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Hydrogels in Periodontal and Craniofacial Regeneration: Current Applications and Next-Generation Biomaterials

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ABSTRACT

Periodontal and craniofacial tissue defects are complex regenerative targets as the reconstitution of tissue heterogeneity, interconnection and function is essential for favorable clinical outcomes. Periodontal tissues are additionally challenged by the bacterial and immunological factors associated with oral regeneration. Hydrogels are extracellular matrix-like hydrated polymer networks that represent a diverse class of regenerative materials. Current applications of hydrogels for periodontal and craniofacial tissue regeneration include either independent or combined approaches including serving as scaffolds to support cell migration, proliferation, differentiation and matrix deposition at the defective site, and/or the delivery of biomolecular therapies. The aim of this review is to highlight and classify the hydrogel strategies currently used in the clinical area for the regeneration of periodontal and craniofacial tissues. In addition, we provide a perspective on emerging hydrogel technologies and regenerative strategies under development that may be utilized to address unmet clinical needs.

1 | Clinical Need and Application

Periodontal and craniofacial diseases present a significant health burden due to their complex structural and functional demands [1]. Periodontitis, one of the most prevalent oral diseases worldwide, not only leads to tooth loss and functional impairment but also contributes to other systemic conditions such as cardiovascular disease, diabetes, and adverse pregnancy outcomes [2]. While early clinical management of periodontal disease emphasizes the importance of non-surgical treatment [3] through improved active therapy, periodontal maintenance, and patient behavior [4], when disease progression continues or structural defects remain unresolved, regenerative interventions become desirable. The regeneration of both periodontal and craniofacial tissues requires re-establishing not only individual tissue components but also their anatomical structure and function [5]. In addition to diseases such as periodontitis, the regeneration of craniofacial defects (which may result from trauma, congenital anomalies, or defects after tumor resections) requires the coordinated regeneration of multiple tissue types to achieve successful clinical outcomes [6]. Surgical regenerative interventions are also commonly indicated in cases involving periodontal intrabony defects, furcation defects, peri-implant defects and mucogingival deformities.

Periodontal and peri-implant surgical interventions utilize a diverse range of biomaterials that support tissue repair and regeneration. Biomaterials act as scaffolds to support cellular behavior (e.g., migration, proliferation, differentiation, extracellular matrix production), provide a favorable microenvironment for cell function, and can enable the delivery of therapeutic agents [7]. As a class of donor-derived biomaterials, autogenous bone grafts have long been considered the gold standard for bone defect repair in periodontal and craniofacial regeneration [8, 9]. Their effectiveness stems from inherent advantages such as osteogenic potential, osteoinductivity, osteoconductivity, and lack of immunogenic response, making them ideal for promoting natural bone formation and integration. Despite these benefits, autogenous grafts are limited by significant clinical drawbacks. Harvesting autogenous bone necessitates an additional surgical procedure, potentially increasing patient morbidity, risk of complications, and postoperative discomfort. Furthermore, autogenous grafts may exhibit rapid resorption, compromising their ability to maintain the volume necessary for successful regeneration [10]. Additionally, external root resorption has been reported, raising concerns about their long-term suitability in periodontal regeneration [11]. Other strategies to utilize autologous regenerative methods, such as autologous blood products (ABP), including platelet-rich fibrin have been explored due to their rich biological factor profiles; however, clinical evidence remains limited [12]. Existing studies on ABP for periodontal regeneration show mixed outcomes, and superiority over control treatments has not been consistently demonstrated, highlighting the need for alternative or complementary biomaterial-based strategies.

Alternatives to autogenous grafts include allografts and xenografts, which circumvent the morbidity associated with additional harvesting procedures. Bone substitutes, primarily derived from bovine, porcine, or equine sources, or allogenic sources offer advantages such as consistent availability, osteoconductive properties, and relatively predictable clinical results [13]. For instance, Bio-Oss (Geistlich, Switzerland), a widely used bovine xenograft, is well established in dental practice and backed by clinical research [14]. Nevertheless, xenografts carry limitations, including variable resorption rates and risks of immunogenic reactions, prompting continuous exploration of safer, more predictable biomaterials.

Hydrogels have become promising alternatives to traditional regenerative materials, due to their biocompatibility and ability to mimic the extracellular matrix [15]. Their fluidity, injectability, and adjustable mechanical properties enable customization for periodontal and craniofacial regeneration. Their injectability allows minimally invasive application, particularly advantageous for periodontal defects where anatomical complexity and limited surgical access necessitate precise material placement [16]. Given these advantages, hydrogels such as Emdogain (Straumann, Switzerland) have increasingly gained attention in clinical and research settings for periodontal and craniofacial tissue regeneration (clinical examples shown in Figure 1). The following sections of this review detail clinically approved hydrogel technologies, highlighting their polymer compositions, mechanisms of action, clinical evidence, and current limitations, with a perspective towards future advancements in the field.

2 | Overview of Hydrogel Technology and Utility in Tissue Engineering

Hydrogels are a class of multifunctional materials composed of cross-linked polymers with high water content, which can exceed 90% in some formulations. The unique hydrated character of these materials allows them to be engineered to emulate characteristics of mammalian extracellular matrix, providing a physical similarity to a diverse range of native tissues and making them highly suitable for biomedical applications [17].

In tissue engineering, hydrogels used are most frequently utilized as space fillers, vehicles for the delivery of bioactive molecules, and as 3D structures (or scaffolds) to promote new tissue formation. Beyond these tissue engineering strategies, hydrogels have been successfully translated into more than 100 medical products (with over 200 active clinical trials), serving a variety of esthetic, wound healing, and therapeutic purposes [17, 18]. Broadly, hydrogels may be classified by both the type of polymer used (natural or synthetic) and by the method of crosslinking (non-covalent or covalent). The choice of these criteria serves to modulate the functional characteristics of tissue engineered hydrogels such that these materials may exhibit a wide range of tissue-specific biocompatibility, mechanical properties (stiffness from 0.5 kPa to 5 MPa) and clinical functionality [19].

While such properties may be achieved with other biomaterials, hydrogels are additionally advantaged by their formation under relatively mild conditions, that may be utilized for chairside gelation or minimally invasive injectable application site (in situ) gelation, which is advantageous in the repair of complex defects. The specific interplay of these facets is already the subject of excellent reviews [19–22]. The following will serve to briefly overview polymer and crosslinking considerations (summarized in Figure 2) as they apply to periodontal and craniofacial tissue regeneration approaches.

Both natural and synthetic polymer-based hydrogels offer distinct advantages and limitations in tissue engineering applications. Hydrogels derived from natural polymers (or biopolymers), including those based on collagen, hyaluronic acid, cellulose, fibrin, gelatin, alginate, and chitosan (among many others) have the advantage of possessing the diverse chemistry present in native tissues, typically yielding naturally biocompatible, bioactive, and minimally cytotoxic hydrogel materials. However, hydrogels based on unmodified biopolymers typically have limited mechanical properties, present batch-to-batch variability in composition, and have a limited ability to modulate material properties [18, 23, 24]. Hydrogels derived from synthetic polymers, such as polyvinyl alcohol (PVA), poly (ε-caprolactone) (PCL), polyethylene glycol (PEG), polyacrylic acid (PAA), polyurethane (PU), and polyacrylamide (PAAM), do not present these disadvantages and may be modified to achieve impressive mechanical properties, synthesized to tight molecular tolerances, and tuned by chemical modifications to achieve tissue-specific properties [25]. Synthetic polymers, however, lack the bio-analogous diversity of natural polymers, and therefore typically require the addition of endogenous factors to promote cell behavior and successful tissue regeneration [26]. To minimize the shortcomings of individual polymers, some clinical materials utilize the combination of multiple biopolymers, functionalization of biopolymers, or blends with synthetic polymers in the development of hybrid network hydrogel materials [27] which have been shown to enable the creation of mechanically resilient and biocompatible scaffolds for improved skeletal muscle regeneration [28].

