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Harnessing biomolecules for bioinspired dental biomaterials

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Abstract

Dental clinicians have relied for centuries on traditional dental materials (polymers, ceramics, metals, and composites) to restore oral health and function to patients. Clinical outcomes for many crucial dental therapies remain poor despite many decades of intense research on these materials. Recent attention has been paid to biomolecules as a chassis for engineered preventive, restorative, and regenerative approaches in dentistry. Indeed, biomolecules represent a uniquely versatile and precise tool to enable the design and development of bioinspired multifunctional dental materials to spur advancements in dentistry. In this review, we survey the range of biomolecules that have been used across dental biomaterials. Our particular focus is on the key biological activity imparted by each biomolecule toward prevention of dental and oral diseases as well as restoration of oral health. Additional emphasis is placed on the structure–function relationships between biomolecules and their biological activity, the unique challenges of each clinical condition, limitations of conventional therapies, and the advantages of each class of biomolecule for said challenge. Biomaterials for bone regeneration are not reviewed as numerous existing reviews on the topic have been recently published. We conclude our narrative review with an outlook on the future of biomolecules in dental biomaterials and potential avenues of innovation for biomaterial-based patient oral care.

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Conflicts of interest

There are no conflicts of interest to declare.

1. Introduction

The clinical need for dental biomaterial therapies is unrelenting. There are 3.5 billion cases of untreated oral conditions and, in particular, 267 million individuals with complete tooth loss globally.[1] An estimated 800 million resin composite, 100 million amalgam, and millions of glass ionomer cement restorations are placed each year and are one of the most prevalent medical interventions in the human body,[2] not to mention the over five million implants placed in the United States each year.[3] The cost for these therapies is immense; the global dental implant market alone is 3500 million USD.[4] Indeed, 141 clinical trials (October 2019; Clinicaltrials.gov) are recruiting or active for dental implants combined with another 201 for dental caries and 81 for endodontic diseases. The combined complexity and prevalence of dental diseases requires well engineered materials to optimize patient outcomes.

Advanced biomaterials are needed to provide the unique functionality required by new devices, scaffolds, and drug delivery systems to keep pace with rapid progress in dental medicine. The range of biomaterial modalities for dental therapies is wide; from load-bearing, nanoparticle-filled, photopolymerized resin composites to soft, degradable collagen membranes for guided bone regeneration. Dental biomaterials, while seemingly “limited” to the small (relative to the rest of the body) oral cavity, are required to interface not only with a diverse set of tissues, from soft oral gingiva to hard, mineralized enamel and bone; but also function under demanding environmental conditions, such as sudden changes in temperature, a wide range of salivary and biofilm-induced pH, antagonistic forces from chewing and wear from hard food debris, and an extraordinarily diverse microflora.[5]

Advances in the general fields of biomaterials and tissue engineering in recent decades have pushed bioengineering principles past cytocompatibility into tailoring specific biological responses; for example, fast and intimate osseointegration of dental implants or the overall commercial success of autologous cell-based therapies (such as for articular cartilage repair or wound healing).[6] Indeed, many traditional dental materials only serve a space-filling role – not a biologically-instructive role – and as a result have little ability to regenerate native tissue.[7] A potent toolkit to unlock specific biological responses is the diverse array of biomolecules nature provides. Biomolecules include a large series of biomacromolecules (for example, proteins, polynucleic acids, lipids, and polysaccharides) and small molecules (for example, amino acids, oligopeptides, monosaccharides, deoxyribonucleotide, and metabolic products) which are essential for physiological processes, such as cell proliferation, migration, differentiation, and overall homeostasis.[8,9] Harnessing the biomolecule toolkit for biomaterial design is a bioinspired and biomimetic approach that offers different molecules with precise biological functions;[10,11] the human proteome contains up to several billion protein species.[12] Advances in biomolecule synthesis over the past decade, such as the now ubiquitous solid phase peptide synthesis,[13] rapid expansion of metaomic technologies,[14] and recombinant technologies,[15] have further driven the ability of tissue engineers and biomaterial scientists to derivatize materials with biomolecules. In any case, harnessing and exploiting the full potential of the biomolecules toolkit to develop more effective, off-the-shelf, preventive and therapeutic materials to address oral diseases requires synergistic collaborations between basic, clinical, and industrial teams (Fig. 1).

In this review, we survey the range of biomolecules used across dental biomaterials with a particular focus on the biological activity of these biomolecules toward prevention of oral disease and/or restoration of oral health. This review is organized by clinical condition to emphasize the design principles needed for each specific disease and biomaterial and the resulting biomolecules used to enhance device function. We conclude our narrative review with an outlook on the future of biomolecules in dental biomaterials and consider potential avenues of innovation using these materials for patient care.

2. Biomolecule-based dental biomaterials

2.1 Antimicrobial dental biomaterials

Infection of medical devices, dental included, is a grand challenge. Indeed, a range of medical devices (from fixation devices to catheters to dental implants) all become infected at unacceptably high rates.[16–19] Infection is particularly difficult to control acknowledging that antimicrobial resistance is rapidly proliferating: the US Centers for Disease Control and Prevention estimates there are more than two million infections in the US each year from antibiotic resistant bacteria resulting in at least 23 000 deaths.[20] The numbers of deaths per year and expense due to device infections is expected to dramatically rise over the coming years.[21] The annual healthcare cost in the US alone for infections due to antibiotic resistant strains is already around $20 billion.[22,23] Challenging regulatory environments, lack of understanding of resistance mechanisms, and reduced financial incentives, among others, have led to reduced development of new antibiotics.[24] This alarm has driven the development of other, non-antibiotic based biomaterials[16,25] for devices outside of dentistry.[17,26,27] Here, we survey a range of biomolecules that have been harnessed to derivatize dental biomaterials with antimicrobial activity toward preventing infection.

2.1.1 Antimicrobial dental implants.—Approximately 178 million Americans are missing at least one tooth thereby causing lost self-confidence and lower self-image.[1,28,29] Conservatively estimated current estimates of an approximately 10%[30–32] dental implant failure rate lead to over one million implants failing worldwide per year.[33] This high failure rates results in functional lifespans of dental implants of around 5 to 11 years[34] yet as much as 23% of the entire adult U.S. population may possess a dental implant by 2026.[35] All the evidence combined strongly suggests that dental implant infection and failure are critical healthcare concerns. Dental implant infection, or periimplantitis, is an inflammatory condition related to infection, biofilm formation, and eventual supporting tissue loss.[36,37] As a result, antimicrobial dental implants are highly desirable.

2.1.1.1 Antimicrobial peptides for dental implants.: Special attention has been recently given to antimicrobial peptides (AMPs) due to their excellent antibacterial, antibiofilm properties, and generally low bacterial strain resistance.[38,39] The latter is an important advantage over commercially-used antibiotics, diminishing the potential risks involved in the use of synthetic drugs (*i.e.*, cytotoxicity, strain resistance, *etc.*).[40] AMPs are typically small (under 50 amino acids) naturally occurring molecules that are generally cationic and amphipathic, though exceptions certainly exist.[41–43] This general structure allows them to act as antimicrobial agents with broad activity spectrum, low cytotoxicity, selectivity

towards microbial membranes, host immunity modulation, and the ability to bind bacterial endotoxins and neutralize their biological effects.[44,45] Despite the existence of thousands of distinct AMPs in nature, which vary in size, structure, sequence, and polarity, only a handful have been applied toward dental implant applications.[46] AMP immobilization onto surfaces like dental implants enhances their stability and increases the local concentration and therefore biological availability for microbe killing.[47–49] Moreover, rationally designed peptides offer the ability to recapitulate the function of proteins and bypass protein's structural complexities and expensive synthesis or isolation.[50] A broad overview of AMP coatings for medical devices in general can be found elsewhere.[51,52] We survey here select AMPs used on dental implants to reduce peri-implantitis.

One well-characterized AMP used to coat dental implants is GL13K, which is a self-assembling, cationic, amphipathic designer AMP derived (and later altered) from the salivary protein BPIFA2.[53,54] Early work with GL13K established it could be anchored on titanium and reduce the load of *Porphyromonas gingivalis*.[55] Subsequent work showed similar antimicrobial activity against *Streptococcus gordonii*[56] without affecting osseointegration in a rabbit model.[57] More recent work[58–60] has shown GL13K's antimicrobial behavior is dependent on the formation of twisted nanoribbon structures that is triggered by neutralization of cationic side groups before surface anchoring. It should be emphasized that AMP mechanisms are not well-established.[61] GL13K has also been anchored on microgrooved substrates to promote soft issue formation with simultaneous antibiofilm activity.[62]

Another AMP used to coat implants is hLF1–11, which is composed of the first 11 N-terminal residues of human lactoferrin (a glycoprotein found in most human fluids[63]).[64,65] hLF1–11 has been covalently anchored and adsorbed to titanium and shown to reduce *Streptococcus sanguinis* and *Lacto-bacillus salivarius* activity.[66] Important work using hFl1–11 has shown that the resultant antimicrobial activity is sensitive to the specific covalent (such as silanization or surface initiated polymerization) anchoring method employed.[67,68] Others have also shown that immobilization methods affect AMP activity.[69] In response, some groups have adopted anchoring chemistry that are chemoselective to tightly regulate AMP orientation.[70,71] A related concept of spacers, or the domain (such as amino acids in the case of AMPs) sometimes placed between the bioactive moiety and the residue(s) used to anchor it, is also important for optimal AMP activity,[72] and has been exploited in different peptides coating configurations, including chimeric peptides.

Chimeric peptides, which are further explained and explored in Section 5, have also been harnessed as AMP coatings for dental implants. These peptides simultaneously present an implant binding peptide, identified using combinatorial phage or cell surface display technologies, and an antimicrobial domain. A common concern of peptide coatings is their durability and the ease, or difficulty, of their clinical application. Chimeric peptides provide a high affinity, material specific binding at the implant interface based on their self-assembly ability while also displaying AMPs on the site. One example showed antimicrobial activity against *Streptococcus mutans*, *Staphylococcus epidermidis*, *and E. coli* using different combinations of AMPs on titanium surfaces.[73] Chimeric peptides have been further applied to titanium in a water-based coating and exert antimicrobial activity against *S. mutans*.[74]

Recently, titanium binding peptides (TiBP) have been combined in chimeric peptides with different AMPs using spacer domains (Fig. 2A–D).[72] Spacer domains[75] are introduced to provide the secondary structural features common to AMPs to enhance the antmicrobial activity of the peptide film on the implant. In this study, chimeric peptides were demonstrated to thoroughly coat titanium sufaces even in the presence of proteins and maintain antimicrobial function following toothbrushing. Correlating the structure–function relationship of the chimeric peptide film resulted in predicting the antimicrobial peptide film properties under competition as well as challenged implant surfaces.

LL-37 is another AMP that has been amply used to coat implants (including its derivatives such as OP-145, P60.4ac, SAAP-148, SAAP-145, and SAAP-276).[76–78] LL-37 is naturally generated through the degradation of the larger human cationic antimicrobial protein (hCAP18).[79] Early work using LL-37 demonstrated contact killing of *Escherichia coli.*[69] Exemplary work showed that LL-37 and closely related derivatives could be immobilized on substrates and retain antimicrobial activity against clinical and multidrug-resistant *Staphylococcus in vivo*.[80] Others have also shown similar *in vivo* activity in rabbit intramedullary nail infection and mouse subcutaneous implant-associated infection models.[81]

A final family of AMPs including Tet-213 (also known as HHC36[82]), Tet-26, Tet-21, and Tet-20[83,84] has been applied toward anti-biofilm implant coatings as well. For example, Tet-213, which was generated computationally, has been incorporated into layer-by-layer assembled structures (LBL; reviewed elsewhere[85]) to reduce biofilm formation of *Streptococcus aureus* and *P. gingivalis.*[86] Earlier work proved the possibility of coating Tet213 on implants with retained antimicrobial activity.[87,88] Fig. 2E–H shows an example of immobilized HHC36 produced with *in vivo* antimicrobial activity,[89] which relatively few studies comprehensively evaluate for antimicrobial surfaces.[90] Indeed, evaluation of antimicrobial surfaces *in vivo* remains an area of active debate. This particular system also features a temperature-sensitive display of AMP (hidden at 37 1C and exposed at 25 1C) to reduce potential cytotoxicity. Melamine (produced by combining portions of the antimicrobial cationic peptides mellitin and protamine[91]) is another surface-immobilized AMP for dental implants that has been tested *in vivo* and shown effective against *P. aeruginosa* and *S. aureus.*[92]

Multifunctional, AMP-based biomaterials have been synthesized as well. Examples include recombinant spider silk proteins (silk generally consists of β-sheet protein structures[93]) fused with a cell-binding domain derived from fibronectin (fibronectin structure detailed later) and anti-biofilm dispersin,[94] bone-regenerating and antimicrobial surfaces,[95–97] and AMP delivery from mineral coated nanotubes for antibiofilm dental implants.[98,99]

2.1.1.2 Antimicrobial elastin-like recombinamers.: Recombinant materials, in general, are an attractive biomolecule synthesis route because of the control in the specific molecular sequence, monodispersity, and ability to scale to large quantities.[100] One example is elastin-like recombinamers (ELRs), which are defined recombinant protein-based polymers (rPBPs) derived from amino acid sequences found in the hydrophobic domains of tropoelastin, the precursor to elastin which is the structural biomolecule responsible for tissue elasticity.[101]

These hydrophobic amino acid domains from tropoelastin are most frequently repeats of the pentamer $(VPGXG)_n$, where X is any amino acid except proline.[102] With greater size than AMPs comes greater functional possibilities and structures. Indeed, ELRs are commonly expressed in heterologous hosts, mainly *E. coli*, due to their large molecular weight.[103] Other domains, such as antimicrobial domains, can be added to ELRs and still retain their fundamental properties, such as reversible temperature-dependent phase-transitional behavior, biocompatibility[104,105] and amenability to a variety of methods for surface functionalization, such as LBL deposition.[106]

Foundational work showed that the antimicrobial peptide ABP-CM4 from the Chinese silkworm could be added to an ELR sequence and show antimicrobial activity.[107] Other work with similar molecules has combined both an antimicrobial peptide and RGD for further multifunctionality.[108] Recent work[109] synthesized an ELR with a typical polycationic backbone, a cysteine-based C-terminal grafting domain for covalent immobilization onto surfaces, and the AMP GL13K on the N-terminus. These ELR-coated surfaces showed anti-biofilm activity against *S. epidermidis* and *S. aureus* (Fig. 3). In a similar fashion, other work from the same group developed antimicrobial ELRs and showed their activity against microcosm biofilms from stocks of oral plaque samples in a drop flow bioreactor to simulate relevant conditions for biofilm formation like that found in the oral cavity.[110]

2.1.2 Antimicrobial biomolecules for dental restorative materials.—Dental restorations, or more colloquially “tooth fillings,” are used for the restoration of carious lesions. Caries occur in almost all adults and the majority of school children.[111,112] Resin composite restoration have particularly short lifespans (around 5 years).[113,114] Constant restoration replacement results in loss of irreplaceable tooth tissue with time.[115] In fact, replacement of failed restorations constitutes about 50% of all operative dentistry work performed by dentists.[116] Restoration failures relate to hydrophilic methacrylate-based adhesive resins infiltrating demineralized, water-rich dentin and acting as semi-permeable membranes.[117] This enables penetration of gingival crevicular fluid and saliva, enzymes, bacteria, and bacterial acidic byproducts into the space between dentin and the restorative material to cause degradation and ultimately recurrent decay and premature failure.[118] One preventative approach in the literature has been the modification of dental restorations using biomolecules to enhance their longevity, for instance, using antimicrobial biomolecules such as AMPs. Section 6 presents alternative approaches for expanding the lifespan of dental restorative materials based on direct modification of teeth tissues using biomolecules with different functionalities.

