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Reconstructing Bone Repair: A Systems-Regeneration Framework Integrating Skeletal Precursor Cells, Mitochondrial Therapeutics, and Organ-Specific Peptide Signaling

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Abstract

Fracture healing is a highly coordinated regenerative process, yet delayed union and nonunion remain important clinical problems, particularly in the setting of severe tissue injury, infection, vascular compromise, aging, and metabolic disease. Increasing evidence indicates that impaired healing reflects disruption of an integrated regenerative system involving skeletal precursor/progenitor cells, osteoimmune regulation, angiogenesis–osteogenesis coupling, mitochondrial competence, and tissue-contextual signaling rather than failure of osteogenesis alone. This review examines these interdependent mechanisms and proposes a systems-regeneration framework in which complementary interventions address distinct biological constraints on bone repair. Skeletal precursor/progenitor cells (PSCs) provide a candidate cellular substrate for osteochondral reconstruction; mitochondrial-directed therapeutics may support the metabolic competence required for progenitor survival, differentiation, vascular function, and matrix production; and tissue-derived peptide biologics represent candidate modulators of osteogenic, immune, vascular, and extracellular matrix (ECM) signaling. Within this framework, the European Wellness platform integrating organ-specific PSCs, Mito Organelle (MO) biologics, and Nano Organo Peptides (NOPs) is evaluated as a candidate implementation of mechanistically coordinated regenerative therapy rather than as an established treatment for fracture repair.

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Its central, testable hypothesis is that cellular reconstruction, metabolic support, and tissue-contextual signaling address nonredundant regenerative bottlenecks and may therefore provide greater benefit when appropriately integrated. Translation of this concept requires rigorous product characterization, mechanism-linked potency assays, demonstration of skeletal target engagement and tissue specificity, factorial testing of component interactions, and validation in clinically relevant fracture models before controlled clinical evaluation. This framework shifts the therapeutic objective from stimulation of isolated osteogenic pathways toward reproducible restoration of anatomically integrated, vascularized, and biomechanically competent bone.

Keywords

Reconstructing Bone Repair; Regeneration; Skeletal Precursor Cells; Mitochondrial therapeutics; Stem cells; Organ-specific peptide signaling.

Introduction

The unmet need for regenerative bone repair

Fracture healing is among the most effective regenerative processes in adult mammals, yet its clinical success remains imperfect [1]. Most fractures ultimately unite, but delayed union and nonunion continue to impose substantial morbidity through prolonged pain, impaired mobility, repeated surgery, loss of productivity, and increased healthcare utilization [2]. Contemporary estimates indicate that approximately 5–10% of fractures develop impaired healing, with considerably higher rates in anatomically complex injuries and patients with adverse biological or mechanical risk factors [3]. Infection, open fracture, severe soft-tissue injury, smoking, diabetes, obesity, vascular compromise, and mechanical instability substantially increase the probability of nonunion [4-6]. Despite major advances in fracture fixation, bone grafting, microsurgical reconstruction, and orthobiologics, persistent nonunion remains a clinically important problem, underscoring the limitations of strategies directed primarily toward mechanical stabilization or individual molecular pathways [7].

Fracture healing requires coordinated activation of injury-responsive skeletal progenitors, temporally regulated osteoimmune signaling, vascular reconstruction, metabolic adaptation, and ECM and peptide-mediated niche signaling [8]. Disruption of these interdependent processes, particularly in severe injury, aging, metabolic disease, infection, or vascular compromise, can prevent progression from inflammatory repair to mechanically competent bone regeneration [9]. Accordingly, impaired union is increasingly understood as failure of a spatially and temporally organized regenerative system rather than deficiency of a single osteogenic pathway.

Current treatment addresses these regenerative requirements incompletely. For example, stable fixation restores mechanical conditions; autologous bone graft supplies osteogenic cells, matrix, and biological signals; recombinant growth factors can augment selected osteoinductive pathways; and cell therapies, biomaterials, EVs, gene-based interventions, and bioactive scaffolds are increasingly being investigated for difficult defects and nonunions [2,10]. Nevertheless, no single modality reliably reconstructs the full osteogenic, vascular, immunological, metabolic, and mechanical environment required for predictable regeneration in biologically compromised fractures [11]. Contemporary reviews of nonunion therefore increasingly frame impaired healing as the consequence of interacting mechanical and biological deficiencies rather than failure of one isolated pathway [12].

This review advances the hypothesis that difficult fracture repair should be approached as a systems-

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regeneration problem in which durable union requires coordinated restoration of three complementary biological domains: 1) an appropriately specified skeletal precursor/progenitor compartment capable of generating cartilage and bone; 2) metabolic competence sufficient to sustain progenitor expansion, osteoblast differentiation, and matrix production; and 3) a regenerative signaling environment that coordinates inflammation, angiogenesis, extracellular-matrix (ECM) remodeling, and osteogenic maturation. Within this framework, skeletal precursor/progenitor stem cells (PSCs) provide the cellular substrate for reconstruction, mitochondrial-directed therapeutics address metabolic constraints on regeneration, and tissue-derived peptide biologics represent candidate modulators of the fracture-healing niche. The European Wellness platform, integrating organ-specific PSCs, Mito Organelle (MO) biologics, and Nano Organo Peptides (NOPs), will be evaluated as one hypothesis-driven implementation of this model, with clear distinction between established fracture biology, mechanistic plausibility, and product-specific evidence.

