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REVIEW

Translational Nanomedicine for Osteoporosis: Bridging Bone Signaling Networks and Targeted Delivery Systems

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Abstract: Osteoporosis is a complex skeletal disorder characterized by reduced bone mineral density and microarchitectural deterioration, leading to an increased risk of fractures. Conventional pharmacotherapies, such as bisphosphonates and selective estrogen receptor modulators, are constrained by poor bioavailability, lack of targeting specificity, and systemic side effects. Unlike previous reviews that examine signaling pathways and nanocarrier design in isolation, this review presents an integrated mechanistic framework wherein specific therapeutic nodes within key bone remodeling pathways—including Wnt/β-catenin, BMP/Smad, and RANKL/RANK/OPG—inform the rational design of nanodelivery systems. Within this framework, four major classes of nanoplatforms—inorganic nanoparticles, polymeric carriers, liposomal systems, and biomimetic vesicles—are systematically evaluated for their ability to engage pathway-specific targets and modulate osteogenesis and osteoclastogenesis. In addition to mechanistic efficacy, each platform is critically assessed for clinical translatability using a multi-dimensional benchmarking approach that encompasses in vivo performance, targeting precision, safety profile, manufacturability, and regulatory readiness. While these nanosystems exhibit significant potential to enhance therapeutic precision, controlled drug release, and safety, challenges such as long-term biosafety, immune interactions, and scalable manufacturing continue to pose barriers to clinical implementation. By integrating mechanistic targeting with translational benchmarking, this review provides a stage-stratified translational roadmap to guide the development of intelligent and clinically translatable nanomedicine strategies for osteoporosis.

Keywords: osteoporosis, nanomedicine, bone-targeted delivery, signaling pathways, translational nanomedicine

Introduction

Osteoporosis is a systemic skeletal disorder characterized by diminished bone mineral density (BMD) and deteriorated bone microarchitecture, which culminates in an elevated risk of fragility fractures, particularly in postmenopausal women and the elderly. The prevalence of osteoporosis is escalating in tandem with global population aging; a 2021 meta-analysis reported a worldwide prevalence of 18.3%, affecting 23.1% of females and 11.7% of males.[1] Projections indicate a substantial future burden, estimating 263.2 million new cases between 2030 and 2034 and forecasting 18.73 million annual hip fractures by 2050.[2,3] Although conventional pharmacotherapies can alleviate symptoms, their clinical utility is frequently constrained by significant side effects, poor bioavailability, and a lack of tissue specificity. Standard-of-care treatments include bisphosphonates, selective estrogen receptor modulators, and RANKL inhibitors like denosumab.[3]

In contrast, nanotherapeutic strategies offer a paradigm shift, presenting significant advantages by enabling targeted delivery to bone tissue, which in turn reduces systemic toxicity.[4] For instance, bisphosphonate-functionalized liposomes have been demonstrated to selectively accumulate at sites of bone resorption, delivering therapeutic payloads directly to

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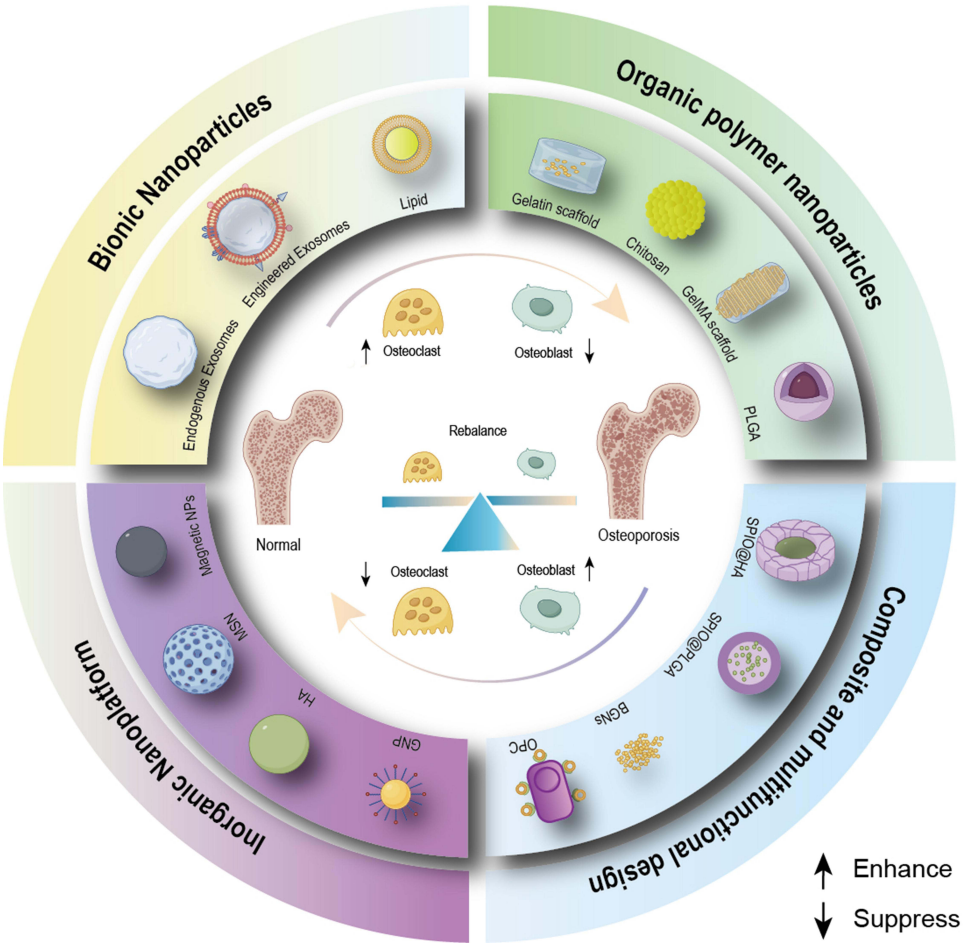
Graphical Abstract



osteoclasts.[5] Such nanomaterials can be engineered to stimulate osteoblast proliferation, repair damaged tissue, and modulate the local microenvironment to foster healthy bone formation, thereby improving bone strength and mitigating fracture risk.[4]

The rational design of effective nanodelivery systems for targeted osteoporosis therapy is predicated on a deep understanding of the regulatory mechanisms that govern bone metabolism and drive disease pathophysiology. Osteoblasts are responsible for secreting and mineralizing the bone matrix, whereas osteoclasts mediate its resorption. These complementary processes are governed by a network of interconnected signaling pathways. For example, the estrogen deficiency characteristic of menopause disrupts the RANKL–RANK–OPG axis, leading to excessive osteoclast activation, while age-related suppression of the Wnt/β-catenin pathway compromises osteoblast function, collectively contributing to bone loss. Current pharmacological therapies aim to restore skeletal homeostasis by either stimulating osteoblast activity or inhibiting osteoclast-mediated bone resorption through multiple delivery routes. An overview of these therapeutic strategies and their cellular targets in bone remodeling is illustrated in Figure 1.

These signaling pathways are therefore not merely regulators of bone metabolism but also represent the most promising molecular targets for therapeutic intervention. While traditional agents such as bisphosphonates function as "blunt instruments" that broadly inhibit osteoclast activity, they lack the precision to selectively modulate specific nodes within these networks, often resulting in systemic side effects.[6] In contrast, nanotherapeutics can be engineered to selectively target specific signaling molecules, an approach that relies on a comprehensive understanding of the bone