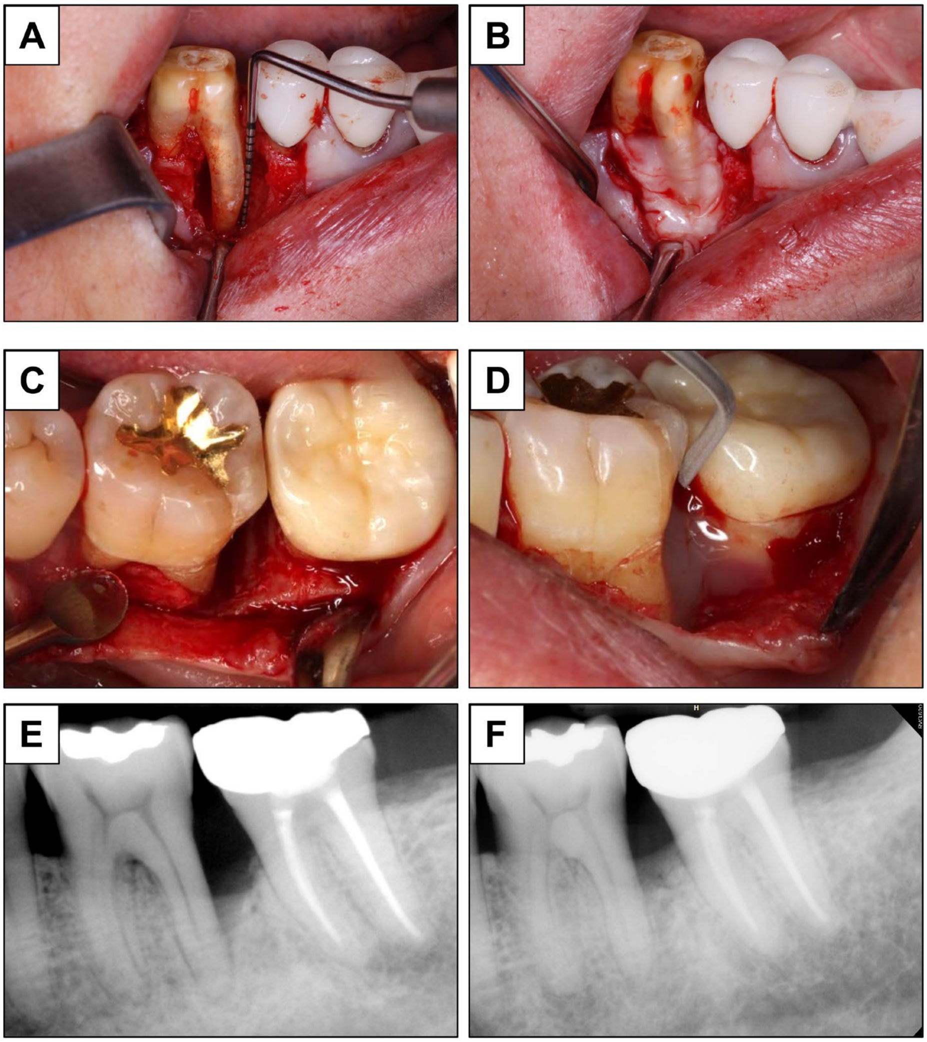

FIGURE 1 | (A, B) Example of the clinical application of Emdogain for the treatment of infrabony and grade 2 furcation defect on tooth #46 (FDI). (C, D) Example of the clinical application of EMD for treatment of infrabony defect interproximal of tooth #36–37 (FDI). (E, F) Radiographic examination 6 months and 1 year following surgical treatment with flap in combination with EMD.

The properties and behavior of hydrogel materials, in addition to the choice of polymer type or blend, are largely dictated by the nature of network formation between the polymeric elements, which can be achieved through both non-covalent (or physical) and covalent (or chemical) crosslinking. Physical crosslinking includes ionic, hydrogen bonding, metal-coordination, and hydrophobic interactions, whereas chemical crosslinking involves network development through the formation of covalent bonds, which may include the formation of imine bonds/acylhydrazone, borate ester, and disulfide bonds (among others) [29–31]. Physical crosslinking is mediated by an increased physical interaction between polymer chains—which may be initiated by elevated temperature, pH, concentration, or the addition of polymer to aqueous media. While this aspect makes physical crosslinking ideal from an ease of use and clinical perspective, the reversible nature of these non-covalent interactions may lead to uncontrolled hydrogel disassembly under physiological conditions, compromising their structural integrity and functionality over time which often restricts their use in load-bearing applications.

Conversely, chemically crosslinked hydrogels are typically endowed with more robust mechanical properties due to the formation of covalent bonds, enhancing their stability and resistance to uncontrolled degradation [32]. Moreover, covalent hydrogels can be engineered to have specific degradation rates, allowing for controlled release of bioactive molecules and facilitating tissue regeneration processes [33]. The chemical crosslinking of polymeric elements has been shown to improve the mechanical properties of both biopolymer blends [34] and biopolymer/synthetic polymer hydrogels [28]. The formation of some chemical crosslinks, however, requires the addition of an initiator (which may be a chemical agent or energy source) and crosslinking agent (typically an additional polymer functional group) to the hydrogel system, which stands to both increase the complexity and reduce the versatility of these materials in certain application spaces (such as the application of an energy source in minimally invasive regenerative approaches). Additionally, the presence of a highly chemically crosslinked network may also impede the penetration of various proteins and inwardly diffusing

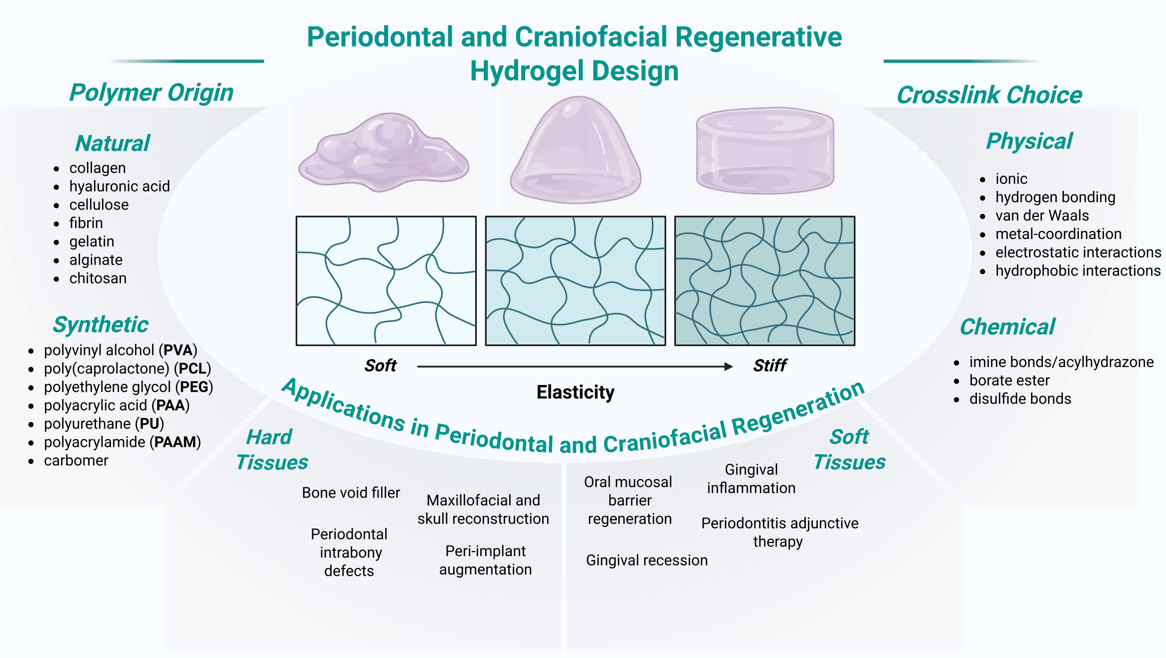

FIGURE 2 | Summary of hydrogel design and clinical applications in periodontal and craniofacial tissue regeneration. Design elements highlighted are representative of those highly prevalent in the literature and are not exhaustive.

enzymes as well as the diffusion of loaded macromolecular drugs (e.g., recombinant proteins and monoclonal antibodies), which constitute an increasing percentage of new drugs approved, with many others under development [35]. To address the shortcomings of both strategies, many emerging tissue regenerative hydrogel strategies utilize both physical and chemical crosslinking mechanisms [36]. One such example is the emergence of methacrylated gelatin (or GelMA), which features the physical crosslinking interactions of gelatin and chemical crosslinking dictated by the level of methacrylate/gelatin conjugation. By optimizing the modification degree or concentration of GelMA, hydrogels have been shown to optimally facilitate cell survival, proliferation, differentiation, and drug delivery [37–39].

The unique properties of hydrogels, such as the ability to be formed in situ, modifiable mechanical characteristics, and biocompatibility, can enable effective healing and restoration of periodontal and craniofacial tissues [40]. In addition to appropriate mechanical properties, other clinically desirable features of hydrogels include their ability to guide the generation of composite periodontal tissues (through gel structure modulation) and their injectability (for minimally invasive interventions) which can be achieved with physically crosslinked, shear-thinning or thermosensitive hydrogels [41, 42]. Biopolymers such as collagen, hyaluronic acid, modified cellulose, and protein cocktail extracts have traditionally been used in these regenerative hydrogels, serving a diverse range of applications from soft tissue regeneration to bone graft adjunct therapies covered in the following section.

For the purposes of this review, we consider hydrogel materials as those that are injectable (to some degree), consisting of a polymeric (natural or synthetic) matrix, are highly hydrated (> 80%) in nature, and possess key features for regeneration endowed by the hydrogel network itself and/or by the delivery of pro-regenerative agents. This precludes the discussion of materials consisting of synthetic or biopolymers in the absence of an aqueous phase, and non-synthetic allo-, xeno- and synthetic bone graft putties, which have been covered at length in an excellent recent review [43]. In the latter cases, water (and often small quantities of polymer) is used minimally for the delivery of solid phase bone graft granules. These pastes, while clinically useful as space-filling materials, do not share the ECM emulative features of hydrogels nor have the ability to be injected into small defect sites in minimally invasive clinical interventions due to their high viscosity. Additionally, clinical materials that utilize pre-formed dehydrated or freeze-dried collagen sponge templates (such as Bio-Oss Collagen [Geistlich, Switzerland] and INFUSE [Medtronic, Ireland]), while primarily polymeric in nature, do not share features such as ECM biomimicry and injectability of hydrogels as classified in this review.

