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Personalised immunomodulatory scaffolds targeting macrophage polarisation in periodontal defects: A review

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Abstract:
Advanced periodontitis causes immune-mediated periodontal destruction and conventional therapies often fail to achieve complete tissue regeneration. Therefore, it is of interest to examine the current evidence on immunomodulatory scaffold design, macrophage polarisation, personalisation strategies and their role in periodontal regeneration. Evidence from *in vitro*, *in vivo* and translational studies was analysed, focusing on biomaterials, surface topography, controlled bioactive molecule release, immune phenotyping, 3D bio printing and stimuli-responsive drug delivery. Natural polymers, decellularised extracellular matrix, synthetic polymer composites, hydrogels and stimuli-responsive scaffolds consistently promoted M2 macrophage polarisation, resulting in improved bone, periodontal ligament and cementum regeneration in preclinical models. Thus, personalised immunomodulatory scaffolds represent a promising strategy for enhancing periodontal regeneration by modulating host immune responses and supporting precision regenerative therapy.

Keywords: Immunomodulatory scaffold, macrophage polarisation, M1 or M2 phenotype, periodontal regeneration, biomaterials, tissue engineering, periodontitis, personalised medicine, cytokine release, 3D bio printing

Background:
Periodontitis is a dysbiotic, immune-mediated inflammatory disease that leads to irreversible destruction of the tooth-supporting apparatus, including the periodontal ligament (PDL), cementum and alveolar bone. Despite substantial advances in debridement techniques and guided tissue regeneration (GTR) procedures, predictable and complete regeneration of the periodontium remains elusive. This is largely because conventional regenerative approaches fail to adequately control the local inflammatory environment that governs the transition from tissue destruction to tissue repair **[1].** The persistence of unresolved inflammation following conventional periodontal therapy frequently impairs the healing cascade and limits the long-term success of grafting materials and barrier membranes **[2].** Macrophages are innate immune effector cells that exhibit remarkable functional plasticity, adopting a spectrum of activation states ranging from classically activated pro-inflammatory M1 macrophages to alternatively activated pro-regenerative M2 macrophages **[3].** In the context of periodontal disease, a sustained imbalance favouring M1 polarisation perpetuates the destructive inflammatory cascade and prevents the resolution phase that is a prerequisite for tissue repair **[4].** Harnessing biomaterial-based strategies to precisely modulate macrophage polarisation within periodontal defects- an approach termed osteoimmunology or osteoimmunomodulation when applied to hard tissue regeneration therefore represents a mechanistically grounded and therapeutically compelling concept **[5].** Immunomodulatory scaffolds, designed to engage and redirect the host immune response rather than passively replacing lost tissue, have attracted increasing attention in regenerative dentistry. These constructs can be tailored with bioactive cues including cytokines, growth factors, gene-silencing agents and physical surface characteristics to guide macrophage behaviour *in situ* **[6].** The additional dimension of personalisation accounting for individual patient immune phenotypes, systemic comorbidities, genetic polymorphisms and microbiome profiles represents the next frontier in this rapidly evolving field **[7].** Therefore, it is of interest to evaluate the role of immunomodulatory scaffolds in regulating macrophage polarisation and enhancing personalised periodontal regeneration.

Macrophage polarisation in periodontal disease pathogenesis:
Macrophages are among the most abundant immune cells within inflamed gingival tissues and constitute the primary cellular interface between the dysbiotic periodontal biofilm and the destructive host response. Upon activation by periodontal pathogens such as *Porphyromonas gingivalis* and *Tannerella forsythia*, tissue macrophages predominantly acquire an M1 phenotype characterised by secretion of TNF-α, IL-1β, IL-6, IL-12 and matrix metalloproteinase (MMPs), which collectively drive alveolar bone resorption and collagen degradation **[8].** This M1-dominant state is further sustained by the pro-inflammatory milieu of active periodontitis, creating a self-reinforcing cycle of tissue catabolism that prevents the transition to the resolution phase required for healing. Sustained M1 dominance in chronic periodontitis prevents the physiological switch to M2-mediated tissue repair, during which M2 macrophages would normally secrete IL-10, TGF-β, arginase-1 and VEGF to restore tissue homeostasis and support angiogenesis and matrix remodelling **[9].** Transcriptomic profiling of gingival biopsies from periodontitis patients has confirmed a significant predominance of M1-associated gene expression signatures- including up regulation of CD80, CD86, iNOS and CXCL10-compared with periodontal healthy controls **[10].** Conversely, M2 polarisation markers such as CD163, CD206, IL-10 and TGF-β are significantly underrepresented in diseased tissues, underscoring the polarisation imbalance as a pathological hallmark of chronic periodontitis rather than an incidental finding **[11].** Critically, successful clinical resolution of periodontitis following treatment

has been associated with a measurable shift towards M2-dominant macrophage phenotypes in the healed periodontium, validating polarisation modulation as a legitimate and clinically relevant therapeutic target **[12].** The Comparative M1 and M2 phenotypic profiles and their periodontal implications are summarised in **Table 1**.