Bone as a Spatially and Temporally Organized Regenerative Organ

Bone regeneration is distinguished from most adult tissue repair by its capacity to restore tissue architecture without permanent scar formation under favorable biological and mechanical conditions [13]. This process is neither uniform nor cell autonomous. Fracture healing proceeds through overlapping phases of hematoma formation and inflammation, progenitor recruitment, soft-callus formation, endochondral and intramembranous ossification, vascular reconstruction, mineralization, and remodeling [14]. The outcome depends on the spatial and temporal coordination of five interdependent biological systems: skeletal PSC activation, osteoimmune regulation, angiogenesis–osteogenesis coupling, metabolic and mitochondrial adaptation, and local peptide/growth-factor signaling [1]. Rather than acting as sequentially independent modules, these systems form a regenerative network in which disruption of one compartment alters the function of the others.

Periosteal and skeletal PSC biology: The cellular substrate for fracture repair is supplied by heterogeneous skeletal stem and progenitor populations distributed across the periosteum, bone marrow, endosteal surface, and surrounding connective tissues [15]. Recent lineage-tracing studies have substantially refined the traditional concept of a generic mesenchymal stem cell by demonstrating that anatomically distinct skeletal PSCs contribute differentially according to injury context [16]. In adult mice, $LepR^{+}$/$Adiponectin^{+}$ bone-marrow stromal populations predominate during steady-state bone formation and repair of selected marrow-associated injuries [17], whereas $Gli1^{+}$ periosteal skeletal PSCs become major contributors after bicortical fracture and can regenerate both bone and marrow stroma [6]. This compartment specificity indicates that effective regenerative therapy should be matched to the biological demands of the injury rather than based solely on broad mesenchymal multipotency [18]. The periosteum is particularly important in traumatic fracture healing because it contains highly responsive progenitors capable of proliferating, migrating into the fracture callus, and undergoing both chondrogenic and osteogenic differentiation [19]. Mechan transduction is integral to this response. Experimental disruption of Piezo1 signaling impairs periosteal stem-cell-mediated fracture repair, establishing a direct link between mechanical cues and progenitor activation [5]. Recent work has further identified BNC2 as an injury-responsive regulator of periosteal stem cell proliferation and endochondral ossification through chromatin remodeling, underscoring that regenerative competence is governed by inducible

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transcriptional and epigenetic programs rather than progenitor abundance alone [20].

Osteoimmunology as a regulator of regenerative timing: Fracture repair begins with inflammation, but inflammation is productive only when it is appropriately timed and resolved [4,21]. Vascular disruption and hematoma formation recruit neutrophils, monocytes, macrophages, lymphocytes, and other immune populations that generate cytokines, chemokines, lipid mediators, and growth factors required for debris clearance, angiogenesis, progenitor recruitment, and callus formation [4]. Macrophages are particularly important because their functional state evolves across the regenerative sequence: early inflammatory macrophage activity supports recruitment and antimicrobial defense, whereas subsequent pro-reparative phenotypes facilitate efferocytosis, angiogenesis, matrix remodeling, and osteoblast differentiation [4,21]. A systematic review of macrophage-directed fracture studies supports the importance of this temporal transition, although the simple M1/M2 binary does not adequately capture the phenotypic heterogeneity observed in vivo [21]. Adaptive immunity also contributes to fracture outcome. Distinct T-cell subsets can promote or inhibit osteogenesis through effects on inflammatory cytokines, osteoclastogenesis, and progenitor behavior, and recent literature increasingly positions T-cell regulation as a component of fracture-healing biology rather than merely a systemic modifier [4,21,22]. Thus, osteoimmunology is not an ancillary feature of bone repair; it is a mechanism through which the injury environment determines whether skeletal progenitors progress toward productive cartilage and bone formation or remain exposed to persistent inflammatory signaling.

Angiogenesis–osteogenesis coupling: Bone formation and vascular regeneration are mechanistically coupled [23-25]. Fracture disrupts local perfusion and creates a hypoxic, metabolically demanding environment in which restoration of blood supply is necessary not only for oxygen and nutrient delivery but also for direct endothelial regulation of osteogenic progenitors [23-25]. Specialized CD31hiEmcnhi endothelium (or type H endothelial cells) vessels are closely associated with osteoprogenitor populations and have emerged as important mediators of angiogenesis–osteogenesis coupling [24-26]. Endothelial cells within these vascular niches communicate with osteoblast-lineage cells through VEGF-, Notch-, HIF, PI3K/AKT-, and other signaling networks that coordinate vascular ingrowth with new-bone formation [27]. The energetic interdependence of these processes is increasingly recognized. Fracture repair requires simultaneous expansion of vascular and osteogenic compartments under changing oxygen availability, and insufficient angiogenesis is strongly associated with impaired union [23,28]. Experimental activation of SIRT1, for example, enhances bone repair by promoting type H vessel formation through PI3K/AKT/FOXO1 signaling, illustrating that vascular and osteogenic restoration can be therapeutically coupled rather than targeted independently [29].

Mitochondrial osteogenic competence: The transition of skeletal PSCs toward mature osteoblasts requires substantial metabolic reprogramming. Osteogenic differentiation increases mitochondrial biogenesis and oxidative phosphorylation to support ATP generation, collagen synthesis, matrix maturation, ion transport, and mineralization. Mitochondrial function also regulates ROS signaling, calcium handling, apoptosis, and the balance between stem-cell maintenance and differentiation [30]. Experimental enhancement of mitochondrial oxidative phosphorylation increases osteogenic differentiation and accelerates fracture repair, whereas inhibition of electron transport abolishes these

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osteoinductive effects, providing causal evidence that mitochondrial competence contributes directly to bone regeneration [31].