2.1.2.1 Dental restorative material modification with AMPs.: One AMP used to biofunctionalize dental restoration materials with antimicrobial has been nisin. Nisin is a cationic peptide from a group of AMPs named lantibiotics.[119] The first variation of nisin was composed of 34 amino acids and derived from *Lactococcus lactis* bacteria.[120] Nisin has since been applied to many industries and produced at industrial scales[121] given its low cytotoxicity.[122] For example, nisin has been incorporated into a dental adhesive for antimicrobial activity against *S. mutans* while not reducing mechanical bonding or photo-

polymerization of the adhesive.[123] Additional work showed this material was also antimicrobial against a saliva-derived microcosm.[124] An alternative approach is the conjugation of AMPs with methacrylates to render them photopolymerizable for incorporation into dental resins. This approach[125,126] has been performed with GH12 (designed *de novo*[127]) and shown to imbue the resins with antimicrobial activity while not affecting bulk mechanical properties. Another group has also incorporated an AMP derived from b defensin-3, a commonly used AMP detailed later, into an adhesive and showed disruption of *S. mutans* biofilms.[128]

2.1.3 Antimicrobial endodontic materials and treatments.—Antimicrobial agents are critical for successful endodontic treatments to combat infection in the intracanal root system and the surrounding periapical area.[129] Unfortunately, around 25 million endodontic procedures are performed each year in the United States.[130] The disinfection process for contaminated teeth consists of removing debris and infected pulp *via* mechanical instrumentation of the main root canal followed by application of irrigant and placement of an intracanal medication.[131] Despite this procedure's success (around a 90% success rate[132]), the root canal system is architecturally complex and secondary canals may remain untreated. Therefore, the absolute, complete elimination of microorganisms and biofilms that invade pulp is critical.[133]

Conventional antimicrobial agents include calcium hydro-xide, phenolic and non-phenolic compounds, biocides, iodine, antibiotics, and natural products.[40,134–136] Overall, calcium hydroxide has been the intracanal dressing most used,[137,138] however, calcium hydroxide may not be effective against all types of bacteria, since some studies have demonstrated that microorganisms like *Enterococcus faecalis*, *Actinomyces radicidentis*, and *Candida albicans* may become tolerant to increased pH produced by calcium hydroxide and result in treatment failure.[139–141] Two other antimicrobials, chlorhexidine (noted for its sustained activity)[142] and sodium hypochlorite dramatically reduce tooth mechanical properties. Another option is triple antibiotic paste (TAP; metronidazole, minocycline, and ciprofloxacin), but TAP is highly toxic and discolors tooth tissue.[143–145] Despite these short comings, many of these existing antimicrobials have been combined with biomolecules in order to enhance the overall biological function. These hybrid materials demonstrate the benefits of combining biomolecules with conventional antimicrobial agents.

Chlorhexidine, perhaps the most ubiquitous endodontic antimicrobial, provides good examples of these hybrid materials. Chlorohexidine has been incorporated into nanotubes and used to synthesize a chlorohexidine-loaded gelatin methacryloyl (GelMA) hydrogel which shows adequate mechanical properties with sustained chlorohexidine release and *in vivo* cytocompatibility (Fig. 4).[146] GelMA is gelatin (degraded collagen) that has been derivatized with photocrosslinkable methacrylates to combine the inherent biological activity of gelatin with the tunable physical properties of a photocrosslinking system.[147] Others have loaded chlorhexidine into cellulose (a polysaccharide derived from plant cell walls[148]) and shown antimicrobial activity against *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *P. gingivalis*, and *Prevotella melaninogenica*.[149] However, despite the ubiquitous nature of chlorohexidine in endodontics, antimicrobial biomolecules – AMPs in particular – have been explored as alternatives to address concerns regarding

antimicrobial resistance and potential cytotoxicity associated with high doses of antibiotics.[150]

2.1.3.1 Antimicrobial peptides for endodontic therapy.: Conventional antimicrobials for endodontic therapies display a range of potential drawbacks, as noted. The most common repertoire of biomolecules tapped for alternative endodontic therapies is AMPs such as nisin. Nisin is more effective against Gram-positive bacteria (*S. gordonii* and *E. faecalis*, for example)[151] and has been combined with low concentrations of sodium hypochlorite to reduce *E. faecalis* biofilm volume and thickness.[152] Importantly, *E. faecalis* does not seem to develop resistance toward nisin.[153] Another AMP with long-confirmed antimicrobial activity against oral pathogens is human b defensin-3 (HBD-3;[154–156] antimicrobial activity includes *S. aureus*, *E. coli*, *Fusobacterium nucleatum*, *Prevotella melaninogenica*, *Peptostreptococcus anaerobius*, *S. mutans*, *Actinomyces naeslundii*, *E. faecalis*, and *C. albicans* species, for example).[157] A smaller variant of HBD-3 (15 amino acids compared to; HBD3-C15[158,159]) is able to reduce fungal growth in an *ex vivo* model of *C. albicans*-infected root dentin with similar effects as chlorhexidine.[160]

Other suggested AMPs for endodontics include human neutrophil peptides 1 and 2, indolicidin, histatins 5 and 8, magainin II, cecropins B and P1, and mastoparan.[150] It should be noted that not all AMPs are broad spectrum; indolicidin, magainin amide, and mastoporan are effective against *Streptococcus milleri* (>90% killing), whereas other listed AMPs displayed reduced antimicrobial activity (<30% killing).[161] Stereochemistry of AMPs also plays an important role as past work has shown differences between L-enantiomeric and D-enantiomeric versions of DJK-5,[162] DJK-2,[162] and 1018[163] against a root canal wall biofilm.[164] D-Enantiomers versions of AMPs are usually more potent against bacteria and biofilms than their L-enantiomers counterparts, which may be associated with the higher resistance of D-enantiomers to enzymatic degradation.[165–167] Finally, a continuing observation is that AMP activity is increased if the application site (usually dentin) is pre-treated with chelating agents.[168] Other considerations for AMPs' usage in endodontic therapy are reviewed elsewhere.[44]

2.1.4 Plant-derived antimicrobial biomolecules for periodontics.—The main entrance of pathogens into the periodontal tissue is the gingival sulcus, *i.e.*, the area of space between a tooth and the surrounding gingiva. Untreated microbial invasion can lead to inflammation (gingivitis) and destruction of anchoring bone tissue.[169] Unfortunately, around 64.7 million American have periodontitis (American Academy of Period-ontology). Nonsurgical therapies for periodontitis combine mechanical scaling and administration of antimicrobials.[170] Similar antimicrobials to endodontics have historically been used. Plant extracts are an exciting source of antimicrobial biomolecules for periodontics because they are rich in secondary metabolites (such as tannins and terpenoids) that have antimicrobial activity and have been used for millennia for wound treatment.[171–173] For example, plant extracts from *Vitis vinifera*, *Pinus* spp., *Coffea canephora*, *Camellia sinensis*, *Vaccinium macrocarpon*, *Galla chinensis*, *Caesalpinia ferrea Martius*, *Psidium cattleianum* have been all demonstrated enhanced anti-biofilm activity against several relevant microorganisms.[174]

Others have shown that extracts from *Azadiracta indica* are as antimicrobial as sodium hypochlorite.[175]

3. Soft tissue healing and attachment

3.1 Biomolecules for dental implant soft tissue integration

The oral mucosa provides protection to periodontal tissues against bacteria and other harsh stimuli in the oral cavity but is disrupted during implant placement.[176] Resulting soft tissue healing and regeneration adjacent to dental implants is para-functional. The implant has a longer biologic width than natural teeth and the implant-associated mucosa is generally fragile.[177] These differences in soft tissue structure and function between implants and teeth strongly contribute to peri-implantitis and implant failure.[178]

The effect of implant surface characteristics (such as topography or chemical composition) on bone progenitor cells and osseointegration is well understood.[179–182] Several well-studied surface modification methods, such as sandblasted and acid-etched (SLA)[183,184] or apatite coatings,[185] offer a bounty of information on this topic.[186] However, the same cannot be said for soft tissue as far fewer studies exist trying to understand surface characteristic on implant soft tissue response.[187] Biomolecules offer a direct, tailored solution to enhance soft tissue healing around implants to prevent their infection and failure.

3.1.1 Peptides for enhancing dental implant soft tissue integration

3.1.1.1 RGD.: RGD[188,189] is the principal integrin-binding domain present within ECM (extracellular matrix) proteins such as fibronectin, vitronectin, fibrinogen, and osteopontin. RGD surface immobilization is now a classic technique[190] for the functionalization of biomaterials surface given its small size and recognition by a variety of cell types. A number of integrins show some binding affinity to RGD, such as α3β1, α5β1, α8β1, αIIbβ3, αvβ1, αvβ3, αvβ5, αvβ6, αv8β, and to some extent α2β1 and α4β1.[191] The use of RGD, as compared with native ECM proteins, minimizes the risk of immune reactivity or pathogen transfer and RGD's small size allows for a range of tunable immobilization to ocurr.[192] A large body of literature exists for RGD functionalized dental implants for osseointegration but only a handful of studies exist for soft tissue.[193] This may be related to the perception of RGD as "dated" and "old-fashioned" even though its simplicity makes it attractive from a manufacturing point of view.[194]

As a means to improve implant soft tissue healing, RGD has been conjugated to poly(L-lysine)-*graft*-poly(ethylene glycol) on titanium and shown to be effective in promoting epithelial and fibroblast growth.[195] Others have developed multilayered coating with type I collagen and RGD-conjugated hyaluronic acid (HA, a nonsulfated glycosaminoglycan[196]). These coatings promoted gingival fibroblast proliferation and adhesion-related gene expression.[197] Silk has been derivatized with titanium binding peptides and an RGD domain to coat titanium.[198] These coatings improved fibroblast adhesion, proliferation, and strengthened mechanical cell adhesion. Some work focusing on zirconia implants immobilized RGD on typical yttria-stabilized tetragonal zirconia and a biocermet.[199] Other work has immobilized linear and cyclized RGD on zirconia and showed enhanced spreading,

proliferation, and focal adhesion formation from gingival fibroblasts.[200] The growing demand of zirconia implants, and the prevalence of restorative abutment made of this tough and aesthetic ceramic, motivates future development of biomolecule coatings for them.[201–204]

3.1.1.2 Laminin-derived peptides.: Oral keratinocytes directly apposing teeth ("directly attached cells") form a basement membrane (BM) compositionally unique to any other BM in the human body: rich in laminin332 (a heterotrimeric glycoprotein[205]) serving as an integrin ligand to form hemidesmosomes (HDs)[206] and missing common BM proteins like collagen IV and perlecans (proteoglycans that crosslink many ECM components).[207] HDs serve as the transmembrane connection between teeth and gingiva as the JE forms a protective barrier for mechanical stability of the tooth, or dental implant, and a physical barrier against biofilm colonization.[176] However, HD formation on dental implants only occurs apically leaving the implant coronal surface vunerable.[176] Given the difficulties in working with laminins (recombinant laminins lack post-translational modification and historical difficulties in isolation and purification from tissue culture),[208] one particular peptide has been derived from the α3 globular domain 3.[209] This peptide has been silanized to titanium and used to induce keratinocyte HD formation toward enhancing implant soft tissue healing.[210,211] This same peptide has also been conjugated to multilayered polyelectrolyte films of poly(L-lysine)/poly(L-glutamic) acid films on titanium and shown to upregulate HD *in vitro* but have limited *in vivo* effects.[212] Another laminin-derived (laminin211 derived; DLTIDDSYWYRI) peptide has been applied toward dental implant coatings as well.[213–215]

A number of other peptide sequences have been isolated from laminins. Laminins are critical in basement membrane assembly and the resulting supramolecular architecture. Thus, laminins are a rich repository of potential cell-signaling motifs for utilization on dental implants.[216] IKVAV, from within the laminin α1 chain and traditionally associated with neurons,[217] has been physisorbed to titanium and shown to increase fibroblast attachment and improve tissue integration in a subcutaneous rat model.[218] YIGSR, derived from the β1 chain,[219] SINNNR, derived from an α chain,[220] and LRE, from laminin β2 chain,[221] are all well studied laminin-derived peptides that may be advantageous for soft tissue integration with dental implants. Indeed, a systematic review convincingly supports the efficacy of laminin-derived coatings for osseointegration and new bone formation around implants.[222] However, implementation for soft tissue remains unresolved. Assembled laminin-based hydrogels have become popular (such as for neural regeneration) in the literature:[223] advances in understanding of laminin from such 3D systems may be useful in designing implant surfaces.