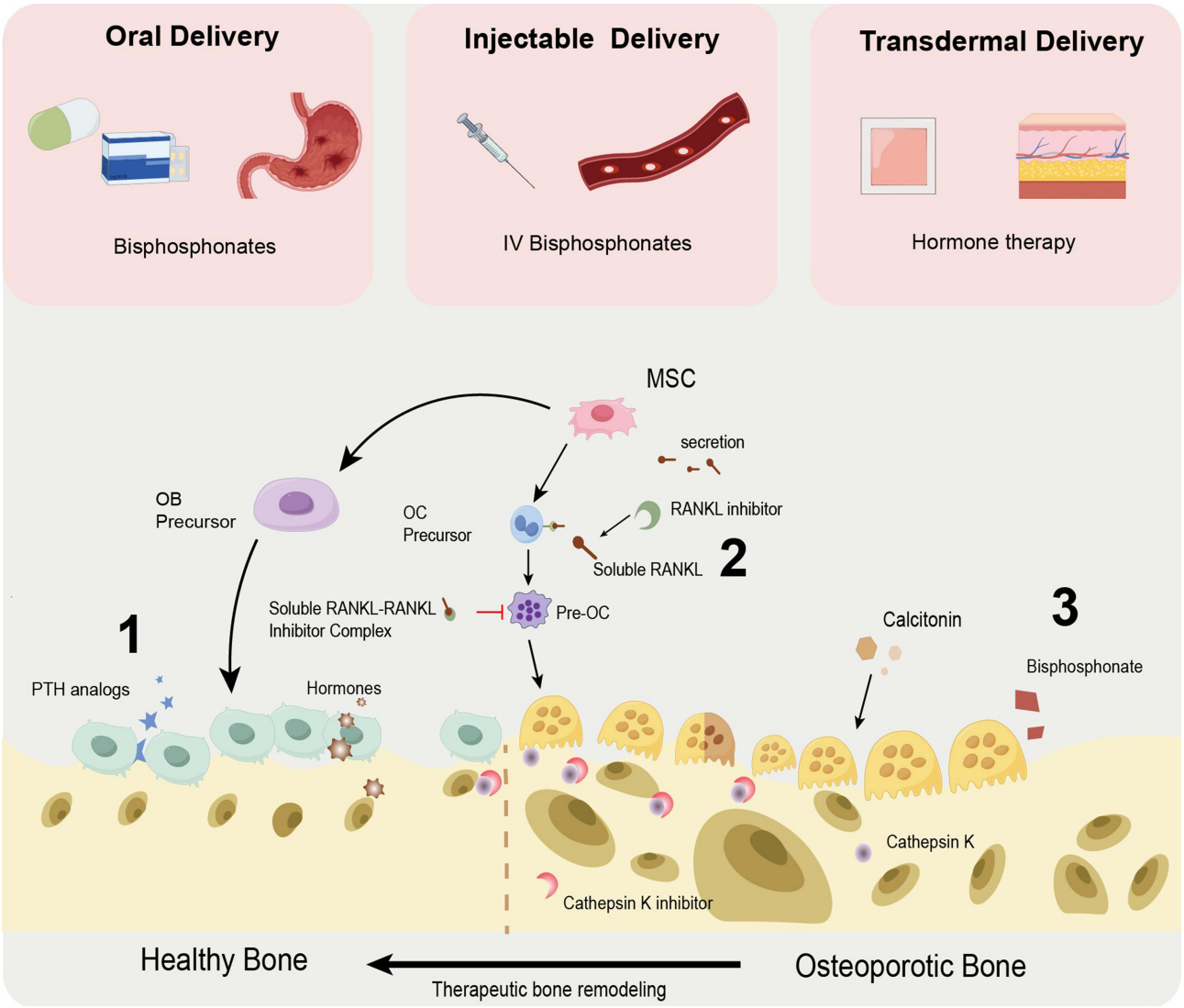


Figure 1 Schematic overview of representative clinical therapies for osteoporosis and their primary targets in bone remodeling. Common administration routes (oral, injectable, and transdermal) are illustrated at the top. (1) PTH analogs promote bone formation by stimulating osteoblast lineage activity. (2) RANKL inhibitors suppress osteoclast differentiation by blocking RANKL–RANK signaling. (3) Antiresorptive agents, including bisphosphonates, calcitonin, and cathepsin K inhibitors, reduce osteoclast-mediated bone resorption. The diagram illustrates the balance between osteoblast-driven bone formation and osteoclast-mediated bone resorption during bone remodeling.
Abbreviations: MSC, mesenchymal stem cell; OB, osteoblast; OC, osteoclast; Pre-OC, osteoclast precursor.

metabolism network. Consequently, elucidating these key pathways is crucial for both uncovering the pathophysiological basis of osteoporosis and guiding the rational design of targeted nanosystems. Key pathways include osteogenesis-promoting cascades, such as the Wnt/β-catenin and Bone Morphogenetic Protein (BMP) pathways; the principal osteoclast-activating pathway, the RANKL–RANK axis; and critical mechanotransduction pathways, represented by the Hippo-YAP/TAZ signaling cascade. This network of interconnected signaling pathways thus presents a rich landscape of molecular targets for the therapeutic management of osteoporosis. For instance, the Hippo pathway's downstream effectors, YAP and TAZ, are critical regulators of skeletal homeostasis; their activation is a promising strategy, as it enhances osteoblast differentiation through crosstalk with Wnt and TGF-β signaling while simultaneously suppressing osteoclast activity, thereby restoring the balance between bone formation and resorption.[7] This pathway exhibits significant crosstalk with BMP and Wnt signaling, wherein BMPs can modulate the expression of Wnt inhibitors such as Sclerostin (SOST) and Dickkopf-1 (Dkk-1).[8,9] These inhibitors have become major anabolic targets, validated by the clinical success of monoclonal antibodies that neutralize them, thereby effectively increasing bone formation by

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liberating the LRP5/6 co-receptor to activate Wnt signaling.[8] Similarly, the mTOR pathway, which involves the distinct complexes mTORC1 and mTORC2, acts as a central energy sensor and plays a nuanced role in bone health. Depending on the cellular context, both its targeted inhibition and strategic activation show potential to regulate osteogenesis, particularly under conditions of metabolic stress such as hyperglycemia, and this pathway is also influenced by BMP signaling.[9,10] Furthermore, targeting RANKL to block bone resorption—a strategy clinically validated by agents like denosumab—remains a cornerstone of anti-resorptive therapy.[11] Emerging strategies also aim to counteract skeletal aging by targeting cellular senescence, either through the use of senolytic drugs to eliminate senescent cells marked by proteins like p16Ink4a or by employing SASP modulators, such as Janus Kinase (JAK) inhibitors, to suppress the pro-inflammatory Senescence-Associated Secretory Phenotype (SASP).[11] Collectively, targeting these key nodal proteins—including YAP/TAZ, SOST, RANKL, and mTOR, as well as targets in other related pathways—offers multifaceted and precise strategies for restoring skeletal homeostasis.

This review will first outline the key signaling networks that govern bone remodeling. Subsequently, the focus will shift to the design and application of various drug-loaded nanosystems engineered to modulate these pathways for the treatment of osteoporosis. Finally, the discussion will address the current challenges and future directions for translating these nanotherapeutic strategies into clinical practice.

Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes

Bone homeostasis is dynamically maintained by a dense regulatory network governing osteoblast and osteoclast activities.[12] Rather than targeting isolated pathways, the modern therapeutic paradigm—particularly in nanomedicine—focuses on modulating specific, therapeutically relevant nodal points within this complex web.[13,14]

Osteogenic Pathways

The canonical Wnt/β-catenin and Bone Morphogenetic Protein (BMP) pathways are the principal drivers of osteogenesis. Both cascades converge to activate master transcription factors like RUNX2 and Osterix (OSX).[15–18] Furthermore, proper skeletal development also relies on the intricate crosstalk between these master transcription factors and auxiliary signaling networks, including Hedgehog, Notch, and TGF-β pathways.[19] From a targeted therapy perspective, the Wnt pathway is highly druggable due to its endogenous secreted inhibitors, such as Sclerostin (SOST) and Dickkopf-1 (Dkk-1). These inhibitors are critical anabolic drug targets, clinically validated by monoclonal antibodies like Romosozumab,[20] and represent prime candidates for nucleic acid or peptide-based nanodelivery systems. Beyond the canonical Wnt and BMP pathways, osteogenesis is intricately tuned by auxiliary networks such as the MAPK cascade, which exerts dual-phase regulation on osteoblastic proliferation and maturation.[21,22] Concurrently, PI3K/AKT/mTOR signaling is critical for protecting mesenchymal stem cells from apoptosis and maintaining their osteogenic commitment through metabolic reprogramming.[23,24]

Osteoclastogenic Pathways

The master regulator of bone resorption is the Receptor Activator of Nuclear Factor-κB Ligand (RANKL)–RANK signaling axis. The binding of RANKL to RANK on osteoclast precursors is the pivotal event driving their activation,[25,26] making RANKL a cornerstone anti-resorptive target (validated by Denosumab).[27] Concurrently, the Mincle receptor acts as a damage-recognition node that initiates NFATC1 activation during tissue necrosis,[28] presenting an alternative target to selectively inhibit pathological bone resorption (Figure 2).

