natural hydrophilic polymers include polysaccharides (alginate, cellulose, heparin, hyaluronic acid (HA), chitosan, etc.) and polypeptides (collagen, gelatin, bovine serum albumin (BSA), poly-L-lysine, poly-L-Glutamic acid, etc.) [74]. Synthetic hydrophilic polymers include alcohol, acrylic acid, and their derivatives (polyethylene glycol (PEG), polyacrylic acid (PAA), polyacrylamide (PAM), etc.) [75]. The hydrogels can be synthesized in a short time through appropriate physical or chemical crosslinking [76]. Physically crosslinked hydrogels can be fabricated by ionic interaction, complementary base pairing, hydrogen bonding, and supramolecular force. Chemical crosslinked hydrogels are produced by Schiff base crosslinking, Diels-Alder reaction, click chemistry, and free radical polymerization (such as photo-initiated, thermal-initiated, and pH-initiated hydrogels) [77].

Hydrogel-based mandibular tissue engineering has been investigated for decades [12]. Natural polysaccharides, chitosan and chondroitin sulfate, are fabricated into 3D porous scaffolds and further modified with apatite coatings and efficient delivery of bone morphogenetic protein 2 (BMP-2) to reconstruct a rat critical-sized (5×5 mm) mandibular defect [78]. In addition, hydrogel made of liposomes takes the advantage of the closed vesicular and amphiphilic structure, improving the delivery efficiency and therapeutic effect of both hydrophilic and hydrophobic pharmaceuticals [79]. A self-assembled liposomal hydrogel is developed to deliver recombinant human BMP-7 for craniomaxillofacial applications [80], a more controlled, linear, and multi-phasic release is demonstrated by this nanogel when compared to the liposome-associated burst and faster release. However, natural hydrogels are sometimes limited by poor mechanical strength and are not suitable for load-bearing sites.

Synthetic hydrogels are more stable. Modification of specific structural units by chemical synthesis can achieve tuned porosity, degradation time, releasing pattern, and mechanical properties [81]. Moreover, stimuli-responsive properties can also be achieved by incorporating specific chemical structures and additives during and after polymerization [82,83]. For example, an injectable thermos-responsive silica nanoparticle (NP)-embedded hydrogel are formulated by adding a specific chemical structure PNIPAAm to the polymer chains, achieving *in situ* gelation at 37 °C and co-delivery of microRNA-222 and aspirin (ASP) in mandibular defect [84]. A boom in research on hydrogels that exhibit responsiveness with various external control triggering mechanisms-pH, temperature, external chemicals, light, and shear stresses will lead to more applications for mandibular reconstruction in the future.

#### 4.3. Seed cells in mandibular tissue engineering

Cell therapies have been expected to bring substantial benefits to patients [85]. The challenges of cell therapy are mainly divided into two parts: internal and external. Success will rely on how to maintain the retention and viability of seed cells internally, and how to recruit or locate external endogenous cells and control their survival, fate, and function within a certain duration following treatment *in vivo*. Hydrogels improve stem cell-based therapies “internally and externally”. Firstly,

the hydrogel as a carrier can restore the seed cells in the defect site and protect them from immune rejection, which circumvents the challenge that less than 5% of the injected cells are maintained at the defect region after transplantation in clinical practice [86]. Secondly, hydrogels releasing stromal cell-derived factor-1 $\alpha$  (SDF-1 $\alpha$ ) can also recruit endogenous cells [87,88]. Finally, hydrogels may control stem cell fate and function through biophysical and biochemical signals such as topography, degradation, mechanics, and adhesion [88].

Hydrogels combined with cell therapies hold great promise in the treatment of mandibular defects. The stem cells used with hydrogel systems for mandibular regeneration mainly include BMSCs [89], adipose-derived stem cells (ADSCs) [90], and dental stem cells (DSCs) [91]. Bone repairs are advanced by BMSCs that migrate to the injured site and undergo differentiation to realize structural and functional repair. This process also exists in mandibular reconstruction [92]. Liu et al. used a sex-mismatched canine model for systemic BMSCs injection and homing to the periosteum-free mandibular defects [93]. Appendicular BMSCs can migrate to craniofacial defects and lead to 20–40% increase of mineralized bone formation [93]. Besides, combined with hydrogel systems, interleukin-4-loaded (assisting in transforming macrophages from the pro-inflammatory M1 phenotype into the anti-inflammatory M2 phenotype) hydrogel scaffold promotes the osteogenic differentiation of BMSCs via TGF- $\beta$ 1/Smad pathway in mandibular defect of rat [94]; More promisingly, hydrogel incorporation enhances the biocompatibility of metal-based scaffolds. The porous Ti6Al4V scaffolds combined with BMSCs-encapsulated Matrigel promote a large amount of new bone formed around and within the scaffold in rat mandibular defect [95].

ADSCs have also been extensively used attributed to their accessibility, abundance, and less invasive procedure for harvesting tissues [96]. Presenting a great osteogenic differentiation potency in mandibular defects [97,98], ADSCs can be incorporated with polymers for enhancing regenerative applications. For example, ADSCs with tricalcium phosphates (TCP) is used for mandible regeneration by facilitating bone extracellular matrix formation and promoting reparative osteogenesis [99]. Moreover, the regenerative effect of ADSCs containing fibrin scaffold and autologous bone graft in rabbit mandibular defect has also been reported, with a significant increase in the thickness of new cortical bone when fibrin glue scaffold combined with ADSCs are used [100]. Besides, ADSCs can potentially improve the current understanding of disease mechanisms, while minimizing tissue rejection when been transplanted back into the host for organ manufacturing [101]. It has been showed that neither the proliferation ability nor the differentiation behavior of the ADSCs is affected by the 3D bioprinting procedures [102]. Various bioactive polymers such as Polyetherketoneketone (PEKK) can be enhanced in tissue integration by functionalizing with ADSCs *in vivo*, improving the cell interaction and osteogenesis of a three-dimensional printed PEKK/ADSC implant within the bicortical critical-sized (1.5 cm × 1.0 cm) mandibular defect in a rabbit model [103]. ADSCs encapsulated in the composite structures remain viable within the hydrogel for more than 14 days and show excellent spreading on the 3D printed PLA microstructure could be readily modulated to simulate the stiffness of the human mandibular condyle [104].

Most interestingly, given that DSCs share the same developmental origin as m-BMSCs and are characterized by self-renewal ability, in recent years, they are often used as seed cells in the regeneration of maxillofacial tissues and periodontal tissues. Dental pulp stem cells (DPSCs) [105], stem cells isolated from human exfoliated deciduous teeth (SHEDs) [106], gingival mesenchymal stem/progenitor cells (GMSCs) [107], and periodontal ligament stem cells (PDLSCs) [108] all demonstrate with self-regeneration and multi-differentiation capacity. Their characteristics, cell surface markers, and applications in maxillofacial tissue regeneration are summarized in Table 2.