3 | Hydrogels Utilized Within Periodontal and Craniofacial Regenerative Medicine

Hydrogels have proven to be valuable tools in the field of periodontal and craniofacial tissue regeneration, which aim to address the global burden of oral disease as well as limited versatility and source considerations for allografting and xenografting approaches. To date, several hydrogel materials have been clinically approved for craniofacial and periodontal tissue regeneration (Table 1). The current suite of hydrogel regenerative therapies available to clinicians can be divided based on both their intended regenerative application (periodontal, peri-implant and craniofacial bone) and tissue target (hard/bone or soft) type. The latter for which organizes the discussion below in describing the materials composition, differing mechanisms of

TABLE 1 | Clinically approved periodontal and craniofacial hydrogel therapies.[a]

Hydrogel therapy	Hydrogel classification	Indicated clinical use	Material limitations	Current regenerative applications	Application sub-type and supporting evidence
Emdogain (FDA, 1996) (Straumann)	Injectable **Active Agent** 3% Enamel matrix derivative **Hydrogel Base** 6.5% Propylene glycol alginate matrix	Originally for the treatment of intrabony defects without fucations (PMA, 1996) Subsequently for furcations, gingival recession defects, and in conjunction with bone graft materials	May not afford the space-maintaining properties necessary for large defects when used alone	Craniofacial Bone	Maxillofacial and skull reconstruction [44]
				Periodontal	Periodontal regeneration – Infrabony defects [45]
					Periodontal – Intrabony defects (ACU) [46–53]
				Peri-implant	Peri-implant augmentation [54–56]
					Peri-implantitis [57]
Actifuse (FDA, 2009) (Baxter) 510 (k) 2009	Implantable[c] **Active Agent** Silicate-substituted calcium phosphate granules **Hydrogel Base** Poloxamer 407 matrix	For the treatment of maxillofacial osseous bone defects (510 (k))	Not appropriate for minimally invasive treatments, requiring a large gauge syringe applicator	Craniofacial Bone	Bone void filler, regenerative grafting [58]
REGROTH (Japan, 2016) (Kaken Pharmaceutical)	Injectable **Active Agent** 0.3% rhFGF-2 **Hydrogel Base** Hydroxypropyl cellulose (HPC)	For the treatment of periodontal pockets and intrabony defects	May not afford the space-maintaining properties necessary for large defects when used alone	Periodontal	Periodontal regeneration [52, 59]
					Periodontal intrabony defects [60–63]

(Continues)

TABLE 1 | (Continued)

Hydrogel therapy	Hydrogel classification	Indicated clinical use	Material limitations	Current regenerative applications	Application sub-type and supporting evidence
Ossigel (Pending) Orquest	Injectable **Active Agent** 0.4% rhFGF-2 **Hydrogel Base** Sodium hyaluronate	Not currently approved clinical use. Indication based on clinical studies is likely intrabony defects	Limited clinical evidence and likely limited space-maintaining properties if used in larger defect sites	Periodontal	Periodontal intrabony defects [64]
Gengigel (FDA, 2007[d]) (Ricerfarma)	Injectable **Active Agent** 7.5% xylitol **Hydrogel Base** 0.2% or 0.8% Sodium hyalaurate	For the treatment of oral mucosal lesions resulting from oral surgery, trauma, or oral mucositis or stomatitis	Currently limited data regarding the release characteristics of the active antimicrobial agent (xylitol) and the effects on oral microbiome	Periodontal	Mucosal barrier, Furcation defects[b] [65] Periodontitis [66] Gingivitis [67]
Aminogam Gingival Gel (CE, 2021[d]) (Professional Dietetics)	Injectable **Active Agent** 2% Amino acids (1% glycine, 0.15% L-leucine, 0.75% L-proline, and 0.1% L-lysine) **Hydrogel Base** 1.3% Sodium hyalaurate	For the protection and regeneration of oral mucosal trauma sites as a result of oral surgery, trauma, or oral mucositis	May not be effective in mitigating infection risk of mucosal wounds necessitating adjunct therapies	Periodontal	Accelerated gingival tissue healing [68–70] Periodontitis [71] Oral mucositis [72]
hyaDENT BG (CE, 2018) (REGEDENT AG)	Injectable **Active Agent** N/A **Hydrogel Network** 1.6% highly crosslinked and 0.2% natural sodium hyalaurate	For the treatment of gingival recession, post extraction healing, intra bony defects and guided bone regeneration (when used in conjunction with bone graft materials)	In the absence of an active agent, regeneration is dependent on the hydrogel network	Periodontal	Periodontal intrabony defects[b] [49] Periodontitis [73, 74]

(Continues)

TABLE 1 | (Continued)

Hydrogel therapy	Hydrogel classification	Indicated clinical use	Material limitations	Current regenerative applications	Application sub-type and supporting evidence
REGENFAST (CE, 2021) (Geistlich)	Injectable **Active Agent** 1% Polynucleotides **Hydrogel Base** 1% Hyaluronic acid	For the treatment of gingival recessions and protection of oral mucosal tissues during trauma or oral surgery	Limited primary as an adjunct therapy to promote healing following oral surgery	Craniofacial Bone	Alveolar Defects[b] [75]
				Peri-implant	Peri-implant augmentation[b] [76]
				Periodontal	Periodontal intrabony defects[b] [77]
					Periodontal pocket closure [78]
Pocket-X Gel (CE, 2021) (Geistlich)	Injectable **Active Agent** 0.625% Octenidine hydrochloride **Hydrogel Base** 0.8% Hyaluronic acid/poloxamer 407 matrix	To promote healing and the protection of oral tissues when used as an adjunct treatment to periodontal therapies	Currently limited data regarding the release characteristics of the active antimicrobial agent (octenidine) and the effects on oral microbiome	Periodontal	Periodontitis [79]

Abbreviations: CE, approved for use in the European Union; FDA, approved for use in the United States; Japan, approved for use in Japan.
[a]Examples are biased towards RCTs, equivalency, and large in vivo validation studies.
[b]Application as an adjunctive therapy.
[c]Large gauge applicator.
[d]Since 2001 the FDA has classified sodium hyaluronate gel base materials as Class I medical devices for the treatment of oral soft tissues.

action, and clinical studies outlining evidence and limitations of clinical utility.

3.1 | Emdogain and Enamel Matrix Derivative

Emdogain is the first clinically approved (FDA, 1996) and one of the most extensively studied hydrogel therapies within craniofacial and periodontal tissue regeneration. In this regenerative material, enamel matrix derivative (EMD) serves as the active biologic agent and propylene glycol alginate (PGA) as the hydrogel local delivery vehicle [80]. The active biologic EMD is a combination of proteins extracted from developing porcine tooth buds consisting primarily of amelogenins (> 90%) and smaller amounts of non-amelogenin proteins such as tuftelin, ameloblastin and enamelin. EMD has been shown independently to promote the osteogenic differentiation of progenitor cells involved in healing periodontal and craniofacial tissues [81].

Other biological effects explored with EMD explored outside of the clinic have included enhanced wound healing, increased cell proliferation, and the promotion of periodontal ligament cell differentiation [82–84]. While EMD has the potential to self-assemble into hydrogels independently, its composition of primarily hydrophobic proteins (including amelogenin) which become insoluble at physiological pH and temperature limits their interactions with oral tissues. Using PGA at an acidic pH allows for adequate loading of EMD, and in a primate study, it was shown to most effectively deliver EMD to treated root surfaces [85].

Emdogain, since its original approved use in the treatment of intrabony defects, has seen utility in a wide range of craniofacial and periodontal clinical scenarios, supported by numerous randomized controlled trials. Among these, Emdogain has demonstrated significant clinical efficacy in promoting periodontal tissue regeneration, where studies have shown the material to stimulate the formation of acellular cementum, collagen fibers, and alveolar bone [86, 87]. Such effects have resulted in statistically significant improvements in clinical attachment level (CAL) and probing depth (PD) reduction compared to placebo and control treatments [46–49], and, advantages over guided tissue regeneration (GTR) procedures, notably with fewer postoperative complications and simpler surgical protocols [44, 50]. In peri-implant procedures, Emdogain has been shown to promote early bone formation at the apical aspects of implants [54], and to be positively associated with implant survival when used as an adjunct therapy in the treatment of peri-implantitis [55, 57]. However, according to a recent RCT [57], the successful treatment of peri-implantitis is difficult to accomplish. Adjunctive use of EMD during peri-implantitis regenerative surgery may not offer long-term clinical or radiographic benefits compared to flap surgery alone [57]. The RCT did state EMD may be positively associated with implant survival and proposed its application as an adjunctive therapeutic may postpone implant failure in advanced peri-implantitis cases that undergo surgery. In the EFP S3 level clinical practice guideline for management of peri-implantitis, there is a lack of evidence and consensus on the selection of biomaterials and biologics for peri-implantitis illustrating the need for additional research [88].

