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3D-printed scaffolds for periodontitis therapy: Spatial programming and microenvironmental regulation

Jingchen Xu^{1*}, Ziyi Xu^{2,3}, Huina He³, Yue Wang³, Yuxuan Sun³, and Haoyang Wu³

¹Department of Dental Medical Center, China-Japan Friendship Hospital, Beijing, 100029, China

²Department of Oral Sciences, Faculty of Dentistry, University of Otago, Dunedin, New Zealand

³State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, Sichuan, China

*Corresponding author:

Jingchen Xu (xjcxjc1995@126.com)

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Abstract

Periodontitis is a chronic inflammatory disease characterized by plaque biofilm dysbiosis, immune dysregulation, oxidative stress, alveolar bone resorption, and impaired wound healing. Although conventional periodontal therapies can reduce microbial burden and slow disease progression, predictable regeneration of the cementum-periodontal ligament (PDL)-alveolar bone complex remains difficult in irregular, infected, and inflammation-compromised defects. Three-dimensional (3D) printing offers a programmable strategy for fabricating periodontal scaffolds with patient-specific geometry, tunable pore architecture, spatially distributed materials, and region-specific biological functions. This review summarizes recent advances in 3D-printed scaffolds for periodontitis therapy and periodontal tissue regeneration, with emphasis on spatial programming and microenvironmental regulation. We first analyze the pathological barriers dictating scaffold design requirements, including persistent biofilms, unresolved inflammation, oxidative stress, disrupted bone homeostasis, and defective healing. We then discuss major printing modalities, material platforms, and biomimetic design strategies, including patient-specific customization, multiphasic compartmentalization, PDL fiber guidance, vascularization-oriented pore networks, and integrated barrier control. Functional strategies involving antibacterial activity, immuno-redox regulation, tissue-specific regenerative cues, neurovascular support, and spatiotemporal delivery are highlighted. Finally, we outline challenges in material optimization, disease-relevant modelling, functional evaluation, manufacturing standardization, and clinical translation. Future 3D-printed periodontal scaffolds should evolve from passive defect fillers into microenvironment-driven precision regenerative systems for functional periodontal reconstruction.

Keywords: Periodontitis; 3D printing; Bioprinting; Scaffold; Spatial programming; Tissue engineering

1. Introduction

Periodontitis is a highly prevalent chronic inflammatory oral disease worldwide and one of the major causes of tooth loss in adults¹⁻³. In 2021, approximately 1.07 billion people globally were affected by severe periodontitis⁴. Pathologically, periodontitis is driven by plaque biofilm-induced dysregulation of host immune-inflammatory responses⁵. This dysregulated response leads to the progressive destruction of periodontal supporting tissues, including the gingiva, periodontal ligament (PDL), cementum, and alveolar bone⁶. As the disease progresses, patients may develop gingival bleeding, periodontal pocket formation, clinical attachment loss, alveolar bone resorption, and tooth mobility⁷. In severe cases, tooth loss may occur, markedly impairing masticatory function, esthetics, and oral health-related quality of life⁸⁻¹⁰. In addition, periodontitis-associated chronic inflammatory burden is closely related to various systemic diseases, including diabetes mellitus, cardiovascular diseases, rheumatoid arthritis, and Alzheimer's disease¹¹.

Currently, periodontitis is mainly managed by plaque control, scaling, and root planing, supplemented by antimicrobial therapy, flap surgery, guided tissue regeneration, or bone substitutes when indicated¹²⁻¹⁴. Although these approaches can reduce microbial burden, control inflammation, and slow disease progression, their therapeutic efficacy in complex periodontal defects is still limited¹⁵. On the one hand, complete debridement is often compromised by deep pockets, furcation involvement, and irregular osseous defects. On the other hand, conventional membranes and bone substitutes remain limited in defect adaptation, space maintenance, mechanical support, and tissue-specific guidance¹⁶. Moreover, authentic periodontal regeneration requires coordinated reconstruction of cementum, PDL, and alveolar bone, together with functional insertion of PDL fibers into the adjacent mineralized tissues¹⁷. Therefore, novel regenerative strategies integrating infection elimination, inflammation modulation, space maintenance, and multi-tissue interface guidance are urgently required¹⁸⁻²⁰.

Three-dimensional (3D) printing is an additive manufacturing technology that builds 3D structures layer by layer from digital models²¹. Compared with conventional scaffold fabrication methods, 3D printing precisely controls scaffold geometry, porosity, pore interconnectivity, local mechanical properties, and spatial material distribution^{22,23}. In particular, it allows the fabrication of patient-

specific scaffolds when integrated with cone beam computed tomography (CBCT), intraoral scanning, and computer-aided design/computer-aided manufacturing (CAD/CAM), making it well suited for periodontal defects with complex morphologies, high individual variability, and constrained anatomical spaces²⁴. Beyond scaffold fabrication, 3D printing offers a programmable platform for spatially regulating periodontal regeneration²⁵. By combining multi-material systems, multiphasic architectures, gradient porosity, and anisotropic fiber alignment, 3D-printed scaffolds can partially mimic the hierarchical organization of cementum, PDL, and alveolar bone, thereby guiding PDL cell alignment, cementum-like matrix deposition, and alveolar bone regeneration²⁶⁻²⁸. In addition, with advances in extrusion-based printing, light-assisted printing, melt electrowriting (MEW), and 3D bioprinting, 3D-printed scaffolds have gradually evolved from simple structural supports into multicomponent functional platforms²⁹. Synthetic polymers, bioceramics, hydrogels, decellularized matrices, cells, growth factors, antimicrobial agents, and extracellular vesicles can be incorporated into printed systems, enabling scaffolds to acquire antibacterial, anti-inflammatory, immunomodulatory, pro-angiogenic, and spatiotemporal delivery functions³⁰.

Accordingly, this review summarizes recent advances in 3D printing technology for the treatment of periodontitis and periodontal tissue regeneration. We first discuss the specific design requirements imposed by the periodontal inflammatory microenvironment, including infection control, inflammation modulation, space maintenance, and cementum-PDL-alveolar bone interface reconstruction. We then summarize the major 3D printing techniques, as well as the material systems for periodontal regeneration such as synthetic polymers, bioceramics, natural hydrogel bioinks, decellularized matrices, and composite scaffolds. Particular attention is given to biomimetic design strategies, such as patient-specific scaffolds, multiphasic architectures, anisotropic fiber guidance, pore network design, and vascularization-oriented structures. We also highlight functionalized 3D-printed systems endowed with antibacterial, anti-inflammatory, and immunomodulatory properties, as well as spatiotemporal drug delivery and stimuli-responsive capabilities. Finally, we discuss current challenges in material design, functional periodontal regeneration assessment, clinical translation, and standardized manufacturing, and provide perspectives on the future application of 3D printing in precision periodontal regenerative therapy.

2. Pathological Barriers to Periodontal Regeneration

Understanding the pathophysiology of periodontitis is fundamental to the rational design of 3D-printed scaffolds for periodontal regeneration. As summarized in **Figure 1**, periodontal regeneration is restricted by five interconnected pathological barriers: persistent plaque biofilms, dysregulated inflammation, oxidative stress, disrupted bone homeostasis, and defective wound healing. These processes collectively impair cell recruitment, angiogenesis, matrix deposition, osteogenesis, cementogenesis, and PDL organization. Accordingly, 3D-printed scaffolds should move beyond passive structural support and osteoconduction toward integrated regulation of infection, inflammation, redox balance, bone remodeling, and multi-tissue interface reconstruction.

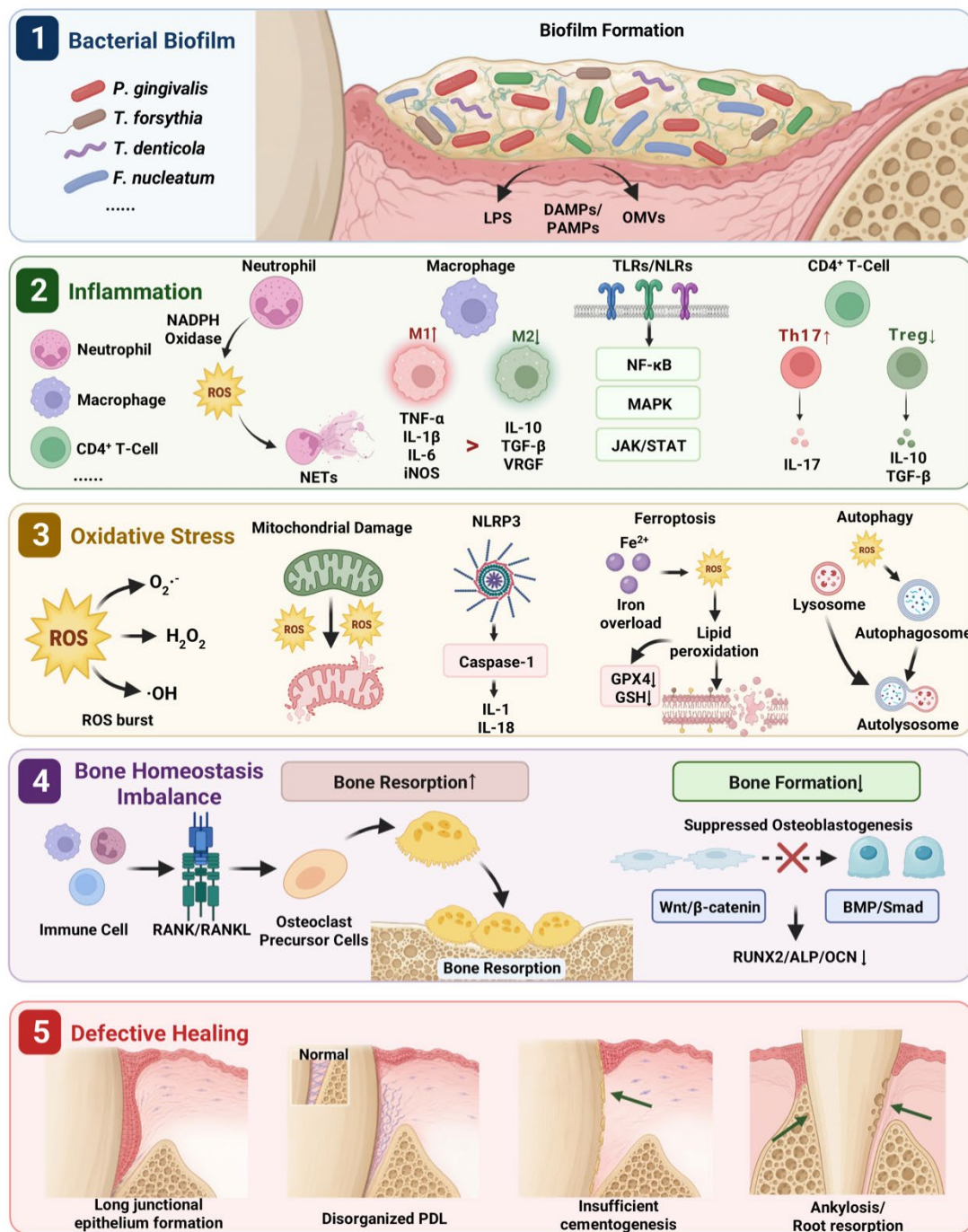


Figure 1. Schematic illustration of pathological barriers to periodontal regeneration, including bacterial biofilm formation, dysregulated inflammation, oxidative stress, bone homeostasis imbalance, and defective wound healing. (Created with BioRender.com).

2.1 Dental Plaque Biofilm

Dental plaque biofilm is a key initiating factor in periodontitis³¹. Unlike planktonic bacteria, periodontal biofilms are highly organized microbial ecosystems where diverse microorganisms are embedded within extracellular matrix (ECM) composed mainly of extracellular polysaccharides, proteins, lipids, extracellular DNA, and host-derived components³². This matrix forms a stable 3D network that promotes bacterial adhesion to tooth surfaces, root surfaces, and periodontal pockets, while creating a protected local microenvironment³³. Spatial gradients of oxygen, pH, nutrients, and metabolic by-products further allow coexistence of bacteria with distinct metabolic profiles, thereby enhancing community stability and environmental adaptability³⁴.

Biofilm-associated microenvironmental changes reshape the subgingival microbial community toward dysbiosis³⁵. Anaerobic and proteolytic pathogens, such as *Porphyromonas gingivalis* (*P. gingivalis*) and *Tannerella forsythia* (*T. forsythia*), progressively expand³⁶. Their virulence factors compromise epithelial barrier integrity and disturb host immune recognition. This process establishes a self-sustaining inflammatory microenvironment³⁷. The pathogenicity of mature biofilms is further reinforced by interspecies cooperation. Early colonizers provide adhesion sites and metabolic support for later anaerobic pathogens, while nutrient cross-feeding, metabolite exchange, quorum sensing, and cooperative virulence enhance community survival³⁸. In addition, the ECM limits the penetration of antimicrobial agents, antibodies, and immune effector molecules, and biofilm-embedded bacteria often adopt low-metabolic or stress-tolerant states, contributing to antimicrobial resistance and persistent colonization³⁹. Therefore, 3D-printed scaffolds for periodontitis treatment should actively interfere with biofilm formation, maturation, and persistence⁴⁰. Incorporating antibiofilm polymers or controlled-release antimicrobial agents into scaffolds can provide local antibacterial effects while helping preserve periodontal microbial homeostasis⁴¹.

2.2 Dysregulated Immunity and Inflammation

In addition to direct bacterial invasion, periodontal tissue destruction mainly results from dysregulated host immune responses under persistent infection. Under physiological conditions, host immune responses restrict microbial dissemination and maintain periodontal homeostasis⁴². Persistent plaque biofilm stimulation, however, shifts this protective defense toward unresolved inflammation and tissue

destruction⁴³. Bacterial pathogen-associated molecular patterns are recognized by host cells through Toll-like receptors, NOD-like receptors, and the complement system⁴⁴. This activation sustains the recruitment of neutrophils, monocytes/macrophages, T cells, and B cells into periodontal lesions⁴⁵.