Table 1: Comparative features of M1 and M2 macrophage phenotypes and their relevance to periodontal disease pathogenesis and regeneration

Feature	M1 Phenotype	M2 Phenotype	Periodontal Relevance
Activation stimulus	LPS, IFN-γ, TNF-α	IL-4, IL-13, IL-10, TGF-β	Biofilm-driven vs. resolution-phase
Key surface markers	CD80, CD86, CD68, iNOS	CD163, CD206, CD209, Arg-1	Histological identification in biopsies
Secreted mediators	TNF-α, IL-1β, IL-6, IL-12, MMPs	IL-10, TGF-β, VEGF, PDGF	Tissue destruction vs. angiogenesis/repair
Metabolic signature	Glycolysis, nitric oxide production	Oxidative phosphorylation, polyamine synthesis	Energy demand of inflammatory state
Tissue effect	Collagen degradation, bone resorption	Matrix remodelling, collagen synthesis	Net outcome for PDL/bone/cementum
Periodontal disease state	Predominant in active chronic periodontitis	Increased after successful therapy	Polarisation shift as therapeutic target

Arg-1 = arginase-1; iNOS = inducible nitric oxide synthase; MMP = matrix metalloproteinase; PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor.

Table 2: Summary of biomaterial platforms investigated for immunomodulatory macrophage polarisation in periodontal regeneration

Biomaterial	Examples	Stiffness Range	Immunomodulatory Mechanism	M2 Evidence	Key Ref.
Natural polymer	Collagen, fibrin, silk fibroin	0.1–5 kPa	Integrin binding, matrikine release	*In vitro, in vivo*	**[19, 23]**
dECM scaffold	PDL-dECM, bone-dECM	Tissue-specific	Tissue-specific bioactive signals	*In vitro, in vivo*	**[20]**
Synthetic polymer	PLGA, PCL, PEG	Tuneable (1–100+ kPa)	Drug release, surface functionalisation	*In vitro, in vivo*	**[21]**
Composite	HA/chitosan, HA/silk fibroin	5–50 kPa	Osteoimmunomodulation + M2 induction	*In vitro, in vivo*	**[22, 23]**
Hydrogel	GelMA, alginate, hyaluronic acid	0.1–2 kPa	Cytokine encapsulation, in situ gelation	*In vitro, in vivo*	**[24]**

DECM = decellularised extracellular matrix; HA = hydroxyapatite; PCL = polycaprolactone; PDL = periodontal ligament; PEG = polyethylene glycol; PLGA = poly (lactic-co-glycolic acid); ROS = reactive oxygen species.

Table 3: Bioactive agents incorporated into immunomodulatory scaffolds for macrophage M2 polarisation in periodontal defects

Bioactive Agent	Class	Signalling Pathway	Delivery System	Periodontal Outcome	Key Ref.
IL-4	Cytokine	IL-4Rα/JAK1/STAT6	PLGA microspheres	Bone fill, M2 shift	**[21, 25]**
IL-13	Cytokine	IL-4Rα/IL-13Rα1/STAT6	Collagen scaffold	Anti-inflammatory	**[25]**
IL-10	Cytokine	JAK1/STAT3	PLGA, GelMA hydrogel	Suppresses M1 activation	**[26]**
Resolvin D1	SPM / Lipid mediator	GPR32/ALX	Lipid nanoparticle-scaffold	Bone regeneration, M2	**[28]**
Resolvin E1	SPM / Lipid mediator	ChemR23	Lipid nanoparticle-scaffold	Efferocytosis, M2	**[28]**
miR-223-3p	microRNA	NF-κB suppression	Scaffold-loaded nanocarrier	Reduced M1, bone repair	**[29]**
miR-21	microRNA	STAT3 activation	Scaffold-loaded nanocarrier	M2 polarisation	**[29]**

GPR = G-protein-coupled receptor; JAK = Janus kinase; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; SPM = specialised pro-resolving mediator; STAT = signal transducer and activator of transcription.

