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Original Article

When Biomaterial Performance Justifies a Claim of Periodontal Regeneration: An Original Translational Framework Connecting Immunomodulation, Vascular Integration, and Functional Periodontal Ligament Reconstruction

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ABSTRACT

Periodontal biomaterials are increasingly engineered to provide antimicrobial activity, immunomodulation, angiogenic support, osteogenic stimulation, controlled degradation, extracellular-matrix mimicry, and spatial guidance of regenerating tissues. Yet favorable performance in any one of these domains does not by itself establish periodontal regeneration. This article develops a translational framework for determining how strongly biomaterial evidence can support a regenerative claim. The analysis distinguishes material performance from biological competence, coordinated tissue reconstruction, functional periodontal-ligament restoration, durability, and clinically demonstrable benefit. Functional regeneration is treated as a multilevel outcome requiring more than bone formation or favorable cellular responses: the regenerated complex must restore biologically appropriate relationships among cementum, periodontal ligament, alveolar bone, vascular supply, and the inflammatory microenvironment. Particular attention is given to immune regulation and vascular integration because both can enable regeneration while remaining insufficient as independent proof of it. Contemporary preclinical biomaterials increasingly combine antimicrobial, redox-regulatory, immunomodulatory, angiogenic, and osteogenic functions, but greater multifunctionality also creates greater evidentiary demands when translating laboratory performance into claims of restored periodontal function. The proposed approach therefore evaluates regenerative claims according to the biological level actually demonstrated and the indispensable evidence dimensions that remain unresolved. This distinction is intended to reduce surrogate-outcome inflation while preserving legitimate lower-level claims about material properties and mechanistic activity. The resulting framework provides a basis for later defining evidence-admissibility boundaries and validation requirements for biomaterials intended to reconstruct the functional periodontium.

Keywords: Periodontal regeneration, Biomaterials, Periodontal ligament, Immunomodulation, Angiogenesis, Tissue engineering

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Introduction

Contemporary periodontal regenerative therapy is evaluated within a clinical environment in which treatment success remains dependent on disease control, defect characteristics, patient-level risk, and the quality of the regenerated supporting apparatus. Evidence-based periodontal guidance accordingly places regenerative interventions within a broader therapeutic sequence rather than treating tissue engineering as an isolated material problem [1]. This clinical context is important because the language used to describe biomaterial performance often develops

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faster than the evidence required to justify corresponding claims of regeneration.

The biomaterial literature now includes membranes, hydrogels, scaffolds, nanoparticles, extracellular-vesicle systems, cell-instructive matrices, and multiphasic constructs designed to influence several stages of periodontal healing. Their reported advantages include improved handling, controlled degradation, cell adhesion, antimicrobial activity, osteogenic differentiation, inflammatory regulation, and delivery of biologically active molecules. Nevertheless, current reviews show that no single biomaterial strategy has eliminated the central difficulty of regenerating the periodontal complex in a clinically predictable manner [2]. A material may perform exceptionally within one experimental domain while leaving another indispensable component of regeneration unresolved.

This distinction becomes clearer when periodontal regeneration is defined biologically rather than rhetorically. Reconstruction of the periodontium requires more than new mineralized tissue. A biologically meaningful endpoint includes appropriate cementum formation, a periodontal ligament with organized fibre insertion, alveolar-bone reconstruction, and restoration of a mechanically competent attachment capable of functioning under physiologic loading [3]. These requirements make the strength of a regenerative claim dependent not merely on whether tissue forms, but on which tissue forms, how it is organized, whether interfaces are restored, and whether the reconstructed system performs its intended biological and mechanical roles.

Methodological guidance for periodontal biomaterials reinforces the need to separate these evidentiary levels. Material fabrication and characterization can establish composition, architecture, degradation, mechanics, surface properties, and other physicochemical characteristics, whereas biological-function testing addresses questions such as cytocompatibility, cell differentiation, immunomodulation, angiogenesis, tissue integration, and in-vivo reconstruction [4, 5]. Neither category alone demonstrates clinically meaningful periodontal regeneration. Their value lies in answering different questions along a translational sequence.

The distinction is especially important as increasingly sophisticated biomaterials move toward personalized, minimally invasive, and multifunctional regenerative strategies. Recent clinical and translational syntheses describe substantial innovation while also emphasizing heterogeneity of the supporting evidence and the continued need for controlled, longitudinal evaluation, particularly for advanced hard-tissue and combined regenerative approaches [6]. The central problem is therefore not whether a biomaterial demonstrates biological activity, but which regenerative claim that activity can legitimately support.