Neutrophils provide early antimicrobial defense through phagocytosis, degranulation, reactive oxygen species (ROS) production, and neutrophil extracellular trap formation⁴⁶. Under chronic stimulation, excessive neutrophil activation causes collateral tissue damage and maintains a pro-inflammatory microenvironment⁴⁷. Macrophages are also reshaped by persistent inflammatory cues⁴⁸. Rather than existing as discrete M1 or M2 populations, macrophages in periodontal lesions exhibit heterogeneous and overlapping functional states⁴⁹. This unresolved innate response further promotes adaptive immune dysregulation. A Th17/Treg imbalance is particularly important in chronic periodontal inflammation⁵⁰. Th17-derived IL-17 stimulates epithelial cells and fibroblasts to amplify inflammation, while Treg-mediated resolution remains inadequate⁵¹. Infiltrating B cells and plasma cells also accumulate and perpetuate chronic inflammation through antibody production, antigen presentation, and cytokine secretion⁵². These innate and adaptive immune populations do not act independently but form an interconnected inflammatory network in which neutrophil recruitment, macrophage activation, Th17/Treg imbalance, and B-cell responses mutually reinforce persistent periodontal inflammation. Continuous release of TNF- α , IL-1 β , IL-6, IL-17, PGE2, and chemokines further amplifies inflammatory cell activation⁵³. Meanwhile, matrix metalloproteinases promote collagen fiber and ECM degradation, disrupting periodontal tissue integrity⁵⁴. Such reciprocal interactions between immune dysregulation and matrix destruction can prevent the inflammatory microenvironment from returning to a pro-resolving and regenerative state. For implanted scaffolds, the pre-existing inflammatory imbalance may be further influenced by the host foreign body response at the material–tissue interface. An appropriately regulated response may support material integration and tissue repair, whereas persistent scaffold-associated inflammation may compromise regeneration. Therefore, ideal 3D-printed periodontal materials should move beyond passive defect filling or barrier function⁵⁵.

2.3 Oxidative Stress

As a prominent pathological feature of the periodontitis microenvironment, oxidative stress serves as

a pivotal mediator connecting infectious stimulation, inflammatory amplification, and cellular dysfunction⁵⁶. Under inflammatory stimulation, neutrophils, macrophages, and other inflammatory cells generate ROS as part of antimicrobial defense⁵⁷. However, oxidative stress occurs when ROS production exceeds the scavenging capacity of local antioxidant systems, causing progressive oxidative damage⁵⁸.

Generally, excessive ROS can induce lipid peroxidation, protein oxidation, DNA damage, and mitochondrial membrane potential collapse, directly damaging periodontal cells and ECM components⁵⁹. ROS further amplify tissue injury by activating inflammatory signaling pathways such as NF- κ B and MAPK⁶⁰. In addition, oxidative stress inhibits the proliferation, migration, and differentiation of periodontal cells involved in osteogenesis and vascularization, thereby interfering with periodontal regeneration⁶¹. Recent studies suggest that inflammation-induced ROS and iron-dependent lipid peroxidation can also induce ferroptosis, a key driver of oxidative injury and persistent inflammation in periodontitis⁶². Ferroptosis releases damage-associated molecular patterns that further amplify local inflammatory responses⁶³. Therefore, 3D-printed scaffolds rationally designed with ROS-scavenging nanomaterials or antioxidants can protect stem cells from oxidative injury and reconstruct the regenerative microenvironment for periodontal regeneration⁶⁴.

2.4 Bone Homeostasis Disruption

Bone homeostasis disruption is another pathological feature of periodontitis, characterized by a persistent imbalance between bone resorption and bone formation². Under physiological conditions, osteoblasts, osteoclasts, osteocytes, PDL cells, and immune cells maintain alveolar bone homeostasis through coordinated intercellular communication⁶⁵. However, persistent microbial stimulation, inflammatory mediator release, and immune cell infiltration shift local bone metabolism toward excessive osteoclast activity and insufficient osteogenesis. This imbalance leads to reduced alveolar ridge height, trabecular bone destruction, and impaired tooth-supporting function⁶⁵.

The RANKL/RANK/OPG axis is central to inflammation-induced alveolar bone destruction⁶⁶. Under inflammatory conditions, increased RANKL expression and relatively insufficient OPG promote osteoclastogenesis and enhance bone-resorptive activity⁶⁷. Multiple inflammatory mediators further

reinforce this osteoclast-dominant state. It is reported that TNF- α , IL-1 β , IL-6, IL-17, and PGE2 upregulate RANKL expression and increase the responsiveness of osteoclast precursors to RANKL stimulation⁶⁸. Sustained inflammation also prolongs osteoclast survival and enhances their resorptive function, leading to degradation of mineralized matrix and collagenous organic matrix⁶⁹. Meanwhile, inflammatory cytokines, oxidative stress, and bacterial virulence factors inhibit osteoblast differentiation and maturation, reducing osteogenic marker expression and interfering with matrix deposition and mineralization^{70,71}. Osteogenesis-related pathways, including Wnt/ β -catenin, BMP/Smad, Notch, and Hippo, are also disrupted, further compromising local bone formation⁷². Accordingly, 3D-printed scaffolds for periodontal regeneration should integrate osteoconductive architectures, pro-osteogenic and osteoimmune properties, and sufficient mechanical stability to preserve regenerative space and support functional periodontal reconstruction.

2.5 Defective Wound Healing

Tissue healing after periodontal therapy does not necessarily result in true periodontal regeneration, but often follows a repair-dominant pattern⁷³. Because the periodontium consists of cementum, PDL, and alveolar bone, functional regeneration requires more than bone filling within alveolar defects⁷⁴. It requires newly formed cementum, organized PDL fibers, and their functional insertion into both cementum and alveolar bone⁷⁵. However, different cell populations exhibit distinct migration rates and biological behaviors during wound healing⁷⁶. Without spatial guidance and tissue-selective regulation, healing may readily shift toward non-functional repair rather than periodontal regeneration.

Long junctional epithelium formation is a common non-regenerative healing outcome after periodontal treatment⁷⁷. Rapidly migrating epithelial cells can proliferate apically along the root surface and occupy the regenerative space⁷⁸. This process prevents PDL cells, cementum-forming cells, and osteogenic cells from participating in new attachment formation. If disorganized fibrous tissue predominates within the defect, soft-tissue filling may occur but fails to restore the mechanical buffering and force-transmitting functions of the native PDL⁷⁹. In addition, insufficient cementum regeneration limits stable PDL fiber insertion, whereas ectopic mineralization may disrupt the non-mineralized PDL space⁸⁰. Therefore, defective periodontal wound healing should be understood as a

spatiotemporal imbalance in multi-tissue reconstruction⁸¹. Accordingly, 3D-printed scaffolds should incorporate multiphasic architectures to block rapid epithelial downgrowth, preserve the PDL space, and guide the coordinated regeneration of cementum, PDL, and alveolar bone.

3. Printing Technologies and Material Platforms

By precisely controlling scaffold microstructure and mechanical properties, 3D printing is well aligned with the regenerative requirements of complex and spatially confined periodontal defects. Currently, diverse 3D printing techniques such as extrusion, photocuring, and bioprinting, as well as material systems including polymers, bioceramics, and composite systems, are utilized for periodontal regeneration. This section summarizes these technical and material foundations and briefly discusses emerging strategies such as in situ/embedded printing, nanocomposite bioinks, stimuli-responsive materials, and 4D printing.

3.1 Printing Modalities

Extrusion-based printing is one of the most widely used 3D printing techniques in periodontal tissue engineering⁸². It fabricates 3D constructs by continuously extruding materials through a nozzle under pneumatic, piston-driven, or screw-driven force⁸³. Depending on the material system, extrusion-based printing can include fused deposition modeling (FDM) for thermoplastic polymers and direct ink writing (DIW) for pastes, hydrogels, and composite inks⁸⁴. For periodontal regeneration, extrusion-based printing enables the construction of scaffolds with regular pore architectures and interconnected networks, thereby supporting cell migration, nutrient exchange, and tissue ingrowth⁸⁵. However, its resolution is largely constrained by nozzle diameter, material viscosity, printing pressure, and layer height⁸⁶. Therefore, extrusion parameters should be optimized to balance material flow, filament stability, shape fidelity, and printing accuracy⁸⁷.

Photocuring-based printing, including stereolithography (SLA) and digital light processing (DLP), relies on light-induced crosslinking of photosensitive materials to generate high-resolution 3D structures⁸⁸. Compared with extrusion-based printing, SLA and DLP generally offer higher fabrication accuracy and better structural consistency, making them suitable for constructing complex

microarchitectures, fine pore networks, and spatially defined hydrogel scaffolds⁸⁹. Gelatin methacryloyl (GelMA), methacrylated hyaluronic acid (HAMA), PEG-based hydrogels, and photosensitive resins are commonly used as photocurable material platforms⁹⁰. Printing performance is determined by optical resolution, layer thickness, exposure dose, photoinitiator concentration, light penetration, and polymerization kinetics. Residual monomers, limited curing depth, radical generation, and post-curing requirements may affect material safety and structural performance and should therefore be carefully controlled^{91,92}.

MEW combines melt extrusion with electrohydrodynamic drawing to produce continuous microscale fibers with precise spatial organization⁹³. Compared with conventional FDM, MEW offers superior control over fiber diameter, orientation, spacing, and layer-by-layer architecture⁹⁴. Since the PDL is characterized by aligned collagen fiber bundles, fiber orientation and insertion between cementum and alveolar bone are essential for functional periodontal regeneration⁷⁹. Thus, MEW has unique advantages in mimicking PDL-like fibrous structures, guiding cell alignment, and reconstructing the PDL-bone interface²⁷. However, this technique mainly relies on thermoplastic polymers such as polycaprolactone (PCL), and the high processing temperature limits direct incorporation of living cells⁹⁵. Therefore, MEW scaffolds are often used as acellular microfibrinous frameworks or combined with hydrogels, bioinks, and surface modification strategies⁹⁶.

3D bioprinting (3DBP) refers to printing strategies in which living cells are incorporated into printable bioinks and spatially deposited together with biomaterials and bioactive factors⁹⁷. Extrusion-based and light-assisted approaches can both be adapted for cell-laden printing, but they introduce additional biological constraints that are not encountered in conventional acellular scaffold fabrication. In periodontal regeneration, 3D bioprinting enables region-specific deposition of PDL stem cells, bone marrow mesenchymal stem cells, dental follicle cells, gingival fibroblasts, endothelial cells, and other regenerative cell populations⁹⁸. In extrusion-based bioprinting, nozzle geometry, bioink rheology, and printing pressure determine the shear stress experienced by cells, whereas light-assisted bioprinting may affect cell viability through photoinitiator concentration, irradiation conditions, and radical-mediated damage^{91,92}. Bioink viscosity and crosslinking density must therefore be balanced to maintain both structural fidelity and cellular function⁹⁹. Periodontal bioprinting ultimately requires coordinated

optimization of printing parameters, crosslinking conditions, post-printing cell viability, spatial accuracy, and tissue-instructive performance.

In situ or handheld printing and embedded printing extend conventional scaffold fabrication by enabling direct deposition within anatomical defects or temporary stabilization of soft inks during printing. In situ printing allows materials to be deposited and cured directly within irregular periodontal defects, potentially improving immediate anatomical adaptation compared with prefabricated scaffolds^{100,101}. Embedded printing, including freeform reversible embedding of suspended hydrogels (FRESH), uses a support bath to stabilize soft or low-viscosity inks and enables the fabrication of delicate hydrogel structures, aligned fibers, and microchannels that would otherwise collapse under their own weight¹⁰². Nevertheless, intraoperative precision, support-bath removal, crosslinking safety, structural reproducibility, and clinical feasibility require further validation. The representative engineering parameters, post-processing requirements, sterilization considerations, and periodontal applicability of the major 3D-printing and bioprinting strategies are comparatively summarized in Table 1.

Table 1. Engineering comparison of major 3D-printing and bioprinting strategies for periodontal scaffold fabrication.

Printing strategy	Representative systems	Resolution / nozzle	Processing window	Pore size	Cell viability	Mechanical range	Post-processing / sterilization	Periodontal applications and limitations	Ref.
FDM/FFF	PCL, PLA, thermoplastic composites	Feature: 100-400 μm ; nozzle: 200-500 μm ; layer: 50-300 μm	PCL: 70-140 $^{\circ}\text{C}$; PLA: 170-220 $^{\circ}\text{C}$; 5-50 mm/s	150-800 μm	N/A; post-print seeding	10 MPa-3 GPa	Cooling/support removal; EtO or validated irradiation	Strong space maintenance and patient-specific shaping; unsuitable for direct cell or protein loading	82-87
DIW/robocasting	Polymer pastes, ceramic slurries, hydrogels, composites	Feature/nozzle: 100-500 μm	20-37 $^{\circ}\text{C}$ for pastes/hydrogels; 10^3 - 10^6 mPa·s; 1-30 mm/s	100-800 μm	N/A for acellular inks	kPa-scale hydrogels to >100 MPa after sintering	Crosslinking, drying, debinding, or sintering; material-specific sterilization	Broad material compatibility; nozzle clogging, collapse, shrinkage, and sintering deformation	82-87
SLA/DLP	Photocurable hydrogels and resins	In-plane: 25-100 μm ; layer: 25-100 μm ; no nozzle	20-30 $^{\circ}\text{C}$; 10-1000 mPa·s; 1-20 s/layer	50-500 μm	N/A for acellular printing	0.1 MPa-3 GPa	Washing/post-curing; aseptic processing or validated low-temperature sterilization	High-resolution barriers, interfaces, and microchannels; residual monomers and limited curing depth	88-92
MEW	Mainly PCL microfibers	Fiber: 2-40 μm ; nozzle: 200-500 μm	70-120 $^{\circ}\text{C}$; 10-150 mm/s	40-1000 μm	N/A; no direct cell loading	0.1-80 MPa; anisotropic	Direct solidification; EtO or compatible irradiation	Precise PDL fiber guidance and bone-PDL interfaces; limited materials and low throughput	93-96

Extrusion bioprinting	Cell-laden GelMA, alginate, collagen, dECM, nanocomposite bioinks	Feature: 100-500 μm ; nozzle: 150-410 μm	20-37 $^{\circ}\text{C}$; 10^2 - 10^6 $\text{mPa}\cdot\text{s}$; 5-30 mm/s	100-500 μm	70%-95%	0.5-200 kPa	Ionic, photo-, thermal, or enzymatic crosslinking; sterile components and aseptic preparation	Regional cell/factor deposition; trade-off among fidelity, viability, and mechanics High-resolution multicellular and multiphasic printing; radical toxicity and limited light penetration Improved adaptation to irregular defects;	97-99
Light-assisted bioprinting	Cell-laden GelMA, HAMA, and PEG-based bioinks	In-plane: 25-100 μm ; layer: 25-100 μm ; no nozzle	20-37 $^{\circ}\text{C}$; 1-300 $\text{mPa}\cdot\text{s}$; 1-15 s/layer	25-300 μm	80%-95%	1 kPa-2 MPa	Secondary curing when required; sterile filtration and aseptic handling	limited surgical precision and intraoperative reproducibility Supports PDL-like fibers and soft interfaces; support removal, dimensional change, and scalability remain concerns	88-92
In situ/handheld bioprinting	Direct defect deposition and handheld systems	Feature: 100-500 μm ; nozzle: 150-500 μm	20-37 $^{\circ}\text{C}$; 10^2 - 10^5 $\text{mPa}\cdot\text{s}$; 1-20 mm/s or operator-controlled	100-500 μm ; less reproducible	80%-95%	1-100 kPa	Rapid in situ crosslinking; sterile components and aseptic delivery		100
Embedded/FRESH bioprinting	Collagen, GelMA, dECM, and cell-rich bioinks in support baths	Feature: 20-200 μm ; nozzle: 100-250 μm	4-37 $^{\circ}\text{C}$; 10 - 10^4 $\text{mPa}\cdot\text{s}$; 5-30 mm/s	50-500 μm	85%-95%	0.5-150 kPa	Support-bath removal; sterile ink/support preparation		101,102

3.2 Structural Materials

Structural materials form the load-bearing basis of 3D-printed periodontal scaffolds, providing the mechanical strength, shape stability, and space maintenance required for complex defects. These materials are commonly used as acellular frameworks or composite load-bearing phases. In periodontal regeneration, commonly used structural materials mainly include synthetic polymers, bioceramics, and polymer/ceramic composites.