**Table 2**  
Properties of dental mesenchymal stem cells.

Dental stem cells	Dental pulp stem cells	Stem cells isolated from human exfoliated deciduous teeth	Gingival mesenchymal stem/progenitor cells	Periodontal ligament stem cells
<b>History (firstly be found or separated)</b>	2000	2003	2010	2004
<b>Surface markers</b>	Positively express Stro-1, CD29, CD44, CD90, CD105; Negatively express CD34, CD45	Positively express Oct4, CD13, CD29, CD44, CD73, CD90, CD105, CD146, CD166; Negatively express CD14, CD34, CD45	Positively express CD90, CD105, CD73, CD44, CD13; Negatively express CD34, CD38, CD45, CD54	Positively express CD10, CD13, CD29, CD44, CD59, CD73, CD90, CD103; Negatively express CD14, CD34, CD45, CD38, CD54, HLA-DR
<b>Multidirectional differentiation ability</b>	Odontoblasts, osteoblasts, endothelial cells, adipocytes, neurons, and chondrocytes	Osteoblasts, neurons, adipocytes, and odontoblasts	Osteoblasts, adipocytes, and chondrocytes	Cementoblasts, adipocytes, osteoblasts, and fibroblasts
<b>Superiority</b>	Great Potentials in bone vascularization	Rich sources; great clinical translational potential	Less painful collection	Strong adhesion, rapid growth, and proliferation; ideal material for regenerating the periodontal tissue defects
<b>Application in bone tissue engineering</b>	[109,110]	[111,112]	[113,114]	[115,116]

#### 4.3.1. Dental pulp stem cells (DPSCs)

DPSCs were firstly isolated from the pulp of extracted third molars, identified as undifferentiated cells derived from the neural crest, that is, originated in the same area as the mandible [117]. Under normal circumstances, DPSCs are quiescent and maintain the replacement of new and old pulp cells. When dental pulp suffers from adverse external stimuli and damage, DPSCs differentiate into odontoblasts to support dental pulp tissue reconstruction [118]. Human mandibular reconstruction by the grafting of autologous DPSCs and collagen sponge bio-complexes (similar to lyophilized hydrogel scaffolds) has been conducted in clinical practice for one year. Compared with traditional direct injection, collagen sponges aid the retention of the encapsulated stem cells by providing biological and physical support as same as the hydrogel systems do [119]. As assessed by clinical probing, X-rays, and histological observations, satisfactory bone regeneration is achieved one year after grafting [109].

#### 4.3.2. Stem cells isolated from human exfoliated deciduous teeth (SHEDs)

Monoclonal SHEDs were firstly obtained from the pulp tissue of deciduous teeth. After *in vivo* transplantation, SHEDs are found to be able to induce bone formation, generate dentin, and survive in the mouse brain along with the expression of neural markers [120]. SHEDs transplantation has an immunosuppressive activity that solves a major concern on stem cell therapies. When human SHEDs from normal exfoliated deciduous teeth are implanted with hydrogel/sponge scaffolds into dog mandibular defects, the new formation of soft tissue, cancellous bone, and compact bone is observed after 12 weeks [111]. SHEDs are noteworthy for easy accessibility from teeth with painless harvest procedures, combined with hydrogel systems for viability and stemness maintenance, which provide a rapid transformation of stem cell-based oral and maxillofacial reconstruction therapy in clinical trials.

#### 4.3.3. Gingival mesenchymal stem/progenitor cells (GMSCs)

Via systemic injection of human GMSCs through the mice tail vein, GMSCs can home to the mandibular defect site and promote bone regeneration by triggering the endogenous MSCs recruitment which is known to be crucial for successful mandibular regeneration [121]. However, up to date, no study has evaluated the contribution of GMSCs migrating from peripheral circulation to mandibular regeneration. To further improve the unmet need for the efficacy of cell therapies and time window, an injectable alginate-based adhesive hydrogel encapsulated GMSCs is developed for bone regeneration around ailing dental implants [113].

#### 4.4. Nanoparticles and growth factors

Hydrogels are also considered ideal delivery carriers for NPs, which

may not only support the sustainable release of drugs and growth factors but also enhance mechanical properties. The extracellular matrix of bone is a biphasic system, one-third of the component is organic substances, two-thirds are composed of inorganic substances. To simulate this biphasic system of natural bone extracellular matrix, biomaterials are developed based on the strategy of “organic macromolecules network (hydrogels) combined with inorganic NPs [122], which is defined as “hybrid hydrogel”. In hybrid hydrogel, this combination of two different types of materials produces structural diversities and brings a variety of enhancements involving mechanical strength and biological response of osteointegration, osteoconduction, and osteoinduction [122].

Organic liposomal microspheres, polymeric microspheres (e.g., PLGA, PVA, gelatin), and inorganic NPs (e.g., nanohydroxyapatite (nHAp), silica NPs, gold NPs, and bio-ceramics NPs) have been used for integration into hydrogel systems in mandibular tissue engineering (Fig. 4). Inorganic NPs has been reported to provide promising outcome in bone healing applications [123]. Among them, the nHAp is the most widely used, which is regarded as a plentiful source of free calcium and a key factor in mineralization and alveolar [124].

NP itself has been also successfully applied to deliver growth factors, genes, and drugs either systemically or locally in a controlled and intelligent manner. This versatility is mainly the result of a wide range of NPs functionalization methods and a large surface area [125]. Antibodies, labeled probes, hydrophobic or hydrophilic molecules, DNA, and oligonucleotides can be conjugated to NPs, allowing customized applications for the desired purpose. For instance, contributing to the intracellular delivery of microRNAs (miRNA), nHAp modified with cationic functional groups 3-aminopropyltriethoxysilane shows the optimal efficiency in miRNA delivery and gene regulation in the human mandibular osteoblasts. Plasmid DNA/c-myc (one transcription factor that supports bone formation) conjugated with CS-gold NPs facilitates the osseointegration of dental implants in mandible osteoporosis rats [126]. Following the same approach, CS-gold NPs carrying peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) plasmid DNA diminishes inflammation and enhances osteogenesis in the mandible around the dental implantation [127]. Besides, tremendous efforts have been made to construct advanced bone fillers with ROS scavenging ability through the functionalization of various types of antioxidants [128]. To endow the gelatin-based hydrogels with high osteoinduction and robust ROS scavenging ability, BMP-2 incorporated poly-dopamine/heparin nanoparticles have been introduced to the optimized hydrogels. The enhanced ROS-scavenge abilities and sustainable release of bioactive molecules has been reported to augment the mandibular regeneration [129].

More interestingly, NPs like superparamagnetic iron oxide nanoparticles (SPIONs) [130], gold NPs [131], and mesoporous silica NPs