Mitochondrial biology therefore links several other regenerative pillars, i.e., hypoxia and revascularization alter substrate availability; inflammatory mediators influence mitochondrial function; oxidative stress modifies progenitor survival; and aging, diabetes, and other metabolic disorders can reduce mitochondrial reserve [32]. The relevant regenerative endpoint is consequently not maximal oxidative metabolism at all stages, but sufficient metabolic flexibility to support changing cellular demands during inflammation, chondrogenesis, osteogenesis, and remodeling [33,34].

Peptide-mediated niche signaling: Bone regeneration is also governed by a dense network of soluble and matrix-derived peptides that regulate progenitor recruitment, osteoblast maturation, osteoclast activity, angiogenesis, and ECM organization [35]. Bone morphogenetic proteins (BMPs) provide the classic example of peptide/protein-mediated osteoinduction, but contemporary studies demonstrate that substantially smaller bioactive peptides can also exert defined skeletal effects [36]. P-15, a collagen-derived peptide, has been investigated as an osteogenic biomimetic that promotes cellular attachment and osteoblast-associated responses, illustrating how matrix-derived peptide sequences can reproduce specific aspects of the native regenerative microenvironment [37]. More direct evidence for endogenous peptide regulation comes from PEPITEM, a physiological peptide recently shown to act through NCAM-1 on osteoblasts, promote osteoblast maturation and new-bone formation, increase osteoprotegerin release, and thereby indirectly constrain RANKL-mediated osteoclast activity [38]. These findings establish a broader principle highly relevant to organ-derived peptide therapeutics: peptide signals can coordinate formation and resorption rather than function solely as nonspecific trophic factors. However, activity demonstrated for a purified peptide cannot be extrapolated to complex tissue-derived preparations without identification of the active constituents and demonstration of equivalent target engagement.

Why fracture healing fails: biological convergence in delayed union and nonunion

Delayed union and nonunion arise when mechanical or biological injury drives the normally coordinated fracture-repair program beyond its regenerative capacity. Rather than representing isolated osteogenic failure, impaired union reflects convergent defects in injury-responsive progenitor recruitment, inflammatory resolution, vascular reconstruction, metabolic competence, and osteogenic signaling. The relative contribution of each defect varies with injury severity, periosteal and soft-tissue disruption, infection, aging, metabolic disease, smoking, vascular compromise, and fixation stability. Accordingly, nonunion is better conceptualized as failure to establish or maintain a regeneration-competent fracture niche than as deficiency of a single osteogenic pathway. Among the systemic conditions that can compromise skeletal integrity and adversely influence the response to fracture, osteoporosis (OP) represents one of the most important.

Osteoporosis as a major contributor to impaired bone integrity and fracture risk

Osteoporosis (OP) is one of the most important systemic skeletal disorders contributing to fragility fractures and is often referred to as a “silent” disease because substantial loss of bone strength may occur before clinical symptoms become apparent. Its prevalence increases markedly with ageing, making

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osteoporosis an important component of healthy-ageing and anti-aging strategies. Epidemiological data from Europe and North America demonstrate a substantial population burden of osteoporosis, while also indicating that a considerable proportion of individuals at high fracture risk remain inadequately diagnosed or treated, including patients who have already sustained a fragility fracture [39-42].

OP can be broadly classified as primary or secondary. Primary osteoporosis includes postmenopausal osteoporosis, predominantly affecting women after menopause, and age-related osteoporosis, which develops in both women and men with advancing age. Secondary osteoporosis results from conditions or external factors that adversely affect bone metabolism. These include endocrine and autoimmune disorders, malignancies, chronic systemic diseases, excessive alcohol consumption, smoking, prolonged immobilization, and medications such as glucocorticoids and some antiepileptic agents [43]. Assessment of skeletal fragility relies on both measurement of bone mineral density (BMD) and estimation of the individual's overall fracture probability. According to recommendations from the International Osteoporosis Foundation (IOF) and the International Society for Clinical Densitometry (ISCD), dual-energy X-ray absorptiometry (DXA) of the lumbar spine and hip remains the standard method for assessing BMD and supporting the diagnosis of osteoporosis. Fracture Risk Assessment Tool (FRAX) provides complementary information by integrating clinical risk factors with, when available, femoral-neck BMD to estimate the probability of future fractures [44].

Dysregulation of bone remodeling in OP

The biological basis of osteoporosis involves disruption of the normally tightly regulated balance between bone resorption and bone formation. Bone remodeling is a continuous process in which old or damaged tissue is removed by osteoclasts and subsequently replaced through osteoblast-mediated matrix synthesis and mineralization. A shift toward excessive resorption or insufficient formation progressively reduces bone mass and compromises skeletal microarchitecture. Osteoclast differentiation and activation are regulated by several interacting signals, among which receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) have central roles. RANKL promotes the differentiation and activation of osteoclast precursors, whereas M-CSF supports their survival and proliferation. Alteration of these regulatory mechanisms can increase osteoclast activity and contribute to pathological bone loss [45].