Table 4: Personalisation strategies for immunomodulatory scaffold design in periodontal regenerative medicine

Personalisation Approach	Tool / Technology	Patient Factor Addressed	Stage of Development	Key Ref.
Immune phenotyping	Peripheral blood macrophage polarisation assay; salivary cytokine panel	Immune dysregulation, comorbidities	Pilot feasibility	**[20]**
3D bio printing	CBCT-guided scaffold fabrication with concurrent cytokine loading	Defect morphology, immune profile	Preclinical / early clinical	**[21]**
Stimuli-responsive release	pH- or ROS-sensitive drug release system	Local inflammatory threshold	*In vitro / in vivo*	**[22]**
Microbiome-guided design	Subgingival microbiome profiling to tailor antimicrobial loading	Dysbiotic biofilm composition	Conceptual / pilot	**[23]**
Genetic profiling	Cytokine gene polymorphism panel (TNF-α, IL-1, IL-10)	Heritable immune response variation	Conceptual	**[24]**

CBCT = cone beam computed tomography; ROS = reactive oxygen species.

Table 5: Summary of key preclinical *in vivo* studies evaluating immunomodulatory scaffolds in periodontal defect models

Animal Model	Defect Type	Scaffold and Agent	Key Macrophage Finding	Regenerative Outcome	Key Ref.
Rat	Intrabony, 1-wall	PLGA/IL-4 microsphere scaffold	↑CD206⁺ macrophages, ↓TNF-α	Enhanced bone fill vs. control	**[21]**
Rat	Intrabony, 2-wall	HA/chitosan composite scaffold	↑Arg-1, ↓iNOS expression	Bone + PDL regeneration	**[22]**
Canine	1-wall intrabony	dECM/PDL scaffold	↑CD163⁺, ↑M2 gene signature	PDL and cementum formation	**[20]**
Rat	Periodontal window	Resolvin D1 lipid nanoparticle scaffold	↑M2 polarisation, ↑VEGF	Alveolar bone regeneration	**[28]**
Rat	Intrabony	miR-223-3p nanocarrier scaffold	↓NF-κB, ↓M1 markers	Reduced bone loss, repair	**[29]**
Rat	Intrabony	ROS-responsive hydrogel scaffold	Autonomous M2 induction at defect	Reduced inflammation, bone gain	**[25]**

PDL = periodontal ligament; ↑ = increased; ↓ = decreased.

Principal of Immunomodulatory scaffold design:

An effective immunomodulatory scaffold must fulfil dual functional requirements: providing structural support for tissue ingrowth while simultaneously delivering immunological cues that redirect macrophage phenotype towards a pro-regenerative state. The physicochemical properties of the scaffold material-including stiffness, surface chemistry, porosity and fibre alignment-profoundly influence macrophage adhesion, morphology and transcriptional programming independent of any incorporated bioactive factors **[13].** Substrate stiffness is particularly consequential: soft substrates with stiffness values approximating native periodontal ligament tissue (approximately 0.5–1.5 kPa) have been shown to preferentially induce M2-like macrophage morphology and cytokine profiles compared with stiffer constructs, mediated through mechanotransductive pathways involving integrin-focal adhesion kinase signalling **[14].** Surface topography exerts an equally significant immunomodulatory effect. Aligned nanofibrous scaffolds fabricated via electrospinning direct macrophage elongation along fibre axes, a physical cue that activates anti-inflammatory signalling through cytoskeletal tension-mediated inhibition of NF-κB. Random fibre orientation, by contrast, promotes macrophage spreading and M1 activation. Surface functionalization with arginine-glycine-aspartate (RGD) peptides, hydroxyapatite nanoparticles and zwitterionic coatings further modulates integrin-mediated signalling to favour M2 polarisation **[15].** Pore architecture also critically influences immune outcomes: macropores of 100–300 μm facilitate macrophage infiltration and support M2 polarisation, whereas microporous architectures tend to restrict macrophage entry and promote foreign body giant cell formation **[16].** These design parameters must be considered in concert to engineer scaffolds that create a coherent pro-regenerative immune microenvironment within the periodontal defect.

Biomaterial platforms for macrophage polarisation modulation:

A broad spectrum of natural and synthetic biomaterials has been investigated as scaffolding platforms for macrophage directed periodontal regeneration. **Table 2** summarises the principal platforms, their immunomodulatory mechanisms and supporting evidence. Collagen based scaffolds, owing to their inherent biocompatibility and capacity to bind and present growth factors, consistently promote M2 polarisation in macrophage culture models and demonstrate reduced pro-inflammatory cytokine secretion compared with synthetic polymer controls **[17].** Decellularised extracellular matrix (DECM) scaffolds derived from periodontal ligament or alveolar bone retain tissue-specific bioactive signals including matrikines and cryptic peptides that preferentially drive M2 macrophage activation and support periodontal cell repopulation **[18].** These natural platforms are particularly attractive because their bioactive signals are inherently compatible with the periodontal tissue microenvironment. Synthetic polymers such as PLGA, PCL and PEG offer tuneable degradation kinetics and mechanical properties, enabling precise temporal control over scaffold resorption and drug release profiles. PLGA microsphere-loaded scaffolds releasing IL-4 and IL-13 have demonstrated robust M2 polarisation and enhanced bone regeneration in rat periodontal defect models **[19].** Composite scaffolds combining hydroxyapatite with biopolymers such as chitosan or silk fibroin have shown synergistic immunomodulatory and osteoinductive effects, simultaneously promoting M2 macrophage phenotype and osteoblastic differentiation of periodontal stem cells **[20].** Hydrogel-based platforms-including alginate, hyaluronic acid and gelatin methacryloyl (GelMA) systems-provide an aqueous, cell-permissive environment well-suited to the sustained delivery of soluble immunomodulatory agents and offer the advantage of minimally invasive injectable delivery that conforms to irregular defect morphologies **[21].**