3.2.1 Synthetic Polymers

Synthetic polymers are among the most widely used structural materials for 3D-printed periodontal scaffolds. PCL, polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA) exhibit favorable processability, biodegradability, and mechanical stability, making them suitable for fabricating space-maintaining 3D frameworks¹⁰³. Among them, PCL is frequently used in FDM and MEW because of its relatively low melting temperature, stable printability, and slow degradation rate, while PLA and PLGA offer tunable degradation profiles and potential for drug incorporation¹⁰⁴. These polymers provide structural integrity and mechanical support, helping preserve defect space while allowing gradual tissue ingrowth¹⁰⁵.

However, synthetic polymers generally lack sufficient cell-recognition motifs and tissue-instructive bioactivity. Their relatively hydrophobic surfaces also limit controlled protein adsorption, cell adhesion, and tissue integration¹⁰⁶. In addition, prolonged degradation, acidic degradation products, and progressive mechanical weakening may compromise long-term regenerative outcomes¹⁰⁷. Therefore, polymer-only scaffolds are often insufficient for periodontal multi-tissue regeneration. They are commonly combined with surface modification, natural polymer coatings, bioceramic fillers, or bioactive factor loadings to improve biological performance and tissue compatibility¹⁰⁸.

Beyond conventional rigid or semi-rigid polymers, biodegradable elastomers have attracted increasing interest for periodontal interface design. Because the PDL is a viscoelastic tissue that buffers and transmits occlusal forces, scaffold materials for ligament-like regions should ideally provide elastic

recovery and mechanical adaptability⁷⁹. Materials such as poly(glycerol sebacate) (PGS), degradable polyurethane-based elastomers, and related composites can help construct mechanically compliant interfacial layers that better simulate the native PDL¹⁰⁹. Compared with rigid scaffolds, these materials improve mechanical transitions at soft-hard tissue interfaces and modulate cell behavior via mechanotransduction¹¹⁰. Thus, biodegradable elastomers represent promising candidates for future PDL-mimetic layers and interfacial buffering structures.

3.2.2 Bioceramics

Bioceramics provide mineral-mimetic and ion-releasing cues for the alveolar bone compartment of 3D-printed periodontal scaffolds. Representative systems, including hydroxyapatite, β -tricalcium phosphate, biphasic calcium phosphate, bioactive glass, and ion-doped inorganic materials, can partially reproduce the inorganic composition of bone and support osteoconduction¹¹¹. These materials release calcium, phosphate, silicon, strontium, magnesium, zinc, or other therapeutic ions based on their composition and dissolution behavior, thereby promoting protein adsorption, cell adhesion, mineral deposition, and bone bonding¹¹². Ion-doped bioceramics can also modulate osteogenic differentiation, angiogenesis, and local inflammatory responses, making them useful for enhancing alveolar bone regeneration within periodontal defects¹¹³.

However, pure ceramic scaffolds are often brittle and lack toughness, which limits their adaptability to irregular periodontal defects and dynamic oral loading¹¹⁴. Besides, their printability depends on particle dispersion, ink viscosity, binder systems, and post-printing sintering or curing, increasing fabrication complexity¹¹⁵. Importantly, periodontal regeneration requires not only bone formation but also preservation of the non-mineralized PDL space. Excessive mineralization near the root surface can impair functional ligament reconstruction. Therefore, bioceramics are more suitable as functional inorganic components in polymer- or hydrogel-based composites rather than as standalone scaffolding materials for the entire periodontal complex¹¹⁶.

3.2.3 Polymer/Ceramic Composite

Polymer/ceramic composite scaffolds can integrate the complementary advantages of both materials.

The polymer phase provides printability, structural integrity, and a degradable framework, whereas the ceramic phase enhances surface bioactivity, mineralization capacity, and osteoconductivity¹¹⁷. For example, the mechanical properties, degradation behavior, and osteogenic potential of PCL/HA, PCL/ β -TCP, PLGA/calcium phosphate, and polymer/bioactive glass systems can be regulated by adjusting ceramic content, particle size, and spatial distribution¹¹⁸. Therefore, polymer/ceramic composite scaffolds can simultaneously provide space maintenance and bone-regenerative properties, making them important candidates for 3D-printed structural scaffold in periodontal bone defects¹⁰⁷.

However, composite design is not a simple additive combination of materials. Insufficient ceramic loading provides limited bioactivity, whereas excessive ceramic content can increase brittleness, reduce printability, obstruct nozzles, and compromise structural stability. Moreover, ceramic particle dispersion, interfacial bonding with the polymer matrix, and particle exposure at the scaffold surface can influence protein adsorption, cell adhesion, and mineralization. Therefore, the key to designing polymer/ceramic composite scaffolds lies in coordinating and optimizing material ratio, particle size, printing parameters, and post-processing strategies to balance mechanical support, printability, degradation behavior, and biological activity.

Piezoelectric and mechanoresponsive materials further expand the functional design of periodontal composite scaffolds¹¹⁹. The oral environment is continuously exposed to mastication-induced forces, PDL tension, and microscale deformation. If incorporated materials can convert mechanical stimulation into local electrical signals, they may provide adaptive antibacterial, immunomodulatory, and osteogenic functions in response to occlusal loading¹²⁰. Barium titanate, poly (vinylidene fluoride) (PVDF), and their composites have shown potential in bone tissue engineering for promoting osteogenesis and mechanotransduction-related responses¹²¹. In periodontal regeneration, these materials can serve as functional components or coatings within composite scaffolds, constructing dynamic systems with mechanical support, interfacial buffering, and force-responsive signals¹²². Nevertheless, their long-term safety, degradation behavior, local electrical output, and true regenerative benefits in periodontitis-associated defects remain to be systematically validated.

3.3 Bioink Platforms

Bioinks are essential for 3D bioprinting because they provide printable and cell-supportive matrices for the spatial deposition of cells, bioactive factors, and ECM-like components¹²³. Unlike structural scaffold materials, bioinks must balance printability, cytocompatibility, crosslinking efficiency, matrix remodeling, and tissue-instructive capacity. For periodontal regeneration, ideal bioinks should preserve cell viability during printing while supporting PDL-, cementum-, alveolar bone-, and vascular-associated cells.

3.3.1 Natural Hydrogel Bioinks

Natural polymer hydrogels are widely used in periodontal bioprinting owing to their high-water content, cytocompatibility, and ECM-mimetic properties¹²⁴. Collagen, gelatin, GelMA, alginate, hyaluronic acid, chitosan, and silk fibroin are commonly used components¹²⁵. Specifically, collagen provides intrinsic cell-recognition motifs and resembles the matrix environment of PDL and bone¹²⁶. GelMA combines gelatin-derived bioactivity with photocrosslinkability. Alginate enables rapid ionic gelation but has limited cell adhesiveness¹²⁷. Hyaluronic acid supports tissue hydration and cell migration, chitosan provides cationic and antibacterial properties, and silk fibroin offers favorable mechanical performance and processability^{128,129}.

However, natural hydrogels often face a trade-off between biological performance and printing fidelity. Low viscosity favors cell dispersion and survival but compromises shape retention, whereas increased viscosity improves filament stability but enhances extrusion resistance and shear-induced cell damage¹³⁰. Besides, the crosslinking method also requires careful optimization: ionic crosslinking is rapid and mild but relatively unstable, while photocrosslinking improves spatial precision but may introduce photoinitiator- or radical-associated cytotoxicity¹³¹. Thus, the design of natural hydrogel bioinks should balance rheology, gelation kinetics, degradation behavior, and cell-matrix interactions.

3.3.2 Decellularized Matrix Bioinks

Decellularized extracellular matrix (dECM) bioinks provide a tissue-mimetic alternative to single-component hydrogels¹³². By removing cellular components while retaining native matrix constituents, dECM preserves collagens, glycosaminoglycans, adhesive proteins, and matrix-bound biochemical

cues¹³³. Compared with purified hydrogels, dECM bioinks offer a more complex microenvironment for regulating cell adhesion, migration, lineage commitment, and matrix deposition¹³⁴. Especially, dECM derived from PDL, dental follicle, dental pulp, or bone can further provide tissue-associated signals, making it attractive for cementum-PDL-alveolar bone interface regeneration⁹⁰.

Nevertheless, dECM bioinks are limited by tissue availability, batch variability, compositional complexity, and weak mechanical properties. Their bioactivity and printability are strongly affected by tissue origin, decellularization protocol, enzymatic digestion, sterilization, and storage conditions¹³⁵. Therefore, dECM is often blended with GelMA, alginate, fibrin, or other crosslinkable hydrogels to improve rheology, gelation, and printing fidelity. Future development should focus on retaining tissue-specific bioactivity while improving standardization, reproducibility, and mechanical robustness of dECM.

3.3.3 Cell-Laden Bioinks

Cell loading distinguishes 3D bioprinting from conventional scaffold fabrication. In periodontal tissue engineering, commonly used cells include PDLSCs, BMSCs, dental follicle cells, gingival fibroblasts, dental pulp stem cells, endothelial cells, and pericytes¹³⁶. Specifically, PDLSCs are associated with PDL-like tissue formation and osteogenic/cementogenic differentiation, BMSCs contribute osteogenic potential, dental follicle cells are related to periodontal development, and endothelial cells and pericytes support vascularization¹²⁶. Through 3D bioprinting, these cells can be spatially distributed within defined regions to support coordinated multi-tissue regeneration¹³⁷.

However, cell-laden bioinks place stringent demands on material design and printing conditions. Shear stress, temperature changes, crosslinking reactions, and light exposure may impair cell viability, while post-printing cell behavior depends on pore structure, nutrient diffusion, matrix degradability, and mechanical cues¹³⁸. Since a single cell type is insufficient to regenerate alveolar bone, PDL, and cementum simultaneously, hierarchical and region-specific bioprinting strategies that spatially organize tissue-specific cellular units are increasingly important¹³⁹. Considering that clinical translation remains constrained by cell sourcing, expansion stability, immune safety, manufacturing complexity, and quality control, cell-free or low-cell-loading bioinks incorporating extracellular

vesicles, chemotactic factors, matrix-derived signals, or immunomodulatory molecules may offer practical alternatives by activating endogenous repair¹⁴⁰.

3.3.4 Nanocomposite and Coaxial Bioinks

Nanocomposite bioinks provide an effective strategy to improve the printability and biological function of 3D-printed scaffolds. Incorporating nanosilicates, bioactive glass nanoparticles, calcium phosphate nanoparticles, metal-organic frameworks (MOFs), MXenes, cerium oxide nanoparticles, or polydopamine nanoparticles can enhance the shear-thinning behavior, self-supporting capacity, and shape fidelity of scaffolds, while introducing ion release, drug loading, ROS scavenging, antibacterial activity, or immunomodulatory effects¹⁴¹. Thus, nanofillers can serve not only as reinforcing agents, but also as functional reservoirs and microenvironmental regulators.

Coaxial printing further expands the spatial delivery capacity of bioinks. Through core-shell nozzles, different materials, cells, or bioactive agents can be positioned in distinct compartments, enabling independent design of structural support and functional release^{127,142}. For periodontal regeneration, such systems are useful for constructing vascular-like channels, PDL-like soft layers, and compartmentalized delivery architectures¹⁴³. To facilitate rational material selection for 3D-printed periodontal scaffolds, the printability, mechanical properties, degradation behavior, sterilization compatibility, storage stability, and major safety concerns of the principal material systems are comparatively summarized in Table 2.

Table 2. Comparison of major material systems for 3D-printed periodontal scaffolds.