Skeletal progenitor function and osteogenic potential

Bone formation ultimately depends on the ability of skeletal progenitor and stromal cell populations to generate functional osteoblasts. MSCs possess multilineage differentiation potential and may give rise to osteogenic, adipogenic, chondrogenic, and myogenic lineages. The balance between these differentiation pathways is influenced by genetic programs, systemic hormones, inflammatory mediators, extracellular signals, and the local bone microenvironment [46]. Ageing can progressively alter this cellular balance. Reduced osteogenic competence, together with increased adipogenic differentiation and cellular senescence, may contribute to declining bone-forming capacity. Transcriptional regulators such as RUNX2 and osterix (Osx) are important for commitment toward the osteoblast lineage, whereas activation of PPARγ promotes adipogenic differentiation. Consequently, disturbances in the regulatory environment surrounding progenitor cells may shift lineage allocation away from osteogenesis and toward

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adipogenesis [46].

Several signaling pathways participate in this process, including Wnt/β-catenin, bone morphogenetic protein (BMP), transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF), parathyroid hormone (PTH), and Klotho-associated signaling. Genetic variation or altered expression of molecules such as RUNX2, LRP5, and COL1A1 may further influence osteogenic capacity and extracellular-matrix formation [47]. These observations suggest that age-related skeletal deterioration cannot be explained solely by excessive osteoclast activity. A decline in the regenerative potential of osteogenic progenitors and changes in their microenvironment may also contribute substantially to the development and progression of osteoporosis.

Osteoblasts, osteocytes, and regulation of bone formation

Following commitment to the osteoblast lineage, these cells synthesize the organic components of bone matrix, including type I collagen, osteocalcin, osteopontin, and other matrix-associated proteins. Alkaline phosphatase activity and subsequent mineralization facilitate maturation of the extracellular matrix. A proportion of mature osteoblasts subsequently becomes embedded within the mineralized matrix and differentiates into osteocytes, which represent the predominant mechanosensory cell population of mature bone [48]. Osteoblast differentiation and function are controlled by a complex network of transcription factors and signaling pathways. RUNX2, Osx, β-catenin, ATF4, AP-1 family members, BMPs, FGFs, TGF-β, IGF-1, Wnt signaling, PTH, and Klotho all participate in maintaining skeletal homeostasis. Disruption of these pathways may impair matrix production, mineralization, or communication between bone-forming and bone-resorbing cells [49].

Osteoclastogenesis and the RANK–RANKL–OPG regulatory network

Osteoclasts are multinucleated cells specialized for the removal of mineralized bone. Unlike osteoblasts, they originate from hematopoietic progenitors of the monocyte/macrophage lineage. Their differentiation requires coordinated stimulation by MSC and RANKL [50]. A central regulatory mechanism is the interaction between RANKL and its receptor RANK on osteoclast precursors. RANK activation initiates intracellular signaling pathways that promote osteoclast differentiation, maturation, and resorptive activity. Osteoblast-lineage cells are an important source of RANKL and therefore participate actively in the regulation of osteoclastogenesis. Osteoprotegerin (OPG) provides an important counter-regulatory mechanism. This soluble member of the TNF receptor superfamily binds RANKL and prevents its interaction with RANK, thereby limiting osteoclast formation and bone resorption [51,52]. OPG is produced by osteoblast-lineage cells as well as by several other tissues and immune-cell populations. Its expression can be influenced by cytokines, hormones, peptides, and pharmacological agents. Consequently, the relative balance between RANKL and OPG is an important determinant of osteoclast activity and overall bone-remodeling dynamics. An increased RANKL/OPG ratio favors osteoclastogenesis and may therefore serve as an indicator of a resorptive skeletal environment [53]. Inflammatory mediators, including TNF-α and signals associated with Th17 cells, can further promote osteoclastogenic activity by modifying RANKL expression and the responsiveness of osteoclast precursors [54]. RANK signaling also has functions beyond skeletal remodeling and participates in immune regulation and other physiological processes. The close interaction between immune cells, MSCs, osteoblast-lineage cells, and

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osteoclasts illustrates the interconnected nature of bone and immune biology. MSCs may influence this environment through paracrine mechanisms, modulation of inflammatory signaling, and regulation of monocyte/macrophage behavior [55].

Extracellular vesicles and intercellular communication in bone

EVs, including exosomes, have emerged as potential mediators of communication between skeletal and immune cells. These membrane-bound vesicles can transport biologically active molecules, including proteins, lipids, messenger RNAs, and regulatory microRNAs, from donor cells to recipient cells. Through this mechanism, EVs may modify cellular behavior without requiring direct cell-to-cell contact [56]. Evidence from experimental models suggests that EV-mediated signaling can influence osteoclastogenesis, osteoblast differentiation, progenitor-cell migration, and the inflammatory environment. Importantly, the biological effect depends on the cellular origin and molecular composition of the vesicles. For example, EVs derived from osteoblast-lineage cells may carry RANKL and thereby promote RANK-dependent osteoclast differentiation under specific experimental conditions [57]. As such, EVs released by adipose-derived stem/stromal cells have been investigated for their potential anti-resorptive and pro-regenerative effects. In osteoporotic animal models, such vesicles have been associated with reduced bone loss, suppression of macrophage-to-osteoclast differentiation, and enhanced migration of bone-marrow-derived MSCs. Experimental depletion of OPG from these vesicles diminished the observed effects, suggesting that OPG-containing EV cargo may contribute to their biological activity [58]. MicroRNAs transported by EVs may provide an additional layer of regulation. By modifying gene expression in recipient cells, these small non-coding RNAs can influence pathways involved in osteogenic and adipogenic differentiation, osteoclastogenesis, and inflammatory signaling. Alterations in specific miRNA networks have therefore been proposed as potential contributors to disturbed bone remodeling and OP [59].