3.1.2 Whole proteins.—The most commonly used biomolecule for soft tissue attachment in the dental implant literature is collagen. Collagen, a protein consisting of a prototypical sequence of repeated G–X–Y sequences hierarchically arranged to form fibers, has numerous structural – particularly in the context of dentistry in dentition and bone – and signaling functions.[224,225] The variety of collagens – there are 28 types of collagen that assemble into a variety of supramolecular structures including fibrils, network-like

structures, and microfibrils – is perhaps underappreciated in the biomaterials literature, where the clear majority of work is focused on type I collagen {[α1(I)]$_2$α2(I)}.[226] A common motivation for immobilizing collagen onto implants is its native RGD and synergy domains. For example, type I collagen has been immobilized *via* silanization on titanium and shown to increase periodontal fibroblast proliferation.[227]

A typical drawback associated with immobilization of entire biomolecules on surfaces is the lack of chemoselectivity and therefore control of the active conformation, *i.e.* biological activity.[228,229] This has been thoroughly demonstrated with type I collagen. For example, fibroblasts respond differently to collagen-laden surfaces that are manufactured with plasma-activation compared to acid etched titanium for later physisorption of collagen.[230] Other work has shown differences in fibroblast behavior on type I collagen-laden titanium immobilized with silanization using either 3-chloropropyl-triethoxysilane (CPTES) or 3-glycidyloxypropyl-triethoxy-silane (GPTES) surface linkers.[231]

Other approaches[232] avoid multi-step silanization and simply use polydopamine to immobilize type I collagen (Fig. 5) and reduce fibrous encapsulation. Polydopamine, a catecholamine, is noted to form polymeric coatings on virtually all tested substrates under mildly alkaline conditions.[233] Polydopamine is reactive toward nucleophiles such as thiol, amino, and imidazole groups under mild basic conditions and derived from sea mussels.[234] Indeed, in this example of type I collagen immobilization (Fig. 5), the poly-dopamine coating process yielded titanium surfaces that increased fibroblast and keratinocyte proliferation, size, focal adhesion formation, and reduced fibrous encapsulation in a subcutaneous rat model. Regardless of the immobilization method (such as simple polydopamine or multi-step silanization), there are evident benefits of presenting an entire biomolecule, with its precisely placed and plentiful binding domains perfected by evolution. However, the use of whole proteins may require strict sourcing of proteins from animal sources, protein recombination, or immunological challenges compared to other approaches.[8]

3.1.2.1 Fibronectin.: Another commonly used biomolecule in biomaterials, fibronectin, has been applied to dental implants for soft tissue healing. Fibronectin is a high molecular weight dimeric glycoprotein that is organized into a fibrillar network on the cell through interactions with surface receptors, and it regulates many cell functions, such as cell adhesion, migration, growth, and differentiation.[235] Fibronectin has been physisorbed to titanium implants and resulted in an increase in proliferation of epithelial and fibroblast cells.[236] Fibronectin has been silanized to titanium and shown to increase fibroblast proliferation, spreading, focal adhesion formation, and soft tissue attachment in a subcutaneous sheep model.[237] Fibronectin has also been used to coat hydroxyapatite-coated porous titanium and increase cell infiltration into the pores.[238] Like collagen, recent work has also suggested the sensitivity the conformation of fibronectin to physiochemical properties that causes downstream signaling effects.[239–243] Like with many whole biomolecules, the individual contribution of each motif from the entire biomolecule can be recapitulated using multiple individual motifs.[244]

3.1.2.2 Histatin-1.: Saliva presents a wealth of biomolecules that offer potential for dental implant therapies. One such molecules is histatin-1, which is a multifunctional histidine-rich peptide (57 amino acids) secreted by salivary glands, a critical molecule for oral mucosal wounds to heal faster and more efficiently than analogous skin wounds.[245] Histatin-1 has been physisorbed to titanium and shown to enhance the attachment and spreading of oral epithelial cells and fibroblasts, and when presented in solution, shown to increase barrier integrity and reduce translocation of bacteria across cell monolayers.[246–248] Other useful molecules may exist for increasing the success of dental implants given saliva's wealth of biomolecules, but they remain unexplored.

3.1.2.3 Growth factors.: Growth factors are biological mediators that regulate important cellular events involved in tissue repair and wound healing.[249] These biomolecules are attractive targets to stimulate soft tissue integration with implants given their role in wound healing. Some examples of this include platelet-derived growth factor (PDGF; induces epithelial proliferation[250]) and enamel matrix derivative (EMD; mostly composed of amelogenins[251]) physisorbed to implants and placed subcutaneously in rats.[252] PDGF increased soft tissue penetration into the implants grooves while simultaneously reducing fibrous connective tissue thickness. Other work[253] has soaked apatite-coated titanium in fibroblast growth factor 2 (FGF2; typically associated with angiogenesis[253]) and placed the implants in rabbit tibias. This FGF2 adsorption enhanced wound healing, reduced inflammation, and induced Sharpey's fiber-like tissue formation.[254]

3.1.3 DNA.—DNA (deoxyribonucleic acid) offers a number of intriguing benefits as a biomolecule to improve dental implant soft tissue integration. DNA is highly charged which allows for sequestering of biomolecules non-covalently (such as a LBL approach).[255,256] Low immunogenicity and tunable immuno-modulation are other benefits of using DNA for bioactivation of dental implant surfaces.[257] Early work for enhanced soft tissue attachment used poly-D-lysine and poly(allylamine) hydro-chloride with DNA for LBL coatings on titanium.[258] These surfaces promoted fibroblast proliferation but showed no effects in a subcutaneous rat model. An alternative approach is the delivery of laminin332 γ2 DNA for uptake and processing by keratinocytes to promote laminin332 production; this approach has been demonstrated effective *in vitro.*[259] Other work has shown similar results using laminin332 α3 DNA on chitosan/collagen coated titanium with nanotube topography *in vivo.*[260] Chitosan, as detailed later, is a natural polymer derived from the shells of shrimp and other crustaceans.[261] Polyethylenimine plasmid DNA nanoplexes encoding for platelet derived growth factor-BB (PDGF-BB) have also been coated on titanium for enhanced soft tissue integration.[262]

3.1.4 Other attractive biomolecules.—Intrinsic to the ability for keratinocytes to form a barrier against bacteria on implant surfaces is cell–cell attachment.[263] For example, in adherens junctions, the transmembrane protein E-cadherin associates with vinculin, which in turn binds catenins to link the complex to the cytoskeleton.[264] Inspired by this, the extracellular domain from E-cadherin has been used physisorbed to titanium and shown to increases metabolic activity, cell area, and attachment of keratinocytes.[265] A protease-activated receptor 4 (PAR4) – activating peptide conjugated to titanium, in combination with

platelet rich plasma, has been shown to induce proliferation and collagen IV secretion, a key molecule for basement membranes, in keratinocytes.[266] Other peptides,[267] such as one derived from ameloblastin – a protein found in enamel and secreted by ameloblasts[268] – has also been used to upregulate HDs when silanized to titanium simultaneously with a peptide from laminin α3 globular domain 3 (Fig. 6).[210]

Given its role in nature, intact laminin332 is perhaps the most intuitive biomolecule to use to enhance soft tissue attachment to dental implants. Indeed, laminin332 has been used to upregulate keratinocyte HD formation after physical adsorption to titanium;[269] passivation prior to adsorption seems to significantly increase the HD formation compared to nonpassivated titanium.[270] Alternatively, controlled adsorption of biomolecules, such as laminin332, on tooth surfaces may be an another way to improve soft tissue interactions.[271]

Phenolic compounds, while typically used for immobilizing or crosslinking molecules, have been used for direct cellular effects. The most common, polydopamine, has been used to coat titanium and increase fibroblast proliferation and collagen and fibronectin synthesis.[272] While simple approaches like this are attractive, some work has shown off-target effects from polydopamine on bone.[273] Other phenolic compounds such as a quercitrin have been silanized to titanium and increased proliferation and ECM production by gingival fibroblasts.[274] Titanium coated with polydopamine and chitosan increases proliferation and type I collagen secretion from fibroblasts.[275]

4. Biomolecules and mineralization for dental biomaterials

Perhaps the most prominent feature of the oral cavity is teeth. The outer covering of teeth, enamel, is the most highly mineralized tissue in the human body and withstands cyclic masticatory loading up to 770 N[276] around one million cycles per year.[277] The fundamental unit of enamel is the enamel prism; highly packed, hard, hydroxyapatite (carbonated calcium phosphate) mineral (approximately 95 wt% of enamel), with around 1 wt% organic matrix and 4 wt% water.[278–281] Underlying enamel as a tougher mechanical support is dentin; mineralized collagen (approximately 45 vol% apatite crystals, 30 vol% collagen, and 25 vol % water).[282] The basic ultrastructure of dentin – mineralized collagen – is structurally similar to bone.[283] The triple-helical collagen molecules (right-handed) are packed in a quasi-hexagonal structure to form nanometer sized microfibrils which further assemble into fibrils.[284] Collagen molecules align in a staggered, parallel array; this arrangement forms a characteristic 67 nm D-periodic banding pattern (“D-banding”) with an overlap zone of 32 nm and a gap zone of 35 nm.[285,286] Hydroxyapatite crystals in dentin and bone are nanometric[287] with their *c* axis preferentially aligned with the long axis of the collagen fibrils, leading to an inter-penetrating organic–inorganic nanocomposite.[288]

A number of major diseases afflict enamel and dentin. Approximately 2.4 billion people worldwide suffer from caries.[111] Dental caries is the most common chronic childhood disease in the United States, disproportionally afflicting low income children.[289] As a result, many approaches have been developed in order to remineralize and restore tooth structure using biomolecules as a biomimetic guide for regeneration. Such synthetic mineralization platforms emulate specific features of natural mineralized supramolecular matrices and may

spur design of materials capable of recreating the structure and function of tissues such as enamel, dentin, or bone.[290]

While a number of models have been developed to mechanistically describe collagen mineralization (such as that observed in dentin),[291] models based on mineralization of collagen with hydroxyapatite using non-classical pathways have been dominant in recent years.[292,293] In nature, the mineralization of collagen is believed to be mediated by interactions between negatively charged complexes of ACP (amorphous calcium phosphate) precursors with the collagen fibers. The ACPs precursors are formed due to interactions between ionic components in the physiological media with soluble templates; proteins that inhibit/promote mineral deposition and phase transformation precipation.[292] The ACP precursors penetrate the collagen fibrillary matrix and then they transform into hydroxyapatite. Indeed, the thorough infiltration of hydroxyapatite in the collagen matrix is considered the foundation of the excellent mechanical properties of hybrid human mineralized tissues, such as dentin and bone.[287,294]

In nature, non-collagenous proteins (NCPs), such as osteopontin (OPN), phosphorylated dentin phosphoprotein (DPP), fetuin and dentin matrix protein (DMP1)[295] regulate the mineralization process of the insoluble collagen matrix, possibly acting as soluble templates.[296] NCPs are intrinsically disordered proteins (IDPs); that is, dynamic, flexible molecules without a well-defined, kinetically stable, folded structure.[297] Moreover, NCPs are highly acidic proteins with a high number of aspartic and glutamic acids and/or phosphorylated residues, such as phosphoserine.[296] As NCPs are highly negatively-charged IDPs, they can sequester ions in solution to form stabilized ACPs that mediate bone mineralization.[296,298–300] The small integrin binding *N*-glycosylated proteins, known as SIBLING proteins,[301] are a family of NCPs that comprises OPN, DMP1,[302] cleavage products of dentin sialophosphoprotein (DSPP),[296] and bone sialoprotein[296] (among others[303]). SIBLING proteins are known to interact with hydroxyapatite through electrostatic and hydrophobic interactions and regulate the biomineralization process of bone and dentin.[296]

Inspired by the role of proteins in the mineralization of dental tissues, a number of biomolecule-based dental biomaterial processes have been developed to help restore mineralization to diseased tissues and idealized as restorative therapies. One synthetic mineralization method is the polymer-induced liquid precursor process (PILP), which substitutes charged naturally-derived macromolecules (such as NCPs) with other macromolecules [most classically poly-aspartic acid (pAsp); a polyanion].[304,305] Densified, crosslinked collagen hybrid matrices can be manufactured with remarkably biomimetic mechanical properties (combined strength and resilience) using PILP.[306] It was discovered in the original study examining the PILP system[307] that pAsp-mediated mineralization could create helical morphologies of calcium carbonate with a spherulitic twisted crystal growth, stabilized by the pAsp. Later, the same authors[305] showed that pAsp triggers a liquid–liquid phase separation alongside the mineral amorphous phase precursor. Similarly, such processes can be applied to other biominerals and solid fibrillary templates, such as silicification of collagen for collagen– silica composite with unique hierarchical structures[308] or cellulose–hydroxyapatite nanohybrids.[309,310] Moreover, alternatives to the use of pAsp as synthetic soluble template in the PILP process have been explored, most

notably poly-acrylic acid (PAA),[311] so that, for instance, fibrillar mineralization can be controlled by modifications of PAA molecular weight and/or concentration.[298] Recently, the synthetic soluble template has been substituted by natural NCPs, such as OPN, *in vitro*.[312–314] The PILP process has also been widely used as a biomimetic system to discern the mechanism by which collagen is intrafibrillarly mineralized in nature.[298,306,309,310,315–317] However, this is a topic under debate. Notably, the versatility of the PILP process has already spurned development of biomineralization processes for restorative dentistry and treatment of hypomineralization-based diseases.[315–317]

A number of biomolecules, mostly derived from NCPs and other IDPs, have been used to control biomineralization processes both as a mechanism of fundamental study and for the creation of therapies for the treatment of dental-related diseases. Below, we survey at few of these biomolecules that have resulted in the restoration of function or regeneration of dental tissues.