Material	Representative forms	Printability	Mechanical properties	Degradation	Sterilization	Storage stability	Major safety concerns	Ref.
PLA	Filaments; rigid frameworks; polymer composites	Good FDM printability; higher processing temperature than PCL; limited direct incorporation of living cells	Higher stiffness and brittleness than PCL; architecture-dependent	Moderate hydrolytic degradation; acidic degradation products	Ethylene oxide or validated irradiation methods; heat-sensitive morphology	Good dry-state stability; moisture- and heat-sensitive during long storage	Brittleness; acidic degradation; inflammatory response to accumulated degradation products	103
PCL	Filaments; porous frameworks; MEW fibers; polymer-ceramic composites	Excellent melt processability; stable FDM/MEW printing; limited direct bioactivity	Relatively high structural stability; flexible-to-semi-rigid; architecture-dependent	Slow hydrolytic degradation; long-term space maintenance	Ethylene oxide, γ -irradiation, or other validated low-temperature methods	High dry-state stability; limited moisture sensitivity	Hydrophobicity; weak cell recognition; prolonged persistence; possible degradation-healing mismatch	105-108
PLGA	Microsphere-loaded inks; porous scaffolds; drug-delivery composites	Limited direct melt printing; more commonly solution-processed or incorporated into composites	Moderate strength; progressive mechanical loss during degradation	Tunable degradation through lactide:glycolide ratio; relatively rapid mass loss	Ethylene oxide or aseptic processing; irradiation may accelerate degradation	Requires dry, low-temperature storage; hydrolysis-sensitive	Acidic degradation; burst release; rapid mechanical weakening; residual-solvent concerns	104, 107

Hydrogels	GelMA; alginate; collagen; hyaluronic acid; chitosan; silk fibroin	Good extrusion or photocuring compatibility; rheology-fidelity trade-off	Low stiffness; highly formulation- and crosslinking-dependent	Enzymatic or hydrolytic degradation; generally faster than structural polymers	Aseptic preparation, filtration, UV, or chemistry-specific sterilization; terminal sterilization often unsuitable for cell-laden systems	Limited hydrated stability; refrigeration or frozen/lyophilized storage often required	Weak mechanics; swelling; batch variability; photoinitiator, radical, or crosslinker toxicity	123-131
dECM	PDL-, dental follicle-, dental pulp-, or bone-derived bioinks	Poor intrinsic shape fidelity; commonly blended with GelMA, alginate, or fibrin	Soft and mechanically weak; source- and concentration-dependent	Enzymatic degradation; tissue- and processing-dependent	Peracetic acid, irradiation, or other validated decellularization-compatible methods	Limited aqueous stability; commonly frozen or lyophilized; batch-dependent shelf life	Residual DNA/cellular antigens; pathogen transmission; batch variability; loss of bioactivity during processing	90,132-135
Bioceramics	HAp; β -TCP; BCP; bioactive glass; ion-doped ceramics	Printable as pastes or composite fillers; often requires binders and sintering	High compressive stiffness; brittle; poor tensile toughness	HAp: slow; β -TCP and bioactive glass: faster dissolution; composition-dependent ion release	Heat, steam, irradiation, or validated low-temperature methods, depending on composition	Generally high dry-state stability; moisture control for reactive powders	Brittleness; particle release; uncontrolled ion release; excessive mineralization near the root	111-116
Nanocomposites	Nanosilicates; BG NPs; CaP NPs; MOFs; CeO ₂ ; PDA NPs in polymer/hydrogel matrices	Often improved shear thinning and shape fidelity; dispersion- and dose-dependent	Enhanced stiffness or toughness at optimized loading; aggregation-dependent	Matrix-controlled degradation plus nanoparticle dissolution or persistence	Determined by both matrix and nanofiller; sterilization may alter surface chemistry or aggregation	Dispersion stability often limited; light, oxygen, moisture, or temperature sensitivity depending on nanofiller	Aggregation; dose-dependent cytotoxicity; ion or particle accumulation; long-term biodistribution and clearance uncertainties	117, 118

3.4 Responsive and 4D-Printable Materials

Periodontitis-associated defects are dynamic pathological microenvironments characterized by pH fluctuation, ROS accumulation, protease activity, persistent inflammation, and residual biofilms. Accordingly, printed materials should move beyond passive structural support and respond to disease-related cues¹⁴⁴. By incorporating pH-, ROS-, MMP-, or enzyme-sensitive linkages, scaffolds or bioinks may achieve on-demand release of antibacterial, antioxidant, or immunomodulatory agents during active inflammation, while subsequently supporting matrix deposition and tissue maturation as the microenvironment improves¹⁴⁵.

4D printing further introduces temporal adaptability into scaffold design. Shape-memory polymers, thermoresponsive hydrogels, or moisture-responsive materials allow scaffolds to be implanted in a temporary compressed state and then recover in response to body temperature, saliva, or local hydration¹⁴⁶. This strategy improves scaffold adaptation to irregular root surfaces, bony walls, and undercut regions¹⁴⁷. However, deformation accuracy, degradation synchronization, mechanical safety, and long-term tissue responses still require systematic validation.

Overall, periodontal 3D printing materials are evolving from static substitutes toward adaptive, instructive, and microenvironment-responsive systems. Future progress depends on the coordinated integration of printing modality, material composition, mechanical behavior, degradation kinetics, biological activity, and disease-responsive function.

4. Spatial Programming of Periodontal Regeneration

Periodontal regeneration requires the ordered, spatial reconstruction of the cementum-PDL-alveolar bone complex within a constrained 3D microenvironment, rather than simple bone filling¹⁴⁸. Because periodontal tissues differ in regenerative rate and cellular origin, conventional osteoconductive scaffolds often lead to non-functional fibrous repair or ankylosis. Thus, the advantage of 3D printing is its ability to spatially program healing in a hierarchical manner, from macroscopic defect matching to microscopic cell and fiber guidance (**Figure 2**).

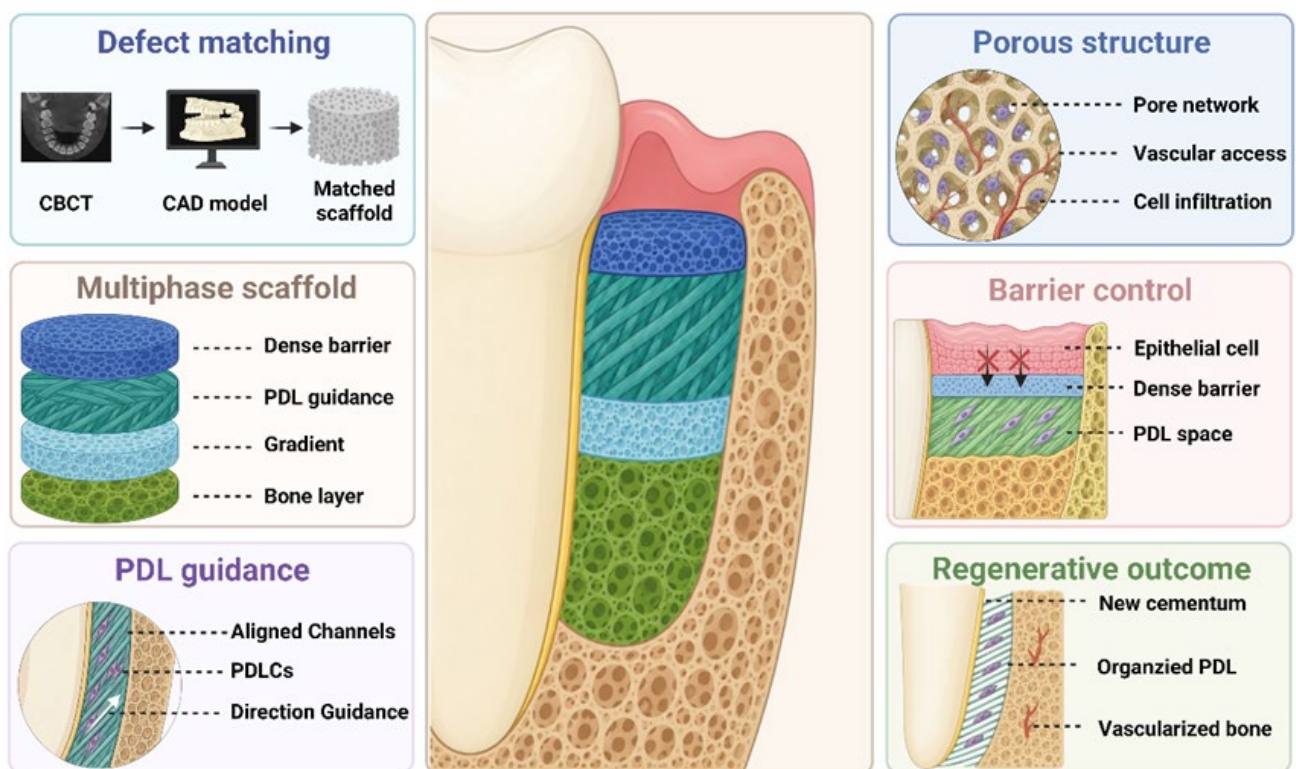


Figure 2. Schematic illustration of spatial programming strategies for 3D-printed periodontal scaffolds, including defect matching, multiphase scaffold design, PDL guidance, porous structure, barrier control, and regenerative outcome optimization. (Created with BioRender.com).

4.1 Patient-Specific Defect Adaptation

Patient-specific defect adaptation facilitates the clinical translation of 3D printing into periodontal regeneration. Periodontal defects are rarely regular osseous cavities, but are shaped by root curvature,

residual bone walls, furcation involvement, soft tissue coverage, and remaining PDL space¹⁴⁹. However, conventional particulate grafts and barrier membranes mainly rely on intraoperative packing or trimming, which can lead to poor marginal fitting, material displacement, clot instability, and premature soft tissue invasion¹⁵⁰. Therefore, precise anatomical adaptation is essential for maintaining regenerative space and improving treatment predictability in complex periodontal defects.

Digital design based on CBCT, intraoral scanning, and CAD/CAM provides a practical method for fabricating patient-specific periodontal scaffolds¹⁵¹. The typical workflow includes image acquisition, defect segmentation, 3D reconstruction, model repair, reverse design, and 3D printing. Through this process, the geometry of scaffolds can be designed according to individual root morphology and bone boundaries. Therefore, the scaffold volume, marginal contour, bone-contacting regions, root-sparing areas, and implantation pathways can be defined before surgery, improving macroscopic adaptation and intraoperative controllability¹⁵². Verykokou et al. established a CBCT-based workflow for periodontal scaffold design and showed that teeth and alveolar bone could be digitally reconstructed, although reliable segmentation of the narrow PDL space remained challenging²⁸. Anderson et al. further demonstrated that CBCT-derived calcium phosphate scaffolds could reproduce digital designs and adapt to complex alveolar defects with clinically relevant accuracy¹⁵³. These studies position anatomical matching as a necessary starting point, but not a sufficient endpoint, for functional periodontal regeneration.

The next step is to convert patient-specific shape matching into patient-specific regenerative programming. Beyond reproducing external defect geometry, 3D-printed scaffolds should incorporate internal pore networks, mechanical gradients, region-specific material distribution, vascular channels, and microenvironment-regulating functions¹⁵⁴. Pantazos et al. provided an example in this direction by developing a CBCT-derived multi-material scaffold that combined properties of defect adaptation, space maintenance, osteoconduction, and local anti-inflammatory release for periodontal bone repair¹⁵⁵. In addition, patient-specific design should also extend from hard-tissue matching to soft-tissue closure. Stable gingival coverage is essential for preventing scaffold exposure, plaque reinvasion, and loss of regenerative space¹⁵⁶. Dai et al. constructed patient-specific full-thickness gingival models from clinical gingival recession images and used artificial intelligence to optimize bioink formulation

and printing parameters¹⁵⁷. Although this strategy primarily addressed gingival reconstruction, it broadened the scope of patient-specific printing from osseous defect filling to coordinated periodontal wound closure. Therefore, future patient-specific scaffolds should integrate root morphology, alveolar bone contour, gingival architecture, and postoperative closure pathways to create more favorable conditions for subsequent cementum-PDL-alveolar bone regeneration.

4.2 Compartmentalized and Multiphase Design

Beyond patient-specific defect adaptation, periodontal scaffolds must address a more fundamental challenge: reconstructing multiple periodontal tissues within one confined defect. The native periodontium is a hierarchically organized soft-hard tissue complex composed of alveolar bone, PDL, and cementum¹⁵⁸. These tissues differ in mineralization degree, cellular origin, matrix composition, mechanical behavior, and regenerative kinetics. Therefore, an advanced periodontal scaffold should not treat the defect as a uniform bone cavity, but should spatially allocate bone-forming, ligament-forming, and cementum-associated microenvironments¹⁵⁹. The bone compartment should provide mechanical support, interconnected porosity, osteoconductive signals, and vascularization-permissive architecture. The PDL compartment should preserve a thin non-mineralized space and guide oriented collagen organization, whereas the root-facing interface should support cementum-like matrix deposition and Sharpey's fiber-like insertion¹⁴⁸.

Multiphase scaffold design provides a direct strategy to translate these region-specific requirements into spatially defined material architectures. Generally, the PDL compartment benefits from anisotropic fibrous structures that guide PDLSC elongation, alignment, and ligament-associated matrix organization¹⁶⁰. By contrast, the alveolar bone compartment requires open porous networks and mineralized components to support cell infiltration, vascularized ingrowth, and new bone formation¹⁶¹. Tissue-specific scaffold systems developed by Daghrery et al. demonstrated that the PDL and bone compartments should be engineered according to distinct structural principles rather than be treated as a single regenerative space¹⁶². These studies also highlighted the need to balance matrix-like support with structural guidance, because excessive hydrogel or collagen filling could mask exposed fibers and weaken PDL alignment¹⁶³. Thus, effective multiphase scaffolds must balance bone-region filling,

biological support, and preservation of anisotropic guidance properties.

Functional periodontal regeneration also depends on the transition between compartments. Abrupt contact between a mineralized bone-like region and a non-mineralized ligament-like region cannot reproduce the gradual structural and mechanical transition of the native periodontal interface¹⁶⁴. Golafshan et al. addressed this issue by developing graded MEW scaffolds containing a magnesium phosphate/PCL bone region, an aligned PCL PDL region, and intermediate transition zones²⁷. Compared with scaffolds lacking a transition layer, the graded design improved continuity between bone-like and ligament-like tissues. This finding highlights the bone-PDL interface as an active design target rather than a passive boundary. Gradient, interlocking, or directionally organized interfaces can buffer the differences in mineral content, elastic modulus, and matrix composition, thereby facilitating soft-hard tissue integration while reducing the risk of ankylosis or direct bone bridging toward the root surface¹⁶⁵.

Hydrogel- and dECM-based multiphasic systems further expand compartmentalized design by introducing tissue-specific biochemical information. Yang et al. developed a GelMA/dental follicle-derived dECM-based 3D-bioprinted periodontal module, in which a DLP-printed PDL module and a DIW-printed alveolar bone module were assembled to mimic the periodontal bone-ligament architecture (**Figure 3**)⁹⁰. This dECM-containing construct improved DFC viability, fibrogenic/osteogenic differentiation, immunomodulation, and periodontal regeneration in a beagle defect model. Related dECM- or cell-derived ECM-incorporated scaffolds also suggested that tissue-associated matrix signatures could provide ligament-relevant biochemical signals¹⁶⁶. These findings indicate that ECM components are not merely biological additives, but mediators that connect scaffold architecture with tissue-specific lineage instruction.