From OP biology to regenerative bone medicine

The mechanisms described above indicate that OP is not simply a disorder of reduced bone density. It reflects a broader disturbance involving bone-cell turnover, progenitor-cell competence, immune regulation, extracellular signaling, and the balance between matrix formation and resorption. Strategies aimed at preserving or restoring skeletal regenerative capacity may complement conventional anti-resorptive and anabolic approaches. An important therapeutic objective may be to maintain the osteogenic potential of skeletal progenitors, limit premature cellular senescence, restore a favorable bone-cell microenvironment, and coordinate the activity of osteoblasts, osteoclasts, osteocytes, immune cells, and vascular components. This concept provides a biological bridge between OP and difficult fracture healing. A skeleton characterized by impaired remodeling, reduced osteogenic competence, altered inflammatory signaling, or compromised vascular and metabolic support may have a diminished capacity to respond effectively to injury. Therefore, OP and age-associated skeletal degeneration may be viewed not only as risk factors for fracture but also as conditions that can reduce the regenerative reserve required for successful bone repair.

Several mechanisms can independently initiate this failure but become increasingly interdependent as healing progresses. Severe periosteal disruption may eliminate or impair injury-responsive skeletal PSCs

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required for callus formation, while failure of mechanosensitive or transcriptional activation can further restrict their expansion and osteochondral differentiation [5,6,20]. Persistent inflammation can prevent transition from the inflammatory phase toward anabolic tissue formation, sustaining tissue injury, osteoclastogenic signaling, and impaired progenitor function [4,9]. These processes are particularly consequential when accompanied by vascular insufficiency: loss of perfusion limits oxygen, nutrients, and cellular recruitment, while inadequate reconstruction of osteogenic vascular niches removes endothelial-derived signals that normally couple angiogenesis to new-bone formation [23-25].

Metabolic dysfunction provides an additional point of convergence. Osteogenic differentiation, matrix synthesis, and mineralization impose substantial energetic demands; consequently, reduced mitochondrial reserve or impaired quality control may prevent otherwise viable skeletal PSCs from executing the programs required for bone formation [60]. This vulnerability may be amplified in aged, metabolically compromised, or ischemic tissues, in which impaired bioenergetic reserve can coexist with inflammation and reduced perfusion [1,4,9,33]. Disruption of developmental, vascular, immune, and matrix-derived signaling can further uncouple cellular compartments that remain viable but are no longer temporally or spatially coordinated. The identification of endogenous osteoregulatory peptides further supports the importance of this signaling environment, while also emphasizing that impaired healing is unlikely to reflect deficiency of any single molecular mediator [61]. These mechanisms therefore converge on a common pathological state in which skeletal PSCs are present or potentially recruitable but cannot generate mechanically competent bone because inflammatory resolution, vascular support, metabolic fitness, and regenerative signaling are insufficiently synchronized. The central therapeutic problem in difficult fracture healing is therefore not simply stimulation of osteoblast activity, but reconstruction of the biological conditions under which endogenous or administered skeletal PSCs can complete organized bone regeneration.

Why current bone-healing therapies remain mechanistically incomplete

Clinical treatment of fracture nonunion appropriately begins with correction of mechanical instability, infection, deformity, and vascular compromise. Revision fixation, compression, debridement, autologous bone grafting, vascularized grafts, bone transport, and selected osteoinductive agents remain indispensable because no regenerative biologic can compensate for gross instability or uncontrolled infection. Nevertheless, even optimized surgical reconstruction may fail when the biological capacity of the fracture environment is severely compromised. Recent reviews therefore increasingly emphasize the need to address the mechanical and biological components of nonunion concurrently [3].

Autologous bone graft remains the clinical benchmark because it simultaneously provides osteogenic cells, osteoconductive matrix, and endogenous signaling molecules [62]. Donor-site morbidity, finite volume, variable cellular composition, and reduced potency in older or metabolically compromised patients have driven development of alternative orthobiologics [63]. Recombinant growth factors can provide potent osteoinduction, but their short-range signaling, supraphysiological dosing requirements, carrier dependence, cost, and potential adverse effects illustrate the limitations of activating individual pathways within a temporally complex regenerative process [64]. Cell-based therapies, including bone-marrow aspirate concentrates, culture-expanded MSCs and skeletal PSCs, offer a cellular source of

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osteogenic and paracrine activity [65]. However, their translation remains constrained by heterogeneous cell identity, donor variability, survival after implantation, lineage fidelity, manufacturing complexity, and a recipient niche that may remain hypoxic, inflammatory, or poorly vascularized. Recent reviews of stem-cell and acellular approaches conclude that these technologies are promising but remain heterogeneous in product definition and clinical evidence [66].

Biomaterial scaffolds, EVs, gene-based therapies, and controlled-release systems can improve spatial delivery and modulate specific aspects of osteogenesis, angiogenesis, or osteoimmunity. Their increasing sophistication is important, but structural support still does not restore progenitor competence nor does angiogenesis ensure osteogenic differentiation or immunomodulation replace lost bone-forming cells. Further, osteoinduction may fail in metabolically compromised tissue. Contemporary nonunion research is therefore moving toward multifunctional constructs capable of coordinating several components of the fracture niche rather than maximizing one isolated biological signal [10].