4.1 Elastin-like recombinamers for mineralization and biomaterials

Elastin-like recombinamers (ELRs), with their positively charged $(VPGXG)_n$ domains, have been mineralized with a PILP-based approach. One factor critical to the ability of ELRs to guide mineralization is a conformational change from disordered random coils into ordered β-sheet structures upon interaction with the developing enamel crystals[318] (the same is also true for IDPs).[319] In fact, the β-spiral structure and an unperturbed fibrillar structure play a critical role in ELR mineralization, more than electrostatic interactions or specific bioactive sequences.[320] This process is highly tunable just based on ELR structure. For example, one can vary ELR crosslinking during manufacturing solvent evaporation to control ELR disorder–order ratios to alter structural hierarchy of the resultant mineralized structures and consequently the properties (mechanical, for example) of the functional material.[318] This approach has also been applied to ELRs with a statherin-derived moiety to form layered and ordered fluorapatite, perhaps useful as an enamel therapeutic.[321] A similar ELR with a statherin-derived moiety promoted bone regeneration *in vivo*.[322] The versatility of the ELR structures also enables the biomimetic mineralization of these molecules in different micro-structures, such as hydrogels,[323] membranes,[318] fibers,[320] and implant surfaces.[324]

4.2 Amelogenin for mineralization and biomaterials

Amelogenin (AMELX) is an IDP shown to play an important role in biomineralization, is the most abundant protein of forming enamel, and is capable of self-assembly to form nanospheres.[325] AMELX is comprised of three domains: a 45 amino acid tyrosine-rich N-terminal domain, a large, hydrophobic central domain, and an 11 amino acid hydrophilic C-terminal domain.[326] Previous work[327] has reported that AMLEX undergoes a structural change from disordered, random coils to ordered β-sheet upon interaction with the developing enamel crystal. The highly conserved N-terminus contains the only post-translational modification in AMELX (phosphorylation of serine-16).[328] Not surprisingly, studies[329,330] have shown the role of this single phosphorylation altering conformation and protein–mineral interactions to improve its capacity to stabilize ACPs.[331] The critical role of pS-16 *vs.* S-16 has also been elegantly shown *in vivo* using a knock-in animal model.[332] Foundational work[319] observed that AMELX self-assembles into “nanospheres” in the

presence of enamel. These nanospheres prevented mineral growth in the *a*- and *b*-axis and promoted crystal formation in the *c*-axis, as is biomimetic. The role of C-terminus has been shown to affect the pre-nucleation clusters and assembly into nanosphere.[333] Another, more applied, example by others[334,335] showed that the distinctive hierarchical structure of mature enamel requires distinct conformational organization of AMELX into amyloid-like nanoribbons. A modular design for amelogenin was suggested correlating the domain of the amelogenin protein with specific mutations using protein engineering and transgenic animal studies.[336,337] Using a bioinformatics scoring matrix, short peptide sequences were identified from the native amelogenin protein. These amelogenin derived peptides were demonstrated to promote formation of a cementum-like hydroxyapatite mineral layer on demineralized root dentin,[338] similar to recombinant AMELX promoting pulp-like regenerative and hard tissue organization in an root apex closure model.[339] A similar peptide approach regulates orientation and regrowth of aprismatic enamel on dentition.[340]

4.3 Statherin for mineralization and biomaterials

Statherin (STATH) is a 43 residue acidic phosphopeptide highly expressed in saliva.[341] The primary sequence of statherin is: D^{1}pSpSEEKFLRRIGRFGYGYGPYQPVPEQPLYPLQPY-QPQYQQYTF; pS are phosphorylated serines. The first five amino acids in the N terminus, and more generally the 15 terminal N terminal amino acids,[342] are critical for adsorption to hydroxyapatite.[343,344] The four basic residues (K and R) are likewise critical for adsorption.[345,346] The C-terminus is also reported to fold into an α-helix upon adsorption.[347] STATH is known to generally modulate mineralization by (1) sequestering calcium ions to suppress immediate calcium phosphate crystallization on mineralized surfaces such as dentin and (2) adsorbing onto/around nucleated crystals to inhibit their further growth.[348] STATH and peptides derived from it have been applied to enamel remineralization for anti-caries applications.[349–353]

4.4 Osteopontin and other natural biopolymers for mineralization and biomaterials

OPN is a highly acidic, disordered protein with many negatively charged amino acids, phosphorylated serine residues, a po-lyaspartic acid cluster, and an acidic serine- and aspartate-rich (ASARM) motif, all of which are known to be critical to its biomineralization properties.[354–356] OPN-mediated biomineralization has been used to direct the formation of nanoscale hydroxyapatite in the interstices of collagen around encapsulated human mesenchymal stem cells in 3D and used as a model to study prostate cancer.[312] Similar worked showed effects of such OPN-mineralized materials on pericyte differentiation and vascularization.[313] This is based in natural processes, for example, where OPN inhibits calcium oxalate growth and kidney stone formation; this process is dependent on OPN's carboxylate groups and phosphorylation status.[357,358] Increased OPN *in vivo* leads to bone hypomineralization,[359] related to upstream pyrophosphate activity and osteoclastogenesis regulation.[360,361] This serves as a reminder that while many of these biomolecules regulate mineralization from a structural perspective [biomolecule/crystal (or pre-cursor interactions)], biomolecules regulate mineralization together with other hormones, transcription factors, regulatory proteins, and enzymes through traditional cellular signal transduction and biochemistry.[362]

Other concepts from these biomineralization systems (and others reviewed in detail elsewhere[290]) have driven development of other advances in biomolecule-based dental biomaterials. For example, chitosan-based extrafibrillar dentin demineralization has been introduced as a bonding strategy to reduce endogenous collagen degradation, prevent water permeation into the hybrid layer, enhance antimicrobial activity, and promote longer bond stability.[363,364] Other possibilities include adapting these collagen biomineralization strategies for more effective remineralization in general, such as caries-preventation.[365–367] Bone-mimetic materials may also be valuable for studying cancer and bone metastases[368] or pre-dentin formation.[369]

5. Chimeric peptides as biomolecules for dental biomaterials

An alternative and attractive approach for generating biomolecules is combining different features of multiple biomolecules into one multifunctional or multi-domain molecules. A chimeric molecule refers to an engineered construct where different functional domains in a biomolecule can be linked to form a novel biological agent.[370–372] This method has historically be applied to drug delivery where one domain is designed to target the cell specific molecule and the other one carries a drug molecule.[373,374] Depending on the nature of the molecules, several linker features have been applied including hydrazine, disulfide moieties, as well as click chemistries where regio-selective moieties cam be integrated in to the design.[375] The concept is similar to fusion proteins where the two domains encoded by different genes can be joined to a transcript and translated as a single polypeptide.[370] Extended examples includes fusion proteins having fusion partners facilitating purification of cloned genes, reporting expression levels and visualization of the proteins in a biological environment. Although this approach been commonly applied to drug delivery, it can facilitate biological activity on an implant, solid material, or tissue interface *via* increased activity and stability of the bioactivity by controlling molecular orientation and facilitating biomolecular interactions. In the last decades, short peptide sequences selected from combinatorial libraries, including phage and cell surface technologies, have emerged as attractive tools to bind to solid materials with high affinity.[376–379] An important aspect of chimeric peptides is their properties can be improved using computational modeling and predictive tools.[380–382] Peptides are particularly attractive for this purpose because of their ease of manufacture.[383] A relatively common way to generate such biomolecules is to pair a bioactive domain (such as growth factor, signaling molecule, *etc.*) with a domain with affinity for a substrate. While we have mentioned a few chimeric peptide examples previously, we spotlight here this class of biomolecule owing to their tunability and multifunctionality.

One exciting set of chimeric peptides is those with affinity to dental hard tissue such as hydroxyapatite. Hydroxyapatite binding peptides (HABPs) selected by phage display, for example, have been conjugated to the N-terminus of a green fluorescence protein variant (GFPuv) to produce GFPuv–HABP used to induce mineralization at the adhesive/dentin interface.[384] Prior work with these HABPs showed that these molecules induced calcium phosphate mineralization by exhibiting control over the mineralization kinetics and particle morphology on hydroxyapatite under specific conditions.[385] In another study, another novel apatite binding peptide identified using phage display[386] was shown to increase adhesion

strength and adhesion specificity of various cell types, as well as control differentiation, to enhance bone regeneration in a mouse model.[387–389] Others have used chimeric peptides composed of cell binding sequence combined with apatite affinity sequence to inhibit osteoblast mineralization.[390]

A relevant type of chimeric peptides for dental applications includes those with affinity for titanium implant materials (titanium binding peptides; TiBPs) to provide titanium with bioactivity or antimicrobial potency, such as the previously shown in Fig. 2. For example, previous examples of TiBPs have demonstrated antimicrobial activity of chimeric TiBPs-AMPs against *S. mutans*, *S. epidermidis*, and *E. coli*[391,392] and enhanced osteoblast activity.[393] Other TiBP-AMP examples showed antimicrobial potency against *S. gordonii*, *Streptococcus oralis*, and *S. sanguinis*.[394,395] The use of chimeric peptides is also an exciting avenue of investigation for drug release systems due to their labile, non-covalent interactions with materials.[396–398] Similar chimeric peptides have also been developed for polymers.[399,400] Another class of chimeric peptides has been developed to bind to titanium and promote soft tissue healing around dental implants.[401] In short, chimeric peptides offer an interesting avenue for multifunctionality within one short peptide sequence and opportunities for new, targeted designs that incorporate the biological activity of chimeras.

6. Oral hard tissue modification with biomolecules

An alternative approach for extending the lifespans of dental restorative materials is not the development of new restorative materials *per se* but rather enhance of the existing tooth structure. This is an attractive approach as decades of work have focused on novel restorative materials that show exciting laboratory results but are then never brought to market.[402] An additional benefit of reinforcing enamel or dentin is the potential universal compatibility with any restorative material.

An alternative approach to protect collagen degradation at the resin/dentin adhesive interface and prevent premature failure of resin composite restorations is collagen crosslinking. Plant-derived proanthocyanidins (polyphenolic compounds that induce intraand inter collagen crosslinking)[403] have been used for extending the lifespans of restorative materials. Proanthocyanidins can be “painted” onto tooth surfaces or encapsulated in dental materials.[404] Application of proanthocyanidins on dentin has been shown to reduce dentin permeability,[405] increase tensile (among many) mechanical properties,[406] reduce degradation due to water and enzymes,[407] and increase bonding.[408] Other work has shown that proanthocyanidins may help protect dental pulp from restoration-associated cytotoxicity.[409] Recent clinical trials have suggested limitations of proanthocyanidin application to extend restoration lifespans.[410,411]

Another dentin modification strategy has featured the AMP GL13K to form robust coatings that take advantage of the amphiphilicity of GL13K with strong affinity for deproteinated, negatively-charged hydroxyapatite-rich peritubular dentin. GL13K thereby forms hydrophobic, antimicrobial, highly stable coatings on dentin that reduce microleakage but do not alter mechanical adhesion between dentin and restorative materials.[412,413] These simple coatings may be able to reduce recurrent caries of existing restorative materials without

tedious and time-consuming restorative product development. Others have developed a peptide combining an AMP domain and a domain with high affinity for hydroxyapatite to engineer antimicrobial enamel.[414–416] Other similar strategies have been developed using monomers.[417,418] Additional work developed a coating process for dentin whereby lysozyme (an antimicrobial enzyme part of the immune system)[419] is emulsified in a solution of PEG (polyethylene glycol) to form amyloid-like lysozyme oligomer aggregates and result in an antifouling coating against proteins and *S. mutans* and induce remineralization under specific conditions.[420] Another well-studied, though not necessarily biomolecule-derived, hard tissue modification, is silver diamine fluoride.[421,422]

7. Oral tissue regeneration using biomolecules in dental biomaterials

The tooth is comprised of hydroxyapatite and soft matter (collagen fibrils, pulp-like cells, and other connective tissue). The outermost layer of teeth is of enamel, which is underlaid by less mineralized dentin and non-mineralized pulp tissue (Fig. 7).[423] The supporting tissues surrounding the tooth (*i.e.*, the periodontium), consist of alveolar bone, cementum, and periodontal ligament.[424] Infections inevitably occur and inflammation leads to endodontic/periodontal diseases that require tissue substitution, repair, or regeneration.[425] Tissue regeneration of dental and periodontal tissues is particularly challenging given that loss of tooth vitality frequently leads to complete removal of the pulpal tissue,[426] and periodontium infection may lead to supra- or subgingival superficial scaling,[427] or even complete tooth removal.[428]

7.1 Pulp regeneration

Tooth vitality relies on a healthy pulp free of microbiology contamination. Nevertheless, dental trauma or caries may result in pulp contamination and inflammation.[429,430] Teeth can lose vitality, become necrotic, and form a periapical lesion. In these cases, necrotic pulp must be removed, the intracanal system disinfected (antimicrobial options for this are discussed in section 2.1.3), and the pulp chamber filled with a restorative material.[426,431] The absence of living tissue in the intracanal space prevents the possibility of pulp regeneration when using conventional endodontic therapy (root canal treatment).[432] Endodontic therapies are performed frequently but the success can vary widely; some reports show long term success rates below 50%.[433] As a result, a number of approaches have been developed toward regenerative endodontic therapies for pulp regeneration.

Pulp regeneration is dependent on the presence of stem cells in the desired site capable of differentiation into specialized cells (*e.g.*, odontoblasts) and the absence of infection/contamination.[429,434] Regeneration is especially relevant in the case of immature permanent teeth.[435] Immature teeth possesses some anatomical characteristics (*e.g.*, wide open apex and fragility) that do not support root canal treatment.[430] Consequently, apexification and the evoked bleeding method are currently used to treat necrotic immature permanent teeth. Both approaches utilize the body's natural biomolecule delivery responses to regenerate pulp.