This article addresses that problem through an original non-empirical translational framework. It first defines the biological requirements that distinguish functional periodontal regeneration from narrower tissue responses. It then examines immunomodulation and vascular integration as enabling components that substantially influence regenerative competence without independently establishing regeneration. Subsequent sections will use these distinctions to identify the evidence gap between biomaterial performance and regenerative claims and to define conditions under which stronger translational claims become scientifically admissible.

Biological requirements for functional periodontal regeneration

The periodontium is an integrated load-bearing organ rather than a collection of independently replaceable tissues. Regenerative strategies must therefore contend with several structurally and biologically distinct regions at once: mineralized alveolar bone, root-surface cementum, the intervening periodontal ligament, gingival and connective tissues, vascular networks, resident and recruited cell populations, and a microbial and inflammatory environment that changes during healing. Scaffold-based periodontal engineering has consequently moved toward designs that recognize tissue interfaces and spatial heterogeneity rather than treating the defect as a uniform void [7].

Experimental work with hierarchical constructs supports this direction. Bilayer architectures can provide different physical and biological environments to adjacent components of a complex defect, illustrating why spatial organization may matter independently of bulk material composition [8]. Related biomimetic strategies have sought not only mineralized-tissue formation but also reconstruction of periodontal-ligament architecture and its relationship to the tooth surface and surrounding bone [9]. Such studies are important because they shift the regenerative question from “does new tissue appear?” toward “does the regenerated tissue occupy the correct location and establish the correct interface?”

Tissue-specific scaffold engineering further demonstrates that hard and soft periodontal tissues may require different microstructural cues. Melt-electrowritten constructs, for example, can be designed to support coordinated regeneration across interfaces

rather than optimizing a single tissue compartment [10]. This approach reflects an essential biological principle: bone formation adjacent to a root does not necessarily imply regeneration of the attachment apparatus. A clinically meaningful periodontal complex requires organization of the intervening ligament and insertion into mineralized interfaces in a manner compatible with physiological force transmission.

Periodontal-ligament architecture is therefore an outcome in its own right. Fibre-guiding scaffold features can influence the direction and organization of developing attachment structures, while layered and biphasic systems can generate distinct microenvironments for tissues that would otherwise compete for space during healing [11-13]. These experimental strategies differ considerably in materials and fabrication methods, but collectively they demonstrate why an undifferentiated measure of tissue fill cannot capture the biological requirements of periodontal reconstruction.

A functional definition must also account for maturation. Newly deposited matrix, early mineralization, or histologic evidence of tissue continuity can represent meaningful regenerative progress without establishing durable function. Cementum-like deposition must ultimately be interpreted in relation to attachment formation; periodontal-ligament organization must be interpreted in relation to orientation and insertion; bone formation must be interpreted in relation to its integration with the attachment apparatus; and all three must be considered under the biological and mechanical conditions in which the tooth will function.

These distinctions support a graded vocabulary of evidence. Repair can describe restoration of tissue continuity without reproduction of the original architecture. Tissue formation can identify regeneration of a specific component, such as bone, without implying reconstruction of the full periodontal complex. Integrated periodontal reconstruction requires coordinated development of several relevant tissues and interfaces. Functional periodontal regeneration, the strongest of these terms, additionally requires evidence that the reconstructed attachment behaves in a biologically and mechanically appropriate manner. These categories are proposed interpretive distinctions rather than validated clinical classifications, but they prevent a narrow experimental endpoint from silently acquiring a stronger meaning than the evidence permits.

The central implication is that the evidentiary burden rises with the biological breadth of the claim. A material can legitimately be described as osteoconductive when the evidence demonstrates that property. It may support periodontal tissue reconstruction when several periodontal compartments are regenerated in appropriate spatial relationships. Calling the same material functionally regenerative requires substantially more because the claim now encompasses organization, integration, maturation, and performance of the attachment complex.

The principal biological distinctions that determine this escalation are summarized in **Table 1**.