The resulting regenerative plateau is therefore best understood as mechanistic fragmentation: existing interventions can correct important components of nonunion biology, but few are designed to restore the interdependent cellular, metabolic, vascular, immune, and signaling functions required for complete repair. This limitation provides the rationale for evaluating complementary regenerative modalities, while recognizing that multimodality itself does not establish superiority; each component must address a demonstrable biological constraint, and combination must produce measurable additive or synergistic benefit.

Skeletal PSCs as the Cellular Foundation of Regeneration

The cellular basis of fracture repair is increasingly understood in terms of spatially restricted skeletal PSC populations rather than a generic “MSC” compartment [6,67,68]. Notably, anatomical source, expression of selected skeletal markers, and in vitro osteogenic differentiation are individually insufficient to establish a therapeutically relevant skeletal PSC identity. Periosteal and marrow-associated progenitors differ in transcriptional identity, injury responsiveness, and contribution to repair, and recent lineage-tracing and single-cell studies have further resolved periosteal subsets that are selectively activated after fracture [6,68]. Itm2a-expressing periosteal skeletal PSCs, for example, contribute directly to fracture callus formation [69], while single-nucleus transcriptomics demonstrates dynamic transitions among periosteal skeletal PSC states during early regeneration [70]. These observations establish an important translational principle: effective skeletal cell therapy should reproduce injury-relevant developmental identity and osteochondral competence rather than rely on undifferentiated proliferative capacity alone.

For most fractures, periosteal progenitors are particularly important because they rapidly proliferate after injury and contribute to both chondrogenic and osteogenic components of the callus [6,68]. Their lineage output is shaped by mechanical, inflammatory, vascular, and developmental signals within the evolving fracture niche; mechanosensitive Piezo1 signaling provides direct experimental evidence that the physical environment can regulate periosteal stem-cell-mediated fracture repair [5]. A therapeutically useful skeletal precursor population must therefore retain injury-appropriate lineage competence while avoiding ectopic or persistent non-osseous differentiation.

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This requirement distinguishes skeletal precursor therapy from conventional MSC administration. MSC preparations are heterogeneous and may exert substantial therapeutic activity through paracrine signaling rather than durable incorporation into regenerated bone. In contrast, a skeletal progenitor intended for structural reconstruction should demonstrate defined cellular identity, clonogenic competence, controlled osteogenic/osteochondral differentiation, matrix production, and capacity to contribute to mineralized tissue. Contemporary skeletal stem/progenitor literature identifies cellular identity, anatomical origin, and developmental hierarchy as important unresolved variables for translation [67,68]. Cellular competence alone, however, is insufficient. Endogenous or administered progenitors must function within an evolving niche characterized by inflammatory signals, mechanical strain, vascular remodeling, changing oxygen availability, and substantial metabolic demand. Functional integration rather than cell retention alone should therefore constitute the relevant therapeutic objective. Mechanism-linked potency assessment should evaluate lineage identity, osteogenic differentiation and mineralization, genomic stability, and contribution to biomechanically competent bone rather than relying solely on viability or nonspecific proliferation. Accordingly, the translational criterion for skeletal PSC therapy is not stemness per se, but reproducible skeletal identity, injury-appropriate lineage competence, metabolic fitness, and contribution to functional bone regeneration.

Mitochondrial competence as a metabolic requirement for osteogenesis

Mitochondrial competence is particularly relevant in biologically compromised fractures because osteogenic differentiation and matrix production impose substantial bioenergetic demands. Experimental enhancement of mitochondrial oxidative phosphorylation increases osteogenic differentiation and promotes fracture repair [30], while regulation of the mitochondrial permeability transition influences skeletal development and fracture healing [71]. These observations support mitochondrial function as a potential regenerative bottleneck rather than merely a marker of cellular stress.

Candidate mitochondrial-directed approaches include modulation of mitochondrial biogenesis and quality control, redox-directed interventions, mitochondrial transfer, and mitochondrial-derived signaling molecules. Notably, macrophage-to-stromal-cell mitochondrial transfer has been experimentally associated with enhanced osteogenic differentiation, providing proof of principle that intercellular mitochondrial biology can influence skeletal regenerative competence [72]. These interventions should not, however, be treated as mechanistically interchangeable: intact mitochondrial transfer differs fundamentally from modulation of endogenous mitochondrial quality control or administration of mitochondrial peptides or organelle-derived molecular fractions.

For fracture regeneration, mitochondrial target engagement should therefore be demonstrated through mechanism-appropriate measures of respiratory function, ATP production, membrane potential, redox state, mitochondrial quality control, and cellular uptake where applicable, coupled to osteogenic and functional endpoints. The relevant question is not whether an intervention alters mitochondrial biomarkers, but whether improved organelle competence enables skeletal progenitors and supporting vascular cells to complete effective bone regeneration.

Peptide-mediated regulation of the bone-regenerative niche

Defined peptide systems provide proof of principle that relatively small molecular signals can regulate

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skeletal regeneration through receptor engagement, matrix mimicry, osteoblast–osteoclast coupling, and canonical developmental pathways. P-15 provides an example of a collagen-derived osteogenic biomimetic [37], while the endogenous osteopeptide PEPITEM promotes osteoblast maturation and new-bone formation through NCAM-1 and increases osteoprotegerin, thereby influencing osteoblast–osteoclast coupling [38]. However, activity of defined peptides cannot be extrapolated to complex tissue-derived peptide fractions; source tissue generates a hypothesis regarding molecular repertoire, not evidence of therapeutic specificity.