Apexification induces apical closure by forming a mineralized barrier (details are reviewed elsewhere[436]) but does not complete root maturation.[430] In contrast, the evoked bleeding

method may induce root maturation.[432] The evoked bleeding consists of performing a laceration of the periapical tissue to provoke bleeding into the canal system, *i.e.*, formation of a blood clot, thus forming a natural, fibrin-based scaffold filling with apical stem cells.[437] This blood clot enriches the site with growth factors FGF2, vascular endothelial growth factor (VEGF; pro-angiogenic[438]), nerve growth factor (NGF; anti-apoptotic[439]), among others.[435,440] However, the regenerated tissues are heterogeneous in morphology, including cementum-, periodontal- and bone-like tissues.[441] In response, treating dentin with a conditioning agent [*e.g.*, chelators like ethylenediaminetetraacetic acid (EDTA)] beforehand can partially demineralize inorganic dentin contents to favor release of growth factors and matrix biomolecules (such as transforming growth factor β1) (TGF-β; enhances odontogensis[442]), bone morphogenic protein-2 (BMP-2; enhances odontogensis[443]), and PDGF.[444–446] These released biomolecules are chemotactic toward dental pulp stem cells (DPSCs)[430] and improve cell attachment to the canal walls and stem cell differentiation.[447,448]

One commonly used cocktail of biomolecules in pulp regeneration is platelet-rich plasma (PRP), or the fraction of a volume of plasma that possesses a greater concentration of platelets and amount of growth factors as compared to peripheral blood.[449–451] One would think it would be highly regenerative considering the high concentration of growth factors (reviewed elsewhere[452–454]), but according to some studies,[449,455] newly formed pulp within PRP-filled root canals is absent of any odontoblasts. Nevertheless, it seems that PRP-based techniques positively influence tooth survival.[456] The recent results of the first randomized, controlled phase I/II clinical trial for delivery of mesenchymal stem/stromal cells (MSCs) encapsulated in platelet-poor plasma (PPP) showed that PPP/MSC treatment increased pulp response compared to a non-regenerative endodontic control.[457]

A wide array of manufactured, biomolecule-based scaffolds has been used for pulp and dentin–pulp complex regeneration.[458] Indeed, the range of biomolecules used for pulp regeneration encompasses the range of biomolecules highlighted in this review. In a series of early, pioneering reports, DPSCs were encapsulated in alginate and placed subcutaneously into the backs of nude mice; histological analysis showed odontoblast-like cells initiated dentin-like hard tissue formation ectopically.[459,460] Others have encapsulated human umbilical vein endothelial cells (HUVECs) and DPSCs in GelMA and showed native cell infiltration with establishment of well-organized neovasculature formation and pulp cells that attached to the inner dentin surface and infiltrated into the dentin tubules.[461] Of note, for encapsulation of HUVECs and DPSCs in GelMA, a light-driven process was used: the hydrogel was incorporated with light-sensitive photoinitiators and then photo-polymerized using ultra-violet (UV) light. Despite being a conventional method, UV light may produce DNA damage and impair cellular function, so that the alternative light sources like the visible-light typically found in dental curing dental devices would contribute for a more biocompatible scenario for pulp regeneration, as suggested by others.[462]

Similar scaffolds have been encapsulated with FGF2 to drive DMP1 and nestin (odontoblast differentiation biomolecule[463]) expression in the dentin defect near the amputated pulp.[464] HA gels fabricated by freeze-drying, when implanted in amputated pulp, showed formation of reparative dentin toward residual dental pulp under the dentin defect to a greater extent

that collagen controls.[465] Other HA-based injectable gel seeded with stem cells from apical papilla (SCAPs) enhance the differentiation of the cells into an odontoblastic phenotype capable of mineralization.[466] Decellularized materials are also attractive materials.[467] Recently, DPSCs have been encapsulated in lowand high-stiffness oligomeric collagen matrices and long-term cell survival demonstrated, as well as endothelial and odontogenic differentiation.[468]

Chitosan has been added to a fibrin hydrogel to promote dental pulp tissue neoformation and collagenous matrix production.[469] Porous silk fibroin scaffolds fabricated using freeze-drying and physically loaded with basic fibroblast growth factor (bFGF) showed pulp-like tissue regeneration with vascularity, matrix deposition, and dentin-like tissue formation.[470] Similarly, silk fibroin scaffolds loaded with RGD and DMP1 showed no hard tissue growth. This negative result suggests that processing and handling protocol of all biomolecules and biomolecule-derived biomaterials may be critical to the final biological activity.[471]

Heparin (a common glycosaminoglycan[472]) has been crosslinked with gelatin in hierarchical nanofibrous microspheres to load and sequester VEGF as an injectable, microsphere system for full-length pulp regeneration.[473] Results showed successful regeneration of pulp-like tissues that filled the apical and middle third root space with notable vascular regeneration in mice. These results claim, for the first time, complete pulp tissue regeneration in a full-length root canal. An alternative strategy is the fabrication of “scaffold-free” 3D constructs composed of DPSCs in their own secreted, biomolecule-rich matrix. These constructs and DPSCs are able to differentiate into odontoblast-like mineralizing cells and form blood vessel-rich pulp-like tissues.[474,475]

7.2 Periodontal tissue regeneration

The periodontal tissue is comprised of cementum, periodontal ligament and the alveolar bone acting together to anchor the tooth.[476] The alveolar bone lining the tooth socket shows a continuous remodeling process; a balance between bone formation and bone resorption.[426,477] Periodontitis is a chronic inflammatory disease induced by bacterial infection and the host response thereto, which may lead to significant destruction of the periodontium.[169] Around 796 million people worldwide have severe periodontitis.[1] Periodontal regeneration was first demonstrated using guided tissue regeneration (GTR) techniques in which epithelial migration into the regenerating area is prevented.[478] GTR techniques vary according to the material used to induce the regenerative process, such as bone grafts (replace the missing alveolar bone); periodontal barriers (cover the remaining alveolar bone present in the defect); and biological mediators (bioactive materials administered into the periodontal defect).[479] Periodontal regeneration remains clinically challenging because of the involvement of the three distinct tissues forming the periodontium.[480] The most notable challenge in periodontal regeneration is ensuring that the periodontal ligament is intercalated, integrated, and inserted into both cementum and bone (*i.e.*, functional Sharpey’s fibers).[481] A noted deficiency in the use of bone grafts and periodontal barriers is their outcomes cannot be predicted. Attempted biological mediators include biomolecules, which may induce effective migration of progenitor cells and their proliferation toward sustainable formation of a new periodontium.[482]

7.2.1 Biomolecules for periodontal regeneration.—Collagen is the gold standard material for periodontal regeneration and has been reviewed elsewhere,[483] but is typically not stiff enough and frequently becomes exposed.[484] In response, relatively advanced biomolecules release systems have been developed with materials other than collagen. For example, core/shell fibrous super-assembled frameworks have been loaded with bFGF and BMP-2 burst release for few days of bFGF followed by a slow and steady release of BMP-2 for up to four weeks. This material showed new bone formation as well as periodontal ligament and cementum regeneration when implanted *in vivo*.[485] Others have combined stromal cell derived factor-1 (SDF-1, a chemoattractant)[486] and BMP-2 with hydrogelator Nap-Phe-Phe-Tyr-OH (NapFFY) by simply dissolving and cooling the mixture to induce assembly.[487] Release profiles were steady through one month and results from a maxillary critical-sized periodontal bone defect showed regeneration of periodontal tissue supporting bone.

More complex mixtures of biomolecules, multi-phasic materials, have been fabricated as well. One example includes tri-layered nanocomposites composed of chitin, bioactive glass, cementum protein 1 (CEMP1, known to induce differentiation of periodontal cells[488]), FGF2, and PRP that were implanted into rabbit maxillary periodontal defects.[489] The results showed formation of new cementum lined with cementoblasts on the root surface, periodontal ligament formation and new alveolar bone formation. Multiphasic constructs are indeed frequently used for periodontal tissue regeneration.[490] Other approaches include a photocrosslinkable HA system enriched with platelet lysate that showed a growth-factor mediated response by periodontal ligament fibroblasts and antimicrobial activity.[491] Platelet lysate has also been encapsulated in HA to increase overall periodontal healing scores and restrict formation of long epithelial junctions.[492] A somewhat unusual biomolecule, wool keratin (usually obtained from low quality wool processing[493]), has been successfully applied to promote similar periodontal tissue regeneration as collagen but while being derived from industrial waste streams.[494] Other work has used polydopamine coatings on poly(ɛ-caprolactone) (PCL)[495] or solvent cast and thermally annealed silk fibroin[496] to regenerate periodontal tissue.

7.2.2 Chitosan for periodontal tissue regeneration.—A common strategy in periodontal tissue engineering, besides multi-phasic approaches, is the use of chitosan. Chitosan is generally antimicrobial (depending on processing)[497] with low cytotoxicity and has been applied to many other fields including biopharmaceutics and food science.[498] Chitosan is noted for its easy processability into hydrogels, fibers, beads, particles, *etc.*, biodegradability, and ability to hydrate wounds.[499] Many studies have demonstrated the beneficial effects of adding chitosan into dental materials to improve their physical, and mechanical properties.[500–505] Perhaps more interestingly, chitosan has been used to enhance periodontal tissue regeneration in many forms.[506]

Some examples of periodontal tissue regeneration using chitosan include fabricating electrospun collagen/chitosan membranes and regenerating periodontal tissue in a rat model.[506] Chitosan and gelatin has also been successfully combined to regenerate periodontal tissue.[507] Multiphasic, oriented chitosan fibers have been created to form a densely mineralized matrix with the new mineral on the dentin surface in a nude mouse model.[508]

Chitosan seems immunomodulatory toward periodontal tissues which may be useful in promoting tissue regeneration.[509] Other have combined chitosan with metallic nanoparticles for enhanced antimicrobial activity[510] or bioactive glass particles for enhanced bone formation.[511]

7.2.3 Gene delivery for periodontal tissue regeneration.—Gene delivery is an advanced biomolecules delivery strategy to yield sustained local production and secretion of proteins to avoid immunological, half-life, and timing problems of classical biomolecule delivery.[512] Delivery constructs can be divided into nonviral vectors (plasmids) and the viral-based vectors.[482] Both vector options are effective but viral options may cause irreversible modifications to the host's DNA.[513] Dosing[514] and proteolysis of vectors[515] remain as a concern, but a few examples of gene delivery for periodontal regeneration exist.

One approach is delivery of vectors encoding growth factors like PDGF-BB or BMP-7 with proved effectiveness for periodontal tissue regeneration in a large alveolar bone defects with similar mechanical properties to native tissue and mature expression of collagen III and periostin (a matricellular periosteum protein).[516,517] Another alternative approach is the reduction of the expression of a particular gene, such as using an adeno-associated virus cathepsin K (Ctsk; an important regulator of osteoclast mineral dissolution[518]) with small hairpin (sh)RNAs.[519] Another study showed that transfecting an adenovirus containing Wnt10b (a Wnt that promotes osteogenesis *via* β-catenin signaling[520]) significantly increased osteogenesis and decreased adipogenesis, which may be useful for periodontal tissue regeneration.[521] Other relevant approaches include *ex vivo* delivery to stem cells for later stem cell therapies for periodontal defect regeneration.[522,523] Vector delivery vehicles include a range of other biomaterials and synthetic polymers.[524]

7.2.4 Bioprinting for periodontal regeneration.—Bioprinting is a fairly novel reconstructive process that holds potential to fabricate three-dimensional, defect-specific vascularized periodontal/bone tissues. In a recent study, bone formation was considerably increased upon the use of a 3D-printable bioink comprised of an ECM hydrogel and amorphous magnesium phosphate particles (Fig. 8).[525] Two distinct concentrations of the foregoing particles were tested (0.5 and 1.0 wt%) and compared to an unfilled ECM. After encapsulation of DPSCs in the bioinks, the cell-laden constructs were tested for osteogenic differentiation potential and for *in vivo* bone regeneration; despite cell viability was similarly obtained as compared with the control, cell morphology features were improved, and mineralization and osteogenic gene expression were increased, leading to gradual bone healing. It is worth mentioning that these modified-bioinks are free of growth factors, and this fact did not prevent bioactivity outcomes to occur. Overall, it was demonstrated that by combining the tested bioink with bioactive compounds (amorphous magnesium phosphate), bone formation is substantially enhanced, so that this manufacturing method shows promise for effective *in situ* bioprinting strategies.

7.3 Biomolecule-based strategies for salivary gland regeneration

Hyposalivation, which is a characteristic of xerostomia (or dry mouth syndrome), can significantly affect the quality of life of patients and is commonly caused by Sjögren's

syndromes, various medications, and side effect of cancer-related radiation therapy.[526] The prevalence of hyposalivation or xerostomia is difficult to estimate but is present in 90–100% of head and neck cancer patients.[527] Treatment to regain full salivary gland function is difficult and typically temporary. As a result, a number of tissue engineering approaches have been undertaken to engineer artificial salivary tissues to mitigate effects of hyposalivation and increase salivation.[528,529]

Many approaches to regenerative salivary glands have used biomolecules in order to mimic the complex structure of salivary glands,[530] which are generally cells from the acini (the basic secretory units of salivary glands) surrounded by ECM:, myoepithelial cells, myofibroblasts, endothelial cells, stromal cells and nerve fibers in addition to the immunological system.[531] As a result of this complex structure – and in particular the necessary ductal structures – almost no examples possess all appropriate vascularization, innervation, and secretory function.[530,532]

Laminin111 derived peptides, which avoid cost and immunological problems associated with whole laminin proteins, have been used as one driver of salivary gland differentiation and development when conjugated to fibrin.[533] Fibrin (a protein formed by proteolytic activity of thrombin on fibrinogen)[534] scaffolds conjugated with these peptides have been able to partially regenerate a damaged mouse submandibular gland.[535] Fibroblast growth factor 7 (FGF7) seems to be responsible for the remarkable new nodes/clusters formation within such fibrin hydrogels.[536] Fibrin is an attractive biomolecule because degradation products have no adverse effects on cell function or viability.[537]

Matrigelt, as in a number of other regenerative medicine applications, has been successfully used to culture salivary gland constructs; particularly as a means to propagate differentiated cell types.[538] However, it should be noted that Matrigelt does not have a well-defined composition[539,540] as it is an assortment of ECM like laminin111, collagen IV and nidogens (crosslink laminins and collagens[541]).[539,540] A perlecan domain IV peptide has been shown to trigger differentiation of salivary gland cells into self-assembling acini-like structures that express necessary biomarkers and secrete α-amylase to a similar extent as Matrigelt and may be a good substitute for Matrigelt.[542] Other work has shown the critical role of FGF7 for branching of salivary gland ducts in 3D.[536]

Other biomolecules used for regeneration salivary glands includes elastin which promotes apicobasal polarization of salivary gland epithelial cells when electrospun (process reviewed elsewhere[543]) with poly(lactic-*co*-glycolic acid) (PLGA).[544] Hyaluronic acid has been crosslinked with mono-2-(acryloyloxy)ethyl succinate to form hydrolytically degradable hydrogels that support multicellular spherical aggregates and stable maintenance of a stem cell phenotype.[545] The addition of polydopamine to hyaluronic acid seems to further support required salivary gland differentiation.[546] Other work with hyaluronic acid hydrogels has generated acini-like structures that activated the salivary fluid production molecular pathway[547] and induced expression of cholinergic neurotransmitter receptors, which are necessary for salivary gland function.[548] Fibronectin has been reported to help differentiation and expression of functional proteins in the acinus and adhesion-related cell markers from human salivary biopsies into acinar cells.[549] Silk fibroin hydrogels aide

salivary gland epithelial cells response to isoproterenol by increasing enzyme release, just as healthy salivary glands do.[550] The many utilizations of chitosan for salivary gland regeneration have been previously reviewed,[551] as have gene delivery approaches.[552]

7.4 Peptide amphiphiles for oral tissue regeneration

The self-assembly of molecules is an attractive strategy for engineering biomaterials because of the highly tunable, free energy-driven process that spontaneously organizes such molecules into finely ordered structures mimicking nature.[553] One class of molecules able to do this is peptide amphiphiles (PA), which first reported to self-assemble into long nanofibers, form hydrogels, and mimic the ECM under the control of pH and presence and concentration of ions.[554,555] A typical fiber-forming PA includes a peptide sequence (normally less than 10 amino acids) linked to an aliphatic tail (at least 10 carbons). This peptide sequence contains a critical domain near the aliphatic tail with a high propensity to form β-sheet secondary structures and charged residues to facilitate self-assembly; bioactive domains can be incorporated, RGD for example.[556]

The first families of PAs were designed to nucleate apatite crystals with specific orientation and mimic the nanostructure of dentin and bone. Since then, other structures have been achieved including spheres, filaments, 2D-sheets, networks, tubes, and helices, among others.[557] A number of functionalities are can be enabled by PAs given their modularity: enzymatically cleavable domains,[558] self-repair,[559] biphasic release profiles,[560] drug-triggered crosslinking,[561] and peptide–DNA hybrids,[562] among others. PAs have been used for a number of regenerative medicine applications including immunomodulation,[563] angiogenesis,[564] neurogenesis,[565] and replication of the multi-hierarchical self-assembly of collagen,[566] among others.