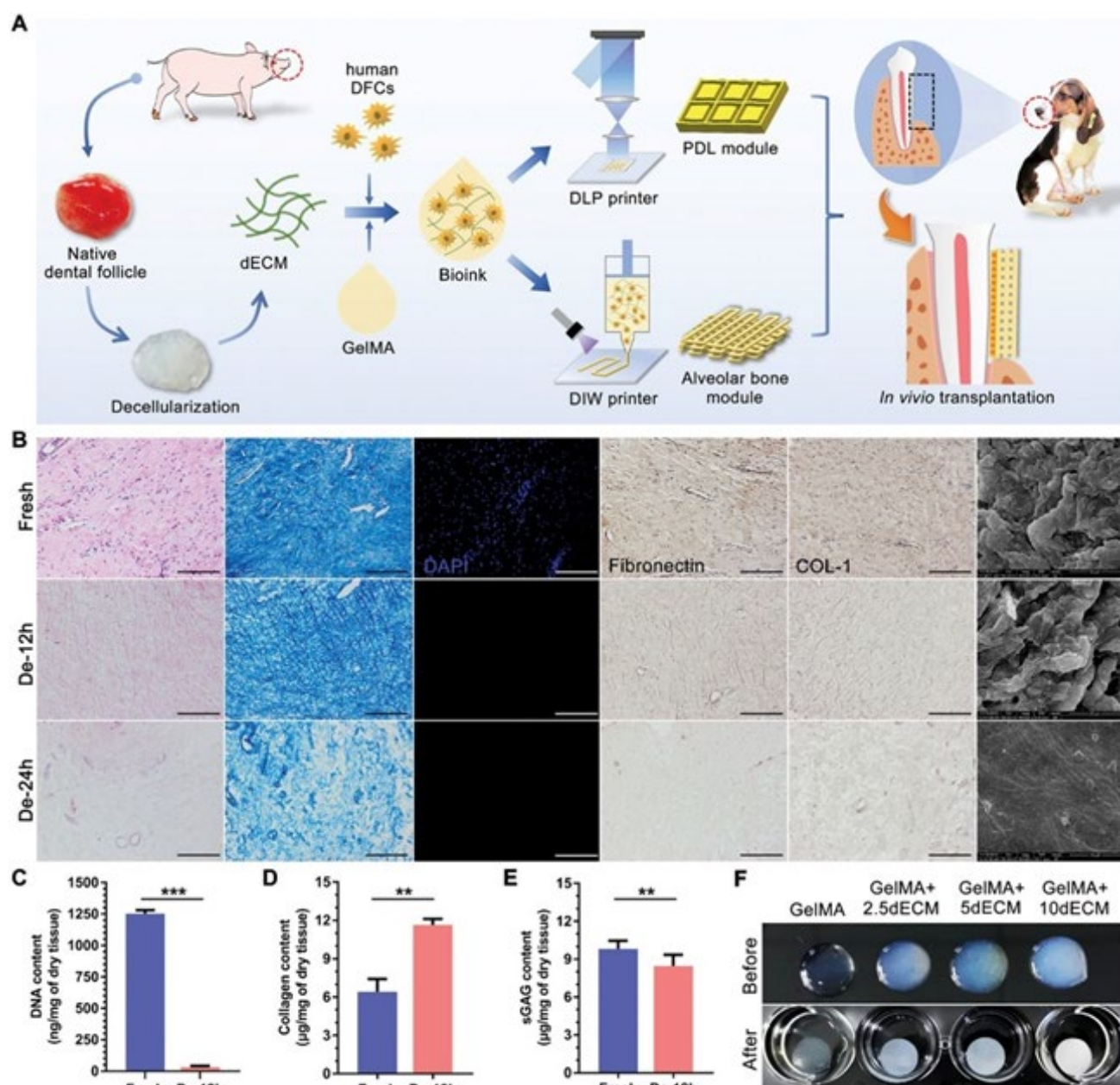


Figure 3. 3D-bioprinted periodontal functional module based on GelMA/dental follicle-derived dECM bioink. (A) Schematic overview of 3D bioprinting periodontal modules using GelMA/dECM bioink encapsulating human dental follicle cells. (B) Characterization of porcine dental follicle-derived dECM by H&E staining, Masson's trichrome staining, DAPI staining, ECM protein staining, and SEM analysis. (C-E) Quantitative analysis of DNA removal, collagen retention, and sulfated glycosaminoglycan (sGAG) content in dECM. (F) Macroscopic appearance of GelMA/dECM bioinks with different dECM concentrations before and after crosslinking. Scale bars: 100 μm. Reproduced with permission from Ref. ⁹⁰. Copyright © Wiley 2023.

Spatial compartmentalization should also extend to the regional delivery of bioactive factors and cells. Although fabricated by electrospinning and directional freeze-drying rather than 3D printing, a triphasic biomimetic scaffold delivering BMP2, CTGF, and rhCEMP1 in distinct compartments demonstrated a valuable design strategy for matching regional biological signals with the regenerative requirements of alveolar bone, PDL, and cementum¹⁶⁷. By contrast, Miao et al. constructed a GelMA/SA/BGM-based bioprinted scaffold incorporating mBMSCs, BMP2, and PDGF to support periodontal bone regeneration and soft tissue healing⁹⁸. These examples show that the value of multiphasic design lies not in layering itself, but in the spatial coordination of material composition, microarchitecture, mechanical transition, ECM information, cellular components, and biological signals¹⁶⁸. Future multiphasic periodontal scaffolds should therefore evolve from static multilayer constructs into spatially programmed regenerative platforms capable of coordinating cementogenesis, PDL fiber insertion, alveolar bone formation, and soft tissue exclusion within a unified periodontal defect microenvironment.

4.3 Fiber Guidance for PDL Regeneration

PDL regeneration is one of the most functionally demanding tasks in periodontal reconstruction. It requires more than forming a soft connective layer between the root and alveolar bone. A regenerated PDL should remain confined within a narrow non-mineralized space, contain directionally organized collagen bundles, and anchor into newly formed cementum and bone to recreate Sharpey's fiber-like attachment⁷⁵. Therefore, microarchitectural control over cell alignment, collagen deposition, and fiber insertion is essential for distinguishing functional PDL regeneration from disorganized fibrous repair.

Microchannel-based scaffolds provide an effective strategy for guiding PDL-oriented tissue formation. Staples et al. developed a fiber-guiding biphasic scaffold with 100 μm channels in the PDL compartment and gradient pores in the bone compartment (100CH scaffold). In a 3D in vitro periodontal attachment model, the 100CH scaffold induced more oblique and perpendicular cell alignment relative to the dentin surface than box-like or sponge-like controls, demonstrating the ability of microscale topography to guide root-facing ligament attachment¹⁶⁹. Subsequent studies further showed that 60-100 μm microchannels promoted cytoskeletal and collagen I alignment toward 60-90°

orientations. In orthotopic periodontal defects, 80 μm channel scaffolds did not markedly increase new bone volume, but better preserved a PDL-like space and promoted more consistent oblique or perpendicular fiber attachment¹⁷⁰. These results indicate that periodontal scaffold evaluation should not rely only on bone quantity, but also on fiber orientation, root-surface attachment, and preservation of a non-mineralized ligament space.

Beyond straight microchannels, biomimetic fiber morphology and anisotropic hydrogel architectures offer additional methods for PDL guidance. Lin et al. used FRESH printing to fabricate wavy collagen microfibers mimicking the crimped pattern of native PDL collagen bundles. Compared with straight fibers, wavy microfibers enhanced PDL cell adhesion, spreading, and periostin expression under fluid shear, indicating that PDL-guiding architectures should consider the nonlinear morphology and mechanical responsiveness of native ligament fibers¹⁷¹. Shao et al. further developed shear-oriented GelMA/PEO embedded bioprinting, in which printing-induced shear aligned hydrogel components along the printing path and enabled continuous microscale fibers, wavy interfaces, and lumen-like structures¹⁷². Such methods provide a technical basis for constructing PDL-like anisotropic hydrogel layers that can be combined with cell loading, factor delivery, and root-surface modification to guide cell alignment, collagen deposition, and functional attachment formation.

Spatial positioning of cells is also critical for PDL-oriented regeneration. Lee et al. printed hPDLSC-laden collagen bioink onto porous titanium scaffolds and found that compared to traditional cell seeding, bioprinting increased the contact ratio between PDL-like soft tissue and the scaffold interface, and promoted more organized soft tissue distribution¹⁷³. Although this model does not fully recapitulate orthotopic PDL regeneration, it demonstrates that precise cell placement at specific interfaces can influence local tissue orientation. Furthermore, de Souza Araújo et al. printed PDLSC-laden collagen scaffolds directly onto root surfaces and generated a soft connective tissue-like layer with a thickness approaching the physiological PDL range in an ectopic root slice model (**Figure 4**)¹²⁶. Therefore, root-surface bioprinting may provide a promising strategy for PDL reconstruction, root-interface repair, and tooth replantation-related tissue engineering.

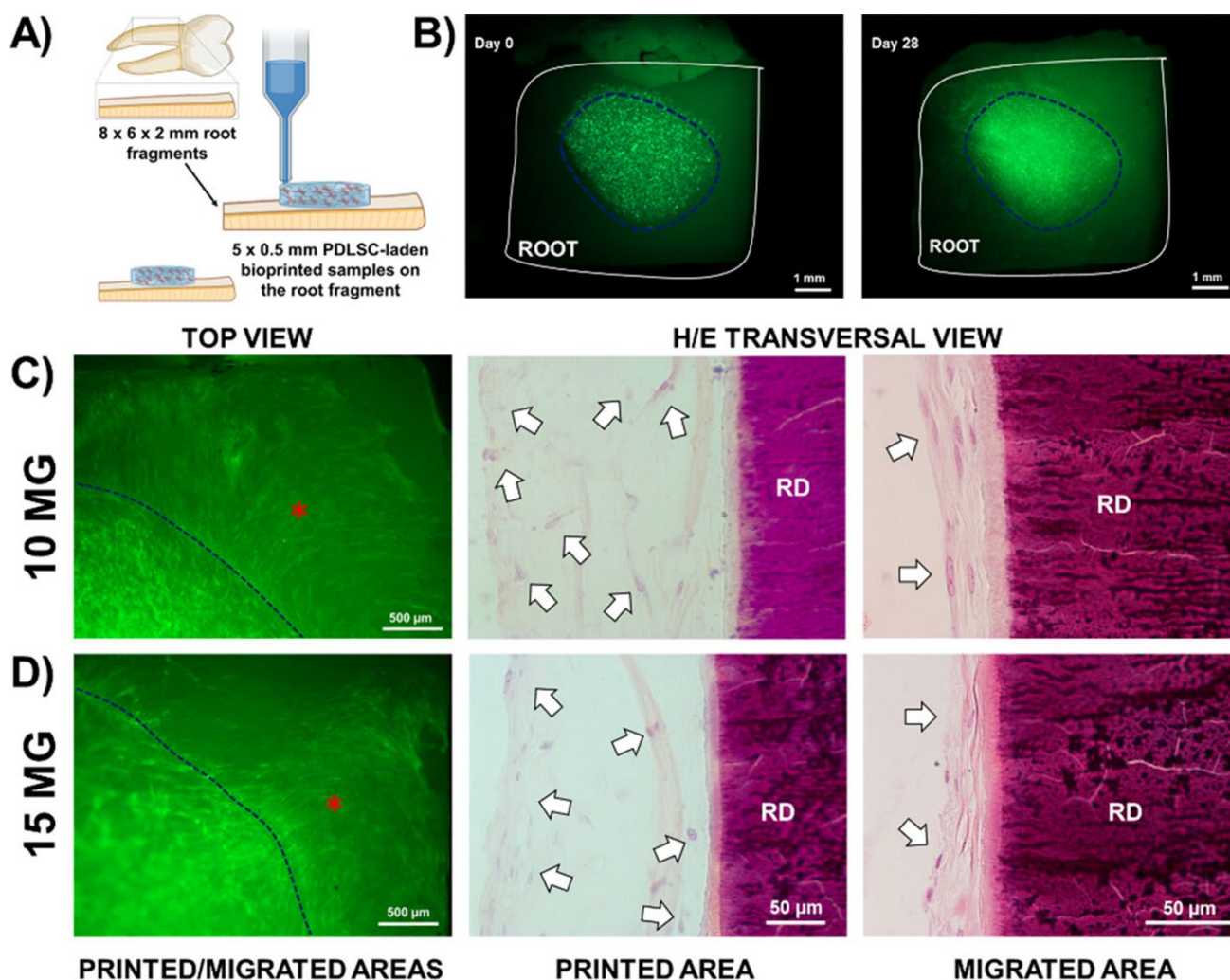


Figure 4. Root-surface bioprinting of PDLSC-laden collagen hydrogels for PDL-like tissue formation. (A) Schematic illustration of the bioprinting process onto the external surface of a root fragment. (B) Representative fluorescence images at day 0 and day 28, showing extensive PDLSC migration from the initially printed region across the root surface. (C) H&E staining after 28 days, showing a soft connective tissue-like layer attached to the radicular dentin, with PDLSCs distributed within the printed scaffold. RD, radicular dentin. Adapted with permission from Ref. ¹²⁶. Copyright © American Chemical Society 2024.

4.4 Pore Networks for Vascularized Ingrowth

Pore networks are not passive voids in 3D-printed periodontal scaffolds, but spatial interfaces that regulate clot stabilization, cell migration, nutrient diffusion, immune cell distribution, vascular invasion, and tissue ingrowth. Compared with randomly porous biomaterials, 3D-printed scaffolds

have predefined pore size, porosity, interconnectivity, channel orientation, regional pore distribution, and fiber spacing²³. This controllability is particularly important in periodontal defects, where the root surface, residual bony walls, and gingival soft tissue create a confined and asymmetric healing space. Therefore, pore design should move beyond uniform pore-size optimization toward regionally programmed and dynamically reshaped pore networks.