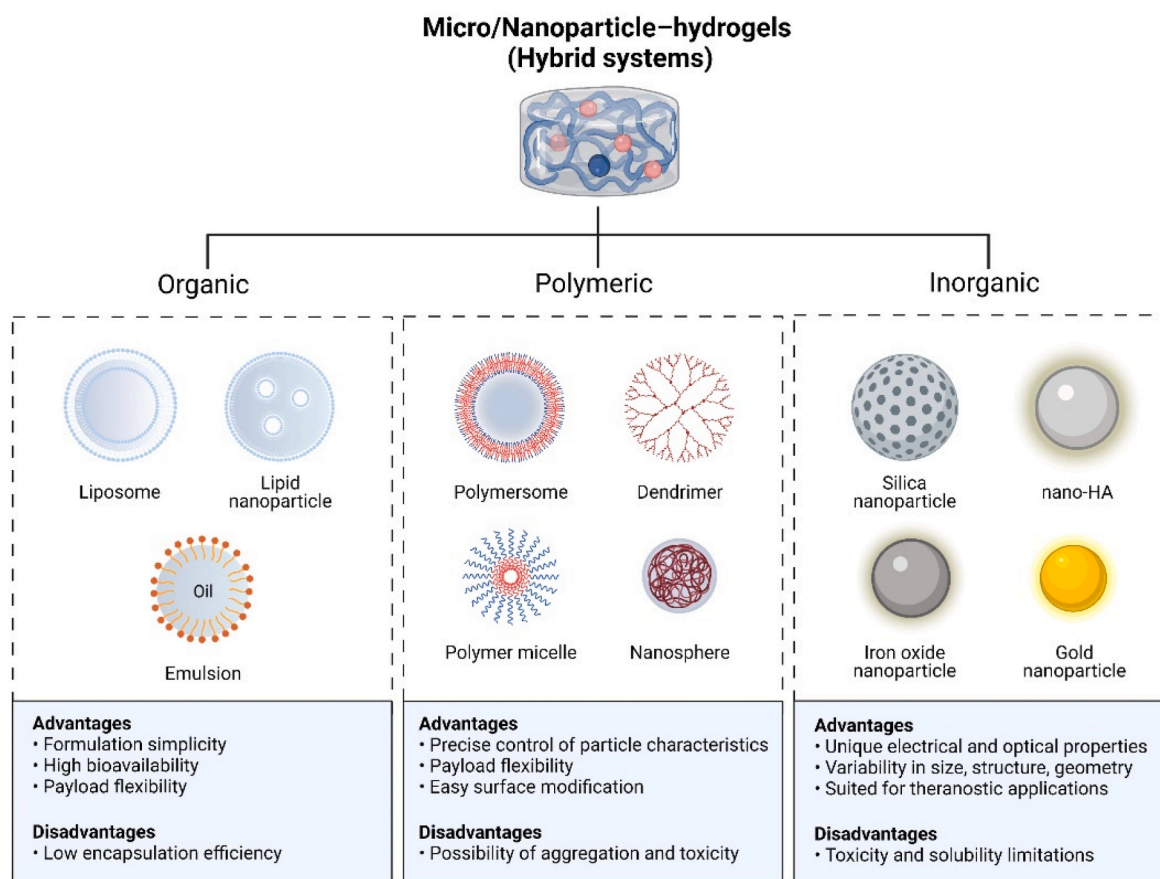


Fig. 4. Potential micro/nanoparticles used in mandibular tissue engineering.

[132], can be used to label cells and to achieve continuous cell tracking, including the biodistribution and migration mode of stem cells after transplantation [133]. There is a significant growth of interest in the use of nanoparticles as non-invasive visual monitoring in diagnostics and healing processes [134]. Making full use of the properties such as

superparamagnetic, high sensitivity, and easy detection are beneficial for regulating and detecting the healing process. For example, SPIONs loaded gelatin sponge not only enhances the mandible formation but also monitors the scaffold degradation and cell integration by imaging the intensity of scaffolds in incisor sockets [135].

Table 3

Applications of Hydrogel systems with seed cells, nanoparticles, and growth factors for mandibular reconstruction.

Materials/Hydrogels	Nanoparticles	Agents/Cells	Animal models	Refs.
Hyaluronic acid hydrogel	Nano-HA	BMP-2	Rat mandibular defect	[147]
Collagen/alginate hydrogel	Nano-HA	NGF	New Zealand white rabbit mandibular defect with distraction osteogenesis	[148]
Collagen sponge/hyaluronic acid hydrogel/PCL outer box PEG hydrogel	–	rhBMP-2/hBMSCs	Rabbit mandibular defect	[149]
Chitosan and chondroitin sulfate	HA/β-TCP	rhBMP-2	Minipig alveolar defect	[150]
Chitosan/collagen hydrogel/Gelatin microsphere	–	BMP-2/ADSCs	Rat Mandibular Defect	[78]
Alginate-fibrin microfibrils	–	rhBMP2	Rabbit mandibular defect	[151]
Calcium alginate hydrogels and polylactic acid (PLA)	Calcium phosphate cement	hBMSCs	Rat mandibular defect	[152]
PLA/gelatin hydrogel	–	hPDLCs/BMSCs	Rabbit mandibular defect	[153]
Mannuronate (SLM) alginate, high guluronate (SLG) alginate, hyaluronan derivative (HApN)	Cyclic RGD conjugated gold NPs	hADSCs	–	[104]
Alginate/hyaluronic acid hydrogels	Collagen-I based recombinant peptide microspheres	BMP-2	Subcutaneously in rats	[154]
Alginate/hyaluronic acid hydrogels	–	BMP-2/hBMSCs	Miniature pig mandibular defects	[155]
Supramolecular hydrogel (SDF-1/BMP-2/NapFFY)	–	Vancomycin, BMP-2	Osteomyelitis rat model	[156]
Gelatin	–	BMP-2, SDF-1	Rat periodontal bone defect	[157]
PEG–PLGA–PNIPAM hydrogel	Silica NPs	Fibroblast growth factor	Rat BRONJ	[158]
N-carboxyethyl chitosan (CEC)/hyaluronic acid-aldehyde (HA-ALD)/adipic acid dihydrazide (ADH)	–	microRNA-222 and ASP	Rat mandibular defects	[159]
CS scaffolds	Nano-HA	–	Mandibular incisors of rat	[160]
Modifying HA with both methacrylate (MA) and 3,4-dihydroxyphenylalanine (Dopa)	Nano-HA/PLGA microspheres	BMP-2/VEGF	Rabbit mandibular defects	[161]
Hyaluronic acid hydrogel	–	–	Maxillofacial tissue	[162]
Hyaluronic acid hydrogel	β-tricalcium phosphate	rhBMP-2	Minipig mandibular defect	[163]



As also shown in Table 3, osteoinductive and angiogenic factors like bone morphogenetic protein (BMP), insulin growth factor (IGF), fibroblast growth factor (FGF-2), transforming growth factor- $\beta$  (TGF- $\beta$ ), stromal cell-derived factor 1 (SDF-1), vascular endothelial growth factor (VEGF), and NGF play crucial roles in mandibular regeneration and have been encapsulated with hydrogel systems [136]. BMP-2 has become the preferred additive for mandibular reconstruction materials [137]. At present, more than 20 kinds of BMPs have been separated, except BMP-1, all belonging to the transforming growth factor  $\beta$  superfamily, among which BMP-2 has the most vital osteogenic ability, which has been extensively used in mandibular reconstruction [138–140]. A review analyzed several cases of BMP-2 used for mandibular reconstruction secondary to tumor resection, trauma, and infection, highlighting the versatility of growth factors-mediated bone regeneration [141]. Moreover, a phase II-randomized controlled study has investigated the safety and efficacy of rhBMP-2 combined with an absorbable collagen sponge versus autograft for maxillary sinus floor augmentation. Such scaffold performed comparable effects to the bone graft in the aspects of maxillary regeneration and functional loading [142], while avoiding the long-term paresthesia, pain, or gait disturbance related to the autograft bone harvest [143]. Clinically, rhBMP-2 sponge collagen or poloxamer-based gel with traditional Ti mesh has achieved better mandibular reconstruction [144,145] (Fig. 5).

## 5. Additive fabrication of novel hydrogels for mandibular reconstruction

### 5.1. Mechanically enhanced hydrogel designs

The mandible participates in various physical activities such as mastication, articulation, speech, and suppling mechanical support. The ultimate compressive strength of the mandibular bone ranged from 0.22 to 10.44 MPa, with a mean value of 3.9 MPa [164]. However, natural polymers such as collagen, gelatin, and chitosan have poor mechanical strength and structural stability [165]. Natural polymers easily deform after implantation and lead to burst degradation during degradation. Here, we introduce several methods for preparing mechanically enhanced hydrogels as bioactive space fillers, aiming at adequate clinical applications for mandibular regeneration.