PAs have also been applied to dentistry. For example, PAs have been used to encapsulate DPSCs with MMP-degradability and RGD to generate mineral for toward dentin repair.[567,568] Others[569] have also suggested the use of PAs for dental pulp regeneration. Dentonin, a peptide shown to help repair dentin,[570] has been incorporated into a PA for dentin repair.[571] Similar work has also incorporated basic fibroblast growth factor (bFGF),[572] TGF-β1,[442] and VEGF into the PA *via* heparin binding for pulp regeneration.[573] Others have used PAs to ectopically generate enamel-like tissue.[574] Similarly, self assembling leucine zipper hydrogel systems have also been applied for regenerative dentistry.[575,576]

8. Future perspectives and conclusion

This review has emphasized the relevant and central role of biomolecules in designing and developing new generations of preventive and therapeutic technologies to address oral health issues both for manufacturing and modifying dental materials. In spite of the specific functional and signaling diversity and specificity of the biomolecules, which justifies the excitement and focus on them, mechanical (elasticity, toughness, *etc.*) and structural (porosity, roughness, *etc.*) characteristics of biomaterials can be overriding signaling cues for cells.[577] Thus, the smart and guided combination of physical and biochemical features in dental biomaterials should be further explored. Release of biomolecules from the biomaterials structural components is another promising technology to control the biological

outcome of biomaterials. However, despite decades of work focusing on biomolecule release kinetics, striking recent work has shown the importance of the temporal and spatial organization and density of biomolecules in their delivery scaffold.[578–581] Patient-specific materials (cells[582] or perhaps even biomolecules, such as is commonly performed with PRP) and their incorporation into therapeutic treatment strategies is another potential avenue for advancement in dental biomaterials.[583] Thus, processing, sourcing, and functional display of biomolecules (release profile, encapsulation, immobilization, *etc.*), with or without cells, can exert strong control over the biological activity of biomolecules.[584,585]

One rising approach to govern biological activity of dental biomaterials is the use of immunomodulatory systems, such as for dental implants[586] given the pivotal role the immune system plays in the response to materials. Strategies such as growth factor sequestration[587] are well-proven routes to take advantage of immunomodulation.

Other classes of biomaterials such as polysaccharides (long chains of carbohydrates) beyond chitosan may further be explored in dentistry given their commonness in other regenerative medicine fields.[588] Proteoglycans [glycosaminoglycan chains covalently attached to protein core (with the exception of hyaluronan) (or hyaluronic acid) that lack a protein core[589]] are widely used in cartilage tissue engineering.[590] However, even though proteoglycans are found in dental pulp and important to odontogenesis, dental biomaterials composed of proteoglycans are scarce.[591,592]

Extracellular vesicles (EVs) are nanoparticles secreted by all cells that contain lipids, proteins, and nucleic acids and function as cell-to-cell communicators; up to 850 different proteins, over 200 mRNAs, and around 60 miRNAs.[593,594] As a result, EVs are functionally active intercellular messengers that may be beneficial for delivering biomolecules towards regeneration[595] and repairing tissue through immune modulation, angiogenesis, inhibition of apoptosis, reduction of fibrosis, and other pathways.[595] One attractive opportunity for EVs is their delivery through biomaterials and tissue engineering constructs.[596–598] EVs play a critical role in development and homeostasis of the oral cavity. For example, ~100 nm exosomes are secreted by the epithelium and mesenchyme of a developing tooth organ where epithelium exosomes induce dentin sialoprotein production and mineralization. Mesenchyme exosomes induce ameloblastin and amelogenin secretion.[599,600] EVs have been used to treat bisphosphonate-related osteonecrosis of the jaw (BRONJ) through promotion of angiogenesis and bone regeneration in rats.[601] Future development in dental biomaterial may exploit this potent delivery mechanism of biomolecules.[602]

Some key factors must be considered as materials move toward translation. The use of different cell types can, due to genetic variability and diversification even with common cell lines, result in different results between investigators.[603] Disparities in biomolecule sources (naturally extracted, recombinant, *de novo* designed, *etc.*) may directly affect biological activity.[194,604] High throughput screening techniques may enable rapid screening of engineering materials to accelerate this pipeline.[605–608] Practicability of the materials for clinicians and potential to scale manufacturing, with environmental constraints, are also realities that promising biomaterial therapies must handle.[609] Strategies to mitigate the relatively short half-lives of biomolecules and transportation and storage of biomolecule-

decorated biomaterials must be faced.[610] Finally, a recent trend has been toward rather complex multi-functional materials.[611] While academically meritorious, financial aspects limit their potential successful clinical translation due to both required manufacturing regulation and sheer cost of all the components.[612] A balance between increased complexity and practicability and cost-effectiveness is likely necessary.

Advantages in dental biomaterials must not be limited to dentistry itself but rather enriched with ideas from the vast field of tissue engineering. Indeed, there were 66 ongoing or completed clinical trials of tissue engineering-related products between 2011–2018 and over $9 billion in sales in 2017 alone.[613] A further, rather concerning challenge in biomaterials is the artisanal nature of current materials, which are neither immediately accessible nor easily sent from lab to lab. This undermines biomaterials exploitation by the entire biomedical community. Filling these gaps and overcoming these knowledge barriers is essential to invigorate the biomaterial and dental communities, with input from and others in the biomedical community at large, toward shared goals and prioritization of the most essential oral and systemic health challenges.

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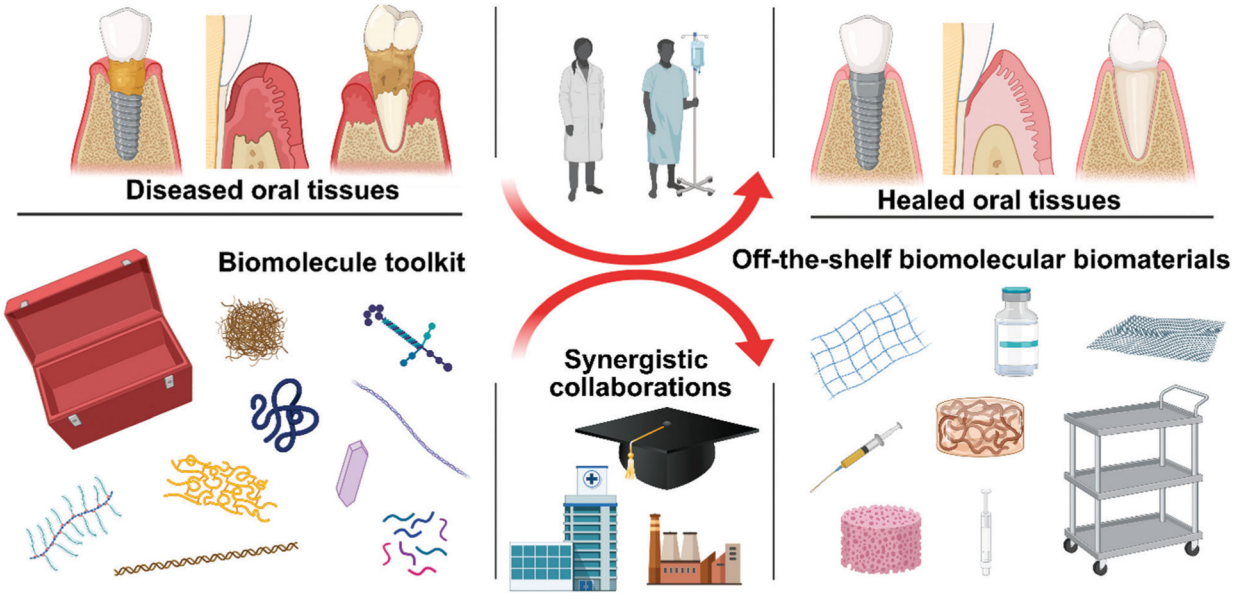

Fig. 1.

Harnessing biomolecules for bioinspired dental biomaterials. Promising and proven biomolecules include hyaluronic acid, DNA, elastin, peptides, proteins, intrinsically disordered proteins, laminin, minerals, and collagen. Dental biomaterials potentially benefitting from biomolecule incorporation include tissue grafts and membranes, adhesives, and regenerative endodontic obturation materials.

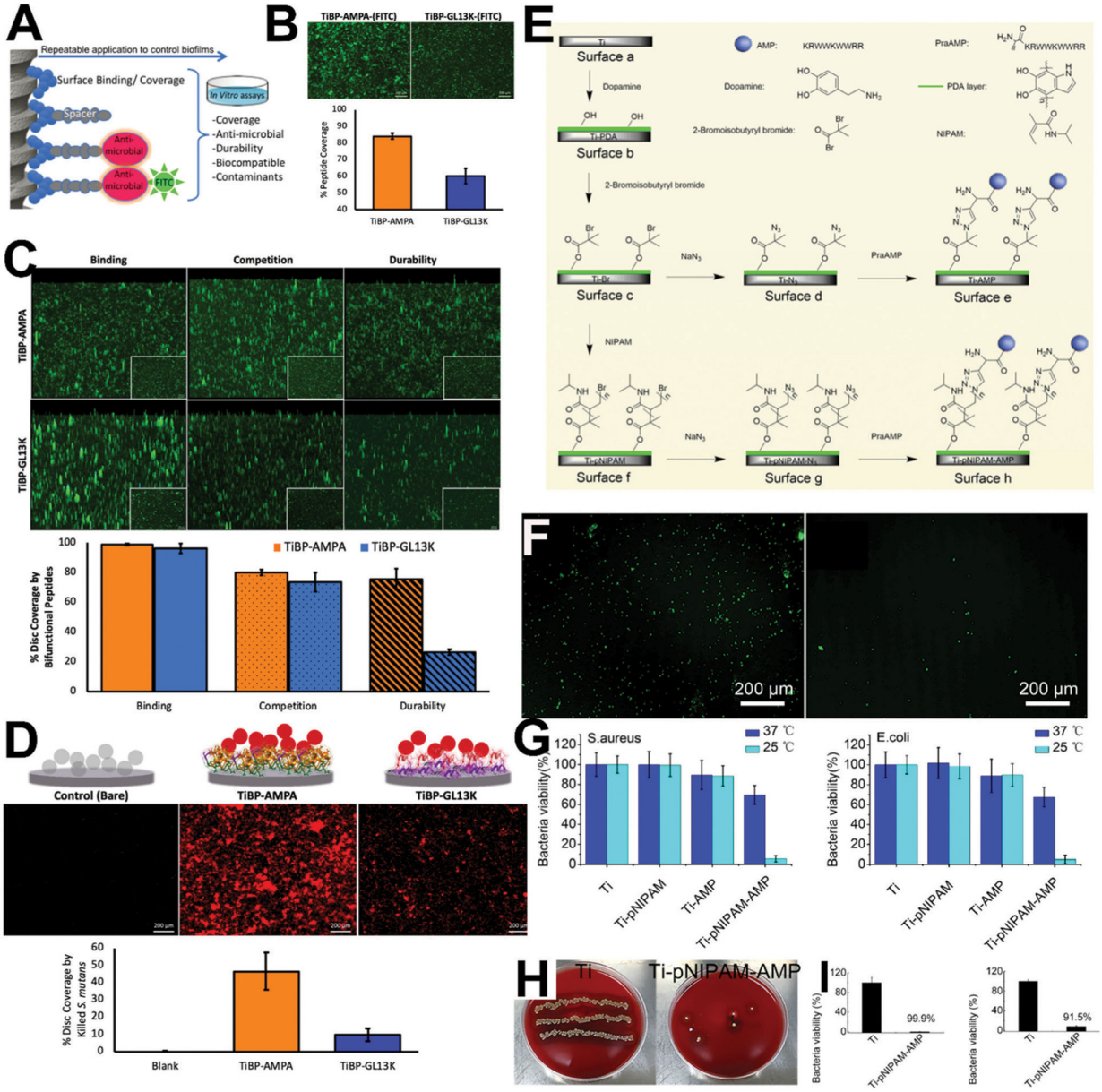

Fig. 2.