Despite its widespread use and documented success, some clinical studies have evidenced limitations to the effectiveness of Emdogain treatment alone, and, to improved treatment outcomes of other biologic-based therapies. For example, one clinical study investigating bone substitutes, found that the use of Emdogain alone results in greater gingival recession at treated sites [51], highlighting the necessitated use of adjunct regenerative materials (such as bone grafts) to optimize outcomes in certain clinical scenarios. Similarly, in a peri-implant study, while Emdogain was shown to result in elevated early bone formation at peri-implant sites, no significant differences were found when evaluating total new bone formation and primary and secondary implant stability compared to the use of bone graft materials alone [54]. One cause of the heterogenous treatment outcomes observed in these clinical cases is the lack of space-maintaining ability of Emdogain, which may be more apparent in larger defect sites [89].

Moreover, in the management of periodontal intrabony defects, clinical evidence has shown that the delivery of recombinant human fibroblast growth factor 2 (rhFGF-2) alone may outperform Emdogain through evaluation of alveolar bone growth in patients with periodontitis [52]. These limitations underscore the need for careful patient-specific selection for use which may include combining Emdogain with space-maintaining materials and the potential use of EMD-alternative biologic agents. These limitations have prompted the development of several other hydrogels for hard tissue regeneration which are highlighted below.

3.2 | Osteoconductive and Osteogenic Hydrogels

Beyond Emdogain, clinicians have had other osteoconductive hydrogels emerge for clinical use in the USA (Actifuse [Baxter, USA]) and Japan (REGROTH [Kraken Pharmaceuticals, Japan]) that illustrate a range of material properties and applications in craniofacial bone and periodontal regeneration.

Actifuse is a hydrogel-based bone graft material with osteoconductive features used in periodontal regeneration primarily for the purposes of space maintenance for bone healing which is a current limitation of the independent use of Emdogain as discussed above. This technology contains synthetic calcium phosphate/hydroxyapatite granules as the active osteostimulatory agent and uses the synthetic polymer poloxamer as the hydrogel matrix. Actifuse is an example of a composite hydrogel, where the bioactive inorganic fillers are used not only to directly impart osteoconduction, but also to improve mechanical properties, which is particularly relevant for bone regeneration applications where space maintenance is essential [90]. Actifuse, based on silicate-substituted calcium phosphate synthetic graft granules, has been well validated in promoting an osteostimulatory effect in spinal and orthopedic applications [58, 91], and has more recently (2018, 510 (k)) been indicated for use in periodontal and craniofacial osseous defects. However, there are currently no active or completed clinical studies investigating the efficacy of Actifuse in periodontal and craniofacial hard tissue regeneration. Perioglas (Novabone, USA), which is another composite material also leveraging the osteostimulatory effects of bioactive ceramic fillers (specifically 45S5 Bioglass) has been approved for clinical use since 1995 (FDA). While functioning as a putty and not meeting our criteria as a true hydrogel therapy, Perioglas has been evidenced to lead to significant improvements in probing depth, clinical attachment level, and bone defect depth in patients with Grade C periodontitis [92] and has been shown to lead to enhanced periodontal osseous defect regeneration compared to open flap debridement alone [93], which may indicate the utility of such a composite material strategy. While Actifuse displays improved space-maintaining ability compared to the independent use of Emdogain, Actifuse is minimally injectable, and currently utilizes a large gauge syringe applicator making for essentially an implantable material.

Periodontal regenerative hydrogel REGROTH, in contrast to Actifuse, utilizes osteoinductive proteins to promote hard tissue regeneration. REGROTH (which was approved for use in Japan in 2016), contains recombinant human fibroblast growth factor-2 (rhFGF-2) as an active agent that is delivered using a hydroxypropyl cellulose (HPC) hydrogel matrix. The use of rhFGF-2 alone has been shown to possess potent angiogenic and mitogenic properties and to have important roles in wound healing and tissue remodeling. Prior to its presence in clinical materials, rhFGF-2 was found to be effective in the regeneration of artificial periodontal defects in large animal models, prompting its integration into clinical materials [94–96]. REGROTH has demonstrated significant efficacy in periodontal regeneration, which, in direct comparison to Emdogain, has shown improved regenerative outcomes (linear alveolar bone growth) in repairing intrabony defects [52]. Indeed, meta-analysis and systematic reviews concerning clinical evidence of rhFGF-2 have suggested greater bone fill density in the treatment of infrabony defects compared to control hydrogel vehicle alone [97, 98]. Clinical studies have also investigated combination therapies utilizing rhFGF-2 alone and REGROTH where the treatment outcomes of infrabony periodontal defects have been shown to be further enhanced by the addition of osteostimulatory agents such as β-tricalcium phosphate, deproteinized bovine bone mineral, and carbonated apatite granules [60–62]. The use of these adjunctive agents is in line with their use in Emdogain, which may address the limited space-maintaining ability of REGROTH in larger defect sites.

3.3 | Hyaluronate-Based Hydrogels

The largest selection of clinically available hydrogel therapies is based on variations of natural base polymers of hyaluronate/hyaluronic acid (HA). As HA is found in higher concentration in the ECM of native periodontal soft tissues compared to hard tissues, such hyaluronate-based hydrogel (HLH) therapies are targeted towards periodontal soft tissue regeneration [99]. HLHs have made for ideal implantable and injectable biomaterials due to their tunability (through altering molecular weight and degree of crosslinking) as well as their bioresorbable and immunomodulatory character [32]. In pre-clinical studies, HLHs have been shown to promote angiogenesis and upregulate periodontal ligament cell proliferation and contractility [100]. The clinical efficacy of Gengigel (Ricerfarma, Italy), Aminogam (Professional Dietetics, Italy), hyaDENT BG (Regedent, Switzerland), Ossigel (Orquest, Spain), REGENFAST (Geistlich, Switzerland), and Pocket-X Gel (Geistlich, Switzerland), which all utilize HLHs, has been established through clinical studies highlighting their material properties and applications in periodontal soft tissue regeneration. While the clinical evidence supporting the use of these HLHs will be highlighted below, additional pre-clinical (in vivo) evidence to support their efficacy can be found in an excellent review by Priyanka et al. [101].

Both Gengigel (available in both 0.2% and 0.8% HA formulations) and Pocket-X Gel (0.8% HA/poloxamer blend) are hydrogels primarily indicated for periodontal applications that utilize antimicrobial active agents xylitol and octenidine, respectively. For Gengigel, low (0.2%) HA formulations are primarily indicated for the non-surgical treatment of periodontitis and periodontal inflammation, which has been shown to result in improvements in clinical attachment level compared to scaling and root planing alone [102, 103]. The more concentrated Gengigel (0.8% HA) formulation is a more viscous HLH that has demonstrated clinical effectiveness when used in conjunction with bone graft materials in the treatment of furcation defects and intrabony defects [65, 66, 104]. For example, combination therapies with β-tricalcium phosphate displayed substantial bone fill and attachment gain in the treatment of intrabony defects, although β-tricalcium phosphate resulted in similar results [105]. Pocket-X Gel has been shown to effectively increase PPD and CAL in patients with stage 3 periodontitis compared to scaling and root planing alone [79]. Currently, the antimicrobial effects of both Gengigel and Pocket-X Gel (and broad-spectrum antimicrobial agents xylitol and octenidine hydrochloride, respectively) have yet to be directly evaluated in clinical studies through pocket sampling and site microbial tests which could serve to better optimize administration protocols and clinical outcomes.

Aminogam (1.33% HA) and REGENFAST (1% HA), in addition to being more viscous than both Gengigel and Pocket-X Gel, are formulated with synthetic amino acids (glycine 1%, L-leucine 0.15%, L-proline 0.75%, and L-lysine 0.1%) and polynucleotides (PN, 1%) as active agents, respectively. Outside of periodontal tissue regeneration, these combination hydrogels have also been used for the viscosupplementation of synovial joints, and, to improve the healing of diabetic ulcers [106, 107]. The addition of synthetic amino acids (as used in Aminogam) has been shown to further enhance the regenerative effects of HLH alone through the promotion of angiogenesis, collagenogenesis and the formation of ECM [108, 109]. PN/HA hydrogels (as used in REGENFAST) have been shown to have a pro-regenerative effect on gingival fibroblasts by stimulating improved cell growth, viability, the production of ECM, and wound healing compared to HA gels alone [110–112]. Clinical trials have demonstrated that Aminogam may accelerate wound healing, and reduce inflammation which can result in more mature connective tissue and collagen when used as an adjunctive therapy compared to ultrasonic debridement alone [71, 113]. Interestingly, in a large split-mouth periodontitis study, the use of REGENFAST in conjunction with subgingival re-instrumentation was found to result in statistically similar CAL gain and PD reduction compared to re-instrumentation alone [78]. Although REGENFAST was not found to improve CAL gain or PD reduction across the split-mouth study, it was found to result in a significant reduction in the modified sulcular bleeding index in patients with baseline PD > 6 mm, perhaps indicating its utility in the treatment of inflammation in deep periodontal pockets.