Mechanotransduction and Microenvironment

Beyond biochemical signals, mechanical forces and systemic inflammation profoundly influence bone mass. The Hippo pathway effectors, YAP and TAZ, act as critical mechanosensitive hubs that translate physical cues into pro-osteogenic signals,[7,29,30] making them promising targets for "mechanotherapeutics" to counter disuse osteoporosis. Notably, these mechanotransducers can also function as a "molecular memory" for BMP signaling, sustaining long-term osteogenic

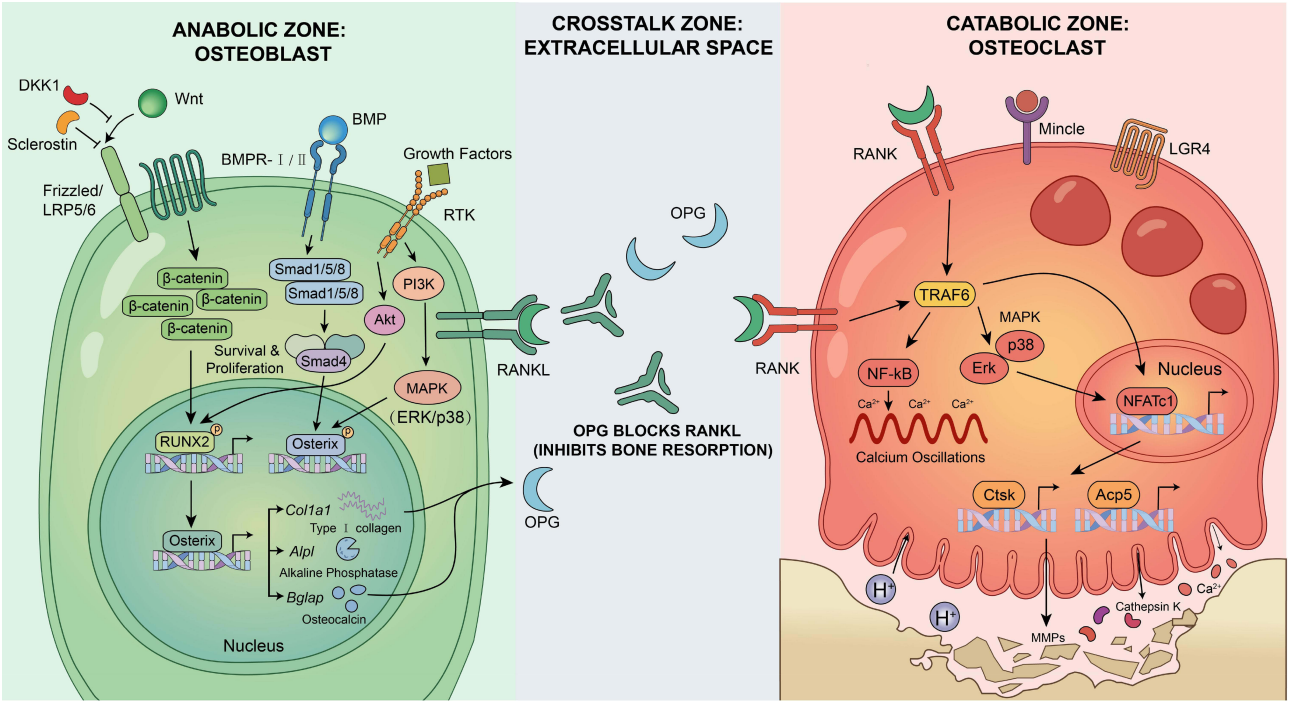

Figure 2 Integrated signaling network governing the dynamic equilibrium of bone remodeling. The diagram is spatially partitioned into three functional compartments. The Anabolic Zone (green, left) illustrates osteoblast-mediated bone formation through three convergent anabolic cascades: the Wnt/β-catenin pathway (transduced via Frizzled/LRP5/6, antagonized by DKK1 and Sclerostin), the BMP/Smad1/5/8 axis (via BMPR-I/II), and the growth factor–RTK–PI3K/Akt/MAPK pathway, all culminating in the nuclear activation of master osteogenic transcription factors RUNX2 and Osterix to drive expression of Col1a1, Alpl, and Bglap. The Catabolic Zone (red, right) depicts osteoclast-mediated bone resorption, initiated by RANK–TRAF6 signaling and amplified via NF-κB, MAPK (ERK/p38), and Ca^{2+} oscillations, leading to NFATc1 nuclear translocation and transcriptional induction of osteoclast effector genes (Ctsk, Acp5) driving H^+ secretion, cathepsin K release, and MMP-dependent matrix degradation. The Crosstalk Zone (center) highlights the pivotal OPG/RANKL/RANK regulatory axis, wherein osteoblast-secreted OPG sequesters RANKL as a decoy receptor, thereby competitively inhibiting RANK activation and attenuating bone resorption. Pointed solid arrows denote activation or downstream signal transduction; blunt-ended lines indicate inhibitory interactions.

commitment even after the initial stimulus has dissipated.[31] Furthermore, addressing the inflammatory microenvironment ("immunoporosis") by targeting cytokines (eg, TNF-α)[32,33] or utilizing reactive oxygen species (ROS)-responsive nanocarriers offers a multi-pronged approach to restoring skeletal integrity.

In addition, skeletal integrity is deeply intertwined with systemic factors, including the "immunoporosis" axis driven by chronic inflammation,[34] the hormonal regulation of RANKL/OPG by estrogen,[35] and metabolic integrators like GSK3β.[36] The landscape of druggable targets also continues to expand with novel negative regulators such as Gprc5a, offering new avenues for anabolic therapies.[37]

Functional Nanoplatforms in Osteoporosis: Classification, Mechanisms, and Clinical Potential

Translating the molecular nodes delineated in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes into clinically effective interventions remains a fundamental challenge for conventional therapeutic agents, which are inherently constrained by insufficient tissue specificity and unfavorable pharmacokinetic profiles. Functional nanomaterials have emerged as a transformative platform to bridge this translational gap. As the field of nanomedicine continues to mature, however, a critical conceptual distinction must be drawn between two broad categories of nanosystems: "drug-loaded" delivery platforms, which function primarily as sustained-release depots to optimize drug pharmacokinetics and bioavailability without intrinsic cellular selectivity, and "actively targeted" delivery systems, which are surface-functionalized with specific ligands to directionally home to discrete cell populations—such as osteoblasts or osteoclasts—within the bone microenvironment.

To effectively modulate the key osteogenic and osteoclastogenic signaling cascades (eg, Wnt/β-catenin, RANKL/RANK/OPG, YAP/TAZ) while circumventing the systemic limitations of conventional therapies, four principal classes of

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nanoplatforms have been developed and extensively investigated. A comprehensive comparative analysis of these platforms—encompassing inorganic nanomaterials, polymeric nanoparticles, liposomal systems, and biomimetic nanomaterials—is presented in Table 1, systematically summarizing their respective drug-loading capacities, active targeting efficiencies, GMP-compatible scalability, inherent advantages, and translational limitations.

The sections that follow will elaborate on how each class of functional nanomaterial is rationally engineered to either exploit passive accumulation mechanisms within bone tissue or actively engage the specific therapeutic nodes outlined in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes, with the overarching objective of restoring the physiological equilibrium of bone remodeling (Figure 3).

Inorganic Nanomaterials for Bone-Targeted Delivery

To engage the specific pro-osteogenic and anti-osteoclastogenic nodal targets established in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes, inorganic nanomaterials—including mesoporous silica nanoparticles (MSNs), nano-hydroxyapatite (nHA), and gold nanoparticles (GNPs)—represent a particularly well-developed class of delivery platforms. Critically, a conceptual distinction must be maintained between systems that function as localized drug-loaded depots by exploiting intrinsic osteoconductivity (eg, unmodified nHA scaffolds), and actively targeted platforms that are surface-functionalized with ligands such as alendronate (ALN) to selectively home to hydroxyapatite-rich resorption sites. Beyond this distinction, these materials collectively offer high physicochemical stability, tunable surface chemistry, and inherent bone-mimetic properties, enabling their deployment across three broad roles: therapeutic agent delivery, direct modulation of cellular behavior, and osteoinductive implant coatings or scaffold additives.