Chimeric antimicrobial peptides and temperature-sensitive immobilized antimicrobial peptides with *in vivo* potency. (A) Schematic representation of AMP designed with an implant/titanium binding domain (TiBP) connected to an AMP domain separated by a spacer. Two peptides designs were used in this study: TiBP-AMPA and TiBP-GL13K, which differed in their respective AMPs (AMPA *vs.* GL13K). (B) Visualization of FITC-labeled peptides using fluorescence microscopy after challenge by *S. mutans* for 24 hours. The percentage of peptide (TiBP-AMPA *vs.* TiBP-GL13K) coverage was determined. (C) Fluorescent microscopy images of peptides (TiBP-AMPA and TiBP-GL13K) binding to titanium implant discs, binding with competition from bovine serum albumin, and durability following 1 minute of brushing with an electric toothbrush. (D) Fluorescence microscopy images and quantification of propidium iodide (PI) staining of dead *S. mutans* bacteria on

implant discs after challenge for 24 hours. (E) Scheme of preparation of temperature-sensitive surfaces on Ti; Ti was treated with dopamine to form surface b (Ti-PDA); then, surface b was treated with 2-bromoisobutyryl bromide to form surface c (Ti-Br); by click chemistry, surface c was first converted into surface d by adding NaN_3, and then into surface e (Ti-AMP); surface e (Ti-AMP) contained AMP but lacked pNIPAM; by atom transfer radical polymerization, pNIPAM was formed on surface c to generate surface f (Ti-pNIPAM); by click chemistry, surface f was converted first into surface g (Ti-pNIPAM-N3) by adding NaN_3 and then into surface h (Ti-pNIPAM-AMP) by adding HHC36. Surface f contained AMP conjugated to pNIPAM. (F) Exposure and hiding of HHC36 (fluorescently labelled in green) at lower (left; 25 °C) and higher temperature (right; 37 °C). (G) Quantitative antibacterial activity of different surfaces after incubation against *S. aureus* and *E. coli* for 2 h at 25 °C (exposed peptide) and 37 °C (hidden peptide). (H) *In vivo* characterization of antimicrobial activity and biocompatibility of samples after implantation in infected rabbit tibiae for 7 days; images of the Petri dishes showing the presence of bacteria (yellow spots) on samples after retrieval (left; plain Ti and right; temperature-sensitive with HHC36). (I) Antimicrobial activity of the surfaces of different samples (left) and the tissues surrounding the corresponding samples (right) after *in vivo* retrieval. Reprinted with permission from ref. 72 (2019) and ref. 89 (2018) American Chemical Society.

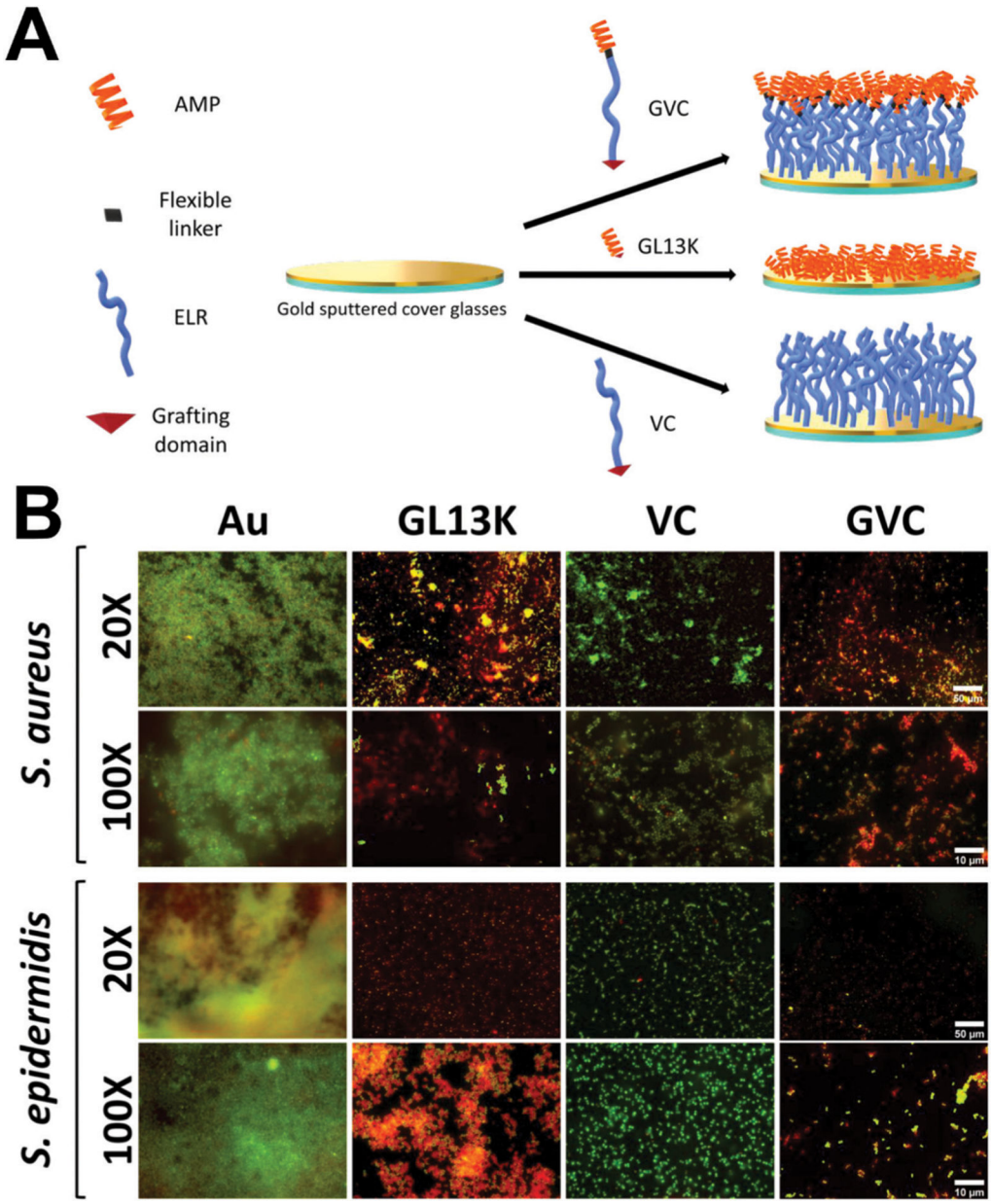

Fig. 3.

Elastin-like recombinamer coatings on dental implants for anti-biofilm potency. (A) Schematic representation of the modular composition of the antimicrobial-ELR (AM-ELR) and production of self-assembled monolayers (SAMs) on gold surfaces. (B) Live/dead staining biofilms (where green is alive and red is dead) for both (*S. aureus* and *S. epidermidis*) after 24 h of culture on negative control gold (Au) surfaces, positive control GL13K peptide surfaces (GL13K), the ELR without an AMP incorporated (VC) and then the antimicrobial AM-ELR (GVC). Reprinted with permission from ref. 109 (2019) American Chemical Society.

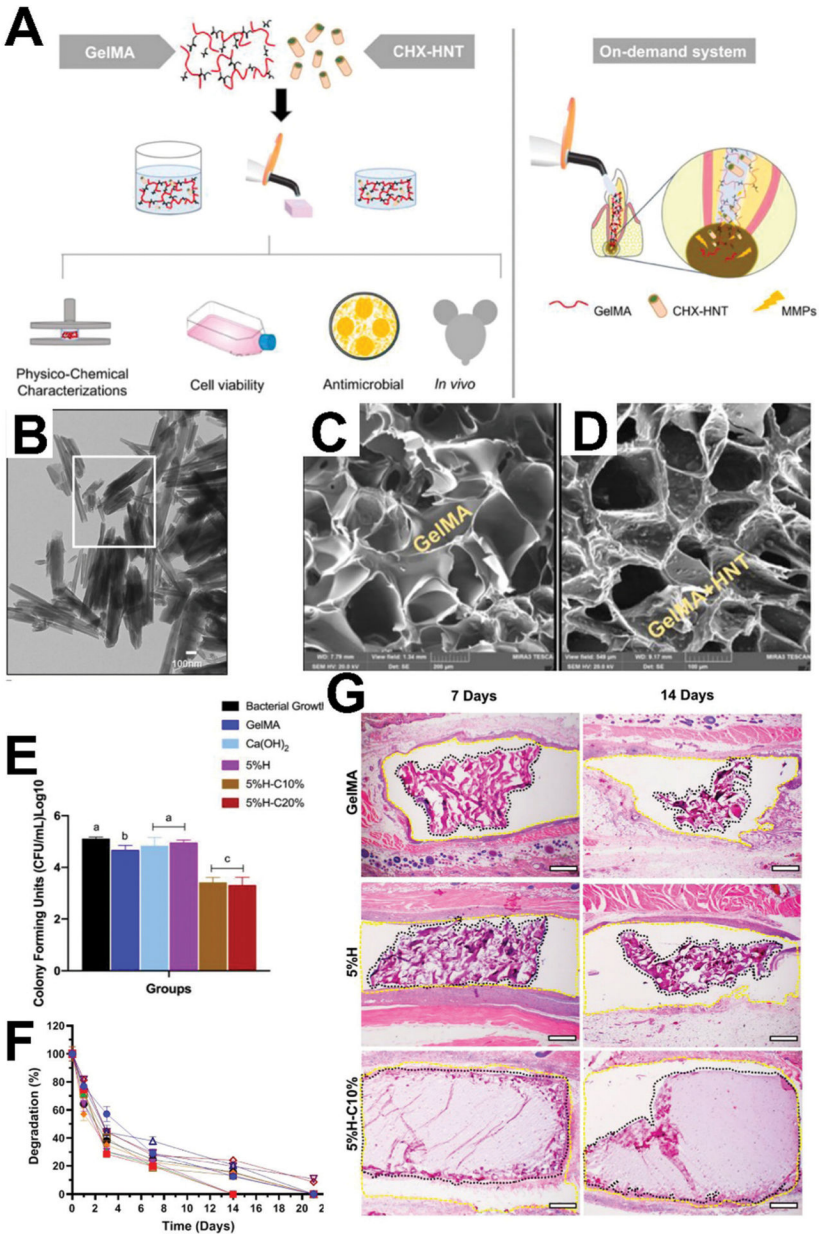

Fig. 4.

Hybrid antimicrobial biomaterial for endodontics. (A) Schematic representation of study design using a photocrosslinkable gelatin methacryloyl (GelMA) hydrogel with halloysite aluminosilicate nanotube (HNT) for release of chlorohexidine (CHX) for on-demand delivery for endodontic infection ablation. (B) Transmission electron micrographs (TEM) of HNTs. (C) Morphology (scanning electron micrographs) of GelMA hydrogel cross-section. (D) SEM cross-section of GelMA modified with CHX-loaded nanotubes. (E) Antimicrobial activity of GelMA with CHX loaded HNTs against a patient-derived oral microcosm. (F) Degradation profile of hydrogels in collagenase type I solution. (G) Histological analysis of the biopsy of the capsule surrounding indicated samples after 7 and 14 days. Reprinted with permission from ref. 146 (2020) American Chemical Society.

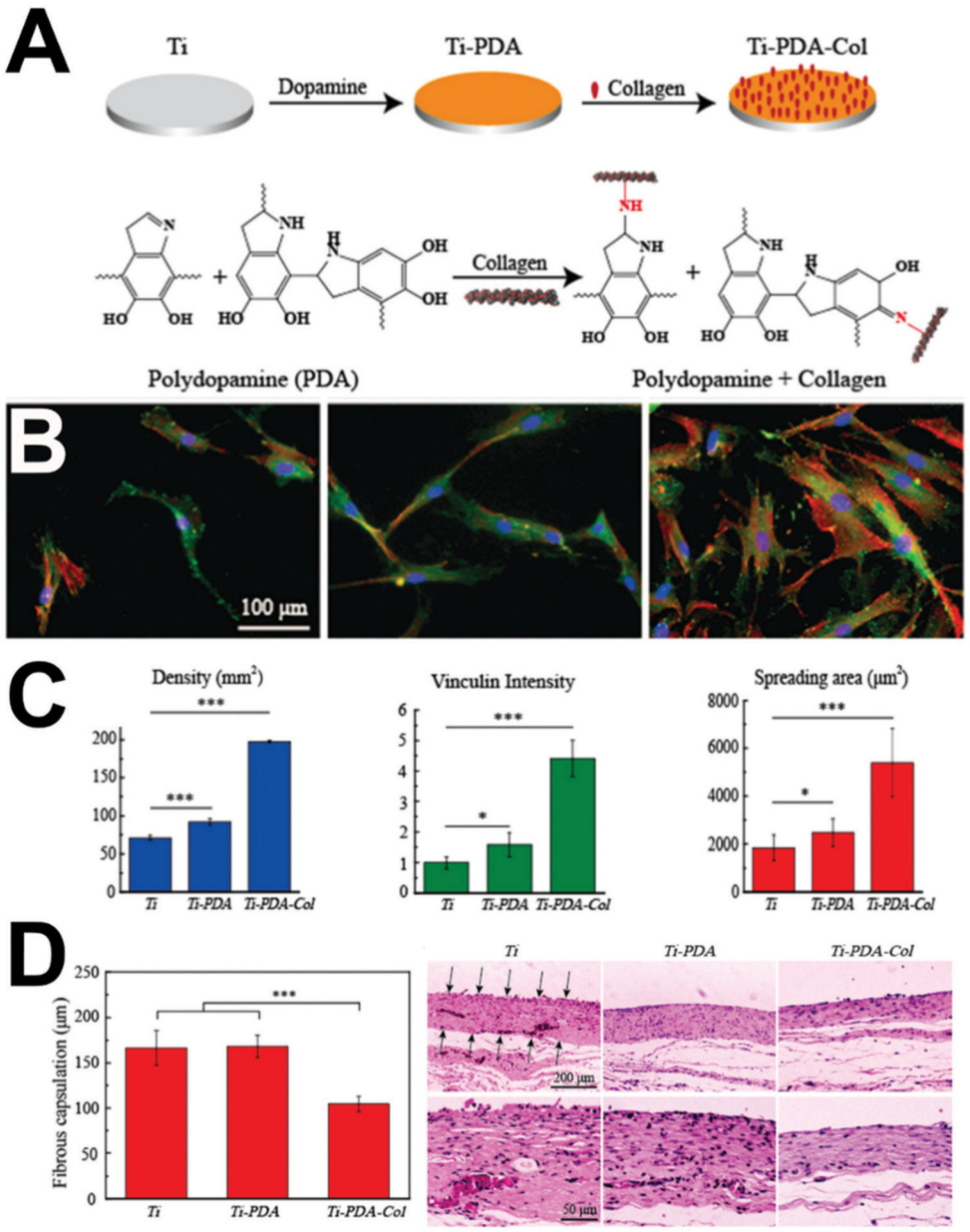

Fig. 5.