HyaDENT BG (1.6% cross-linked and 0.2% natural HA), represents the most viscous HLH currently clinically available that has displayed promise primarily within adjunctive gingival and bone grafting applications. In this material, HA serves as both the active agent and hydrogel matrix, which may be used effectively in combination therapies. For example, in a combination therapy with a subepithelial connective tissue graft, HyaDENT BG was shown to lead to improved root coverage compared to the use of tissue graft alone in the treatment of clinical gingival recession [114, 115]. In another clinical study, the treatment of intrabony defects with HyaDENT BG in conjunction with Emdogain and deproteinized porcine bone mineral granules was shown to lead to improved clinical attachment and a reduction in pocket probing depth and gingival recession [49, 73]. When used independently, HyaDENT BG has also shown clinical effectiveness in the treatment of periodontitis, acting to reduce periodontal inflammation (measured by bleeding on probing) compared to control treatments [74].

Ossigel (low viscosity, high molecular weight HA) represents the only HLH therapy formulated with a biologic (rhFGF-2) as an active agent to improve tissue regeneration. Compared to REGROTH, Ossigel contains a slightly higher concentration of rhFGF-2 (0.4% vs. 0.3%) and utilizes a HA hydrogel network more specifically oriented toward soft-tissue regeneration (compared to HPC). In addition to the elevated levels of HA in periodontal soft tissues, hyaluronate and rhFGF-2 have displayed innate synergies that have been shown to enhance the regenerative potential of periodontal ligament cells in vitro [116]. Elements of the regenerative potential of HLH/FGF-2 systems have also been shown in a large animal osteotomy model, which led to significant improvements in fracture healing [117]. One clinical study investigating Ossigel has illustrated its effectiveness in the treatment of intrabony defects, displaying significantly improved clinical attachment levels and reduced probing pocket depths compared to surgical interventions alone [64]. Despite this clinical evidence, the regulatory status of Ossigel is still pending.

3.4 | Summary of Approved Hydrogel Technologies for Clinical Application

The therapeutic needs of periodontal and craniofacial regenerative medicine have spurred the development of several clinically available hydrogel-based approaches each with distinct mechanisms and limitations that shape their clinical application. Emdogain, as the first FDA-approved regenerative hydrogel in this space, has demonstrated significant efficacy in promoting periodontal tissue regeneration but has displayed limitations when used independently in challenging applications where space maintenance is essential (such as craniofacial defect regeneration). Actifuse, a composite hydrogel, features inorganic osteoconductive filler particles which lead to better space maintenance but limit the injectability of these materials. REGROTH utilizes osteoinductive protein rhFGF-2 as an active agent which has demonstrated promising outcomes, but faces similar adjunct use limitations as Emdogain. HLHs, including Gengigel, Aminogam, hyaDENT BG, Ossigel, REGENFAST, and Pocket-X Gel, primarily target soft tissue regeneration (due to the natural presence of HA in periodontal soft tissues) with varying degrees of success and more limited clinical evidence regarding their efficacy as adjunctive hard tissue therapies. The distinct limitations of contemporary hydrogels discussed above highlight the ongoing need for continued development and refinement of hydrogel-based regenerative therapies in periodontal and craniofacial applications, which are the subject of the following section.

4 | Emerging Hydrogel Regenerative Strategies to Address Outstanding Clinical Needs

While the hydrogel-based therapies discussed above have undoubtedly aided in improving the outcomes of periodontal and craniofacial regeneration, significant gaps remain. Indeed, while improved clinical outcomes may be found through these clinical interventions, such contemporary therapies often fail to completely restore the original structure and function of periodontal and craniofacial tissues, where in many cases even when used within indication, complete defect closure (including intrabony and furcation defects) is seldom achieved. Additionally, most contemporary therapies typically achieve positive treatment outcomes as defect site size decreases, where significant outcome heterogeneity is observed in the treatment of large or complex defects or in patients with specific comorbidities [118]. The regeneration of the human periodontium and craniofacial bone is challenging due to their dynamic, complex, and tooth-specific character that relies on specific tissue architecture and interconnection to regain appropriate function and health. Many emerging regenerative hydrogel therapies are attempting to better address the regenerative complexity of periodontal and craniofacial tissues towards improving clinical outcomes.

Specifically, these developments have aimed to address the complexity of periodontal tissue and craniofacial bone regeneration by going beyond the primary use of contemporary hydrogels as passive drug delivery systems, and instead use alternative hydrogel compositions, gelation strategies and architectures and through improved direction/modulation of the respective healing environment using biomolecular cues. There are already several excellent reviews that comprehensively discuss the body of emerging pre-clinical regenerative hydrogel technologies for periodontal tissue and bone regeneration [118–123]. The following text will aim to highlight and define these emerging themes and their relation to addressing the clinical gaps of currently available therapeutic hydrogel materials.

4.1 | Emerging Regenerative Hydrogel Network Technologies—Injectable

Currently available hydrogel therapies often rely exclusively on physical crosslinking for network formation including those which are primarily regulated by temperature control. One common challenge associated with physically crosslinked hydrogels is their potential lack of structural integrity which often restricts their application in load-bearing and space-filling applications without high contents of filler materials (such as bone graft materials). An optimal clinical hydrogel should be both injectable and endowed with suitable degradation and mechanical properties for each respective periodontal and craniofacial regenerative application. A comprehensive summary of contemporary and emerging injectable hydrogel network formulations and crosslinking strategies is already the subject of an excellent review [124]. In contrast to clinically available hydrogel therapeutics, emerging strategies are utilizing more sophisticated in situ gelation strategies and a diverse range of composite hydrogel network polymers. Such composite systems also include those incorporating bioactive nanoparticles (e.g., 45S5 bioactive glass [125]) as fillers. These inorganic fillers not only enhance bioactivity but also improve the mechanical properties of polymer hydrogels, which is particularly relevant for bone regeneration applications.

Emerging hydrogel network forming strategies in periodontal and craniofacial tissue engineering include those that are more directly thermo-responsive or photocurable [119]. Additionally, while current hydrogel therapies rely on a single polymer for network formation, many injectable hydrogels under development are utilizing hybrid network formation to better modulate the degradation and mechanical properties of developed materials. In one example, Wu et al., developed a hybrid hydroxypropyl methylcellulose, hyaluronic acid, and glycerol based injectable hydrogel [126]. The use of a hybrid hydrogel network allowed for the improved modulation of gelation time, transition temperature, and injectable viscosity compared to the use of hydroxypropyl methylcellulose alone, which may be more suitable for minimally invasive periodontal regenerative applications.

Another emerging trend is the development of self-healing injectable hydrogels. Such hydrogel materials can temporarily fluidize under shear stress which can allow for the use of small gauge administration of hydrogel materials in minimally invasive treatments [127]. In one strategy, utilizing a combination of dynamic non-covalent crosslinking strategies (Schiff base and metal coordination), Guo et al. developed a chitosan/HA self-healing hydrogel as an injectable drug delivery vehicle to promote periodontal regeneration [128]. In this work, the self-healing chitosan/HA hydrogel was found to be injectable from a 25-gauge needle, and when loaded with ginsenoside Rg1 and amelogenin (the most abundant protein in EMD), it was found to better repair alveolar bone loss compared to control treatments in a rodent periodontal defect model.

4.2 | Emerging Regenerative Hydrogel Network Technologies—Implantable

While some contemporary implantable hydrogel therapies utilize polymers of biological origin (such as collagen and HA) they are not yet structured to match that of the regenerative tissue target. Emerging implantable hydrogel technologies have focused on the recapitulation of the complex and hierarchical structure of periodontal and craniofacial tissues utilizing contemporary 3D bioprinting techniques (which also benefit from self-healing hydrogel technologies). 3D printed resorbable polymeric scaffold materials have already proven to be effective in the regeneration of periodontal tissues, with patient-specific designs being used to fill large osseous and alveolar bone defects in humans [129–132]. Using 3D bioprinting, similar constructs can be developed using hydrogel matrices that may serve to further emulate the complex composition and structure of native tissues. For example, Sowmya et al. developed a tri-layered biomimetic hydrogel scaffold intended to emulate the structure of the cementum-periodontium-alveolar bone complex [133]. By using such a hierarchical hydrogel, complete defect healing was observed in vivo and illustrated favorable formation of new cementum, fibrous PDL, and alveolar bone. Specific architectural cues in tissue-directed scaffolds have also been achieved using advances in 3D bioprinting, with several emerging therapies utilizing periodontal and craniofacial progenitor cell-laden hydrogel matrices [134–138]. In one example, Yang et al. developed a 3D printed periodontal scaffold using a methacrylate gelatin (GelMA) and decellularized ECM cell-laden bioink (Figure 3) [139]. Using this hybrid hydrogel network, mechanical and architectural guidance were manipulated to achieve enhanced biomimetic regeneration of periodontal tissues. In a beagle periodontal defect model, the cell-laden hybrid hydrogel was found to suppress M1 macrophage activation as well as better induce biomimetic periodontal fiber orientation and osteogenesis compared to a GelMA hydrogel control, showing promise in enhancing periodontal regeneration.