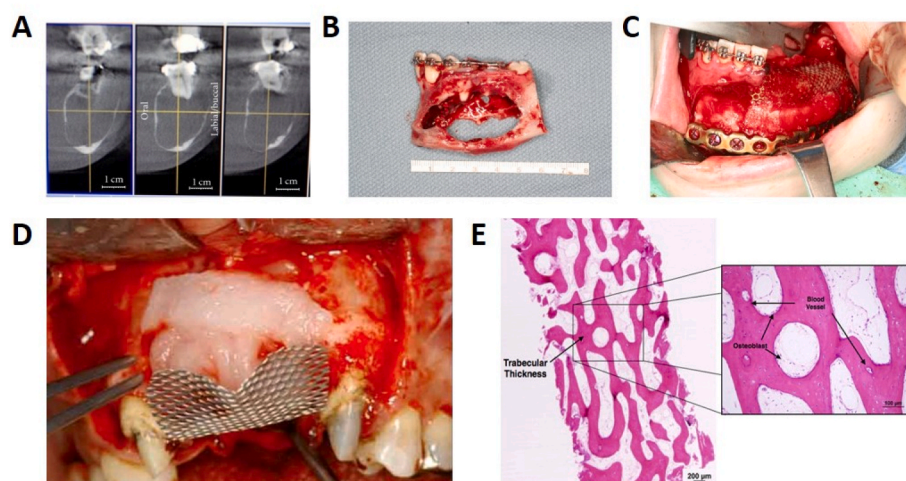
Compared with traditional single network hydrogels, the mechanical properties of double network (DN) hydrogels are significantly improved. It is an interpenetrating network formed by two polymers with different properties. One is a polyelectrolyte network structure with high cross-link density performing rigid and brittle, and the other is a neutral network structure with loose crosslink performing soft and tough. The polyelectrolyte network structure provides a “sacrificial bond” for the

DN hydrogel to disperse external stress, while the flexible neutral network structure fills in the polyelectrolyte network structure, providing a scaffold and maintaining the shape of the DN hydrogel. It has been almost 20 years since Gong et al. reported the first fabrication of DN hydrogel [166]. Suggesting that the PAMPS-PAAm DN hydrogels hold up to nominal stress of 17.2 MPa, while the PAMPS gel and PAA gel break only at 0.4 MPa and 0.8 MPa, respectively [167]. Given the mechanical enhancement, DN hydrogels are widely used in bone, including mandible tissue engineering.

In order to improve the mechanical strength and stable network of traditional gelatin methacryloyl (GelMA) hydrogel, DN hydrogels doped with magnesium ions have been successfully prepared by two cross-linked including *in situ* free radical polymerization and magnesium ionic coordination strategies. With the introduction of DN networks and POSS-Mg composite, the maximum compressive strengths are enhanced by about 6-folds, showing a promising bone formation and vascularization in calvarial defect of rats [168]. One novel DN hydrogel is constructed by physical cross-linking of medical-grade PVA (synthetic polymer) and CS (natural polymer). The obtained hydrogel demonstrates excellent tensile strength (0.24 MPa), elongation at break (286%), and high compressive strength (0.11 MPa on the strain of 60%) compared to the single network hydrogels. This mechanically enhanced hydrogel shows excellent biocompatibility *in vitro* and a significantly accelerated simultaneous regeneration of bone defects in rabbits [169]. Besides, the complex network of the DN hydrogel does not affect the loading and release of seed cells and growth factors. *in situ* gelling DN Alginate/HA hydrogels can tune the gelling rate to achieve a controllable mechanical strength by supplementing different concentrations of HA. The DN hydrogel also allows BMP-2 encapsulating and sustained releasing, thus greatly enhanced bone regeneration in mandibular defects of miniature pigs [155].

The mechanical properties can be improved by adding nanoparticles and nanostructures into hydrogels, called nanocomposite (NC) hydrogels. Metal NPs, carbon-based NPs, and ceramic NPs all can be incorporated into hydrogels through *in situ* polymerization, *in situ* formation of NPs, and physical mixing [170]. Due to the hydrogen bonds or van der Waals interactions between the nanoparticles and polymer chains, the network of hydrogels can be strengthened to obtain nanocomposite hydrogels with stable structure and improved mechanical properties.

The most widely used inorganic NPs in NC hydrogels for bone tissue engineering are calcium phosphates, including hydroxyapatite (HAp),  $\beta$ -TCP, and their mixtures – bidirectional calcium phosphate (BCP). HAp constitutes the inorganic phase of the natural bone and is one of the most biocompatible phosphate molecules. The addition of nHAp in hydrogels exhibits excellent mechanical properties with the tensile stress in the range of 0.21–0.86 MPa, and its compressive strength can reach 35.8



**Fig. 5. Clinical application of hydrogel in mandibular reconstruction.** (A) CT image of the mandibular lesion. (B) Tumor specimen. (C) Bio-implant (rhBMP-2/Absorbable collagen sponge) inserted and covered by titanium mesh (A-C, Copyright © 2011 Alan S. Herford et al. Ref [141]). (D) Another clinical case used absorbable collagen containing rhBMP-2 in the concave area of the titanium mesh. (E) Histology showed a large amount of newly formed bone and bone marrow/connective tissue in the rhBMP-2-containing collagen implanted area (D-E, Copyright © 2022 Elsevier B-V., Ref. [146]).

MPa, which has already exceeded the ultimate compressive strength of human mandibular trabecular bone (ranged from 0.22 to 10.44 MPa) [171]. While maintaining high mechanical strength and bioactivity, the hydrogel can still retain its responsiveness and injectability. HA-based hydrogels containing nHAp have been fabricated to achieve mandibular bone augmentation in rats through minimally invasive surgery, holding a great clinical translational potential in oral implantation [172]. To improve the responsiveness, an injectable thermosensitive hydrogel containing Zn-doped CS/nHAp/β-glycerophosphate (Zn-CS/nHAp/β-GP) is prepared and characterized, in which nHAp accelerates bone formation *in vivo* as evident by the depositions of apatite and collagen. Moreover, to overcome the limitations on inferior mechanical properties as well as the high biomimetic requirement during the 3D bioprinting process, a novel NC hydrogel with bioactive GNPs, reinforcing a 3D printed microstructure via fused deposition modeling has been developed. The stiffness of the composite hydrogel can be readily modulated to simulate the stiffness of the human mandibular condyle [104]. DN and NC hydrogels have also been combined to enhance its mechanical properties. The same mechanical strength can be achieved with a few nano composites. In carbon dots/nano-HA/PVA hydrogels, the results show that 0.6% of solid content nHAp containing could optimize the compression properties to 3.462 MPa of compression strength [153].

Besides, by changing component concentration, molecular weight, or fiber structure of the hydrogel system, the mechanical properties of the hydrogel, such as Young’s modulus, stress, deformation, strength, and other indicators, can be improved to varying degrees. However, the mechanical enhancement will inevitably slow down the degradation, and the toxicity of ingredients will be another concern. So, in the future, extensive efforts are needed for preparing mechanical strength-adjustable hydrogels for mandibular tissue engineering, aiming to obtain ideal mechanical properties and restore the hydrogels’ advantages.