Polydopamine and whole proteins for improving soft tissue healing around dental implants. (A) Schematic of surface modification of Ti–6Al–4V (Ti). Polished titanium was first coated by a poly-dopamine (PDA) film by self-polymerization of dopamine; then, type I collagen was bonded with the PDA film *via* a Michael addition or Schiff base reaction. The possible structure of PDA and mechanism of the reaction between PDA and collagen is shown. (B) Adhesion of fibroblasts on (from left to right) Ti, Ti-PDA, and Ti-PDA-Col after 1 day of culture; fluorescent micrographs stained with vinculin in green, actin in red, and nuclei in blue. (C) Fibroblast surface density, vinculin intensity, and cell spreading area after 1 day of culture. (D) Histological (H&E) analysis of the biopsy of the capsule surrounding indicated

samples after 30 days of implantation in rats and quantification. Reprinted with permission from ref. 231 (2019) The Royal Society of Chemistry.

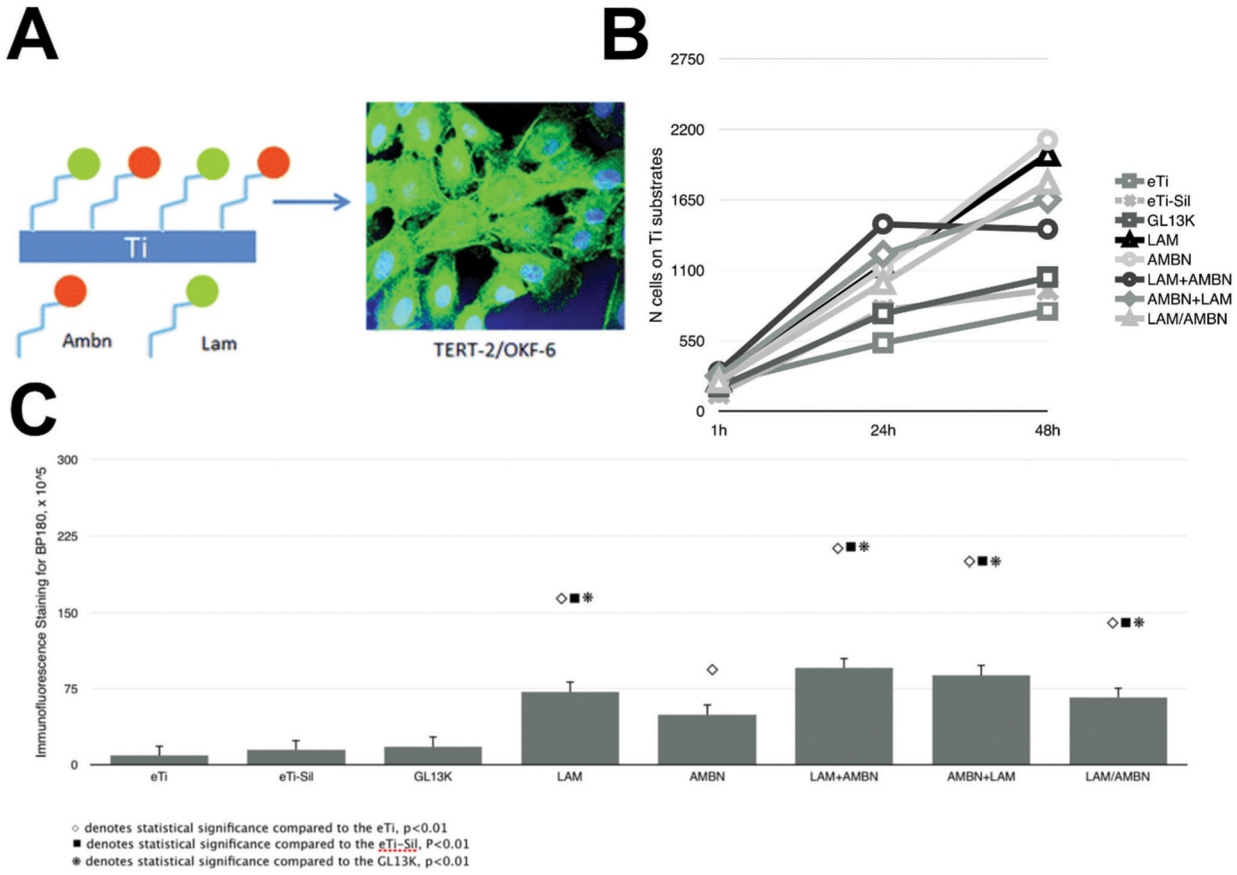

Fig. 6.

Peptides for enhancing dental implant soft tissue healing. (A) Schematic of surface modification co-immobilizing a peptide derived from ameloblastin (denoted as ABMN) and the laminin α3 globular domain 3 (denoted as LAM) to upregulate hemidesmosome formation on titanium for percutaneous devices such as dental implants. (B) Proliferation of keratinocytes through 48 hours (2 days) of culture on mono- and co-immobilized surfaces. (C) Hemidesmosome formation (immunofluorescence of collagen XVII) after 1 day of culture. Reprinted with permission from ref. 210 (2018) The Royal Society of Chemistry.

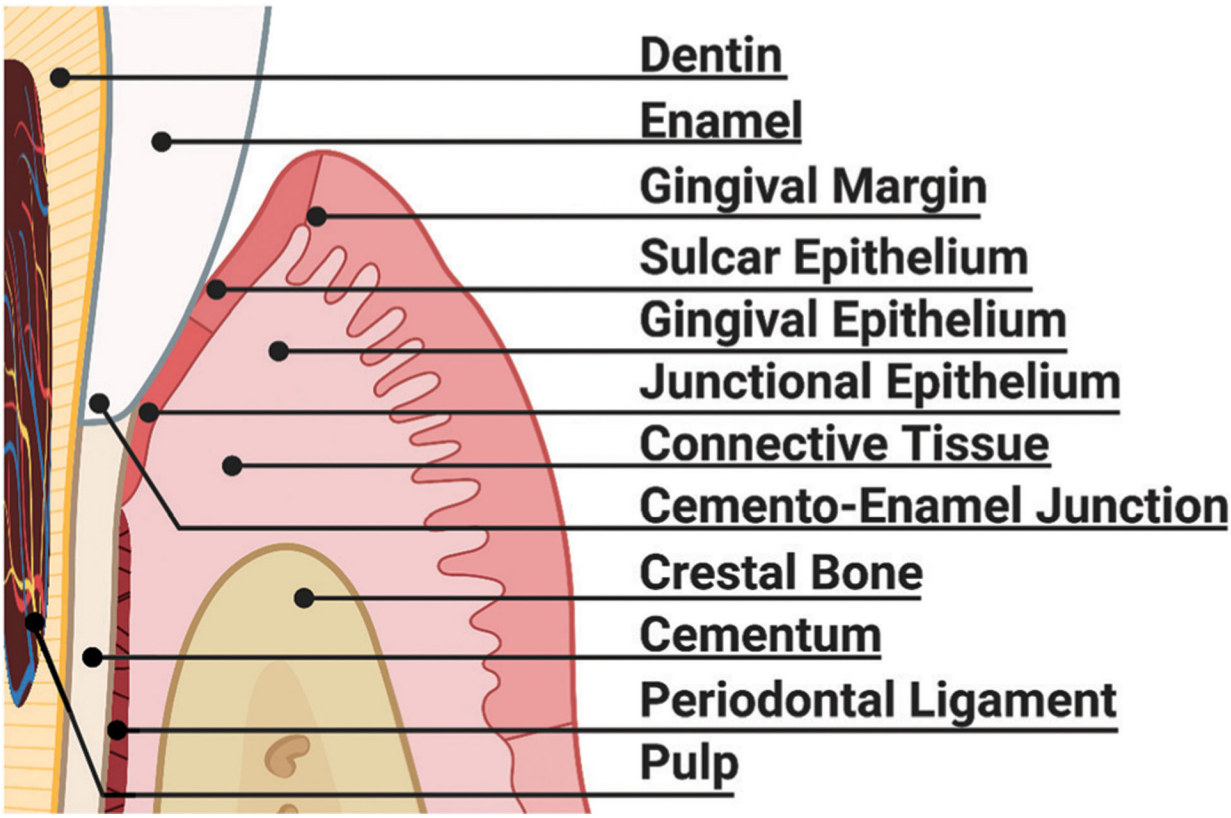

Fig. 7.

Hard and soft periodontal tissues susceptible to disease and infection necessitating bioinspired dental biomaterial therapies. The tooth, primarily composed of enamel and dentin, is filled with blood vessels and is innervated. The tooth root is covered in cementum and partially anchored into the oral cavity through periodontal ligaments as the tooth sits in a bone socket. The surrounding gingiva, composed of sulcar epithelium and connective tissue, seals the tooth from the harsh oral cavity at the junctional epithelium, near the cemento-enamel junction, and is marked by a distinctive gingival margin and epithelium in healthy individuals.

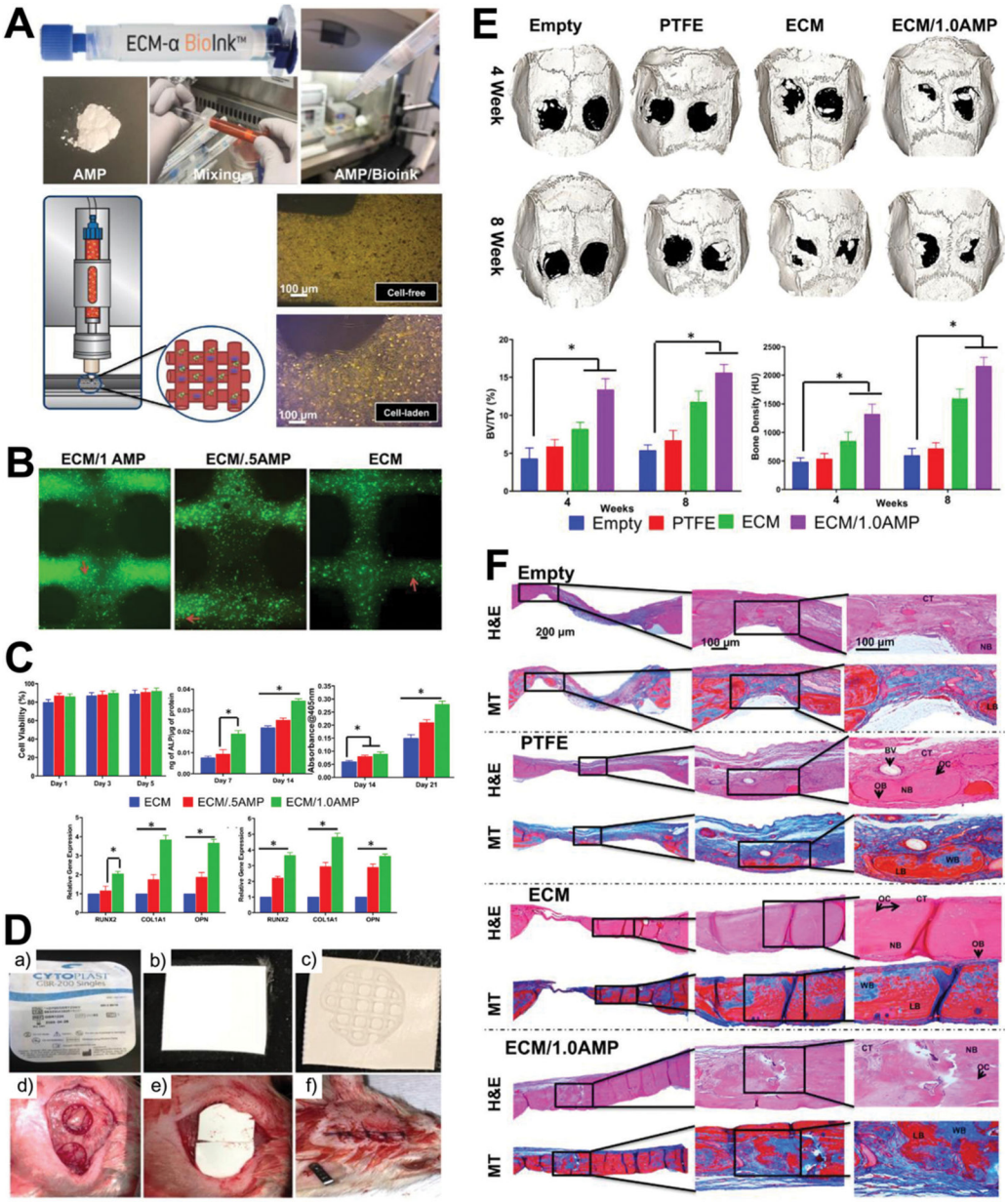

Fig. 8.

Novel bioink biomaterial for increasing bioactivity and bone healing. (A) Representative macrophotographs (upper images) showing the formulation process of the extracellular matrix/amorphous magnesium phosphate (ECM/AMP) bioink, and schematic of the ECM/AMP cell-laden bioink printing and the optical images (lower images) of the cell-free/cell-laden, AMP-based composites with and without cells. (B) Calcein AM (green) and PI (red) staining assay for live and dead analysis of dental pulp stem cells (DPSCs) after short period (1 day) in the cell-laden ECM and ECM/AMP-bioprinted constructs, showing more elongated morphology for DPSCs when combined with the AMP-modified constructs (red arrows denote dead cells). (C) Graphs showing similar cell viability among the tested bioink constructs, but a significant overall increased osteogenic differentiation (alkaline

phosphatase activity, Alizarin Red S absorbance, and osteogenic gene expression at days 14 [lower left graph] and 21 [lower right graph]) for the ECM/AMP-modified bioinks as compared with the AMP-free control. (D) Representative macrophotographs for the application of the tested constructs in the *in vivo* rat model, showing the polytetrafluoroethylene (PTFE) membrane (cytoplast) used as a carrier for the printed constructs (a), its cutting into square-shaped pieces (7×7 mm^2) (b) and combination with the constructs (c), and implantation in prepared defect (d and e) and suture (f). (E) Micro-CT results showing rat skull 3D rendering at 4 and 8 weeks for defects left empty or filled with the PTFE membrane alone, ECM and 1.0 wt% ECM/AMP-modified (ECM/1.0AMP) constructs; bone volume per total volume (BV/TV) and bone density were substantially higher for defects treated with the AMP-modified material. (F) H&E and MT staining after 8 weeks of implantation of tested groups and controls, indicating healing of the defects with new bone formation restricted to the area close to the border of the defects, with the ECM and ECM/1.0AMP groups showing thicker bone formation; inset legends – connective tissue (CT), osteoblast (OB), new bone (NB), blood vessel (BV), osteocytes (OC), woven bone (WB; blue), lamellar bone (LB; red). Reprinted with permission from [ref. 514] (2020) American Chemical Society.