Osteoblast-directed strategies predominantly aim to enhance viability, differentiation, and matrix mineralization capacity. MSNs coated with polyethyleneimine (PEI) and loaded with pleiotrophin enhanced viability and mineralization in both MC3T3-E1 cells and human mesenchymal stem cells (MSCs), with a 5 kDa PEI coating demonstrating acceptable biocompatibility and superior outcomes relative to free pleiotrophin.[38] In a more mechanistically targeted approach, MSNs co-functionalized with PEG and ALN for the co-delivery of SOST siRNA and osteostatin successfully activated Wnt/β-catenin signaling—a central anabolic node identified in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes—producing superior bone regeneration in ovariectomized (OVX) mice compared with conventional PTH treatment.[39] Thiol-functionalized MSNs demonstrated effective ROS scavenging, achieving over 90% clearance within 48 hours in vitro and improving wound closure, suggesting utility in oxidative-stress-driven bone loss.[40] Dexamethasone-loaded MSN-ALN-Gd platforms enabled traceable, sustained osteogenic stimulation extending to 22 days in vitro.[41] Targeting estrogen receptor signaling—another nodal axis in postmenopausal osteoporosis—ALN-functionalized nHA loaded with genistein improved bone microarchitecture in OVX rats in vivo.[42] Polydopamine-assisted nHA coatings enhanced bone formation under oxidative stress conditions and improved bone-implant contact in relevant in vivo models.[43] Alginate–hydroxyapatite microspheres designed for the co-delivery of cells and quercetin supported osteogenesis in MC3T3-E1 cultures.[44] Demonstrating a dual mechanism, SPIO@HA composites exerted concurrent anti-resorptive and osteogenic effects, successfully preventing bone loss in OVX models in vivo.[45] Double-layered GNP coatings on titanium implants enhanced osseointegration in OVX rabbits by upregulating RUNX2 via p38 MAPK activation.[46] Bioactive glass nanoparticles (SiO_2–CaO) released calcium and silicon ions that activated RUNX2 and osterix, yielding improved bone formation in zebrafish models in vivo.[47] Finally, PTH(1-34)-loaded PMBG/TCP scaffolds regulated bone homeostasis and accelerated cranial defect repair in rats, illustrating the utility of inorganic composites in localized regenerative contexts.[48]

Critical appraisal of these osteoblast-directed inorganic strategies reveals several recurring limitations. First, the majority of studies are conducted in ovariectomized (OVX) rodent models which, while an established preclinical standard, fail to recapitulate the multifactorial complexity of human osteoporosis, including chronic low-grade inflammation, age-related osteoblast exhaustion, and polypharmacy interactions common in elderly patients. Second, outcome metric heterogeneity across studies—ranging from in vitro mineralization assays to micro-CT trabecular parameters—impedes head-to-head comparison and prevents identification of which nanoparticle design features most reliably drive in vivo efficacy. Third, the predominant reliance on short-term treatment windows (typically 4–8 weeks) provides insufficient insight into long-term nanoparticle retention, off-target organ accumulation, and potential chronic toxicity

Table 1 Comparative Characteristics of Nanosystems for Osteoporosis Therapy

Nanoplatform Type	Drug Loading Capacity	Targeting Strategy & Efficiency	Manufacturing Scalability (GMP)	Key Advantages	Primary Limitations & Translational Hurdles
Biomimetic Materials (eg, Exosomes)	Up to ~33% (eg, paclitaxel)	**Very High (Active/Intrinsic)**; natural homing ability or engineered surface specificity.	**Low**; complex isolation, poor yield, and extreme batch-to-batch variability.	Supreme biocompatibility, minimal immunogenicity, innate ability to cross biological barriers.	Nearly insurmountable GMP scaling hurdles; prohibitive costs; biological heterogeneity.
Polymeric Nanoparticles (eg, PLGA)	Typically 5–20% (eg, simvastatin)	**High (Active)**; highly tunable surface for grafting bone-targeting peptides/ligands.	**Moderate-High**; mature synthesis methods, but maintaining consistency in ligand conjugation is challenging.	Excellent biodegradability, tunable sustained release, FDA-approved polymer components.	Limited mechanical strength; acidic degradation byproducts may trigger local inflammation.
Inorganic Nanomaterials (eg, MSNs, Gold NPs)	Broad range, up to ~85% (eg, SCT in HAP NPs)	**High (Passive/Active)**; innate physicochemical affinity for hydroxyapatite or active surface functionalization.	**Moderate**; synthesis is scalable, but achieving strict uniformity at industrial scale is demanding.	Superior structural stability, osteomimetic properties, highly controlled pore sizes.	Unacceptable long-term biopersistence; risk of chronic toxicity due to accumulation in the RES.
Liposomal Systems	Variable, ~10–90% (eg, PA in TLipo)	**High (Active)**; readily modifiable lipid bilayer for attaching targeting moieties (eg, alendronate).	**High**; mature industrial-scale continuous manufacturing (eg, microfluidics) is highly feasible.	High biocompatibility, capable of co-delivering hydrophilic/ hydrophobic cargos, established clinical precedents.	Prone to in vivo instability (leakage); susceptible to rapid clearance by the immune system without stealth coatings.

Abbreviations: FDA, Food and Drug Administration; GMP, good manufacturing practice; HAP, hydroxyapatite; MSNs, mesoporous silica nanoparticles; NPs, nanoparticles; PA, pomolic acid; PLGA, polylactic-co-glycolic acid; RES, reticuloendothelial system; SCT, salmon calcitonin; TLipo, targeted liposomes.

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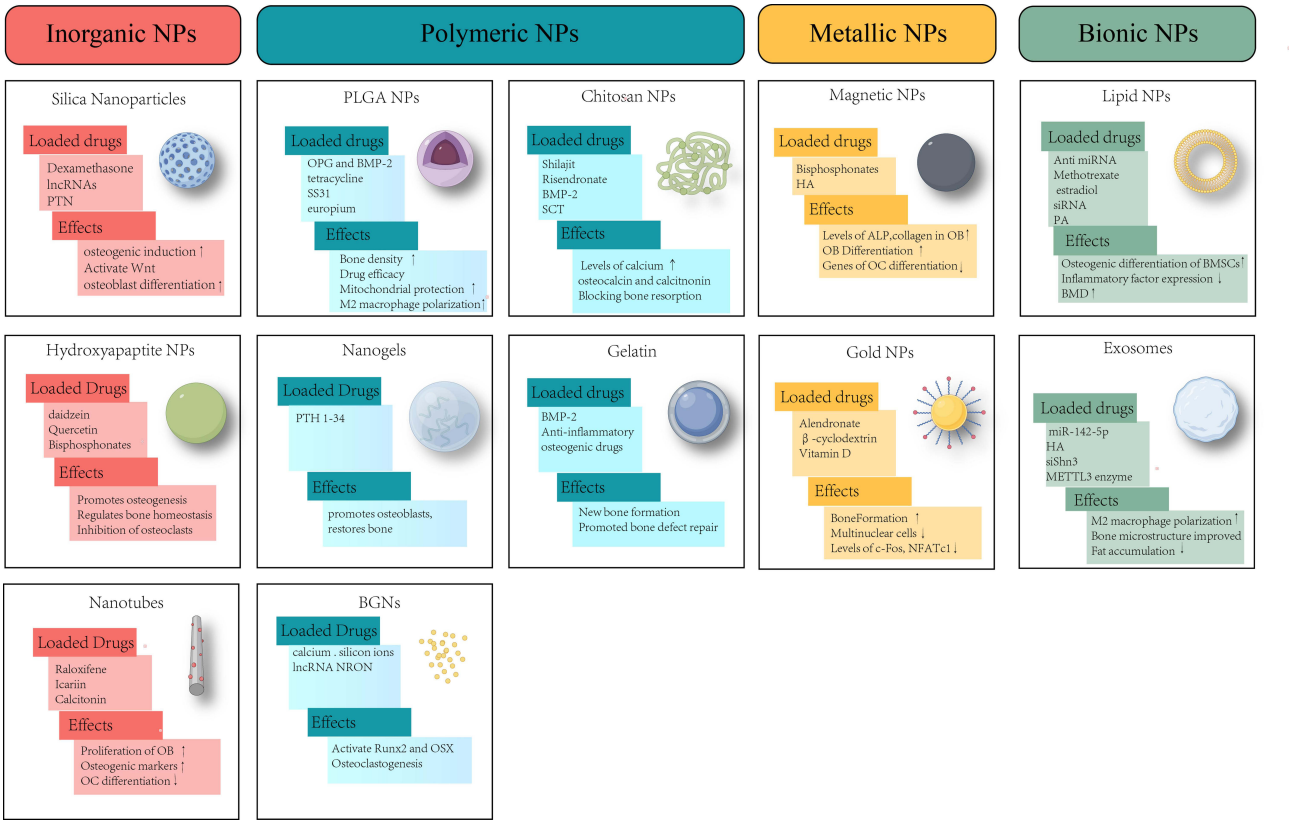