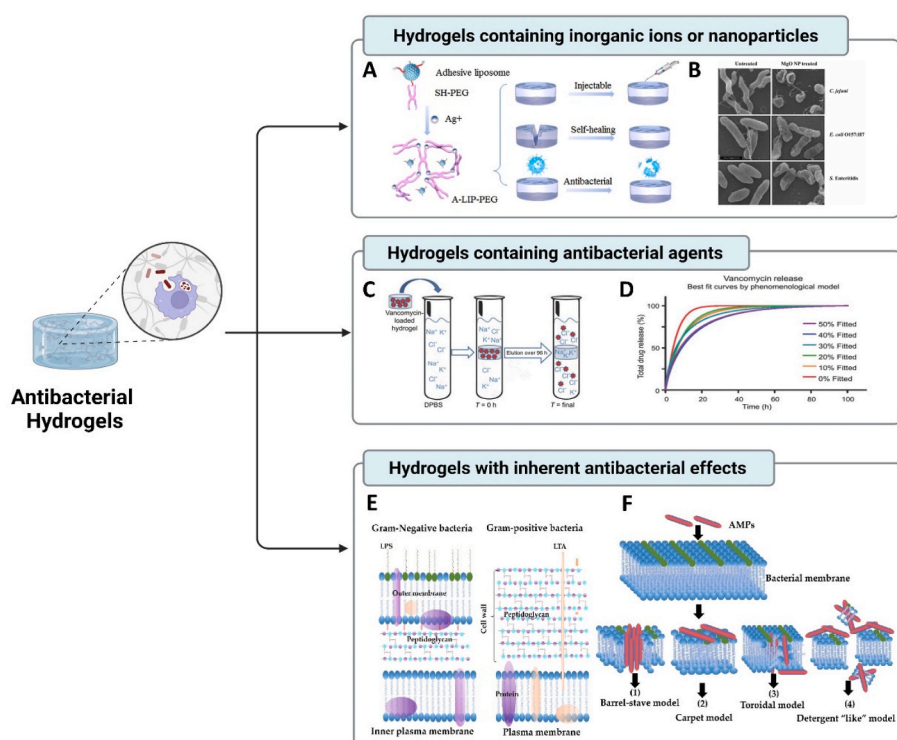
### 5.2. Antibacterial hydrogel designs

More than 700 bacterial species or phylotypes have been so far detected in the oral cavity. Once the tooth loses, microorganisms from oral fluids tend to accumulate at the exposed roots and form solid biofilms [173]. These biofilms may cause persistent infection around the implant, and severe alveolar bone resorption [174,175]. Surgical debridement, mandibular decortication, or resections combined with long-term systemic antibiotics are traditionally necessary procedures for adequate removal of osteonecrosis or tumor of the mandible and prevention of recurrent infections [176].

The development and application of antibacterial materials are limited by the problems of drug resistance and short antibacterial effect [177]. Hydrogels can be used as antibacterial agent carriers based on their inherent capabilities such as hydrophilicity and porosity. According to the classification of hydrogel matrix and antibacterial agents, the antibacterial hydrogels are divided into three types: (i) hydrogels containing inorganic ions or metallic oxide NPs, (ii) hydrogels containing antibacterial agents, and (iii) hydrogels with inherent antibacterial effects (Fig. 6).

In the first category, the hydrogel containing the antibacterial inorganic substance functions by adding metal ions or metallic oxide NPs. Metal ions (e.g., Ag<sup>+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Co<sup>2+</sup>), metal or metallic oxide NPs including silver NPs (Ag-NPs) [178], magnesium oxide (MgO) NPs [179], zinc oxide (ZnO) NPs [180] and Ti dioxide (TiO<sub>2</sub>) NPs [181] are widely combined with hydrogels refer to their broad-spectrum antibacterial properties and non-resistance to antibiotics. In addition to the local release of the metal ions, metallic oxide NPs also hold an antibacterial effect mainly by (i) oxidative stress via the generation of reactive oxygen species (ROS) on the surfaces of NPs; (ii) physicochemical and morphological properties to bind or damage the bacterial cells [182].

The hydrogel laden with inorganic antibacterial materials enhances the antibacterial performance and maintains antibacterial activity for the long term, thereby reducing the possibility of bacterial resistance. For example, a dynamic supramolecular hydrogel is formed assembly by



**Fig. 6. Antibacterial hydrogels for potential oral and maxillofacial applications.** (A) Adhesive liposome, SH-PEG, and Ag<sup>+</sup> constructed an adhesive, self-healing, and antibacterial hydrogel (Copyright © 2022 Springer Nature Limited, Ref [184]). (B) SEM images of bacterial cells treated (right panel) with MgO NPs (Copyright © 2022 BioMed Central Ltd, Ref [196]). (C) Controlled delivery of Vancomycin via charged hydrogels for combating surgical site infections. (D) Best fit of data calculated by the phenomenological mathematical model described in the text. (C-D, Copyright © PLOS, #C2354500, Ref [197]). Bacterial membrane structures (E) and mechanisms of action of AMPs (F) (Copyright © 1996–2022 MDPI unless otherwise stated, Ref [198]).

sodium tetraborate, PVA, Ag-NPs, and tetraethyl orthosilicate, and composited with pTi as an implant system, which serves as an ideal dental implant for contaminated alveolar bone defects [183]. Besides, incorporating adhesive liposomes into PEG hydrogels based on the coordinated cross-linking principle of SH-PEG and Ag<sup>+</sup> creates an injectable, antibacterial, and self-healing drug delivery system in bone [184].

In the second category, antibacterial agents-containing hydrogel is most extensively used in mandibular reconstruction. Combining antibiotics or antibacterial drugs (ciprofloxacin, gentamicin, vancomycin, cephalosporin, or other synthetic antibacterial drugs) into hydrogels is the current development mainstream of mandibular substitutes in pre-clinical studies [185]. For instance, local antibacterial treatment with an injectable gentamicin-collagen hydrogel shows a higher amount of bone area at 4 weeks post-operation in mandibular osteomyelitis of rabbits [186]. Besides, combined with polymer scaffolds as a functional space maintainer, gelatin microparticles with antibiotic colistin containing are incorporated with porous polymethylmethacrylate constructs for rabbit mandibular defect reconstruction [187]. A clinical study reported that the protective hydrogel (DAC®; Novagenit Srl. Mezzolombardo, Italy) composed of hyaluronic acid and antibiotics performed a beneficial effect in maxillofacial surgery fixation. This protective hydrogel is not only for prevention but also in cases of replacement of infected implants due to biofilm or any other source of infection [188].

The last category, a hydrogel with inherent antibacterial effects, can be mainly divided into two types: containing antibacterial polymers or antibacterial peptides (AMPs) [189]. Specifically, some polymers with antibacterial fragments can also be used to form hydrogels. For example, a new hydrogel composed of thermo-responsive Poly (N-isopropylacrylamide (PNIPAAm) and redox-responsive poly (ferrocenesilane) (PFS) macromolecules exhibits strong antibacterial activity at the same time maintaining good biocompatibility with cells [190].

AMPs-based hydrogels are also widely reported. It is synthesized by antibacterial amino acids or peptides as structural components. AMPs are the primary defense against a broad spectrum of microorganisms, especially for antibiotic-resistant bacterial infections [192]. Generally, AMP has an amphiphilic structure with a hydrophobic core and a polycation surface, promoting interaction with negatively charged bacterial membranes. AMPs destroy bacterial membranes, inhibit cell wall and nucleic acid synthesis, change the formation of cell plasma membrane membranes, inhibit protein synthesis, and cause bacterial death. Based on these characteristics, a modified histatin-5, one antimicrobial peptide, is formulated into a bioadhesive hydrogel to treat oral candidiasis caused by the fungal pathogen *Candida albicans* [193]. Antibacterial hydrogels by self-assembling the tripeptide (<sup>D</sup>Leu-Phe-Phe) and the antibiotic ciprofloxacin exhibit a mild antibacterial activity against Gram-negative bacteria [194]. Moreover, to produce an antimicrobial hydrogel that can strongly adhere to hard and soft oral surfaces, an antibacterial adhesive hydrogel based on visible-light-activated gelatin and an AMP (Tet213) is developed for dental peri-implant disease, the adhesion strength and antibacterial effect is stronger than that of the commercially available adhesive product (CoSeal™, Baxter, Deerfield, Ill., USA) to porcine gingiva. It also supports the growth of autologous bone after sealing calvarial bone defects in mice [195].

It is inevitable to cause some contradictions between encapsulating the antibacterial agents and the stem cells in the development of hydrogel systems. In fact, for the mandibular reconstruction secondary to trauma and deformity, highlighting the versatility of stem cell-mediated bone regeneration, wrapped stem cells into hydrogel is to mimic a “bio-tissue” to achieve self-mineralization and recruit endogenous cells to accelerate bone regeneration. However, for the mandibular reconstruction secondary by infections or osteonecrosis under bacteria or verification environment, it has more heed in successfully addressing growing concerns of antimicrobial resistance to conventional therapeutic approaches, so hydrogel systems present as a “bio-carrier” to sustaining-release drugs into the lesions and maximize the efficiency of bone regeneration. Since the latter has no concern for immune response

and medical ethics, hydrogel is more frequently applied as a carrier in the development of current clinical products nowadays.