Table 1. Biological requirements that progressively strengthen a claim of periodontal regeneration

Regenerative component	Biological question that must be resolved	What a positive finding can legitimately establish	What remains unresolved if assessed alone
Defect-compatible material environment	Can the material maintain a biologically tolerable space and structural environment for healing?	Suitability of the material environment for further regenerative testing	Formation of specific periodontal tissues and functional attachment
Alveolar-bone reconstruction	Is mineralized supporting tissue restored within the periodontal defect?	Bone-regenerative activity within the tested model	Cementum formation, periodontal-ligament architecture, fibre insertion and functional load transfer
Cementum/root-interface reconstruction	Does newly formed mineralized tissue establish an appropriate root-surface interface?	Reconstruction of a component required for new attachment	Quality and orientation of the intervening ligament and durability of attachment
Periodontal-ligament reconstruction	Does a ligament-like connective tissue form between root surface and alveolar bone?	Reconstitution of the soft-tissue compartment of the attachment apparatus	Correct insertion, orientation, maturation and mechanical competence
Spatially coordinated cementum–PDL–bone integration	Are the principal periodontal tissues reconstructed in anatomically appropriate relationships?	Integrated structural regeneration in the evaluated model	Long-term mechanical function, durability and reproducibility in patients

Vascular and cellular integration	Are regenerating tissues supplied by viable vascular and cellular networks capable of supporting maturation?	Biological competence of the reconstructed environment	Proof of durable attachment function or clinical superiority
Mechanical and temporal maturation	Does the reconstructed attachment remain organized and competent under physiologic loading over time?	Evidence approaching functional periodontal regeneration	Transportability across defects, patients, treatments and long-term clinical settings
Comparative patient-level benefit	Does the regenerative strategy improve clinically important outcomes beyond an appropriate comparator?	Clinical evidence supporting the intended therapeutic claim	Universal applicability outside the tested indication and population

Table 1 deliberately separates tissue-specific success from the stronger claim of a reconstructed functional organ. The distinction also explains why biological regulation of the healing environment deserves separate analysis. Even an appropriately designed scaffold cannot produce integrated regeneration if inflammation, cellular dysfunction, vascular insufficiency, or adverse host conditions prevent the required tissues from developing and maturing.

Immunomodulation and vascular integration

Periodontal biomaterials are implanted into an environment shaped by microbial exposure, tissue injury, inflammatory signalling, recruited immune cells, resident stromal populations, and changing metabolic conditions. Consequently, the biological performance of a scaffold is not determined solely by whether cells adhere to it or whether it supports mineral deposition. Regenerative competence also depends on whether the local immune environment permits progenitor-cell survival, matrix organization, vascular development, and progressive tissue maturation.

Macrophage behaviour is one important component of this environment. Experimental hydrogels designed to combine stem-cell recruitment with modulation of macrophage responses demonstrate that regenerative materials can influence both cellular recruitment and inflammatory state [14]. Such findings support the view that immunity is not merely an obstacle to regeneration but an active determinant of the conditions under which regeneration occurs. At the same time, macrophage biology cannot be reduced to a rigid M1/M2 binary. Phenotypes vary over time and across tissue contexts, so a shift in selected markers is more appropriately interpreted as evidence of immune modulation than as proof that a regenerative program has been completed.

Paracrine signalling provides another route through which regenerative competence may be altered. Mesenchymal-stem-cell-derived exosomes can enhance periodontal-ligament-cell functions and improve regenerative responses in experimental systems [15]. These observations are biologically plausible because extracellular vesicles can transport regulatory molecules between cells, but the hierarchy of evidence remains important. Improved proliferation, migration, differentiation, or signalling constitutes mechanistic evidence; it does not independently demonstrate reconstruction of a durable periodontal attachment.

Vascularization introduces a related but distinct requirement. Periodontal tissues undergoing regeneration require delivery of oxygen, nutrients, circulating cells, and signalling molecules while metabolic waste is removed. Biomaterials that couple osteogenic and angiogenic properties therefore address a biologically important limitation of tissue engineering [16]. Yet angiogenic marker expression, endothelial behaviour, or early vessel formation should not automatically be described as stable vascular integration. The stronger claim requires evidence that vascular structures persist, integrate with regenerating tissues, and support their maturation.