Figure 3 Taxonomic classification and therapeutic profiles of functional nanoplatforms for osteoporosis treatment. The schematic systematically categorizes bone-targeted drug delivery systems into four major classes: Inorganic NPs (silica nanoparticles, hydroxyapatite NPs, nanotubes), Polymeric NPs (PLGA NPs, nanogels, chitosan NPs, BGNs, gelatin matrices), Metallic/Composite NPs (magnetic NPs, gold NPs), and Bionic NPs (lipid NPs/liposomes and exosomes). For each platform, representative therapeutic cargo and key pharmacological outcomes are annotated. Small upward arrows (↑) denote enhancement or upregulation of designated biological markers or functional endpoints; downward arrows (↓) indicate suppression or downregulation.

—a critical knowledge gap for a disease demanding lifelong management. Studies that demonstrate in vitro efficacy without subsequent in vivo validation should be interpreted with particular caution, as the complex biological environment of osteoporotic bone frequently attenuates effects observed under idealized cell culture conditions.

Osteoclast-directed strategies aim to attenuate differentiation or resorptive activity. Chitosan–pectin core-shell MSNs loaded with salmon calcitonin were engineered as an oral delivery platform, demonstrating improved bioavailability and osteogenic outcomes under simulated gastrointestinal conditions.[49] Cerium oxide-doped MSNs combined intrinsic antioxidant activity with pro-osteogenic effects, inhibiting osteoclastogenesis in vitro.[50] Iron oxide-doped nHA, in combination with specific microRNAs and static magnetic field exposure, promoted osteoblast function, suppressed inflammatory cytokine production in macrophages, and inhibited osteoclast differentiation in vitro—converging on multiple immunomodulatory nodes simultaneously.[51] High-loading salmon calcitonin-hydroxyapatite (SCT-HAP) nanoparticles (~100 nm) improved serum biomarkers, bone mass, and mechanical strength in vivo, while also enabling noninvasive sublingual delivery as a patient-friendly administration route.[52]

Despite these promising osteoclast-directed outcomes, several mechanistic and translational limitations warrant emphasis. Osteoclastogenesis is governed by concurrent signaling through RANKL/RANK, reactive oxygen species (ROS), and inflammatory cytokine networks; strategies targeting a single node risk compensatory pathway upregulation that single-target preclinical models typically fail to reveal. The oral and sublingual calcitonin delivery systems, while patient-friendly in concept, face a substantive hurdle: salmon calcitonin is inherently susceptible to enzymatic degradation in the gastrointestinal tract, and bioavailability improvements demonstrated under simulated gastrointestinal conditions may not reliably translate to the dynamic in vivo environment, particularly in elderly patients with altered gut physiology, reduced mucus integrity, and variable gastric pH. Furthermore, the absence of direct head-to-head

comparisons between these novel platforms and existing anti-resorptive gold standards (bisphosphonates, denosumab) limits the ability to contextualize reported efficacy within the existing clinical landscape.

Indirect mechanisms, including microbiota modulation and antimicrobial action, represent an emerging frontier. Curcumin-loaded MSNs demonstrated enhanced antibacterial and antiviral activity alongside improved wound healing compared with free curcumin.[53] Gold nanospheres ameliorated OVX-induced bone loss in vivo, in part by modulating the gut microbiota and reducing circulating TMAO levels.[54] GNPs (~60 nm) increased short-chain fatty acid production by enriching beneficial microbial taxa, modulated macrophage polarization, reduced pro-inflammatory cytokines, and mitigated cartilage and subchondral bone damage through the microbiota-gut-joint axis.[55] Silver nanoparticles exhibited stronger suppression of osteoclast markers than GNPs at equivalent concentrations, significantly reducing the expression of TRAP, CTSK, c-Fos, and NFATC1.[56]

The microbiota-targeting and antimicrobial strategies described in this subsection represent an intellectually compelling but mechanistically undercharacterized frontier. While the reported improvements in bone parameters are notable, the causal chain linking gut microbiota modulation—through nanoparticle-mediated compositional shifts—to skeletal outcomes involves multiple biological layers (microbial metabolite production, intestinal barrier integrity, systemic immune modulation) that have not been causally resolved in the reviewed studies. The correlational nature of microbiome-bone axis evidence makes it premature to designate gut microbiota modulation as a validated therapeutic target for inorganic nanomaterials without rigorous mechanistic dissection, germ-free animal validation, and longitudinal studies in aged models. Similarly, the superiority of silver over gold nanoparticles at equivalent concentrations for osteoclast suppression, while interesting, raises unresolved cytotoxicity concerns given silver's well-documented non-specific cellular toxicity profile at therapeutic concentrations.

In summary, owing to their mechanical rigidity, inherent osteoconductivity, and capacity for sustained local release, inorganic nanoplatforms are most appropriately deployed in localized interventions—such as implant coatings, bone defect scaffolds, and periosteal applications—where their structural permanence confers a distinct advantage. However, their translation to systemic intravenous targeted delivery for osteoporosis is substantially constrained by limited biodegradability and the attendant risk of long-term off-target accumulation in organs such as the liver and spleen. Furthermore, while ALN functionalization remains the predominant targeting strategy owing to its high hydroxyapatite affinity, this approach is inherently passive and indiscriminate, failing to distinguish between sites of active bone formation and active resorption. Emerging strategies employing osteoblast-selective peptides or aptamers hold greater promise for precision targeting of active remodeling zones. Accordingly, rigorous long-term biodistribution, genotoxicity, and clearance studies remain essential prerequisites for advancing inorganic nanomaterials toward meaningful clinical translation, detailed in Table 2.

Polymeric Nanocarriers in Osteoporosis Therapy

To modulate the anabolic signaling axes (eg, BMP/Smad, Wnt/β-catenin) and inflammatory microenvironment pathways identified as key therapeutic nodes in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes, polymeric nanomaterials—including poly(lactic-co-glycolic acid) (PLGA), chitosan, polyethylene glycol (PEG), and gelatin—offer highly tunable and functionally versatile platforms. Crucially, delivery strategies employing these polymers have undergone a marked conceptual evolution: from simple sustained-release drug-loaded matrices that rely on passive accumulation, toward sophisticated actively targeted vehicles that exploit mechanisms such as CXCR4-overexpressing cell membrane cloaking to actively home to the bone marrow niche. Beyond this targeting dimension, these carriers accommodate a diverse cargo spectrum—spanning small molecules, peptides, nucleic acids, and cellular secretomes—to simultaneously promote osteogenesis and suppress excessive bone resorption across a range of preclinical models.