Additional evidence demonstrates that peptide-responsive pathways participate directly in fracture repair. Formyl peptide receptor-1 deficiency reduces osteogenic differentiation and impairs bone healing [73], while MAGP2 promotes osteogenic differentiation during fracture healing through interaction with β-catenin signaling [74]. Together, these observations establish biological precedent for peptide-mediated skeletal regulation but do not establish the efficacy of complex bone-, periosteal-, marrow-, vascular-, or other organ-derived peptide preparations.

For bone-directed peptide biologics, the central translational questions are therefore compositional and mechanistic. Complex preparations require molecular definition by mass spectrometry, molecular-weight profiling, source authentication, quantitative batch fingerprinting, and appropriate purity, stability, and safety testing. Functional assays should establish dose–response relationships and pathway engagement in relevant skeletal populations, while comparative testing against appropriately selected non-skeletal preparations is necessary if organ specificity is claimed. Potency assays should be linked to the proposed mechanism of action and distinguish osteogenic, osteoimmune, vascular, and matrix effects from nonspecific proliferative activity.

Ultimately, the strongest evidence would require demonstration that a defined peptide preparation improves fracture repair in vivo and that depletion, inhibition, or enrichment of candidate bioactive constituents correspondingly modifies the biological effect. Peptide-mediated niche regulation therefore represents a plausible therapeutic domain alongside skeletal progenitor reconstruction and mitochondrial support. The relevant scientific question is not whether tissue-derived fractions are intrinsically regenerative, but whether reproducibly characterized preparations contain defined molecular signals that engage specific osteogenic, immune, vascular, or matrix pathways and improve functional fracture repair.

European Wellness as an Integrated Platform for Skeletal Systems Regeneration

The European Wellness (EW) regenerative platform provides a translational framework for integrating three biologically distinct components of fracture repair: skeletal PSCs as the cellular substrate for bone formation, MO biologics as candidate modulators of metabolic competence, and NOPs as proposed tissue-contextual signaling preparations. The critical test of the platform is therefore not whether each modality exhibits biological activity in isolation, but whether their integration resolves mechanistically distinct constraints on repair. This distinction converts the PSC–MO–NOP model from an empirical combination strategy into a falsifiable systems-regeneration hypothesis. For skeletal regeneration, this framework maps naturally onto the principal biological constraints established in the preceding sections. Regionally appropriate skeletal PSCs are required to generate cartilage and bone, but their regenerative output

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depends on immune resolution, vascular support, mechanical context, and metabolic fitness. Recent lineage-tracing studies show that skeletal PSC populations are anatomically heterogeneous and that periosteal populations make injury-specific contributions to fracture repair, arguing against the assumption that generic mesenchymal "stemness" is sufficient for osseous reconstruction. Within an EW-type platform, an organ-matched skeletal PSC preparation would therefore require direct demonstration of skeletal identity, osteochondral competence, and injury-relevant function; tissue origin alone would not establish equivalence to experimentally defined periosteal or marrow skeletal stem cells.

MO biologics occupy a distinct mechanistic position. Fracture regeneration requires substantial metabolic coordination between osteogenic and vascular compartments, and experimental evidence increasingly supports mitochondrial function as an active determinant of osteogenic differentiation and fracture repair. Mitochondrial transfer from macrophages to MSCs has been shown experimentally to enhance osteogenic differentiation and accelerate fracture healing, while mitochondrial permeability-transition regulation can influence skeletal development and repair. These data provide biological precedent for targeting mitochondrial competence, but they do not establish the activity of EW MO preparations. The latter must be defined according to composition, intact organelles, organelle fractions, proteins, peptides, metabolites, or mixed preparations, and evaluated using mechanism-linked measures of respiratory function, ATP generation, membrane potential, redox state, uptake, persistence, and effects on osteogenic differentiation. The experimentally testable proposition is that improving metabolic fitness may increase the capacity of endogenous or administered skeletal progenitors to complete bone formation under regenerative stress. NOPs address a third domain: molecular communication within the fracture niche. Peptide-mediated regulation is already established as a genuine component of skeletal biology. Defined peptide-receptor pathways influence osteogenic differentiation and fracture repair; for example, loss of formyl peptide receptor-1 impairs osteogenesis and bone healing, while matrix-associated signaling proteins can interact with canonical β-catenin pathways to regulate osteogenic differentiation [75]. The organ-specific NOP concept extends this principle by proposing that tissue-derived low-molecular-weight fractions may contain combinations of signals reflecting developmental and physiological characteristics of their source tissue. EW publications have advanced this broader model across multiple organ systems, including musculoskeletal tissues, while acknowledging the need for quantitative proteomic and mechanistic validation [76-82]. For skeletal applications, the critical question is whether defined bone-, periosteal-, marrow-, vascular-, or related NOP preparations reproducibly contain bioactive constituents that engage skeletal regenerative pathways at therapeutically relevant exposures.