Even seemingly subtle material characteristics can affect these processes. Chiral nanoscale surfaces have been reported to influence periodontal regenerative responses, illustrating how physicochemical properties can become biologically instructive rather than merely structural [17]. Redox-active materials provide another example. Cerium-oxide-containing nanofibrous systems can regulate oxidative conditions while supporting bone-regenerative processes [18], and glutathione-peroxidase-mimicking nanozymes can reduce reactive oxygen species within inflammatory periodontal environments and improve periodontal-bone regeneration experimentally [19]. These findings establish plausible mechanisms through which biomaterials can modify hostile microenvironments, but reduction of oxidative stress is an enabling action rather than a complete regenerative endpoint.

Physical stimulation can also intersect with cellular metabolism and inflammation. Piezoelectric hydrogels

developed for periodontitis treatment suggest that mechanically responsive biomaterials may modify bioenergetic and regenerative behaviour rather than functioning only as passive matrices [20]. Similarly, functionalized nanofibrous membranes have been designed to influence macrophage polarization through PI3K/AKT and NF-κB-related signalling while simultaneously supporting periodontal regeneration [21]. At the cellular level, nanosilicates can activate PI3K-AKT-related pathways in periodontal-ligament cells and promote regenerative phenotypes [22]. Together, these studies show that material–cell interactions occur across several regulatory levels, from surface and mechanical cues to intracellular pathways.

The expanding literature on mesenchymal stromal cells and their derivatives reinforces the same interpretation. Reviews of MSC-mediated periodontal regeneration describe immunomodulation as an important component of their potential biological value [23]. Exosome-focused syntheses likewise identify interactions among immune regulation, cell signalling, and tissue-repair mechanisms [24]. However, these literatures remain heterogeneous in cell source, isolation methods, cargo, delivery systems, disease models, and outcome definitions. The mechanistic convergence is therefore stronger than the current basis for broad clinical claims.

Inflammatory signalling can also directly constrain the regenerative competence of periodontal-ligament stem cells. Experimental targeting of cGAS-STING-associated inflammatory activity has shown that an adverse inflammatory state can impair osteogenic function and that biomaterial-based modulation can partially restore a more favorable regenerative environment [25]. A related strategy using L-arginine-modified mesoporous bioactive glass combines reactive-oxygen-species scavenging with nitric-oxide release and affects inflammatory, macrophage, and osteogenic responses in experimental periodontitis [26]. These systems illustrate why regenerative biomaterials increasingly target microenvironmental control rather than tissue replacement alone.

The growing field of nanotherapeutic immune modulation similarly emphasizes the possibility of restoring local immune homeostasis, while also highlighting delivery, safety, complexity, and translational limitations [27]. Vascular biology adds another layer. Recent mechanistic work with periodontal-ligament stem cells indicates that scaffold-related molecular organization can couple osteogenic differentiation with proangiogenic signalling [28]. Such coupling is important because bone and vascular development interact during regeneration, yet it remains necessary to distinguish signalling evidence from the demonstration of a mature, perfused and functionally integrated vascular network.

The newest multifunctional systems take this integration still further. Magnetoelectric platforms, temporally orchestrated microneedle–nanosheet systems, and morphology-engineered hydroxyapatite constructs have been designed to combine antibacterial activity, immune regulation, vascular support, and osteogenic regeneration within the same therapeutic environment [29-31]. Their sophistication makes them particularly informative for translational reasoning. Multifunctionality can strengthen biological plausibility because several known constraints are addressed simultaneously, but it does not reduce the need for validation. Indeed, the more biological functions a platform is claimed to coordinate, the more carefully each contribution, interaction, temporal sequence, and downstream endpoint must be demonstrated.

The resulting evidence supports an important distinction: immunomodulation and vascular integration are enabling dimensions of periodontal regeneration, not substitutes for it. A material may successfully attenuate inflammatory signalling yet fail to reconstruct the cementum–periodontal-ligament–bone interface. It may promote angiogenic signalling without establishing durable vascular integration. It may enhance osteogenic differentiation while leaving fibre insertion unresolved. Conversely, a construct that generates organized tissues but does so within a persistently dysregulated inflammatory environment may lack the biological stability required for durable function.

This means that immunological and vascular endpoints should be interpreted according to what they directly demonstrate. Their strongest value arises when they can be linked to subsequent tissue organization, interface maturation, and sustained functional reconstruction rather than being treated as independent proof of regeneration. **Table 2** therefore organizes commonly reported biomaterial endpoints according to their legitimate interpretive role and the unresolved question that prevents premature escalation to a stronger regenerative claim.