4.3 | Emerging Regenerative Hydrogels as Delivery Vehicles

In addition to serving as ECM-emulative biomaterials, hydrogels can act as effective delivery systems for the localized and sustained release of pro-regenerative and tissue directive biologics. This is the primarily used case of contemporary therapeutics described earlier which function to provide localized delivery of biologics such as EMD and rhFGF-2 to periodontal and craniofacial wound sites to promote tissue regeneration. One outstanding challenge is the lack of controlled and sustained delivery of these biologics throughout the course of wound healing. Due to the lack of controlled and sustained release character of these hydrogel materials, biologics are often delivered at concentrations that are orders of magnitude larger than those found physiologically, which can lead to variable clinical outcomes and increase the cost of materials considerably. For example, INFUSE which is an implantable collagen therapy formulated with growth factor rhBMP-2 at supraphysiological concentrations that exceed more than 10^6 times the BMP-2 protein concentration found under normal bony defect regeneration [140]. Such elevated concentrations of rhBMP-2 have been shown in some cases to lead to adverse healing events including severe gingival swelling as well as structurally abnormal bone and increased inflammation [141–143]. Additionally, clinicians currently have an abbreviated suite of biologic-loaded hydrogels to serve the complex regenerative needs of periodontal tissues which omit several pro-regenerative biologics, antimicrobial compounds and agents to modulate immune response. Therefore, emerging regenerative hydrogel developments are currently exploring more sophisticated controlled/triggered release strategies and the integration of novel pro-regenerative cargo.

4.4 | Controlled and Stimuli-Responsive Release Systems

To address the challenges of the burst release of cargo, research has been driven to develop more advanced controlled/

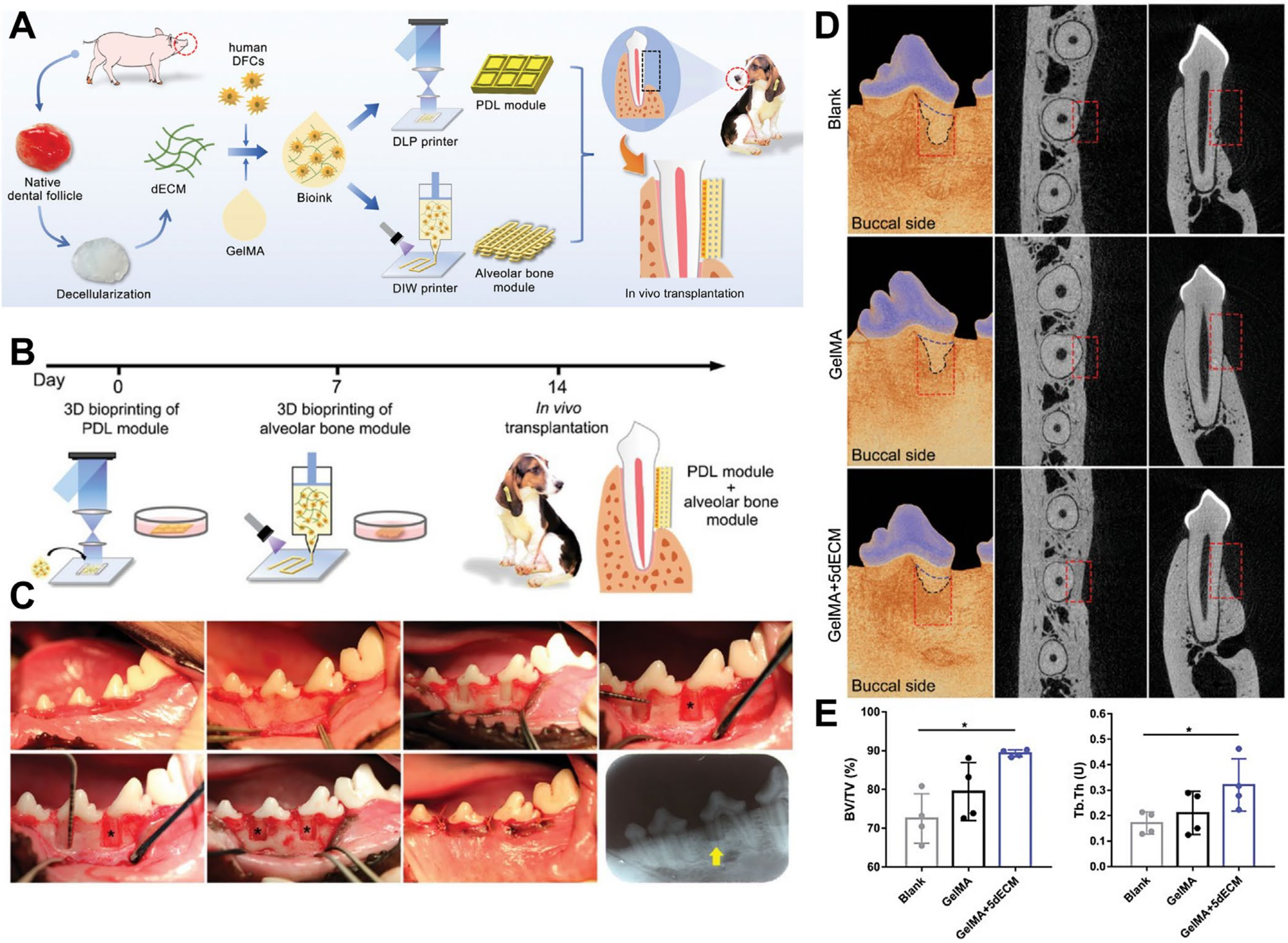

FIGURE 3 | (A) Schematic overview of the 3D bioprinting of periodontal modules with GelMA/dECM bioink encapsulating human dental follicle cells for periodontal regeneration. (B) Periodontal module construction. (C) Surgical procedure (black asterisk: Transplanted periodontal module) and X-ray image of the periodontal defect (yellow arrow) after surgery on day 0. (D) Micro-CT scanning of the periodontal defect 3 months after transplantation (red dotted line: Defect area; blank dotted line: The boundary of new bone; blue dotted line: Natural bone height). (E) Quantitative analysis of BV/TV and Tb.Th at 3 months post-surgery based on micro-CT scanning (BV/TV: *$p = 0.0301$; Tb.Th: *$p = 0.0280$). Adapted from Yang et al. with permission from copyright CC BY 4.0 [139].

triggered hydrogel release platforms. These have included patient-tailorable drug-loaded hydrogels [144] as well as so-called "smart" or stimuli-responsive hydrogels [145]. Stimuli-responsive strategies have included those that promote the release of cargo in response to pH, reactive oxygen species, enzymes, and small molecules (such as glucose) [146–150]. These strategies take advantage of the known physiology of the wound healing environment to trigger cargo release. For example, pH-responsive hydrogels have been designed to release anti-inflammatory cargo in response to inflamed wound sites that become slightly acidic (pH <6) [151]. Yu et al. using this strategy, developed a chitosan-based hydrogel loaded with N-phenacylthiazolium bromide, which was found to tailor more rapid release in the presence of a slightly acidic wound environment, downregulate inflammation-related pathways, and lead to improved therapeutic outcomes in a small animal periodontitis model [152]. In another pH-responsive strategy, Cai et al. utilized a Carboxymethyl Chitosan-Oxidized Dextran to facilitate the delivery of Embelin in inflamed periodontal microenvironments (Figure 4) [153]. The stimuli-responsive release of Embelin was found to modulate macrophage polarization and suppress inflammatory cytokine expression which promoted bone regeneration in a small animal periodontitis model.

4.5 | Emerging Pro-Regenerative Active Agents and Cargo

Clinicians currently have a limited suite of pro-regenerative hydrogel materials available to address increasingly complex clinical cases. To expand the suite of clinically available pro-regenerative hydrogel materials, the integration of human platelet-derived growth factor-BB (PDGF-BB) and bone morphogenetic protein 7 (BMP-7) has been explored. Both PDGF-BB and BMP-7 have been extensively studied in the regeneration of periodontal and craniofacial tissues, resulting in clinically (FDA) approved technologies GEM 21S (Geistlich, Switzerland) and Osigraft (Olympus Biotech, USA), respectively [154]. Ammar et al. explored the integration of rhPDGF-BB within an injectable thermo-responsive chitosan/β-glycerol phosphate (CS/β-GP) hydrogel, which was shown to provide sustained release for up to 2 weeks and increase