### 5.3. Injectable hydrogel designs

Additional consideration includes the special aesthetic challenges posed by the restoration of facial structures and minimally invasive surgery has attracted much attention in maxillofacial reconstruction [199]. Profited by the low-risk infection and high acceptance of patients, the increasing demand for minimally invasive surgery has inspired researchers to focus on the development of injectable biomaterials [200].

Injectable hydrogels are particularly attractive samples in mandibular reconstruction. Except for delivering the therapeutic cell population and bioactive factors, they can cure under various environmental stimuli which provides a board of design strategies to respond to the *in-situ* environments. The conventional curing mechanisms can be divided into physical and chemical gelation (Fig. 7). Physical gelation includes ionic crosslinking gelation, thermo-induced phase transition, and self-assembled gelation. Chemical crosslinking includes conjugated effect and free radical polymerized gelation [9]. The physical gelation hydrogels can eliminate the use of crosslinking agents so always maintain good biocompatibility. However, its effectiveness is limited. Chemical crosslinking hydrogels provide greater sustained release kinetics and superior mechanical properties [201]. Here, we review the curing mechanisms and related corresponding injectable hydrogel applications in mandibular tissue engineering.

**Ionic crosslinking gelation** refers to the interaction of charged polymers with oppositely charged multivalent ions or polymers. Since some natural polysaccharides and their derivatives are polymer polyelectrolytes, they cross-link under normal conditions or in response to pH stimulation. Alginate is a representative polymer of the ionic crosslinking hydrogel. Since its polysaccharide structure consists of 1,4-linked β-D-mannuronic acid and α-homopolymer blocks, it can be crosslinked with calcium, zinc, or other cations at different positions of the alginate chain [202]. Alginate hydrogels can be easily injected and often served as the encapsulating carrier of growth factors. Cao et al. locally injected NGF via alginate containing hydrogel to enhance the bone consolidation and myelinated fiber density of the inferior alveolar nerve during mandibular distraction osteogenesis of rabbits [148]. However, the main limitation of injectable alginate hydrogels attributes to their poor mechanical properties, which cannot ensure the structural shape and mechanical maintenance for a certain period [203–205]. Therefore, alginate is usually chemically modified or combined with other polymer scaffolds or NPs to improve its mechanical and biological behavior. A drug-loadable calcium alginate hydrogels have been developed with a PLA scaffold supporting high plasticity and favorable biological properties to enhance oral bone regeneration [206].

**Thermo-induced phase transition** refers to the polymer solution that forms a hydrogel due to the manipulation of temperature. When the temperature changes, the physical entanglement of polymer molecular chains forms a polymer network. Such hydrogels can be injected into the body in liquid form, gelation *in situ*, and their crosslinking point temperature can be adjusted to be close to body temperature around 37 °C [207]. The common feature of thermo-induced phase transition hydrogels is the coexistence of hydrophilic/hydrophobic groups [208]. Hydrophobic groups include methyl, ethyl, and propyl. Hydrogels are generally liquid at low temperatures and possess a low critical solution temperature (LCST). When the temperature is lower than LCST, the enthalpy change plays a leading role, and the polar groups in the molecular chain form hydrogen bonds with water molecules to dissolve the polymer in water. When the temperature is higher than LCST, the entropy change (hydrophobic effect) plays a leading role, the hydrophobic isopropyl group is dehydrated during the transformation, causing polymer molecules to precipitate in the water [209].

The typical representative of thermo-induced phase transition hydrogel is PNIPAAm [210] and Pluronic (PEO-PPO-PEO) [211].

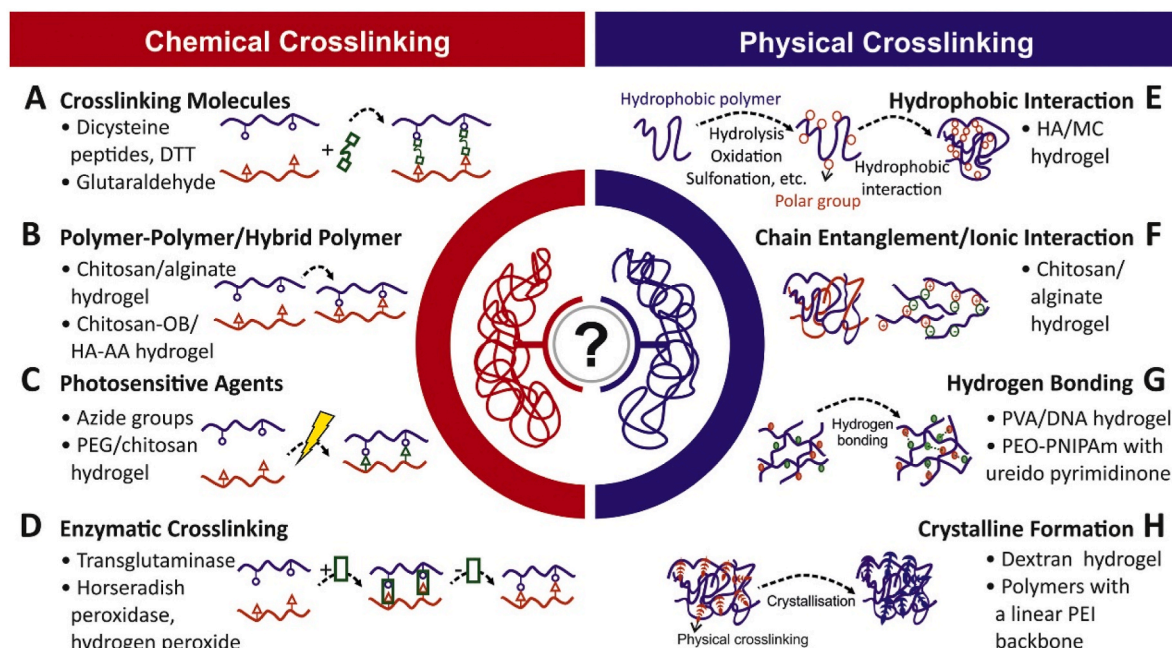


Fig. 7. Physical and chemical crosslinking of hydrogel synthesis (Copyright © 2022 Elsevier B.V., Ref [228]).

Generally, PNIPAAm and Pluronic can be combined with a degradable polymer in the form of the copolymer or chemical grafting to obtain a temperature-sensitive hydrogel scaffold with controllable injection and biocompatible for the survival of cells [212]. For instance, PNIPAAm-grafted gelatin is synthesized, exhibiting a sol-to-gel transformation at physiological temperature. It also protects cells from harsh shear stress due to the liquid form during the injection and presents an enhanced bone formation incorporating with BMSCs in a cranial defect model [213]. Besides, an injectable thermo-responsive PEG–PLGA–PNIPAAm hydrogel is designed for the microRNA-222 and aspirin minimally invasive surgical delivery, which stimulates bone regeneration in the rat mandibular defect model, displaying the nerve innervation in bone defects with high expression of neuronal protein Tuj1 and glial protein S100 [159].