The EW platform scientific value is dependent upon consistent demonstration of nonredundant component activity and mechanistic interaction. Factorial studies are requisite to determine whether skeletal PSCs, MO preparations, and NOPs independently (and/or interactively) affect lineage formation, metabolic competence, and niche signaling, respectively, and whether pairwise or triple combinations produce effects exceeding those predicted from the components alone. Such studies should incorporate periosteal and marrow progenitor cultures, osteochondral organoids, macrophage–progenitor and endothelial–osteoblast cocultures, metabolically compromised models, and mechanically standardized fracture or critical-size defect models. Angiogenesis is particularly important because fracture repair

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depends on energetic and signaling coupling between vascular and osteogenic compartments [8]. Accordingly, organ specificity should be treated as a falsifiable biological property, not an attribute inferred from source tissue. A skeletal preparation would demonstrate organ specificity only if molecular profiling and comparative functional assays showed preferential engagement of osteogenic, chondrogenic, vascular, or fracture-repair programs relative to appropriately selected non-skeletal preparations. Similarly, claims of synergy require formal interaction analysis; co-administration alone demonstrates exposure to multiple agents, not systems regeneration. The current EW evidence base is best regarded as conceptual and translational rather than definitive for fracture healing. Its principal contribution is the organization of cellular, metabolic, and tissue-signaling modalities within a common regenerative framework. The next scientific step is progressively stricter validation such that product identity precedes mechanism, mechanism precedes combination testing, and target engagement precedes claims of enhanced fracture regeneration.

Translational priorities and experimental validation

Translation of this framework requires modality-specific standards. Characterization of skeletal PSC preparations by source, viable-cell composition, single-cell molecular identity, clonogenicity, genomic stability, osteogenic and chondrogenic differentiation, and functional mineralization is essential. Release criteria should distinguish true skeletal progenitor activity from generalized stromal-cell viability and should include evaluation of ectopic differentiation, senescence, immunogenicity, and tumorigenic risk. MO preparations require equally explicit definition. If intact mitochondria are present, membrane integrity, mitochondrial DNA quality, respiratory-chain activity, oxygen-consumption rate, ATP generation, respiratory-control ratio, and cellular uptake are critical. If the preparation is predominantly peptide-, protein-, membrane-, or metabolite-derived, those products require different potency assays. Mechanistic studies should determine whether treatment improves progenitor mitochondrial reserve, osteoblast differentiation, endothelial function, or immune-cell metabolism rather than relying on nonspecific antioxidant endpoints. NOP development should prioritize high-resolution mass spectrometry, peptide sequencing, molecular-weight distribution, source-tissue authentication, stability, batch fingerprinting, and quantitative assessment of major constituents. Pharmacokinetics and biodistribution must establish whether biologically relevant concentrations reach the fracture microenvironment. Mechanism-linked potency assays should interrogate periosteal progenitor activation, RUNX2/SP7-dependent osteogenic differentiation, matrix mineralization, osteoblast–osteoclast coupling, macrophage resolution, endothelial angiogenesis, and relevant receptor or signaling pathways. Integrated testing should then proceed through factorial designs comparing PSCs, MO biologics, and NOPs individually, pairwise, and in combination. Mechanically standardized fracture models should be complemented by models of biologically difficult healing, including aging, diabetes, vascular compromise, critical-size defects, and appropriately selected infected or ischemic injury models. The primary endpoint should not be increased callus volume alone, but restoration of mechanically competent union, assessed by quantitative imaging, histomorphometry, vascularization, tissue composition, and biomechanical testing. Only after component-specific activity, target engagement, and interaction have been demonstrated should controlled clinical trials evaluate whether the platform improves time to union, nonunion rates, reoperation, function, pain, and return to activity. Prospective studies should predefine product identity, mechanism-linked potency, target engagement, and interaction criteria before efficacy

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testing, thereby reducing the risk that post hoc biological associations are interpreted as evidence of mechanism.

Conclusions

Difficult fracture healing is increasingly understood as a failure of the regenerative system rather than an isolated deficit in osteogenesis. Successful union requires coordinated progenitor activation, inflammatory resolution, vascular reconstruction, metabolic competence, and tissue-level signaling within an appropriate mechanical environment. When these processes become uncoupled, viable progenitors and osteogenic signals may remain present yet fail to generate structurally organized, mechanically functional bone. This systems perspective helps explain why interventions directed toward individual components of fracture repair can improve selected biological endpoints without reliably resolving biologically complex nonunion.

A systems-regeneration strategy therefore requires complementary interventions directed at distinct regenerative constraints. Skeletal PSCs provide a candidate cellular substrate for osteochondral reconstruction; MO biologics represent a potential means of supporting the metabolic competence required for progenitor survival, differentiation, and matrix formation; and NOPs provide a testable approach to tissue-contextual modulation of osteogenic, vascular, immune, and matrix signaling. The PSC–MO–NOP model should not, however, be considered advantageous simply because it is multimodal. Its central hypothesis is that each component addresses a mechanistically distinct bottleneck and that their integration produces additive or synergistic regeneration beyond that achieved by the individual modalities.

The EW platform represents a candidate implementation of this three-domain architecture, but its relevance to fracture repair remains to be established experimentally. Translation will require rigorous definition of product identity and composition, demonstration of skeletal target engagement and mechanism-linked potency, comparative validation of proposed tissue specificity, and factorial studies distinguishing independent from combinatorial effects, followed by testing in clinically relevant fracture models and controlled human trials. Claims of systems regeneration should therefore remain contingent on demonstration of functional tissue restoration rather than mechanistic plausibility alone. The relevant translational benchmark is not generalized biological activity, increased callus volume, or modulation of surrogate biomarkers, but reproducible restoration of anatomically integrated, vascularized, and biomechanically competent bone.

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