Table 2. Biomaterial endpoints that inform immune–vascular periodontal regeneration and the interpretive limits of each endpoint

Observed biomaterial endpoint	Biological process represented	What the endpoint can support	Why it remains insufficient for a complete regenerative claim
Reduced inflammatory mediator activity	Modification of the inflammatory microenvironment	Evidence that a material can attenuate selected inflammatory pathways	Does not establish restoration of periodontal tissues, interfaces or function
Altered macrophage phenotype or signalling	Immune-cell response to the material and wound environment	Evidence of immunomodulatory activity	Macrophage states are heterogeneous and dynamic; marker changes do not prove durable regeneration
Improved periodontal-ligament-cell viability, migration or differentiation	Cellular competence within the regenerative environment	Evidence that the material supports relevant periodontal cells	Cellular response remains upstream of integrated tissue reconstruction
Extracellular-vesicle-mediated signalling	Paracrine regulation of immune and regenerative cell behaviour	Mechanistic evidence for cell–cell communication and biological instruction	Product composition, persistence, delivery and tissue-level consequences remain context dependent
Reactive-oxygen-species reduction	Control of oxidative stress within an inflammatory lesion	Evidence of improved redox conditions for healing	Oxidative control alone does not determine tissue identity or functional attachment
Increased osteogenic differentiation	Promotion of bone-forming cellular programmes	Evidence supporting osteogenic potential	Bone-oriented activity does not demonstrate cementum formation or periodontal-ligament reconstruction
Increased angiogenic signalling	Promotion of endothelial recruitment or vascular-development pathways	Evidence supporting proangiogenic potential	Signalling or early vessel formation does not prove mature, stable and functionally integrated vasculature
Coupled osteogenic and angiogenic responses	Interaction between mineralized-tissue development and vascular support	Stronger biological plausibility for coordinated tissue development	Still does not establish complete cementum–PDL–bone reconstruction or long-term mechanical competence
Combined antimicrobial and immunomodulatory activity	Simultaneous reduction of microbial pressure and inflammatory dysregulation	Evidence that multiple barriers to healing are being addressed	Multifunctionality does not establish the relative contribution, durability or clinical necessity of each function
Temporally programmed biological activity	Intended matching of material function to changing stages of healing	Evidence that timing is being treated as an explicit design variable	Experimental timing cannot be assumed to reproduce the temporal biology of human periodontal healing
Integrated immune–vascular–osteogenic modulation	Coordinated influence across several regenerative mechanisms	High-level preclinical evidence of a biologically instructive microenvironment	Strong mechanistic integration remains distinct from verified functional periodontal regeneration and comparative patient benefit

The evidence developed through these first three sections establishes the biological foundation for the manuscript's subsequent translational analysis. Material performance can create a permissive environment, guide tissue organization, regulate inflammatory responses, support vascular development, and stimulate specific regenerative cell programmes. None of these observations should be discounted; each represents a legitimate level of evidence. The unresolved problem is how far those findings permit investigators to move from a material-performance statement toward progressively stronger claims of periodontal regeneration. That question requires explicit comparison between the endpoint demonstrated and the biological or clinical meaning assigned to it.

Evidence gap between biomaterial performance and regenerative claims

The translational problem becomes most visible when biologically plausible interventions are tested against comparative clinical outcomes. In a pilot clinical trial of intrabony periodontal defects, adding autologous periodontal-ligament-derived mesenchymal stem cells

to a xenogeneic bone substitute was feasible and safe, yet did not produce a statistically significant additional improvement in clinical attachment level or probing-depth reduction over the control treatment [32]. The study was small and cannot exclude clinically meaningful benefit, but its importance is conceptual: additional biological sophistication does not guarantee incremental clinical efficacy.

The same caution applies to increasingly responsive biomaterials. Injectable hydrogels can be engineered for controlled release, environmental responsiveness, cell recruitment, and tissue support, but their regenerative interpretation remains dependent on mechanics, degradation, delivery, defect anatomy, and the biological state of the periodontal wound [33]. Strong alveolar-bone formation likewise represents a narrower endpoint than reconstruction of the entire attachment apparatus. Multifunctional microspheres that enhance bone regeneration in experimental periodontal defects provide valuable evidence of osteogenic performance without independently demonstrating cementum formation, organized periodontal-ligament insertion, or durable physiological force transmission [34].