**Self-assembled gelation** refers to some amphiphilic polymers displaying gelation properties due to their complexation as a result of desolation, collapse, and intermolecular association of nonpolar segments of the monomers [214]. Supramolecular hydrogels rely on small molecules that self-assemble in water through the cooperative effect of the intermolecular forces including electrostatic, hydrogen bonding, and Van Der Waals forces. Supramolecules are ubiquitous, such as enzymes and their substrates, hormones and their receptors, and inclusion compounds of crown ethers and certain metals [215,216]. The process of those kinds of supramolecular self-assemblies through hierarchical growth to form a hierarchical structure is similar to that of a protein from a primary structure to a tertiary structure [217]. Many studies based on heterodimeric peptide/protein or host macrocyclic interactive systems have demonstrated the revelation of shear-thinning ability and self-healing (rapid network recovery) to develop injectable hydrogels [218].

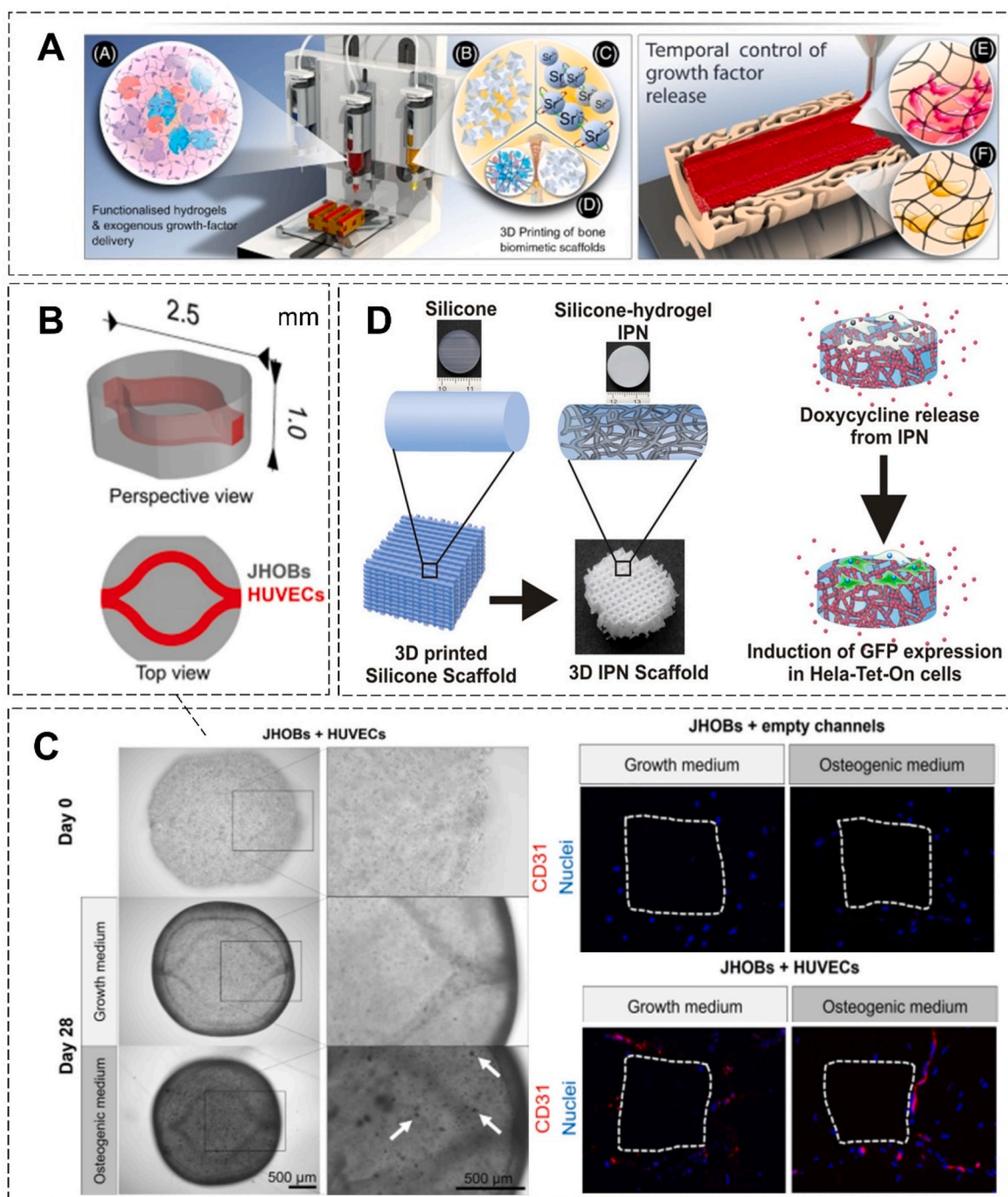
Among the various types of supramolecular forces, the macrocyclic host-guest recognition force has attracted more attention, because it usually contains a variety of forces and exerts a wealth of environmental responsiveness [219]. This dynamic crosslinking provides mechanical protection for delivered cells from the shear damage during injection, as well as maintains the retention and integrity of the implant *in vivo* [220]. The previous study prepared a supramolecular injectable hydrogel via the efficient host-guest complexation between the aromatic residues of gelatin and free diffusing photo-crosslinking acylated  $\beta$ -cyclodextrin

monomers for the rat calvaria bone defect [221]. This weak crosslinking also facilitates the infiltration and migration of the endogenous cells. So, the self-assembled hydrogel can be used as a combined medical device with metal materials to improve their biocompatibility. 3D inorganic-organic supramolecular bioactive interface consisting of a stiff 3D printing porous metal scaffold and injectable supramolecular polysaccharide hydrogel is constructed for osseointegration enhancement in the osteoporotic microenvironment [222].

**The conjugated effect** refers to an electronic effect that changes the distribution of  $\pi$  electrons (or p electrons) in the system due to the mutual influence between atoms. The preparation of injectable hydrogels based on this mechanism is a hot topic, mainly including Michael addition (the nucleophilic addition of a carbanion or another nucleophile to an  $\alpha$ ,  $\beta$ -unsaturated carbonyl compound) [223], Schiff base (aldehyde groups condense with amino groups to form amide bonds) [224], Diels-Alder “click” reaction (conjugated dienes react with substituted olefins to form substituted cyclohexenes), and other click chemistry [225]. These crosslinking processes are carried out under mild conditions, independent of chemical additives. Many natural polymers contain polysaccharides with adjacent hydroxyl groups, such as alginate, chondroitin sulfate, hyaluronic acid, and cellulose, which can be oxidized by periodate to obtain aldehyde groups, when mixed with water-soluble macromolecules containing amino groups like BSA, chitosan, polylysine, an injectable crosslinking hydrogel scaffold can be formed *in-situ* based on Schiff bases [226]. Diels-Alder click chemistry and dynamic acyl hydrazone bond cross-linking are employed for chondroitin sulfate-based hydrogel formation, aiming to improve the necessary strength and precise mechanical tunability to fit for the maxillofacial bone reconstruction [227].

#### 5.4. 3D bioprinting hydrogel designs

The ideal scaffold resembles the structure and composition of human bone, provides nourishment to graft cells, delivery of bioactive factors, and tube-like structures to allow vascularization, advantages that can positively impact bone graft success (Fig. 8A). Many studies have been dedicated to developing a suitable hydrogel bioink to satisfy the merit of viscosity for fluent printability, the hardness, and stiffness, to support the subsequent layers [229]. During 3D bioprinting, polymer



**Fig. 8. Hydrogel system-based mandibular reconstruction by 3D bioprinting.** (A) Multiple-components 3D bioprinting used to generate ‘Print-and-Implant’ scaffold for bone repair (Copyright © 2022 Elsevier Inc., Ref [238]). (B) CAD file of the jawbone model. (C) (Left) Microscopic images of the prints on day 0 and after 28 days of cultivation. (Right) Immunohistochemical staining of CD31 in the bioprinted human jawbone models *in vitro*, the surface of the constructs is marked with white dotted lines. (B-C, Copyright © 2022 Springer Nature Limited, Ref [235]). (D) 3D Printed silicone-hydrogel interpenetrating polymer network (IPN) with biomolecules delivering and cell fate directing (Copyright © 2022 American Chemical Society, Ref [239]).

concentration is the key determinant. A high concentration of polymer can improve the viscosity and mechanical properties of the composite. In contrast, a low concentration may offer better efficiency for cell proliferation and differentiation of osteogenesis and chondrogenesis. The viscosity suitable for print is in the range of 300–30000 cps, which requires the printing concentration of alginate should be in the range of 2–4% [230,231]. However, under this concentration, it is challenging to achieve the hardness and strength of implanted bone only using 3D bioprinted hydrogel. Therefore, many studies suggest employing stiff polymers such as PCL, PLGA, and PVA combined with the 3D bioprinted

hydrogels [232]. Indeed, hybrid strategies achieve the balance of desired compression modulus for mandible reconstruction while retaining the biological properties of hydrogels.