In the alveolar bone compartment, pore architecture coordinates vascularized ingrowth with early host responses. Interconnected pores provide routes for reparative cells and vessels, whereas pore geometry and strand spacing influence oxygen availability, inflammatory cell accumulation, and fibrous encapsulation¹⁷⁴. In a general bone regeneration model, PCL/PEG/HA composite scaffolds with pores of approximately 600 μm reduced inflammatory infiltration and fibrous tissue formation while promoting M2-like macrophage polarization, vascular ingrowth, and new bone formation¹⁷⁵. These findings indicate that pore architecture can function as an osteoimmune and vascular-regulatory cue rather than a purely structural parameter¹⁷⁶. In addition, the regenerative function of pores also depends on the biological activity of their boundaries. In ordered MEW scaffolds, $0^\circ/90^\circ$ fiber arrangements with defined strand spacing provide templates for cell bridging and inward tissue growth. When combined with fluorinated calcium phosphate nano coatings, the pore walls acquire mineralization-inductive, ion-releasing, and cell-adhesive functions¹⁷⁷. Thus, the pore walls can be transformed into active regenerative interfaces where clot stabilization, vascular invasion, cell attachment, and bone deposition are spatially coupled.

Furthermore, the dynamic pore networks allow scaffold architecture to adapt to the healing process. Rigid frameworks maintain early defect space, but their internal pores lack matrix-like adhesion sites for continuous tissue formation. Evidence from general bone repair and in vitro models further shows that incorporating RGD-functionalized alginate into HA/PLGA scaffolds can improve cell migration, collagen deposition, vascularization, and bone ingrowth¹⁷⁸. Similarly, Mg/Sr co-doped calcium silicate/PCL scaffolds with regular printed pores can synergize with pro-osteogenic and pro-angiogenic ion release, while HA-PLA scaffolds with different infill densities show different pore connectivity, nutrient diffusion, and osteogenic behavior^{113,179}. These findings provide transferable design principles for optimizing the bone-facing region of periodontal scaffolds. In aMF-CPC scaffolds, degradable

alginate microfibers generate secondary pores and interconnected channels within calcium phosphate cement matrices, thereby improving space availability for cell extension and vascular penetration¹⁸⁰. Although not evaluated in a periodontal defect, this dynamic pore-forming strategy illustrates how printed scaffolds may balance early structural stability with subsequent vascularized tissue ingrowth.

Importantly, the requirements for pore structure differ among the bone, PDL, and barrier regions. The bone compartment benefits from larger interconnected pores supporting vascularized bone ingrowth, whereas the PDL compartment requires a narrow, continuous, and non-mineralized space that guides ligament-like tissue organization instead of uncontrolled bone bridging¹⁶⁹. The soft tissue-facing region, in contrast, should provide a relatively low permeability to delay rapid epithelial and gingival connective tissue invasion¹⁸¹. Therefore, an ideal periodontal scaffold should not employ a uniform pore architecture throughout the construct. Instead, it should integrate large vascularization-permissive pores in the alveolar bone region, microchannel or aligned pore structures in the PDL region, and dense or semi-permeable barrier structures toward the gingival side¹⁸². Such region-specific pore programming can help coordinate vascularized bone regeneration, PDL space preservation, fiber-guided ligament formation, and soft tissue exclusion within the same periodontal defect.

4.5 Integrated Barriers for Healing Control

Barrier integration is essential for regulating the sequence of periodontal tissue regeneration. After periodontal surgery, epithelial and gingival connective tissue cells migrate rapidly and occupy the regenerative space, before PDL-derived cells, cementum-associated cells, and osteoprogenitor cells establish new attachments¹⁸³. Therefore, the role of periodontal barriers should not be limited to wound coverage or passive separation. It should control the direction, timing, and selectivity of cell migration within a spatially confined defect.

Conventional guided tissue regeneration membranes mainly function as physical barriers against soft tissue invasion; however, their two-dimensional geometry often requires intraoperative trimming and may lead to poor adaptation, collapse, displacement, or exposure in irregular periodontal defects¹⁵⁶. 3D printing provides a strategy to embed barrier function directly into scaffold architecture. By spatially regulating pore size, porosity, and material distribution, a dense soft tissue-facing region can

restrict epithelial downgrowth, whereas an open bone-facing region can support clot stabilization, vascular invasion, and osteogenic cell migration¹⁸³. Vahdatinia et al. developed a gradient-pore membrane in which the small-pore side delayed epithelial and gingival connective tissue invasion, while the large-pore side facilitated vascularized tissue ingrowth¹⁸⁴. Similarly, *dos Santos* et al. developed a 3D-printed ChW/GelMA-based bilayer membrane incorporating LNPs@SIM-GSE, integrating soft tissue exclusion, porous tissue ingrowth, and antibacterial, antioxidant, anti-inflammatory, and osteogenic activities (**Figure 5**)¹⁸⁵. Because periodontal regeneration occurs in an open oral environment, barrier design should also support gingival sealing and wound closure¹⁸⁶. Wang et al. developed a bilayer hGF-laden collagen/SrCS scaffold combining hard-tissue support with gingival fibroblast-associated soft-tissue regulation¹⁸⁷, while Liu et al. developed an ADM/gelatin/alginate gingival scaffold with a dense barrier layer and a porous tissue-instructive layer¹⁸⁸. Together, these examples suggest that barrier-integrated scaffolds should shift from passive exclusion toward selective permeability, soft-tissue closure, and coordinated hard-tissue regeneration.

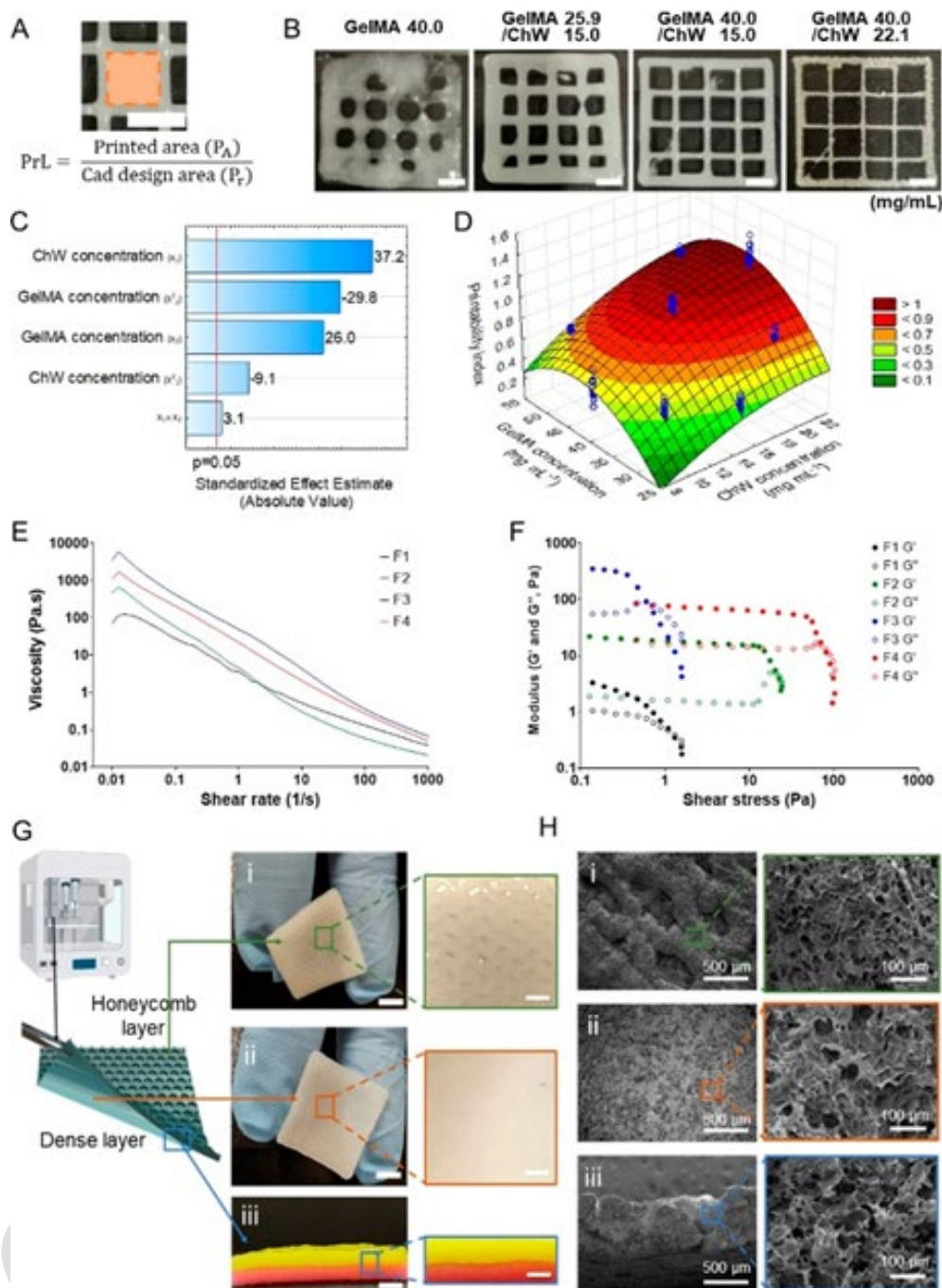


Figure 5. 3D-printed ChW/GelMA-based bilayer membrane incorporating LNPs@SIM-GSE for periodontal regeneration. (A, B) Printability index calculation and representative printed grid patterns of different ink formulations. (C, D) Pareto and response surface analyses showing the effects of ChW and GelMA concentrations on ink printability. (E, F) Flow curves and amplitude sweeps showing shear-thinning behavior and viscoelastic properties. (G) Photographs of the printed bilayer construct, including honeycomb, dense, and lateral views. (H) SEM images showing the honeycomb layer, dense layer, and bilayer cross-sectional morphology. Reproduced with permission from Ref. ¹⁸⁵. Copyright

Overall, ideal 3D-printed periodontal barriers should establish selective permeability in specific region, rather than simply maximizing impermeability. The soft tissue-facing side should delay epithelial and gingival connective tissue invasion, while the bone-facing side should permit vascular and osteogenic ingrowth. The PDL region should preserve a non-mineralized space while preventing direct bone bridging toward the root surface. Future barrier-integrated scaffolds should coordinate dense and porous architectures, degradation kinetics, pore networks, ligament-guiding structures, antibacterial effects, and anti-inflammatory functions. Therefore, they can guide periodontal healing from early soft tissue sealing and space maintenance toward vascularized bone regeneration, PDL organization, and stable multi-tissue interface reconstruction.

5. Functional Programming of 3D-Printed Scaffolds

Beyond spatial reconstruction, 3D-printed periodontal scaffolds must actively regulate the pathological microenvironment of periodontitis. As discussed above, residual biofilms, persistent inflammation, oxidative stress, immune dysregulation, impaired vascularization, and unstable soft tissue sealing collectively compromise cementum-PDL-alveolar bone regeneration¹⁸⁹. Therefore, functionalization should not be viewed as the simple addition of antibacterial agents, osteogenic factors, and cells, but as a stage-adapted strategy that couples scaffold architecture with microenvironmental regulation. By integrating antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, pro-vascular, and tissue-instructive cues, 3D-printed scaffolds can coordinate early infection control, intermediate inflammatory resolution, and late-stage multi-tissue interface reconstruction.

5.1 Antibacterial and Antibiofilm Control

Antibacterial and antibiofilm activity is a key feature distinguishing 3D-printed scaffolds for periodontitis from conventional bone-regenerative constructs¹⁰. Periodontal defects are not sterile osseous cavities where scaffolds remain exposed to saliva, gingival crevicular fluid, residual plaque,

and inflammatory exudates after implantation¹⁸⁹. Once bacteria colonize scaffold surfaces or internal pores, the regenerative space will become a biofilm-retentive niche that perpetuates inflammation and compromises tissue ingrowth¹⁹⁰. Therefore, 3D-printed scaffolds should establish a regeneration-compatible antibacterial window that suppresses early postoperative colonization, while promoting host cell adhesion, vascularization, mineralization, and periodontal interface reconstruction.

Local antimicrobial delivery provides a direct route for early infection control. Theodoridis et al. incorporated tetracycline hydrochloride into thermoplastic PCL to fabricate an extrusion-printed antibacterial scaffold. The scaffold released approximately 45% of the drug within the first 2 h and an additional 30% over the following 2-72 h, generating an early antibacterial window and producing an inhibition zone of approximately 23 mm against *S. aureus*¹⁹¹. In an apical periodontitis-related bone repair setting, Li et al. further incorporated PLGA microspheres with antimicrobial peptide KSL-W into a collagen/silk fibroin/nano-hydroxyapatite scaffold, which maintained antibacterial activity against *E. faecalis* and *P. gingivalis* for at least 10 days¹⁹². These studies demonstrate the feasibility of sustained local antimicrobial delivery, although their efficacy against mature multispecies subgingival biofilms remains to be established. However, release-based antibacterial scaffolds must balance antimicrobial efficacy with regenerative compatibility. In the PCL-tetracycline system, early burst release enhanced short-term antibacterial activity but reduced osteoprogenitor cell viability, indicating that excessive local drug exposure may impair subsequent tissue formation¹⁹¹. Accordingly, scaffold evaluation should include release kinetics, cytocompatibility, antibiofilm durability, and compatibility with later-stage tissue regeneration, rather than just inhibition zones and planktonic bacterial killing efficacy.

Furthermore, the composition and interfacial properties of scaffolds should directly regulate bacterial adhesion and biofilm formation. Suo et al. developed carbon nanotube/chitosan/sodium alginate scaffolds that combined the cationic antibacterial activity of chitosan with the mechanical reinforcement of carbon nanotubes. The results showed that increasing carbon nanotube content enhanced the inhibitory effect on the adhesion of *P. gingivalis*¹⁹³. However, the excessive loading of carbon nanotube reduced human PDL cell viability, again highlighting the need to define a safe functional dose window. In contrast, Daghrery et al. proposed a milder antifouling strategy using

fluorinated calcium phosphate-coated melt-electrowritten scaffolds. The ordered PCL microfibers and F/CaP nanocoating of scaffolds modestly inhibited *P. gingivalis* growth and early biofilm formation, while supporting hPDLSC adhesion, cell bridging, and mineral deposition¹⁷⁷. Such regeneration-compatible antibacterial interfaces are more suitable for periodontal scaffolds than aggressively bactericidal surfaces that compromise host tissue integration.