At the higher end of preclinical evidence, engineered extracellular-vesicle systems have produced native-like cementum–periodontal-ligament–bone organization in experimental models [35]. Such findings substantially strengthen a claim of integrated periodontal reconstruction because they move beyond isolated cell markers or bone formation. They nevertheless remain separated from human functional regeneration by species transfer, durability, biomechanical loading, manufacturing reproducibility, and comparative clinical performance. Contemporary analyses of smart periodontal biomaterials similarly emphasize that microbial burden, inflammatory instability, multi-tissue interfaces, mechanical forces, and model validity remain major translational barriers [36].

The central evidentiary gap is therefore not a simple opposition between “laboratory” and “clinical” evidence. It is a sequence of non-equivalent questions. A material may be well characterized but biologically ineffective; biologically active but spatially incapable of reconstructing the attachment apparatus; structurally regenerative but mechanically immature; or functionally promising without demonstrated comparative patient benefit. A regenerative claim becomes vulnerable whenever terminology advances beyond the strongest level directly supported by the evidence.

Table 3 formalizes these claim-specific requirements without converting them into a numerical score or universal threshold.

Table 3. Evidence requirements that constrain progressively stronger periodontal regenerative claims

Intended claim	Minimum evidence that directly supports the claim	Evidence that strengthens but does not independently prove it	Critical unresolved question before escalation
Material is suitable for periodontal regenerative investigation	Verified physicochemical, structural, mechanical, degradation and compatibility characteristics appropriate to the intended use	Favorable cell interaction or controlled release	Does the material produce biologically relevant effects in a periodontal context?
Material is biologically instructive	Reproducible influence on relevant periodontal cells, immune pathways, vascular biology or regenerative signalling	Multimodal activity across several pathways	Do these effects alter tissue reconstruction rather than only surrogate markers?
Material supports periodontal tissue regeneration	Demonstrated formation of one or more periodontal tissues in an appropriate model	Immunomodulatory, angiogenic or antimicrobial activity	Are the regenerated tissues anatomically coordinated and appropriately interfaced?
Material supports integrated periodontal reconstruction	Coordinated cementum, periodontal-ligament and alveolar-bone reconstruction with appropriate spatial relationships	Native-like architecture and vascular integration	Does the reconstructed attachment mature and function under physiological loading?
Material supports functional periodontal regeneration	Integrated reconstruction plus evidence of mature attachment organization, durability and biomechanical competence	Strong mechanistic and advanced animal evidence	Is function reproducible across relevant defects and sustained over time?

Material provides clinically meaningful regenerative benefit	Appropriate human comparative evidence showing patient-relevant benefit for the intended indication	Consistent mechanistic and preclinical evidence	Is benefit durable, safe, reproducible and applicable beyond the tested population?

These levels should not be interpreted as a rigid development ladder. A study can legitimately support an important lower-level claim even when evidence for a stronger claim is absent. The purpose is to prevent evidence obtained at one level from being rhetorically transferred to another without an explicit scientific bridge.

The interaction among biological requirements, immune and vascular conditions, tissue organization, and evidentiary boundaries is summarized in **Figure 1**.