Osteoblast-directed strategies converge on the anabolic nodes outlined in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes. PLGA nanoparticles co-functionalized with alendronate (ALN) and loaded with osteogenic growth peptide (OGP) restored bone homeostasis in ovariectomized (OVX) rats in vivo by activating BMP2, RUNX2, and ALP signaling, yielding measurable improvements in matrix mineralization and trabecular microarchitecture.[57] Chitosan–quercetin conjugates enhanced osteogenesis and angiogenesis in glucocorticoid-

Table 2 Inorganic Nanomaterials for Osteoporosis Therapy: Preparation, Agents, Release Profiles, and Targeting Strategies

Nanoplatform & Cargos	Targeting Strategy	In vivo Efficacy Metrics	Clinical Trial Status	Est. Manufacturing Cost & Regulatory Pathway	Ref.
MSN@PEI + PTN	**Active**: Cationic surface charge-mediated	Increased BMD, improved trabecular microarchitecture	Preclinical (Animal)	**Cost**: High **Reg**: Combination Product (Nanomedicine)	[38]
MSNs-PA@PEI + SOST siRNA/ osteostatin	**Active**: ALN-modified PEG for bone targeting	Synergistic promotion of bone formation and reduction of bone resorption	Preclinical (Animal)	**Cost**: Very High **Reg**: Complex Biologic Combination	[39]
MSN-SH + Si ions	**Active**: Thiol-mediated adhesion	Enhanced early osteogenesis in vitro/ in vivo	Preclinical	**Cost**: Moderate **Reg**: Novel Nanomaterial/ Device	[40]
MSN-ALN-Gd + Dexamethasone	**Active**: ALN-conjugated bone targeting	Enhanced targeted bone accumulation, rescued BMD loss	Preclinical (Animal)	**Cost**: High **Reg**: Theranostic Combination Product	[41]
Gen-ALN-nHA + Daidzein	**Intrinsic/Active**: nHA affinity + ALN	Restored OVX-induced BMD decline	Preclinical (Animal)	**Cost**: Moderate **Reg**: Combination Product	[42]
nHA (Dopamine-assisted) + ROS scavenging	**Localized**: Implant-tissue interface	Promoted local osseointegration, reduced oxidative stress	Preclinical (Animal)	**Cost**: Low to Moderate **Reg**: Class III Medical Device	[43]
Alg/Quer-HAp + Quercetin	**Localized**: Injectable microspheres	Promoted localized bone regeneration in defects	Preclinical (Animal)	**Cost**: Moderate **Reg**: Device/Combination Formulation	[44]
SPIO@15HA + SPIO core	**Intrinsic/Active**: Dual OB/OC targeting	Rebalanced bone remodeling, enhanced MRI tracking	Preclinical (Animal)	**Cost**: High **Reg**: Theranostic Device	[45]
GNPs (implant) + Surface silanization	**Localized**: p38 MAPK activation	Enhanced local bone matrix mineralization	Preclinical (Animal)	**Cost**: Moderate **Reg**: Medical Implant Coating	[46]
SiO2-CaO BGNs + Ca2+, Si4+ ions	**Passive**: Clathrin-mediated endocytosis	Stimulated osteoblast differentiation and bone formation	Preclinical (Animal)	**Cost**: Low **Reg**: Bone Substitute (Medical Device)	[47]
PMBG/TCP-PTH + PTH (1–34)	**Localized**: 3D scaffold + FAP inhibition	Enhanced trabecular bone regeneration	Preclinical (Animal)	**Cost**: High **Reg**: Device + Biologic Combination	[48]
PCB@MSN + Salmon calcitonin	**Passive**: Oral, mucoadhesion	Modest reduction in bone resorption markers	Preclinical (Animal)	**Cost**: Moderate **Reg**: Peptide Formulation	[49]
Ce@MSNs + Ce antioxidant	**Passive**: Mitochondrial ROS scavenging	Protected osteoblasts from oxidative damage	Preclinical (Animal)	**Cost**: Moderate **Reg**: Novel Nanomedicine	[50]
nHAp/IO + miR-21, miR-124	**Active**: Magnetic guidance	Synergistic OB promotion and OC suppression	Preclinical (Animal)	**Cost**: Very High **Reg**: Complex Biologic Combination	[51]
SCT-HAP-NPs + Salmon calcitonin	**Intrinsic/Active**: HAp + calcitonin receptor	Sustained suppression of OC activity, preserved BMD	Preclinical (Animal)	**Cost**: High **Reg**: Biologic Combination Product	[52]
Cur@MSN-PVP NFs + Curcumin	**Active**: Surface charge-mediated	Increased bone volume fraction, reduced inflammation	Preclinical (Animal)	**Cost**: Moderate **Reg**: Complex Drug Formulation	[53]
GNS (Oral) + Direct action	**Passive**: Gut microbiota-dependent	Altered gut microbiota, indirect bone protection	Preclinical (Animal)	**Cost**: Moderate **Reg**: Novel Oral Nanomedicine	[54]

(*Continued*)

Table 2 (Continued).

Nanoplatform & Cargos	Targeting Strategy	In vivo Efficacy Metrics	Clinical Trial Status	Est. Manufacturing Cost & Regulatory Pathway	Ref.
GNPs (Oral) + Direct action	**Passive**: Microbiota-gut-joint axis	Reduced systemic inflammation and bone loss	Preclinical (Animal)	**Cost**: Moderate **Reg**: Novel Oral Nanomedicine	[55]
SNPs + Passive uptake	**Passive**: Size-dependent macrophage targeting	Modulated osteoimmune microenvironment	Preclinical (Animal)	**Cost**: Low **Reg**: Novel Nanomedicine	[56]

Abbreviations: Alg, alginate; ALN, alendronate; BGNs, bioactive glass nanoparticles; Ce, cerium; CTAB, cetyltrimethylammonium bromide; Cur, curcumin; DTPA, diethylenetriaminepentaacetic acid; FAP, fibroblast activation protein; Gd, gadolinium; Gen, genistein; GNPs, gold nanoparticles; GNS, gold nanostars; HAP/nHA, (nano) hydroxyapatite; IO, iron oxide; MAPK, mitogen-activated protein kinase; MPTMS, (3-mercaptopropyl)trimethoxysilane; MSNs, mesoporous silica nanoparticles; NFs, nanofibers; PA, polyacrylate; PCB, pectin-chitosan beads; PEG, polyethylene glycol; PEI, polyethylenimine; PMBG, phosphorus-rich mesoporous bioactive glass; PTH, parathyroid hormone; PTN, pleiotrophin; PVP, polyvinylpyrrolidone; Quer, quercetin; RES, reticuloendothelial system; ROS, reactive oxygen species; SCT, salmon calcitonin; SNPs, silica nanoparticles; SPIO, superparamagnetic iron oxide; TCP, tricalcium phosphate.

induced osteoporosis models in vivo by upregulating RUNX2 and type I collagen while attenuating inflammatory signaling, thereby supporting the coordinated repair of bone and its associated vasculature.[58]

A critical appraisal of these osteoblast-directed polymeric strategies reveals a consistent pattern: efficacy demonstrations are predominantly anchored to single-agent, single-target systems evaluated in OVX rodent models with short observation periods of 4–8 weeks. While this framework provides proof-of-concept evidence, it underrepresents the clinical scenario in which osteoporosis arises from concurrent deficits in osteogenesis, osteoclast suppression, and vascular support simultaneously. Critically, the magnitude of BMD improvements reported across studies—typically 15–30% relative to OVX controls—while statistically significant in young ovariectomized rodents, may not translate proportionally to the aged human skeleton, where intrinsic osteoblast number, activity, and responsiveness to anabolic signals are substantially diminished. The absence of aged animal models or large-animal validation in these studies represents a significant translational blind spot that limits confidence in extrapolating these results to the target clinical population.

The evolution toward bio-integrated, actively targeted systems is most clearly exemplified by biomimetic nanogels cloaked with bone marrow MSC membranes overexpressing RANK and CXCR4. By leveraging the natural marrow-homing capacity of the source cells, these constructs achieved active targeting of the bone microenvironment, delivering PTH(1–34) to increase bone mass by approximately 62.5% and achieving greater than 90% RANKL clearance in postmenopausal models in vivo—directly engaging the RANKL/OPG axis identified in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes.[59] In a complementary cell-free approach, endothelial cell membrane-coated PLGA nanoparticles with CXCR4 overexpression delivered MSC secretome factors (OPG, BMP-2), increasing bone mineral density (BMD) by 18.3% in OVX rats in vivo and circumventing the instability concerns associated with live stem cell therapies.[60]

The biomimetic cell membrane-cloaking strategy represents a qualitative advance in targeting sophistication, but its clinical scalability demands critical scrutiny. Fabrication of RANK/CXCR4-overexpressing MSC membrane-coated nanogels requires extensive cell culture, genetic modification, membrane extraction, and nanoparticle coating steps—each introducing potential batch-to-batch variability, regulatory complexity, and contamination risk. More fundamentally, the 62.5% increase in bone mass reported for PTH(1-34)-loaded constructs was achieved in young OVX mice; PTH receptor signaling capacity and osteoblast responsiveness to anabolic stimulation are markedly attenuated in aged subjects with senescent osteoprogenitor pools, raising substantive questions about whether equivalent efficacy can be achieved in the actual target population of elderly postmenopausal women. This age-dependent efficacy attenuation represents a translational risk that is systematically underexplored in current polymeric nanoparticle literature.