Overall, antibacterial 3D-printed scaffolds for periodontitis are moving from simple bactericidal platforms toward infection-inflammation-regeneration coordinated systems. Antibiotics, antimicrobial peptides, intrinsically antibacterial polymers, nanofillers, and antifouling coatings can each contribute to infection control, but their periodontal contribution depends on timing, dose safety, host-cell compatibility, and long-term regenerative integration¹⁹⁴. Future studies should move beyond short-term single-species assays and incorporate mature multispecies biofilms, in vivo bacterial burden, inflammatory resolution, microbiome remodeling, and functional periodontal regeneration as integrated evaluation endpoints.

5.2 Immuno-Redox Regulation

Regeneration within periodontal defects is hindered not only by residual bacteria, but also by persistent inflammation, oxidative stress, and osteoimmune imbalance⁶. Chronic biofilm stimulation sustains inflammatory and bone-resorptive signaling, while excessive ROS damages periodontal cells and amplifies NF- κ B-, MAPK-, and inflammasome-related pathways². Within this complex immune microenvironment, macrophages exhibit dynamic and heterogeneous functional states shaped by microbial signals, oxidative stress, local metabolism, and material interfaces, rather than conforming to a simple M1/M2 dichotomy¹⁹⁵. Their responses are further influenced by neutrophil activity, Th17/Treg balance, B-cell-mediated inflammation, and the host response to implanted materials. Therefore, immuno-redox functionalization of 3D-printed periodontal scaffolds should aim not merely to alter individual macrophage markers, but to shorten the destructive inflammatory phase, promote coordinated resolution, and redirect the local microenvironment toward tissue repair.

Scaffold architecture itself can participate in immune regulation. Pore size, interconnectivity, fiber arrangement, and surface topography influence macrophage adhesion, spatial distribution, and

phenotypic transition¹⁹⁶. Using rat subcutaneous implantation and mandibular critical-sized defect models, Li et al. showed that PCL/PEG/HA scaffolds with pores of approximately 600 μm reduced inflammatory cell infiltration, fibrous capsule formation, and collagen deposition in the subcutaneous setting, while promoting vascular ingrowth and new bone formation in mandibular defects¹⁷⁵. These findings indicate that pore architecture can regulate the broader foreign body response and subsequent tissue integration, rather than affecting macrophage-associated phenotypes alone. Lower MyD88 expression in the large-pore group further suggested the possible involvement of TLR/MyD88-related signaling, although this association was based on immunohistochemical evidence and was not confirmed through pathway-specific intervention¹⁷⁵.

Complementing these in vivo findings, Daghrery et al. developed ordered melt-electrowritten scaffolds and showed that regular fiber organization and pore topology helped maintain IL-10 expression, upregulate MRC1, and reduce M1-associated markers under lipopolysaccharide stimulation¹⁶². Together, these studies support the concept that structural programming can attenuate early inflammatory responses and create a host environment more permissive to tissue ingrowth. Nevertheless, because the immune conclusions were primarily derived from selected cytokines and macrophage-associated markers, they should be interpreted as evidence of structure-associated immunomodulatory phenotypes rather than definitive macrophage reprogramming.

Material functionalization further strengthens the coupling between inflammatory resolution and tissue regeneration. For example, PCL/chitosan/L-arginine/ β -TCP composite scaffolds integrate structural support, natural polymer bioactivity, arginine-associated immunomodulation, and inorganic osteogenic cues within a single printed platform¹⁹⁷. This system reduced pro-inflammatory cytokine expression and increased repair- and osteogenesis-associated factors, indicating a repair-associated immune profile.

These designs highlight the close coupling between immune regulation and osteogenesis, as unresolved inflammation suppresses bone formation and limits the effectiveness of osteogenic stimulation. Beyond printed scaffolds, a non-destructive magnesium abrasion and electro-dissolution strategy further coordinated biofilm removal, early immune regulation, bone regeneration, and

secondary osseointegration in infected implant models¹⁹⁸. Hu et al. combined DLP-printed micropillar structures, TGF- β 1, and FTY720 to construct a biomimetic PDL complex⁵⁵. RNA sequencing further revealed Card9 downregulation and NF- κ B inhibition, providing transcriptomic support for the immunomodulatory mechanism beyond selected inflammatory markers⁵⁵. This strategy demonstrated that inflammatory resolution should be coordinated with ligament-space preservation and fiber organization.

Redox modulation represents another essential dimension of periodontal scaffold functionalization. Excessive ROS suppresses periodontal cell proliferation, migration, osteogenic differentiation, and endothelial activity, thereby impairing both bone formation and vascularized repair¹⁹⁹. Although the SDF-1/metformin delivery system developed by Wang et al. was not based on a typical 3D-printed scaffold, it provides a relevant design rationale by sequentially coupling cell recruitment, redox regulation, and osteogenic restoration. In this system, stromal cell-derived factor-1 promoted BMSCs recruitment, while metformin alleviated ROS accumulation and activated AMPK/ β -catenin signaling, thereby improving periodontal bone repair²⁰⁰. In a critical-sized bone defect model, dual-stage metformin release from the aMF-CPC scaffold similarly reduced inflammatory cytokine expression and supported regenerative tissue formation¹⁸⁰. Together, these studies illustrate how immuno-redox regulation may be integrated with scaffold-based tissue repair, although the aMF-CPC strategy still requires further validation in inflammatory periodontal defects.

Overall, immuno-redox regulation allows functionalized 3D-printed periodontal scaffolds to be instructive platforms that coordinate host response, oxidative balance, vascularization, and tissue repair²⁰¹. Future studies should clarify the temporal interplay among scaffold architecture, degradation behavior, ion release, antioxidant activity, and immunomodulatory cues, while integrating broader immune-cell profiling with transcriptomic, pathway-level, and spatial analyses. Scaffold evaluation should further extend beyond cytokine and macrophage-marker expression to include vascularized bone formation, PDL organization, root-surface attachment, and long-term functional periodontal regeneration²⁰².

5.3 Tissue-Specific Regenerative Cues

As discussed above, functional periodontal regeneration requires coordinated reconstruction of alveolar bone, cementum, and PDL, together with stable soft-hard tissue attachment, rather than simple alveolar bone filling²⁰³. Cementum and PDL regeneration require tissue-specific ECM cues, developmental interactions, and paracrine regulation²⁰⁴. Tang et al. used GelMA-based bioprinting to reconstruct interactions between Hertwig's epithelial root sheath cells and dental pulp cells, mimicking epithelial-mesenchymal crosstalk during mineralized tissue formation²⁰⁵. Yang et al. incorporated dental follicle-derived dECM into GelMA to construct periodontal functional modules for PDL-bone interface formation⁹⁰. Blaudez et al. further combined human osteoblast-derived bone-like ECM with hPDL cell sheets to generate a biphasic ECM scaffold, providing distinct matrix cues for the bone-facing and ligament-facing regions²⁰⁶. These ECM-informed strategies may help preserve PDL-like space, support ligament-associated matrix organization, and reduce the risk of ankylosis.

Cell-free paracrine cues further expand tissue-specific programming by regulating cell-matrix interactions without direct cell transplantation. Han et al. embedded hPDLC-derived or hGF-derived small extracellular vesicles into GelMA scaffolds and showed that hPDLC-derived vesicles could effectively promote oral MSC adhesion, focal adhesion formation, mechanotransduction, and ligament-, osteogenic-, and cementogenic-related differentiation²⁰⁷. These findings suggest that tissue-derived extracellular vesicles can provide cell-free biochemical cues for coordinating PDL organization and mineralized tissue formation.

Beyond paracrine regulation, incorporating bioactive inorganic components into printable hydrogels provides another strategy for supporting multi-tissue periodontal regeneration. Mei et al. incorporated mesoporous bioactive glass into GelMA, improving the shape fidelity, surface roughness, and Si/Ca/P ion release of the scaffold, and promoting osteogenic/cementogenic differentiation of hPDLCs²⁰⁸. Miao et al. further introduced bioactive glass microspheres containing mBMSCs, BMP2, and PDGF into a GelMA/SA bioprinting system to support bone formation, cell migration, vascularization, and soft tissue repair in periodontal defects⁹⁸. In addition, the hGF-laden collagen/SrCS bilayer scaffold discussed above illustrated how hard-tissue ionic cues and soft-tissue paracrine support can be regionally combined to promote vascularized periodontal repair¹⁸⁷. These studies indicate that inorganic bioactivity should be integrated with scaffold architecture, vascular support, and

compartment-specific healing requirements.

Overall, tissue-specific regenerative cues should shift 3D-printed periodontal scaffolds from osteogenesis-centered regeneration toward regionally programmed reconstruction. Specifically, mineral and ion-releasing components are most suitable for the alveolar bone region. ECM-derived signals and vesicle-based cues can support PDL organization and interface remodeling. And cementum-associated cues can guide root-surface attachment. Future functionalized scaffolds should integrate material composition, printed architecture, and biological signaling according to the cementum-PDL-alveolar bone hierarchy, enabling functional periodontal attachment rather than isolated bone regeneration.

5.4 Neurovascular Support

Insufficient vascularization remains a critical bottleneck in functional periodontal regeneration. In deep or large defects, delayed vascularization can restrict tissue formation to the defect margins and make the scaffold core vulnerable to nutrient deprivation, fibrous encapsulation, and delayed remodeling²⁰⁹. Because alveolar bone and PDL regeneration both require oxygen supply, immune-cell trafficking, progenitor-cell recruitment, and ECM turnover, vascularization should be considered a core design requirement rather than an auxiliary function of 3D-printed periodontal scaffolds.

Pro-vascular scaffold design should integrate architectural, biochemical, and cellular cues. As discussed above, interconnected macropores, vascularization-permissive pore networks, and degradable microchannels can provide physical routes for nutrient diffusion, cell migration, and vessel invasion¹⁷⁸. Meanwhile, ion-releasing components, growth factor signaling, and cell-laden bioinks can further promote endothelial activity and osteogenic-angiogenic coupling²¹⁰. Therefore, vascular design should not be separated from scaffold architecture or osteogenic programming, but should be incorporated into the spatial organization of periodontal repair.

Beyond vascular ingrowth alone, bone-vessel-nerve co-regeneration has emerged as a potentially transferable concept for periodontal scaffold design. Zhu et al. developed a 3D-bioprinted alginate microfiber-calcium phosphate cement scaffold integrating a human PDLSC-based tri-culture system

with two-stage metformin release (**Figure 6**)¹⁸⁰. In a critical-sized bone defect model, this platform promoted coupled bone, vascular, and neural tissue formation, which provides a useful proof-of-concept for incorporating neurovascular modules into future periodontal scaffolds. In a complementary non-periodontal model, a 3D-bioprinted RGD-Alg/GelMA/PCL scaffold laden with Schwann-like cells supported peripheral nerve regeneration, providing a transferable strategy for integrating cell-laden hydrogels with polymer reinforcement in future neural-supportive periodontal constructs²¹¹.

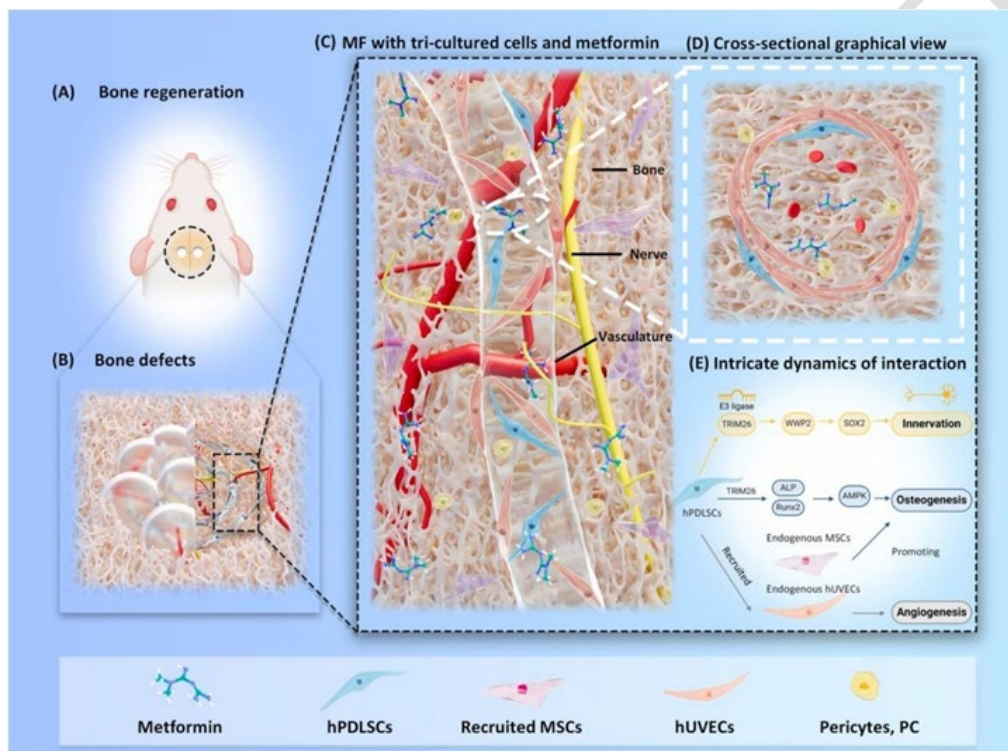


Figure 6. 3D-bioprinted aMF-CPC scaffold for bone, vascular, and nerve regeneration. (A) Application of the aMF-CPC scaffold for critical-sized bone defect repair. (B) Scaffold-mediated regeneration of bone, vasculature, and nerves. (C) hPDLSC-based tri-culture system comprising hPDLSCs, hUVECs, and pericytes. (D) Cross-sectional view of vessel ingrowth within the tri-culture system. (E) Cellular interactions in the tri-culture regenerative microenvironment. Reproduced with permission from Ref. ¹⁸⁰. Copyright © KeAi Communications Co. Ltd. 2025.

Overall, vascularization represents an important component of periodontal tissue repair, whereas direct evidence for neural regeneration in 3D-printed periodontal scaffolds remains limited. Findings from general bone defect models nevertheless provide useful design principles for integrating vascular and neural cues into future periodontal constructs. Further studies in disease-relevant periodontal models

are required to determine whether these strategies can improve functional cementum-PDL-alveolar bone reconstruction.