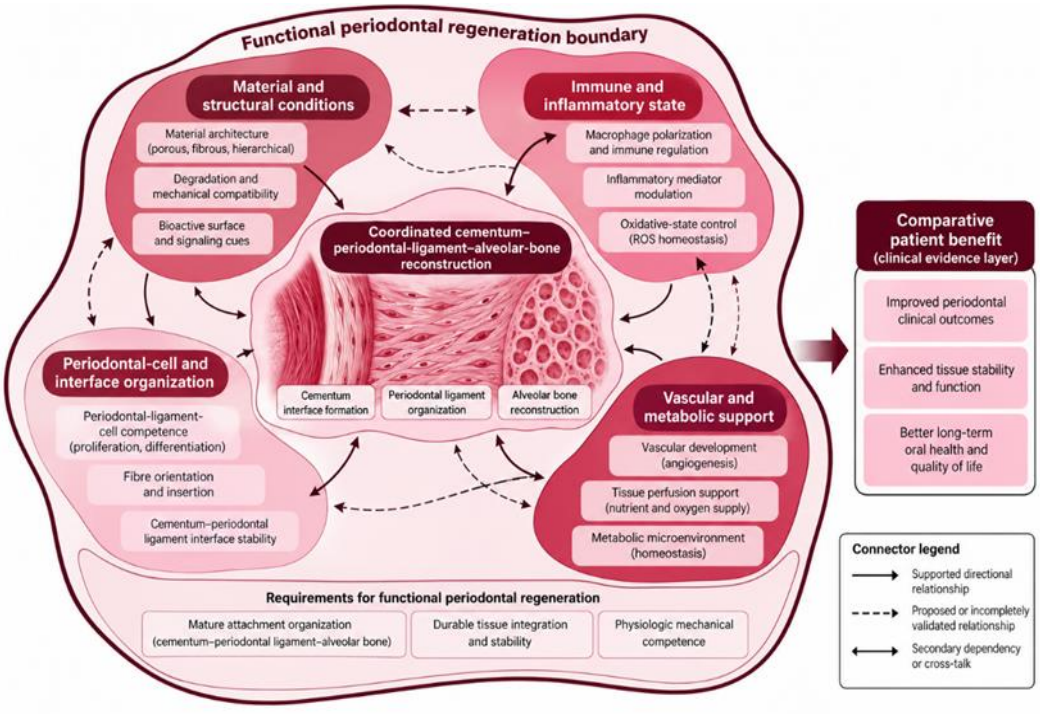


Figure 1. Biological dependencies that distinguish periodontal tissue response from functional reconstruction

A translational evidence-admissibility framework

The preceding evidence supports a simple but restrictive principle: the admissible strength of a regenerative claim is limited by the most important unresolved evidence dimension required by that claim. This does not mean that every study must demonstrate every biological and clinical endpoint. Instead, the wording of the claim must remain within the evidence actually obtained.

For a material-characterization claim, structural, chemical, mechanical, and degradation evidence may be sufficient. A claim of biological instruction requires additional evidence that the material alters relevant periodontal cells or biological pathways. A claim of integrated regeneration requires evidence that distinct periodontal tissues are reconstructed in anatomically coherent relationships. Functional regeneration requires a further bridge to attachment maturation, biomechanical competence, and durability. Claims of patient benefit require appropriate human comparative evidence.

The framework therefore treats material properties, immune regulation, vascular integration, tissue reconstruction, function, and clinical benefit as related but non-interchangeable dimensions. Evidence can accumulate across them, but strength in one dimension does not compensate automatically for absence in another when that missing dimension is indispensable to the proposed claim. This prevents two opposite errors: inflating a surrogate endpoint into a clinical conclusion, and dismissing valid material or mechanistic findings merely because clinical evidence has not yet been generated.

Figure 2 expresses this claim-limiting logic as a conditional map rather than a quantitative grading system.