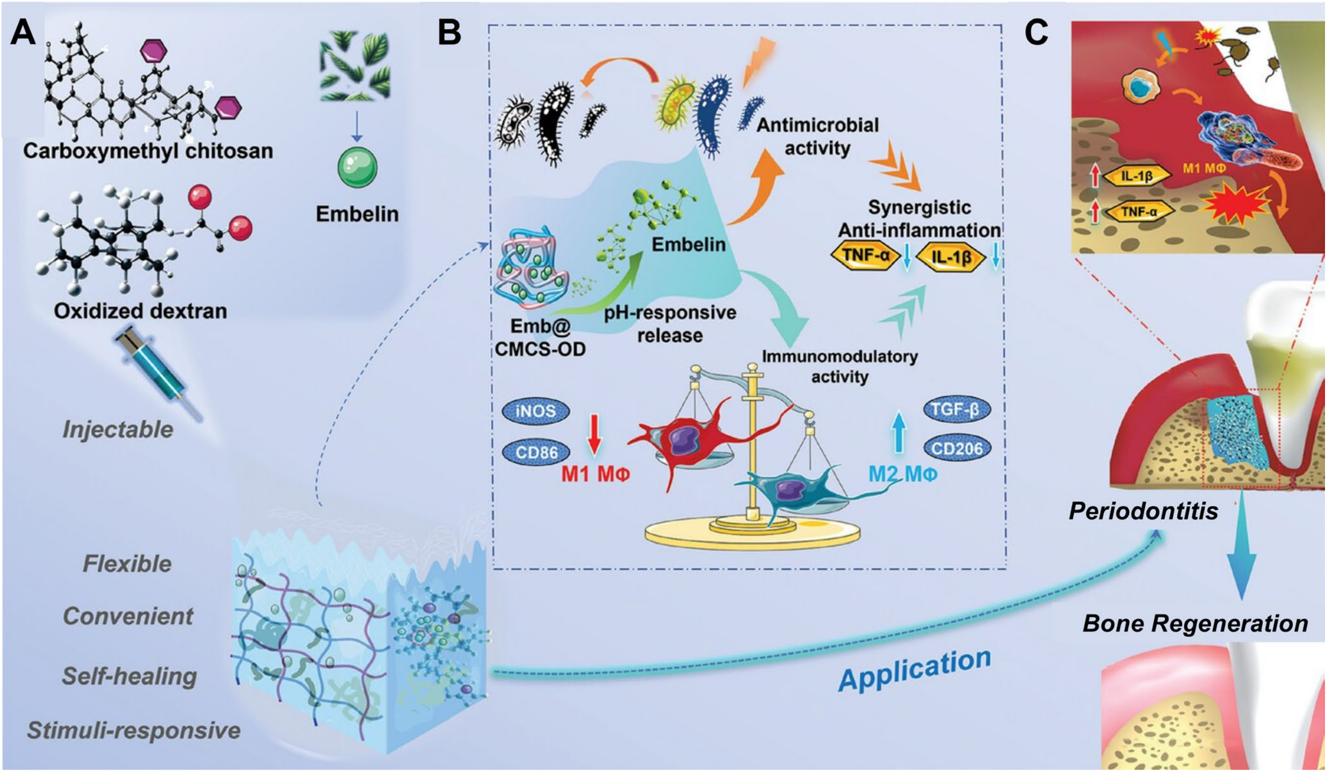

FIGURE 4 | The schematic illustration of periodontal regenerative Emb@CMCS-OD hydrogel. (A) Constituents and structural representation of Emb@CMCS-OD hydrogel. (B, C) Proposed regenerative mechanism of Emb@CMCS-OD hydrogel. Emb@CMCS-OD was designed to address microbial infection and rectify immune imbalances, especially hindering the infection by *P. gingivalis*, stimulating the shift of macrophage from the M1 to M2 phenotype and suppressing the expression of TNF-α and IL-1β, thereby promoting the regeneration of periodontal bone. Adapted from Cai et al. with permission from copyright CC BY 4.0 [153].

periodontal ligament stem cell viability in a preclinical study [155]. In a separate large animal study, Zang et al. investigated the use of a similar CS/β-GP injectable hydrogel as a delivery system for rhBMP-7 [156]. In this study, the rhBMP-7 loaded CS/β-GP hydrogel achieved cargo release for up to 11 days and successfully improved the regenerative outcomes in a Class III furcation defect model. While neither system explored a controlled release mechanism (both experiencing > 60% burst release in 24 h) they provide an improved platform in comparison to the delivery of free protein. In another example, Maio et al. demonstrated the potential of a combined hierarchical designed and growth factor loaded hydrogel (Figure 5) [157]. Their system, composed of GelMA, sodium alginate, and bioactive glass microspheres loaded with rhBMP-2 and rhPDGF-BB, achieved significant regeneration of multiple tissue types in large animal models.

In addition to the delivery of pro-regenerative biologics, current strategies are additionally considering the dynamic regulatory and immune microenvironment of wound sites which serve to determine the temporal dynamics and success of periodontal regeneration. In pro-inflammatory periodontal wound sites, the unique presence of microorganisms and interactions with host immune cells primarily drive compromised periodontal healing and bone resorption [158, 159]. In consideration of these facets, both emerging injectable and implantable hydrogel technologies have begun utilizing antimicrobial and immunomodulatory agents to drive successful wound healing.

Given the constant exposure to high microbial load and prevalence of diseases related to microbial dysbiosis, such as periodontitis, regenerative hydrogels with antimicrobial features are among the most frequently explored emerging regenerative hydrogel technologies [160]. While the literature on these materials is extensive, one emerging subtheme is the use of natural antimicrobial agents (as opposed to traditional antibiotics) as a strategy. In a clinical trial investigating the effectiveness of periodontitis treatment methods, Bhatia et al. found that Pluronic F-127 hydrogel loaded with 1% curcumin was able to reduce the growth of pathogenic periodontal bacteria including *Fusobacterium nucleatum* and *Porphyromonas gingivalis* and improvements in clinical attachment level and probing pocket depth [161]. In another clinical trial exploring a natural antimicrobial strategy, a carbopol hydrogel material loaded with flax seed oil was found to improve clinical attachment level and probing pocket depth compared to control treatments in patients with chronic periodontitis [162].

As a direct immunomodulatory strategy, emerging work has begun to explore the use of hydrogel platforms as vehicles to deliver progenitor cells or progenitor cell secretome components as an immunomodulatory strategy. Mesenchymal stem cells (MSCs) have unique low immunogenicity and the ability to suppress immune cell functions and regulate both innate and adaptive immune responses [163, 164]. Gingival mesenchymal stem cells (GMSCs), particularly in periodontal contexts, have shown to be useful inflammatory modulators, displaying enhanced stability and maintained stemness under inflammatory conditions,