Bioactive cues and controlled release strategies for M2 polarisation:

The incorporation of specific immunomodulatory bioactive molecules into scaffold systems enables targeted manipulation of macrophage polarisation. **Table 3** summarises the principal bioactive agents employed, their signalling mechanisms, delivery systems and periodontal outcomes. IL-4 and IL-13 are prototypic M2-inducing cytokines that signal through the IL-4Rα/JAK1/STAT6 axis to unregulated arginase-1, CD206 and anti-inflammatory mediators. Their controlled release from scaffold systems at physiologically relevant concentrations (1–10 ng per mL) has been demonstrated to shift macrophage phenotype in periodontal defect environments without the systemic side effects associated with parenteral cytokine administration **[25].** IL-10, a potent anti-inflammatory cytokine, has similarly been incorporated into PLGA and GelMA scaffolds to suppress M1 activation and promote reparative macrophage function **[22].** Beyond cytokines, specialised pro-resolving mediators (SPMs) derived from omega-3 fatty acids-including resolvins, lipoxins and protectins-offer cost-effective and

pharmacologically stable alternatives for scaffold loading. Resolvin D1 and E1, incorporated into lipid nanoparticle-scaffold composites, activate G-protein-coupled receptors on macrophages to promote efferocytosis, dampen NF-κB signalling and drive phenotypic switching from M1 to M2 states, with promising M2-polarising activity and enhanced periodontal bone regeneration in preclinical models **[27, 28].** MicroRNA-loaded scaffolds targeting M1-promoting transcription factors-including miR-223-3p (suppressing NF-κB) and miR-21 (activating STAT3)-represent an emerging nucleic acid-based approach to epigenetically reprogramed macrophage polarisation at the defect site without sustained protein delivery **[23].**

Personalisation strategies in immunomodulatory scaffold development:

A fundamental challenge in translating immunomodulatory scaffold research to clinical practice is the substantial heterogeneity of immune responses across individual patients. Factors including age, systemic disease burden (particularly diabetes mellitus and autoimmune conditions), tobacco use, genetic polymorphisms in cytokine genes (TNF-α, IL-1, IL-10) and the composition of the subgingival microbiome profoundly influence macrophage behaviour and the inflammatory milieu of periodontal defects **[24].** A scaffold designed to induce M2 polarisation in an immunocompetent, non-smoking patient may be insufficient or even counter-productive in a diabetic patient with chronically dysregulated macrophage function and impaired resolution capacity **[25]. Table 4** summarises the principal personalisation strategies under investigation. Pre-implantation immune profiling using peripheral blood macrophage polarisation assays and salivary cytokine panels enables patient stratification by immune phenotype and informs scaffold composition and cytokine loading decisions**.** Three-dimensional bio printing technologies now permit the fabrication of patient-specific scaffold geometries precisely matched to CBCT data of individual defect morphologies, with concurrent loading of personalised cytokine cocktails determined by immune phenotyping results **[25].** Smart, stimuli responsive scaffolds incorporating pH- or reactive oxygen species (ROS) sensitive drug release mechanisms add a further layer of personalisation by releasing M2-polarising agents only when inflammatory thresholds are exceeded within the defect environment, creating an autonomous feedback-regulated immunomodulatory system that adapts dynamically to the evolving immune landscape of the healing defect **[26].**

Pre-clinical evidence and translational considerations:

A growing body of preclinical evidence supports the efficacy of immunomodulatory scaffold strategies in periodontal defect models. **Table 5** summarises the key *in vivo* studies, including model type, scaffold design, macrophage findings and regenerative outcomes.

Conclusion:

Immunomodulatory scaffolds promoting M2 macrophage polarisation enhance bone, periodontal ligament and cementum regeneration compared with conventional regenerative approaches. Personalising scaffold design according to immune phenotype, defect characteristics and systemic conditions may improve regenerative outcomes in periodontal defects. Future clinical translation requires standardised preclinical models, long-term *in vivo* validation and well-designed clinical trials.

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The authors declare no conflict of interest.

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