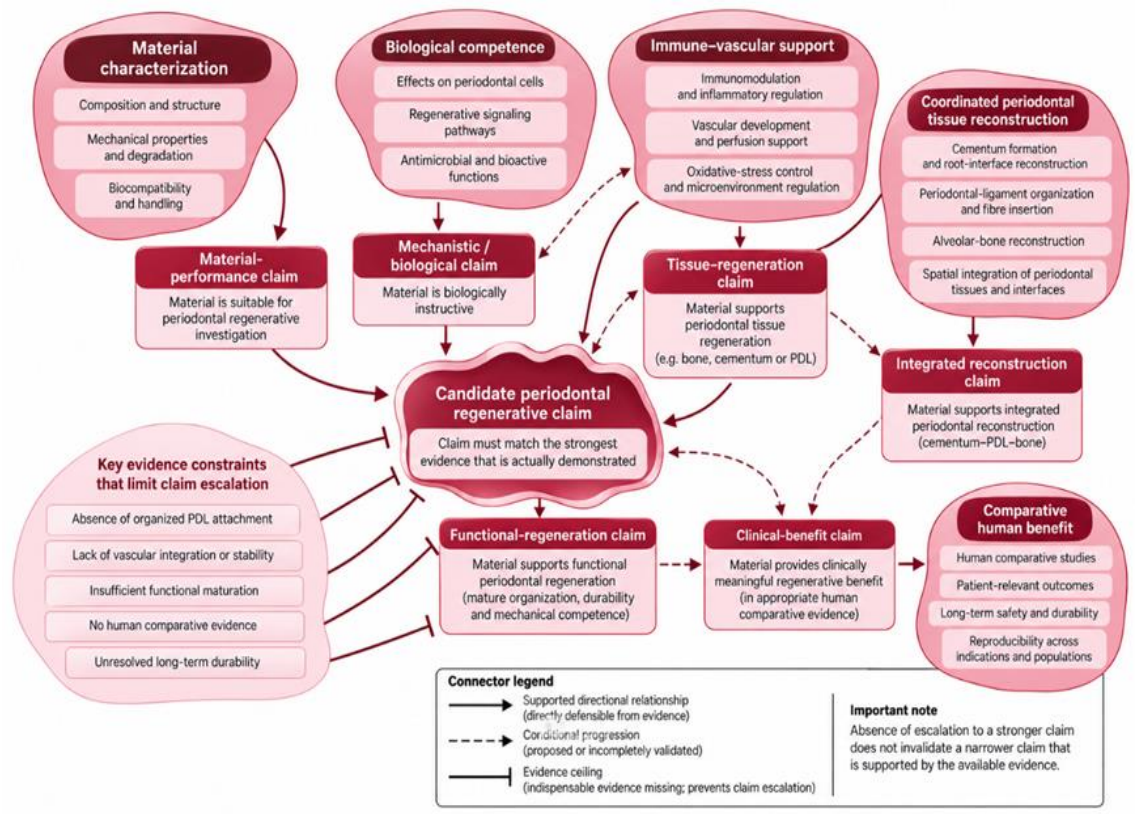


Figure 2. Evidence ceilings governing escalation from biomaterial performance to periodontal regenerative claims

Experimental validation needs, clinical translation, and limitations

The framework becomes useful only if it can guide validation rather than merely classify language. Experimental design should therefore target the unresolved evidence dimension that prevents the intended claim from becoming admissible. A material with strong physicochemical and cellular evidence may require an appropriate defect model rather than additional repetitions of the same in-vitro endpoint. A construct that produces bone and ligament-like tissue may require better evidence of fibre insertion, maturation, and mechanical function. A platform with compelling animal reconstruction may require comparative human evaluation before claims move toward clinical benefit.

Functional periodontal-ligament reconstruction deserves particular attention because it is one of the easiest components to under-specify. Histologic proximity of connective tissue to a root surface is not equivalent to a mature ligament capable of transferring physiologic forces. Future validation should integrate tissue identity, fibre organization, insertion at mineralized interfaces, maturation, and durability under relevant loading without imposing unsupported universal force thresholds.

Clinical translation presents a different evidentiary problem. Human trials are not necessary to support every material or mechanistic statement, but they become indispensable when the claim concerns patient benefit, treatment superiority, or predictable clinical regeneration. The pilot MSC trial illustrates why this distinction matters: plausible regenerative biology did not automatically produce demonstrable incremental clinical benefit [32]. Clinical evaluation must therefore be matched to the strength of the claim rather than treated as a ceremonial final step.

Several limitations apply to the proposed framework. Periodontal models differ in defect morphology, species biology, microbial conditions, loading environment, treatment sequence, and measured endpoints. Immune and vascular processes are dynamic, and experimental markers provide incomplete representations of those systems. Biomaterials also vary in manufacturing complexity and reproducibility. Most importantly, no validated quantitative weighting exists that would justify converting the present framework into a universal score. Its purpose is interpretive: to expose which evidence supports a claim, which evidence merely strengthens plausibility, and which missing dimension still limits translation.

Conclusion

Biomaterial performance justifies a claim of periodontal regeneration only when the wording of that claim remains proportional to the biological and translational evidence actually demonstrated. Physicochemical quality, immunomodulation, vascular support, cellular activity, bone formation, and even sophisticated multi-tissue reconstruction each provide legitimate evidence, but they are not interchangeable with functional periodontal regeneration or patient benefit.

A stronger regenerative claim requires progressively stronger evidence of coordinated cementum–periodontal-ligament–alveolar-bone reconstruction, attachment maturation, biomechanical competence, durability, and, when clinical benefit is claimed, appropriate human comparative outcomes. Immunomodulation and vascular integration are therefore best understood as enabling components within a larger regenerative system rather than independent proof of success. The proposed evidence-admissibility framework preserves meaningful lower-level findings while preventing surrogate or preclinical outcomes from silently acquiring stronger clinical meaning. Its value lies not in assigning a score, but in making the evidentiary boundary of each regenerative claim explicit and testable.

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