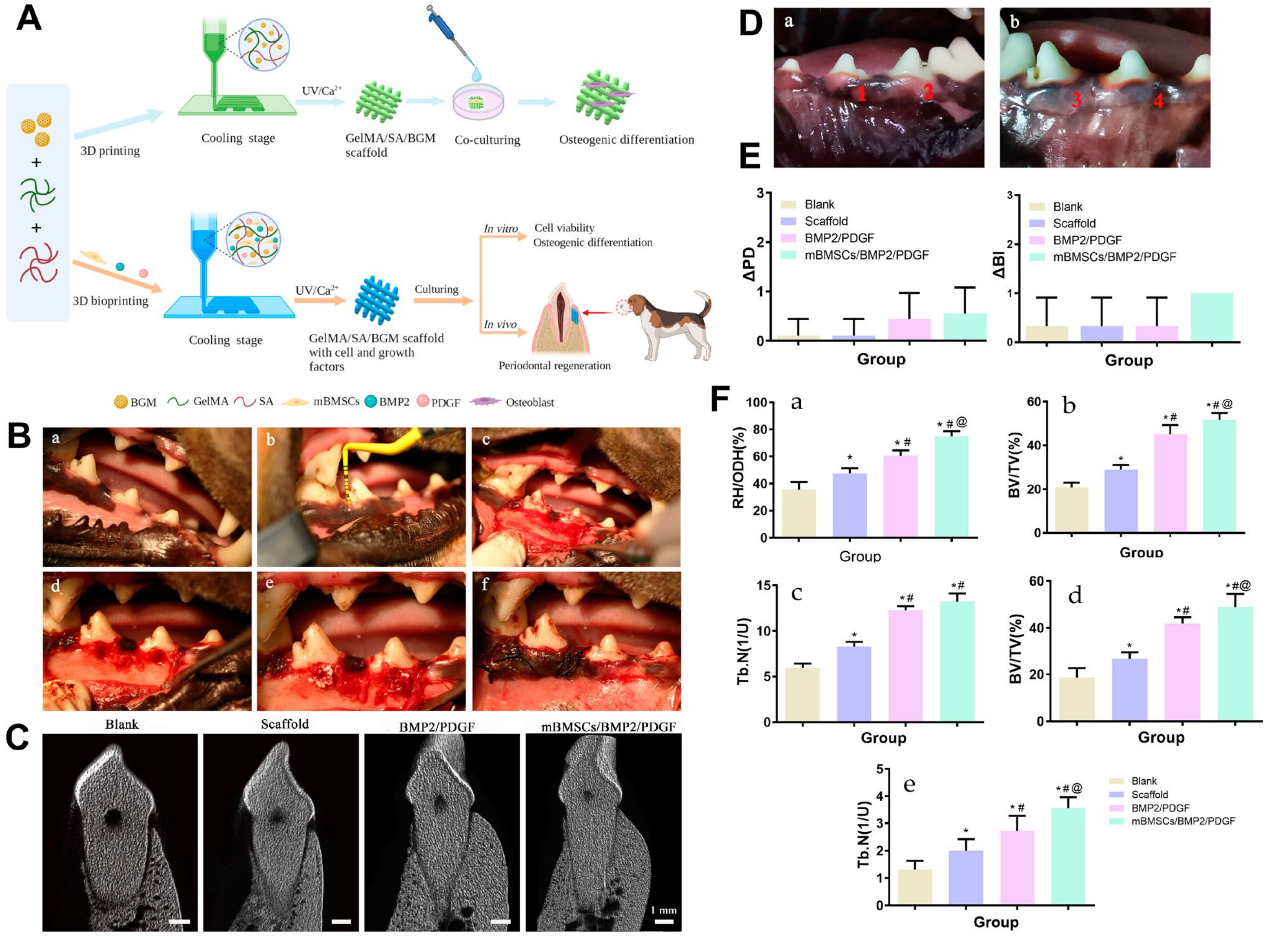

FIGURE 5 | (A) Fabrication and characterization of 3D-printed GelMA/SA/BGM hydrogel scaffold and 3D-bioprinted cell- and growth factor-laden GelMA/SA/BGM scaffold. (B) Construction of acute periodontal defect in beagle dogs, (a) preoperative photograph, (b) periodontal examination, (c) flap, (d) construction of 5 mm × 5 mm bone defect, (e) scaffold implantation, (f) suture. (C) Buccal-lingual micro-CT reconstruction 8 weeks after surgery. (D) Intraoral photographs at 8 weeks after surgery. (a): [1] blank group, [2] scaffold group; (b): [3] BMP2/PDGF group, [4] mBMSCs/BMP2/PDGF group. (E) Periodontal status at 8 weeks after surgery. (F) Micro-CT analysis: (a) RH/ODH, (b) 2D analysis of BV/TV, (c) 2D analysis of Tb.N, (d) 3D analysis of BV/TV, (e) 3D analysis of Tb.N. *$p < 0.05$ vs. blank group, $^{\#}p < 0.05$ vs. scaffold group, $^{@}p < 0.05$ vs. BMP2/PDGF group. Figure adapted from Maio et al. with permission from copyright CC BY 4.0 [157].

and producing a variety of anti-inflammatory cytokines such as PGE2, IDO, and IL-10 [165–168]. Despite their established immunomodulatory character, the direct delivery of progenitor cells using hydrogel vehicles has remained challenging in vivo. In periodontal defect models, such cell-laden hydrogel therapies have either shown a lack of improvement over the hydrogel vehicle control, or, in an interesting case, show improved regenerative capacity of therapies even in cases where cells were not localized in the defect site [169, 170]. In the later study, improvements in newly formed bone were suggested to be attributed to the paracrine mechanisms of the delivered progenitor cells. Considering these findings and the regulatory challenges associated with progenitor cell-based therapies at large, many emerging strategies have utilized hydrogels as a vehicle for progenitor cell secretome components. In one example, Shen et al. utilized a chitosan hydrogel incorporating dental pulp stem cell-derived secretome, which was found to reduce inflammation and improve healing in a small animal periodontitis model [171]. In another secretome-based strategy, Chew et al. utilized a collagen hydrogel incorporating mesenchymal stem cell secretome which was found to improve the regenerative outcomes in a small animal periodontal defect model [172].

4.6 | Challenges Facing the Clinical Translation of Emerging Hydrogels

Despite the promise of emerging hydrogel technologies, significant challenges must be overcome to successfully reach the clinic. These hurdles include effective mechanical properties, regulatory barriers, and clinical adoption.

The current mechanical limitations of contemporary hydrogels are particularly apparent in hard tissue applications. This can be highlighted, for example, by the need to combine technologies like Emdogain and REGROTH with bone graft materials, as these hydrogel materials alone lack the mechanical robustness and space-maintaining ability required for larger or load-bearing defects. While these materials both utilize physical crosslinking (which results in minimal control of deformation), emerging strategies using chemical crosslinking, hybrid polymer networks, and inorganic fillers (as seen in Actifuse) are being developed to enhance mechanical strength. However, the use of the latter strategies remains a challenge while maintaining the appropriate degradation kinetics and injectability that make contemporary hydrogel clinically desirable.

Navigating the regulatory landscape towards the approval of emerging regenerative hydrogels poses additional barriers for clinical translation. Advanced hydrogels, particularly in combination technologies that include biologics (such as rhPDGF-BB and rhBMP-7) or human cells, currently face a complex and costly approval process. These emerging technologies require both extensive preclinical and clinical data to prove both safety and efficacy which demands substantial investment. This is a challenge that extends beyond periodontal and craniofacial regeneration, where there are still very few examples of clinically approved biomedical hydrogels with active biologics or cellular cargo [17]. Within periodontal and craniofacial regeneration, the use of rhFGF-2 in conjunction with a hydrogel carrier (such as in REGROTH, which is only regulated for use in Japan) is currently not found in any FDA-approved clinical hydrogels despite nearly 10 years of clinical use. Steps are currently being made by regulatory bodies to address these challenges. One includes the FDA beginning to encourage the use of animal-alternative models to support preclinical evidence of material efficacy and safety. This stands to remove in vivo preclinical models in favor of more resource-efficient (and in some cases, more physiologically representative) models, such as emerging organ-on-chip microphysical systems [173].

Even if clinically approved, emerging hydrogel technologies are faced with practical challenges for clinical adoption. These include factors that relate to clinical ease of use and the cost of the new materials, which serve to affect clinical uptake. Additionally, widespread clinical adoption may be limited by materials that demonstrate marginal or similar clinical benefits over contemporary materials. This may be demonstrated by the retained clinical preference for materials such as Emdogain, which, despite its limitations, clinicians favor biomaterials that offer straightforward application protocols and predictable outcomes. These clinical considerations pose additional engineering design criteria that must be met to develop novel regenerative hydrogels for periodontal and craniofacial regeneration.

4.7 | Summary of Emerging Hydrogel Technologies for Periodontal and Craniofacial Regeneration

Current hydrogel-based therapies, while undoubtedly useful for periodontal and craniofacial regeneration, still face limitations in achieving complete tissue restoration, particularly when treating large or complex defects and complex clinical cases, which has prompted the development of emerging hydrogel-based strategies to address these challenges. While these developments are currently faced with additional translational challenges, the space remains rich with technological advancement and exciting supporting pre-clinical evidence. While traditional injectable hydrogels are constrained by their reliance on the physical crosslinking of single polymers, newer approaches utilizing sophisticated in situ gelation strategies and hybrid polymer networks have shown evidence of improved gelation control and mechanical properties. Additionally, advances in 3D bioprinting have also seen the emergence of implantable hydrogel technologies that better recapitulate native tissue architecture, which may be tailored to fit within site and patient-specific tissue niches. The design of hydrogels as delivery vehicles for pro-regenerative cargo has begun to address the limitations of burst release through the integration of stimuli-responsive systems that respond to environmental cues associated with the wound healing environment. Emerging developments have also seen the integration of biologics such as rhPDGF-BB and rhBMP-7 as well as natural antimicrobial and immunomodulatory agents, which show promise in addressing the complex wound healing environment.

5 | Conclusions

The field of periodontal and craniofacial tissue regeneration has seen significant advancement through the development and clinical implementation of hydrogel-based therapies. The fundamental properties (high water content and ability to mimic extracellular matrix characteristics) and versatility of hydrogels have made them an ideal regenerative biomaterial platform. This review has examined the clinical need for regenerative hydrogels, as well as clinically available and emerging technologies which attempt to improve the complex regeneration of periodontal and craniofacial tissues.

Currently available hydrogel therapies in periodontal and craniofacial regeneration are limited to 9 approved technologies and have shown varying degrees of success. EMD-based material Emdogain has demonstrated significant efficacy in promoting periodontal tissue regeneration, while other bone-graft hydrogels such as Actifuse and REGROTH have provided important osteoconductive or osteoinductive properties. Hyaluronate-based hydrogels, including Gengigel, Aminogam, and hyaDENT BG, have also shown promise in the regeneration of periodontal soft tissues and as adjunctive therapies with bone graft materials. While indeed these materials have improved treatment outcomes compared to most traditional bone grafts (such as autologous bone grafts), they still face limitations in achieving complete tissue restoration, particularly in the regeneration of large or non-contained defects and in complex cases.

Emerging hydrogel technologies are actively seeking to address the shortcomings of contemporary materials through enhanced consideration of the dynamic, complex, and patient-specific periodontal and craniofacial wound healing space. Promising advancements include injectable hydrogel systems with improved hybrid polymer gelation, the integration of 3D bioprinting in the development of implantable hydrogels, and improved hydrogel technologies for drug delivery including stimuli-responsive delivery systems and the incorporation of novel biologics and immunomodulatory agents. While these strategies represent promising directions to enhance therapeutic outcomes the complexity of periodontal and craniofacial regeneration likely requires the interplay of several of these emerging strategies. The combination of such strategies, however, may stand to limit the translation of hydrogel due to its increased complexity. For example, the regulatory pathway for biologic-laden hydrogels is particularly challenging, as evidenced by the limited number of active clinical trials (9) of all regenerative hydrogel technologies currently investigating such strategies [17]. The increased complexity of these systems, in addition to needing to display clear clinical advantages for adoption, stands to introduce additional hurdles and cost burdens towards regulatory approval.

In conclusion, while current hydrogel technologies have established a foundation for periodontal and craniofacial tissue regeneration, emerging strategies may stand to further improve treatment outcomes and address the shortcomings of contemporary therapies.

Disclosure

AI Statement: This manuscript did not use artificial intelligence in any capacity.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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