5.5 Spatiotemporal Delivery

Periodontal regeneration is a stage-dependent healing process rather than a single event of tissue filling. Early healing requires residual infection control, clot stabilization, and inflammatory restriction. The intermediate phase depends on cell recruitment, vascular initiation, and osteogenic activation, and late-stage regeneration requires cementum deposition, PDL maturation, and soft-hard interface stabilization¹⁷. Therefore, the value of 3D-printed delivery systems lies not in maximal cargo loading, but in synchronizing release kinetics, spatial localization, and therapeutic function with the evolving biological requirements of periodontal repair.

Compared with conventional films, gels, or particulate carriers, 3D-printed scaffolds enable delivery behavior to be programmed through layer sequence, polymer distribution, pore architecture, and scaffold-cargo interactions²¹². Denizhan et al. developed metronidazole-loaded chitosan/alginate periodontal films using semi-solid extrusion printing and showed that multilayer configuration and chitosan-alginate polyelectrolyte complexation regulated swelling, adhesion, and drug release behavior²¹³. This example illustrates that the temporal profile of local delivery can be tuned by printable polymer architecture rather than by changing the therapeutic agent alone.

Protein and growth factor delivery further demonstrates how printed scaffolds can spatially organize bioactive signaling within structurally stabilized regenerative niches. Lee et al. used rhBMP-2-loaded 3D-printed PCL/ β -TCP scaffolds with heterogeneous pore architectures and fixation wings for canine mandibular reconstruction, showing that osteogenic cues can be positioned within a defect-adapted and mechanically stabilized scaffold microenvironment²¹⁴. Liu et al. incorporated recombinant human erythropoietin into low-temperature-printed silk fibroin/collagen/hydroxyapatite scaffolds, achieving early release followed by sustained delivery and improved bone repair in rabbit mandibular defects²¹⁵. Collectively, these mandibular defect studies demonstrate how anatomical placement, pore architecture, scaffold stability, degradation behavior, and release kinetics can be coordinated within factor-loaded printed scaffolds to support vascularized bone regeneration, providing useful design

principles for future periodontal delivery systems.

Extracellular vesicle delivery provides a cell-free strategy that more closely approximates paracrine regulation and further expands spatiotemporal delivery design. Sun et al. combined human umbilical cord mesenchymal stem cell-derived exosomes with 3D-printed silk fibroin/collagen I/nano-hydroxyapatite scaffolds, enhancing endothelial cell activity in vitro and promoting angiogenesis and osteogenesis in alveolar bone defects in vivo²¹⁶. Compared with single-factor delivery, extracellular vesicles carry multiple regulatory signals and may coordinate angiogenesis, immune regulation, and tissue maturation in a stage-adapted manner²¹⁷. Collectively, these findings highlight the potential of extracellular vesicle-loaded printed scaffolds as cell-free delivery platforms for vascularized alveolar bone repair and provide a valuable basis for their further application in periodontal regeneration.

Overall, 3D-printed periodontal delivery systems should move beyond cargo-loaded scaffolds toward spatiotemporally programmable regulatory platforms²¹⁸. Ideally, early release should control residual infection and destructive inflammation, intermediate release should promote cell recruitment, vascularization, and osteogenic initiation, and late-stage cues should support cementogenesis, PDL maturation, and interface stabilization²¹⁹. By coupling release kinetics with scaffold degradation, pore remodeling, vascular invasion, cell migration, and tissue replacement, printed delivery systems can provide stage-adapted regulation for functional periodontal regeneration.

6. Challenges and Future Perspectives

Although 3D printing has provided new opportunities for periodontitis therapy and periodontal regeneration, current evidence remains insufficient for predictable clinical translation²⁶. Periodontal regeneration occurs in an open pathological environment exposed to polymicrobial biofilms, persistent inflammation, oxidative stress, gingival crevicular fluid, and dynamic mechanical loading. Its ultimate goal is not simple bone filling, but coordinated reconstruction of cementum, PDL, alveolar bone, and their functional interfaces. Future 3D-printed periodontal scaffolds should establish systematic design principles integrating manufacturability, tissue-specific bioactivity, disease-relevant modeling, functional evaluation, and translational quality control instead of simply improving structural complexity and bioactive cargo loading¹⁴⁰.

(1) Balancing printability, mechanical stability, and biological activity. Nowadays, a central challenge of 3D-printed periodontal scaffolds is to reconcile material processability, mechanical support, degradation behavior, and biological function²²⁰. Synthetic polymers, such as PCL, PLA, and PLGA, provide stable printability and space maintenance, but show limited bioactivity, slow degradation, and high-temperature processing restrict direct incorporation of cells or labile factors. Natural hydrogels and bioinks, including GelMA, collagen, alginate, ADM, and dECM-based systems, can mimic the ECM and support cell survival, migration, and differentiation, but often lack mechanical strength and long-term shape fidelity²²¹. Bioceramics, bioactive glasses, and therapeutic ion-releasing materials can enhance osteogenesis and angiogenesis, yet may impair rheology, toughness, and printing accuracy with excessive inorganic loading. Future material design should therefore shift from searching for a single ideal material to developing region-specific multi-material integration, endowing the bone, PDL, root-facing, and soft tissue-facing regions with distinct mechanical, degradative, and biological functions.

(2) Linking scaffold architecture to tissue-specific regeneration. Although patient-specific scaffolds, multiphasic constructs, microchannels, aligned fibers, gradient pores, and bilayer membranes have shown promising effects in tissue regeneration, the quantitative relationship between architecture and periodontal tissue outcomes remains unclear²²². Pore size, porosity, fiber spacing, channel geometry, interfacial transition, stiffness, and degradation rate collectively regulate cell migration, vascular ingrowth, PDL fiber orientation, bone formation, and soft tissue exclusion²¹⁰. Larger pores favor vascularized bone ingrowth but weaken mechanical stability and increase soft tissue invasion. By contrast, microchannels can guide PDL alignment provided that the guidance architecture is not obscured by excessive hydrogel filling. Future studies combining computational modeling, finite element analysis, fluid transport simulation, in situ imaging, and multiparametric experiments should move scaffold design from empirical optimization toward predictive structural programming²²³.

(3) Establishing standardized criteria for functional periodontal regeneration. Well-established clinical and histological frameworks are available for evaluating periodontal regenerative outcomes, although a universally accepted composite endpoint specifically for 3D-printed periodontal scaffolds has not yet been established. Clinically, regenerative efficacy is commonly assessed by probing depth

reduction, clinical attachment level gain, gingival recession, tooth mobility, and radiographic bone fill. However, these clinical and radiographic improvements do not alone confirm true periodontal regeneration. Histologically, functional regeneration requires the formation of new cementum, a preserved non-mineralized PDL space, functionally oriented PDL fibers inserted into both the new cementum and alveolar bone, and newly formed alveolar bone without ankylosis or root resorption^{154,224}. Therefore, scaffold evaluation should integrate clinical periodontal measurements, radiographic or micro-CT analysis, histomorphometry, PDL-space measurement, collagen-fiber orientation analysis, region-specific molecular markers, and, where feasible, mechanical loading tests. Because histological confirmation is generally unavailable in routine human clinical studies, future investigations should clearly distinguish clinical improvement, radiographic bone repair, and histologically verified functional periodontal regeneration.

(4) Developing disease-relevant and dynamic testing models. Most current studies use acute surgical defects, ectopic implantation, calvarial defects, or healthy alveolar bone defect models *in vivo*, which cannot fully simulate the pathological states of periodontitis²²⁵. Clinical periodontal defects involve mature multispecies biofilms, chronic immune activation, excessive ROS, osteoclast-dominant bone resorption, soft tissue competition, crevicular fluid flow, and continuous oral exposure. Patient-related factors such as diabetes, smoking, occlusal trauma, poor plaque control, and systemic inflammation further alter the infection control, vascularization, scaffold degradation, and tissue maturation. Thus, future studies should adopt ligature-induced periodontitis, diabetic periodontitis, furcation defects, vertical intrabony defects, and large-animal models. Periodontium-on-a-chip and microfluidic biofilm-host co-culture systems can also provide realistic platforms for evaluating the antibacterial, immunomodulatory, ROS-responsive, and stimuli-responsive capacities of scaffolds²²⁶. The major experimental models for evaluating periodontal regenerative scaffolds are comparatively summarized in Table 3, with emphasis on disease relevance, principal evaluation outcomes, limitations, and potential clinical value.

Table 3. Comparison of experimental models and evaluation frameworks for periodontal regeneration.

Model	Disease relevance	Key outcomes	Advantages	Limitations	Clinical value
In vitro models	Low to moderate; reproduce selected cellular, microbial, or inflammatory features	Antibacterial activity; cytocompatibility; inflammation; ROS; cell migration and differentiation	Controllable, reproducible, and suitable for mechanistic screening	Lack systemic immunity, vascularization, mechanical loading, and complete periodontal anatomy	Early screening and mechanism validation
Ectopic implantation	Low; does not reproduce the oral or periodontal environment	Foreign-body response; degradation; vascularization; ectopic tissue formation	Simple preliminary in vivo evaluation	Lack oral biofilms, occlusal loading, and native periodontal interfaces	Preliminary safety and tissue-forming assessment
Healthy alveolar defects	Moderate; reproduce local anatomy but not chronic periodontitis	Bone fill; BV/TV; BMD; vascularization; scaffold integration; periodontal tissue formation	Orthotopic assessment of adaptation and regeneration	May overestimate efficacy under non-inflammatory conditions	Baseline regenerative and surgical evaluation
Ligature-induced periodontitis	High; reproduces plaque-associated inflammation and bone loss	Bacterial burden; inflammation; CEJ-ABC distance; bone regeneration; PDL and cementum formation	Evaluates antibacterial, immunomodulatory, and regenerative effects in a diseased environment	Variable severity and possible spontaneous resolution after ligature removal	Disease-relevant preclinical evaluation
Diabetic periodontitis	High; reproduces metabolic dysfunction and impaired healing	Inflammation; oxidative stress; angiogenesis; bone regeneration; periodontal reconstruction	Tests efficacy under clinically relevant compromised healing	Complex, costly, and biologically variable	Evaluation for high-risk patients with diabetes

Large-animal models	High; high anatomical and surgical relevance	Scaffold fit; soft-tissue closure; radiographic bone fill; histological periodontal regeneration; safety	Human-like defect size and surgical procedures	High cost, ethical constraints, and limited sample size	Advanced preclinical and translational validation
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(5) Addressing manufacturing, quality control, and regulatory translation. Patient-specific 3D-printed periodontal scaffolds require CBCT acquisition, defect segmentation, 3D reconstruction, CAD design, printing, post-processing, sterilization, quality testing, and intraoperative fitting. Each step introduces variability. Current CBCT resolution remains insufficient for accurately reconstructing the narrow PDL space, cementum boundary, thin alveolar plates, and inflamed soft tissue margins, while metal artifacts and irregular defects further reduce model accuracy. Unlike standardized products, personalized scaffolds are difficult to validate through conventional batch-based quality control. Critical quality attributes should include external shape accuracy, pore fidelity, mechanical performance, degradation behavior, sterilization effectiveness, drug-release profiles, and retention of biological activity²²⁷. For drug-, growth factor-, cell-, or EV-loaded constructs, dose consistency, release stability, immune safety, storage, transport, and long-term toxicity must also be defined. Early translation may therefore begin with acellular patient-specific bone scaffolds, functional GTR membranes, or soft tissue sealing constructs, and then move toward more complex cell- or EV-based active systems.

(6) Moving from material-driven design to microenvironment-driven therapy. Future 3D-printed periodontal scaffolds should be designed according to the dominant pathological features of each defect²²⁸. For example, defects with high plaque burden require antibacterial, antibiofilm, and anti-inflammatory functions; diabetic or highly oxidative microenvironments require ROS scavenging, metabolic regulation, and stem cell protection; large intrabony defects require vascular channels, osteoconductive frameworks, ion release, and mechanical support; and defects with severe PDL loss or root exposure require aligned microstructures, cementogenic cues, and preservation of a non-mineralized ligament space. The AI-assisted segmentation, reverse defect design, toolpath optimization, stimuli-responsive materials, 4D printing, dynamic pore networks, EV-based cell-free delivery, and in situ bioprinting can further enable phenotype-matched scaffold design²²⁹. Ultimately, 3D-printed periodontal scaffolds should evolve from static defect fillers into integrated regenerative systems that coordinate anatomical adaptation, tissue compartmentalization, immune regulation, vascularization, soft tissue sealing, and functional attachment reconstruction.

7. Conclusion

3D printing has introduced a new strategy for periodontitis therapy and periodontal tissue regeneration. Unlike conventional grafts or barrier membranes, 3D-printed scaffolds can integrate patient-specific defect adaptation, spatially defined architectures, programmable pore networks, compartmentalized material distribution, and localized delivery of bioactive cues. These advantages make 3D printing particularly suitable for periodontal defects, where regeneration requires the coordinated reconstruction of cementum, PDL, soft tissue sealing, and functional soft-hard tissue interfaces.

Current advances indicate that the role of 3D-printed periodontal scaffolds is shifting from passive space maintenance toward active spatial and microenvironmental regulation. Through multiphasic design, fiber-guiding architectures, barrier integration, and region-specific pore programming, printed scaffolds can guide cell migration, vascular invasion, PDL fiber orientation, and tissue compartmentalization. Meanwhile, loading antibacterial agents, immunomodulatory factors, antioxidant components, pro-vascular signals, extracellular vesicles, and stimuli-responsive systems further enables scaffolds to address the pathological features of periodontitis, including biofilm persistence, chronic inflammation, oxidative stress, impaired vascularization, and defective wound healing. Nevertheless, predictable periodontal regeneration remains challenging. Future studies should move beyond osteogenesis-centered evaluation and establish more rigorous criteria for functional periodontal reconstruction. Meanwhile, developing disease-relevant models, standardized manufacturing workflows, quality-control systems, and translationally feasible product pathways is required to bridge the gap between experimental scaffold design and clinical applications.

Ultimately, the next generation of 3D-printed periodontal scaffolds should not be viewed as customized bone substitutes, but as instructive regenerative platforms that coordinate anatomical adaptation, tissue-specific spatial programming, immune-redox regulation, vascularization, soft tissue sealing, and functional attachment reconstruction. By integrating digital design, advanced biomaterials, responsive delivery, and microenvironment-driven therapeutic strategies, 3D printing may enable a transition from partial structural repair toward predictable and precision-oriented functional periodontal regeneration.

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Conflict of interest

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Availability of data

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