Gelatin-based scaffolds and nanoparticles activated canonical BMP-Smad and Wnt/β-catenin pathways using ultra-low BMP-2 doses, upregulating RUNX2 and promoting bone defect repair in vivo while reducing the requisite BMP-2 dose by more than 97%—a clinically meaningful reduction given BMP-2's dose-dependent adverse effects.[61] High-

strength gelatin hydrogels capable of co-delivering anti-inflammatory and osteoinductive agents remodeled chronic inflammatory niches within osteoporotic bone, markedly enhancing new bone formation in vivo.[62] Functionalized gelatin scaffolds incorporating magnesium or zoledronic acid enabled sustained localized release on implant surfaces, suppressing osteoclast activity and preventing excessive peri-implant resorption.[63]

The gelatin-based strategies described in this section, while mechanistically compelling, introduce a distinct set of translational constraints. The greater than 97% reduction in BMP-2 dose achieved through gelatin nanoparticle encapsulation is clinically meaningful in principle, but this figure derives from localized bone defect models rather than the systemic, diffuse bone loss characteristic of osteoporosis; whether equivalent dose-sparing efficacy is achievable through systemic delivery—where BMP-2 encounters serum proteases, non-target receptor binding, and rapid clearance—remains undemonstrated. Similarly, the high-strength gelatin hydrogels and functionalized scaffolds incorporating magnesium or zoledronic acid are inherently local delivery platforms optimized for surgical implant contexts, and their applicability to the predominant clinical presentation of osteoporosis—generalized vertebral and hip fracture risk without discrete bone defects—is limited. This localized-versus-systemic applicability gap represents a fundamental scope constraint that must be explicitly acknowledged when evaluating the clinical relevance of scaffold-based polymeric strategies for osteoporosis management.

Osteoclast-directed and anti-inflammatory strategies further illustrate the dual-action potential of polymeric platforms. Chitosan nanoparticles loaded with Himalayan shilajit extract reduced oxidative stress and IL-6 levels in vivo, redirected adipose-derived stem cells toward the osteoblast lineage, and improved bone microarchitecture in glucocorticoid-induced osteoporosis models.[64] Liposomal-PLGA hybrids modified with an α8 integrin antibody and co-loaded with dexamethasone and captopril exerted systemic anti-inflammatory and anti-fibrotic effects, providing an indirect but meaningful benefit to bone health.[65]

The anti-inflammatory and osteoclast-directed polymeric strategies reviewed here reveal a recurring paradox: systemic anti-inflammatory agents such as dexamethasone, while effective in acute inflammatory contexts, carry intrinsic risks of immunosuppression and, critically, glucocorticoid-induced bone loss with prolonged exposure—an ironic liability for an osteoporosis therapeutic platform. The reviewed formulations partially mitigate this through encapsulation and targeted local delivery, but long-term safety data for repeated systemic administration under chronic disease conditions are largely absent, representing a critical translational gap. Furthermore, the Himalayan shilajit extract system, while demonstrating multi-pathway activity in vivo, lacks the standardized chemical characterization required for regulatory-grade quality control; natural product extracts with undefined active constituent profiles pose substantial challenges for batch consistency, dose-response characterization, and drug-drug interaction assessment in a clinical setting.

Emerging innovations in this class are increasingly directed at enhancing targeting precision and achieving multifunctionality through intelligent material design. Tetracycline-grafted mPEG-PLGA micelles chelate calcium within hydroxyapatite to actively enhance bone accumulation and improve the solubility of hydrophobic anabolic agents such as astragaloside IV, reportedly yielding a 62.7% increase in BMD in vivo.[66] ALN-functionalized PLGA nanoparticles with membrane-mimetic coatings were engineered for ROS-responsive delivery of the mitochondrial protective peptide SS31, producing a 32% increase in bone volume fraction (BV/TV) in OVX mice in vivo—directly addressing the oxidative stress node identified in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes.[67] Polymer–inorganic composite carriers are also gaining traction for synergistic bioactivity: ZOL-PLGA-Yoda1-SPIO constructs activated Piezo1 and YAP/β-catenin signaling, promoted angiogenesis, and enhanced bone regeneration in OVX models in vivo.[68] Europium-doped SPIO-PLGA nanocomposites induced M2 macrophage polarization, enhanced osteogenesis, and suppressed osteoclastogenesis in OVX rats in vivo.[69]

The increasingly sophisticated multifunctional polymeric constructs described in this subsection—combining bone-targeting ligands, stimuli-responsive release triggers, magnetic components, and immunomodulatory payloads—raise a fundamental translational concern: manufacturing complexity scales non-linearly with functional sophistication. Each additional component introduces new synthesis steps, characterization demands, and potential failure points for quality control. The ZOL-PLGA-Yoda1-SPIO construct, for instance, integrates four distinct functional elements; none of the reviewed studies address the reproducibility of this multi-step fabrication at scales beyond laboratory synthesis, nor the regulatory classification challenges posed by such combination products. Similarly, the ROS-responsive release

mechanism, while elegantly designed, assumes a level of oxidative stress consistency at bone remodeling sites that may vary substantially between patients and even between skeletal sites within the same patient—a pharmacokinetic unpredictability that has not been systematically characterized.

Relative to the mechanically rigid inorganic platforms described in Inorganic Nanomaterials for Bone-Targeted Delivery, biodegradable polymers—particularly FDA-approved PLGA—are substantially better suited for systemic targeted delivery, owing to their superior biocompatibility, tunable degradation kinetics, and established manufacturability for both local and systemic therapeutic strategies, detailed in Table 3. A defining trend in this class is the conceptual advancement beyond simple ALN-mediated passive targeting toward intelligent biomimetic strategies, such as cell membrane cloaking, that actively exploit the natural homing mechanisms (eg, CXCR4) and immune-evasive properties of source cells. This represents a qualitative leap over the targeting sophistication achievable with inorganic carriers. Polymeric platforms further demonstrate a clear advantage in the delivery of biologics—including peptides and cell secretomes—which remain technically challenging for inorganic systems. However, the in vivo robustness of these multi-step targeting cascades (eg, marrow homing followed by ROS-triggered release) in the complex human physiological environment remains to be rigorously validated in large-animal models and clinical trials. Critically, despite their biodegradability advantage, the acidic monomeric byproducts of PLGA degradation can inadvertently provoke local inflammatory responses—a deleterious outcome in a chronic inflammatory disease context such as osteoporosis, and one that demands precise formulation-level control. Accordingly, careful attention to long-term degradation profiles, immunocompatibility of byproducts, and mechanical reinforcement for load-bearing applications will be indispensable for advancing polymeric nanoplatforms toward clinical translation.

Liposomal Systems for Bone-Specific Drug Delivery

To execute precise, cell-specific interventions against the osteoblast and osteoclast regulatory nodes established in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes, liposomal systems—particularly lipid nanoparticles (LNPs)—have emerged as highly versatile platforms for bone-targeted therapeutics. A critical conceptual distinction must be maintained, however, between basic LNPs that function merely as passive drug-loaded vesicles, and modern actively targeted liposomal constructs that achieve cell-level specificity by grafting surface moieties such as bone-homing peptides (eg, $AspSerSer_6$), osteoblast-selective aptamers (eg, CH6), or bisphosphonate ligands (eg, ALN) to actively recognize and engage osteogenic or resorptive microenvironments. Within this framework, a substantial body of research has focused on LNP-mediated targeting of mesenchymal stem cells (MSCs) and bone marrow stromal cells (BMSCs)—the progenitor populations of mature osteoblasts—with the dual aims of stimulating bone regeneration and suppressing osteoclastogenesis, detailed in Table 4.