3D bioprinting opens new possibilities for site-specific arrangements of multiple cell types and the generation of fine features embedded in structures for mandibular reconstruction [233,234]. This allows for multicellular hydrogel fabrication and different polymers assembling. Constructs are bioprinted containing primary jaw-derived osteoblasts and vasculature-like channel structures harboring primary endothelial cells. The *in vitro* mandibular construct shows mineralization and hinted

at differentiation to an osteocyte phenotype (Fig. 8B–C) [235]. Moreover, 3D printed PCL/hydrogel has been also incorporated with small molecules to target several types of bone cells to fabricate regenerated mandibular constructs. Accompanying with the release of dual drugs (resveratrol and strontium ranelate, RVS, and SrRn), scaffolds significantly promote *in vivo* mandible formation after 8-week implantation [236]. Besides, the 3D cultural environment provided by the bioprinted hydrogel constructs reflects a more distributed integrin usage and enhanced biological activity, directing the cell fate in proliferation and differentiation (Fig. 8D).

As mentioned, 3D bioprinting also lays down a solid foundation tangible for a promising future of more “personalized” treatment of mandibular reconstruction. Combined with clinical CT imaging and mechanical control technology, a 3D bioprinted biomimetic tissue is fabricated with human amniotic fluid stem cells (hAFSCs)-laden hydrogel for large-scale mandibular reconstruction [237]. Patterning of 3D architecture includes multiple cell-laden hydrogels and supporting PCL polymer. The printing process does not affect cell viability and validates strong osteogenic ability via *in vitro* experiment [237]. ADSCs encapsulated in the composite structures remains viable within the hydrogel that shows excellent spreading on the 3D printed PLA microstructure and simulates the stiffness of the human mandibular condyle [104]. Descriptions and research outcomes of 3D bioprinted constructs especially with hydrogel involved used for mandibular reconstruction are summarized in Table 4.

## 6. Challenges and perspectives

Several hydrogel-based applications have received FDA approval and are currently available for clinical use in oral-maxillofacial trauma surgeries. For example, INFUSE® bone graft (Medtronic Sofamor Danek

**Table 4**  
3D bioprinted constructs used for mandibular regeneration.

Type of constructs	Models	Outcome	Ref.
HAp/epoxide acrylate maleic artificial implants	Patients with craniomaxillofacial bone defects	Enhanced aesthetic results and functional recovery	[240]
3D bioprinted PEKK scaffolds combined with ADSCs	Rabbit mandibular defects	Enhanced integration and bone formation	[103]
PCL/CS hydrogel with HAp coating custom scaffolds with orthogonal interconnected channels	<i>In vitro</i>	Well mimicking human mandibular condyle	[241]
3D bioprinted bone constructs of PCL/HA and SVF-derived cell (SVFC)-laden hydrogel bioink	<i>In vitro</i>	Successfully microvessel formation <i>in vitro</i> and <i>in vivo</i> . Great promising applications for craniofacial bone defects	[242]
3D bioprinted PCL/TCP scaffolds combined hAFSCs-laden hydrogel with a Pluronic F127 temporary support	<i>In vitro</i>	Successful fabrication of mandible, calvarial bone, cartilage, and skeletal muscle	[237]
3D bioprinted Multicellular (osteoblasts and endothelial cells) GelMA/PEGDA scaffold	<i>In vitro</i>	Successful biofabrication of a human jawbone model	[235]
3D bioprinted PCL/hydrogel scaffold with RVS and SrRn sustained releasing	Rat mandibular defects	Enhanced mandibular bone formation after 8-week implantation	[236]

USA, Inc.), a collagen-based hydrogel containing rhBMP-2, has been tested for mandibular reconstruction of structure and function in patients without using iliac crest graft because of the advanced age and comorbidities of the patients [243]. However, some challenges must be overcome before it becomes widely used.

Firstly, there is a conflict between high biocompatibility and poor mechanical strength. Sometimes a compromise in mechanical strength is necessary for using high biocompatible hydrogels as tissue-engineering scaffolds. Although several approaches have been developed to enhance their mechanical properties as we mentioned above, the toxicity of polymers and NCs added during this process, and the inevitable increase of the degradation time, pose risks to bone regeneration. So, hydrogel-related applications are mainly used as independent or composite bone fillers. The load-bearing area still needs to be fixed surgically with metallic materials.

Other concerns are on the uncontrolled release of loaded bioactive factors and stem cells, that is, the burst degradation will lead to burst release. Recently, intelligent hydrogel systems can achieve controllable delivery by sensing stimuli in their external environment and making corresponding changes. In addition to the traditional triggering mechanisms like pH, temperature, and light, hydrogels responsive to biochemical stimuli like enzymes, antigens, and ligands have also been explored [244]. Of note, the more complex functions generate higher cost.

Biosafety and stability should be considered in the whole process of hydrogel production, storage, and transportation [245]. In addition, there is no standardized bone disease model(s) for the current complex hydrogel types to verify their effects, and almost all the hydrogels are not irreplaceable with similar component combinations, gelation mechanisms, and bioactive functions.

Despite the significant challenges that we are facing, the development of hydrogel-based systems for mandibular construction has broadened the scope of craniofacial tissue reconstruction. Such advanced hydrogel systems hold enormous promise for future clinical translations. Based on in-depth understanding of hydrogels, bone regeneration, and their interactions, we will be able to push hydrogel systems toward effective therapy for mandibular reconstruction.

## 7. Conclusion

Advanced hydrogel systems represent a new series of materials arising from an urgent need in mandibular reconstruction to improve the regenerative capacity and functional recovery stemming from osseous. A comprehensive understanding of the remodeling of mandible and hydrogel design strategies is vital for developing innovative therapeutic strategies with better therapeutic efficacy. The faster bone formation rate of the mandible requires the synchronization of biodegradation and new bone ingrowth as the hydrogels show. This review introduces the hydrogel system designs combined with growth factor delivery, NP enhancement, and cell therapy. Autologous dental stem cells are emphasized as the promising ingredients of hydrogel systems for their easy accessibility and stemness maintenance. Besides, additional considerations include the routine presence of bacterial contamination from the oral and the special aesthetic restoration of facial structures, we highlight that the ideal hydrogels are expected to possess the enhanced mechanical property, antibacterial ability, injectable form via minimally invasive surgical intervention, or especially programmable and 3D bioprinted to suit the mandibular defects under various causative situations. With the continuous progress of material technology and 3D bioprinting manufacturing, we anticipate that in terms of constructing multicellular-mediated osteogenic and irregular bone regeneration, advanced hydrogel systems may lay down the solid foundation tangible for a promising future of more intelligent and personalized treatment in challenging mandibular reconstruction.

## Ethics approval

No ethics approvals are needed.

## Declaration of competing interest

The authors declare no conflict of interest.

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