MSC/BMSC-directed osteogenic strategies directly engage the progenitor-level anabolic nodes discussed in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes. LNP-mediated delivery of siRNA targeting GNAS significantly enhanced the osteogenic differentiation of MSCs in vitro, offering a promising nucleic acid-based anabolic strategy for mitigating bone loss.[70] ALN-modified LNPs co-loaded with anti–miR-378a-3p suppressed osteoclast formation in OVX mice in vivo, yielding a 35.2% increase in BMD—a clinically meaningful magnitude of response.[71] Endothelial cell–targeting LNPs carrying siRNA against ZEB1 promoted angiogenesis-dependent bone formation in OVX mice in vivo through activation of the Notch signaling pathway, effectively reversing osteoporotic bone loss and illustrating the value of coupling vascular and skeletal regeneration.[72]

While these nucleic acid delivery achievements are scientifically significant, their translational context demands critical assessment. The in vitro GNAS-siRNA results, though demonstrating clear osteogenic enhancement, lack the in vivo pharmacokinetic data necessary to assess systemic delivery feasibility—specifically, siRNA cargo stability under serum conditions, LNP biodistribution to bone versus off-target organs (particularly liver and spleen), and the immunostimulatory potential of the LNP-siRNA complex after repeated dosing. A broader mechanistic caution also applies: the remarkable efficacy of LNP-mRNA platforms in vaccine contexts was achieved through intramuscular injection targeting highly vascular, phagocyte-rich tissue—a fundamentally different delivery challenge compared to bone-targeted siRNA delivery, which requires systemic circulation, active bone homing, cellular internalization by osteoblast

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Table 3 Polymeric Nanomaterials for Osteoporosis Therapy: Targeting Strategies, in vivo Efficacy, Clinical Status, Cost, and Regulatory Pathways

Nanoplatform & Cargos	Targeting Strategy	In vivo Efficacy Metrics	Clinical Trial Status	Est. Manufacturing Cost & Regulatory Pathway	Ref.
AL-PLGA NPs + OGP/ALN	**Active**: ALN-mediated hydroxyapatite targeting	Increased BMD and BV/TV in OVX rat model	Preclinical (Animal)	**Cost**: Moderate **Reg**: Combination Product (Drug/Device)	[57]
Chitosan-quercetin	**Passive**: Modulation of bone remodeling	Enhanced trabecular thickness and bone regeneration	Preclinical (Animal)	**Cost**: Low **Reg**: Standard small-molecule formulation	[58]
Chitosan nanogel + PTH (1–34)	**Biomimetic**: CXCR4/SDF-1 axis (BMSC membrane)	Increased BMD, prolonged bone retention	Preclinical (Animal)	**Cost**: Extremely High **Reg**: Complex Biologic/Cell-derived product	[59]
MSC-Sec/CXCR4 NP	**Biomimetic**: CXCR4-mediated microenvironment targeting	Increased BMD, decreased osteoclast number in OVX mice	Preclinical (Animal)	**Cost**: High (Secretome isolation) **Reg**: Biologic pathway (highly stringent)	[60]
Gelatin-CaSO4/HA + BMP-2	**Localized**: Targeted to calvarial bone defects	Accelerated localized defect healing	Preclinical (Animal)	**Cost**: Moderate **Reg**: Class III Medical Device + Biologic	[61]
Gelatin NPs + Rosuvastatin	**Localized**: HIF-1 alpha pathway (3D printed)	Enhanced local osteogenesis and angiogenesis	Preclinical (Animal)	**Cost**: High (3D printing scale-up) **Reg**: Combination Product	[62]
GelMA-AS + Mg2+	**Localized**: Osteoporotic defect delivery	Increased bone volume fraction, enhanced repair	Preclinical (Animal)	**Cost**: Low to Moderate **Reg**: Combination Product/Device	[63]
Chitosan-NPs + Shilajit extract	**Intrinsic/Active**: Nanochitosan bone affinity	Increased BMD, restored trabecular architecture	Preclinical (Animal)	**Cost**: Low **Reg**: Botanical/Supplement formulation	[64]
DXMS/CAP@PLGA	**Active**: alpha 8 integrin antibody-mediated	Synergistic restoration of bone mass	Preclinical (Animal)	**Cost**: High (Antibody conjugation) **Reg**: Targeted Biologic/Combination	[65]
TC-mPEG-PLGA + Astragaloside IV	**Active**: Tetracycline-hydroxyapatite complexation	Increased BMD, improved biomechanical strength	Preclinical (Animal)	**Cost**: Moderate **Reg**: Combination Product	[66]
ALN@BMSCM@PLGA + SS31	**Biomimetic/Active**: BMSC membrane + ALN	Enhanced ROS scavenging and osteoblast survival	Preclinical (Animal)	**Cost**: Extremely High **Reg**: Cell-derived Biologic Combination	[67]
ZOL-PLGA@SPIO + Yoda1	**Active/Physical**: Zoledronate + magnetic guidance	Increased targeted bone accumulation and BMD	Preclinical (Animal)	**Cost**: High **Reg**: Complex Combination (Drug/Device)	[68]
SPIO:Eu@PLGA	**Physical**: Magnetically assisted trabecular delivery	Enhanced tracking and localized retention	Preclinical (Animal)	**Cost**: Moderate to High **Reg**: Medical Device/Imaging Agent	[69]

Notes: In vivo efficacy metrics generally represent findings from preclinical ovariectomized (OVX) rodent models unless otherwise specified.

Abbreviations: ALN, alendronate; AS, astragaloside IV; BMD, bone mineral density; BMP-2, bone morphogenetic protein-2; BMSC(M), bone mesenchymal stem cell (membrane); BV/TV, bone volume/tissue volume ratio; CAP, captopril; CXCR4, C-X-C chemokine receptor type 4; DXMS, dexamethasone; Eu, europium; GelMA, gelatin methacryloyl; HA, hydroxyapatite; NPs, nanoparticles; OGP, osteogenic growth peptide; OVX, ovariectomized; PLGA, polylactic-co-glycolic acid; PTH, parathyroid hormone; Reg, regulatory pathway; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor 1; Sec, secretome; SPIO, superparamagnetic iron oxide; TC, tetracycline; ZOL, zoledronate.

Table 4 Liposomal Nanoplatforms for Osteoporosis Therapy: Targeting Strategies, in vivo Efficacy, Clinical Status, Cost, and Regulatory Pathways

Nanoplatform & Cargos	Targeting Strategy	In vivo Efficacy Metrics	Clinical Trial Status	Est. Manufacturing Cost & Regulatory Pathway	Ref.
LNP-siRNA + siRNA (Sequence D)	**Passive**: Size-mediated accumulation (50 nm LNPs)	Enhanced MSC transfection and local osteogenesis	Preclinical (Animal)	**Cost**: High **Reg**: RNAi Therapeutic Formulation	[70]
Antagomir@ALN-Lipo + Antagomir-378a-3p	**Active**: ALN-mediated hydroxyapatite targeting	Increased BMD and trabecular thickness	Preclinical (Animal)	**Cost**: High **Reg**: Targeted Biologic Combination	[71]
Lipo-ZEB1-GFP + ZEB1-GFP plasmid DNA	**Passive**: Metaphyseal vasculature accumulation	Promoted type H vessel formation and osteogenesis	Preclinical (Animal)	**Cost**: Very High **Reg**: Gene Therapy Delivery System	[72]
Na2HPO4@Lipo-pOCm + Na2HPO4	**Biomimetic**: Pre-osteoclast membrane fusion	Reduced osteoclastogenesis, preserved bone mass	Preclinical (Animal)	**Cost**: Extremely High **Reg**: Cell-Derived Biomimetic Device	[73]
AM@OPC/AE@OPC + MTX, Estradiol (E2)	**Active**: OPC recruitment via CXCL12/CXCR4 axis	Reduced bone destruction, restored remodeling balance	Preclinical (Animal)	**Cost**: High **Reg**: Complex Drug Combination Product	[74]
DSS-lip-ant132 + miRNA-132-3p inhibitor	**Active**: (AspSerSer)6 peptide targeting	Increased bone formation at resorption sites	Preclinical (Animal)	**Cost**: High **Reg**: Peptide-Targeted Biologic	[75]
CXCR4-EXO/Lipo NPs + Antagomir-188	**Biomimetic**: Exosome-guided SDF-1/CXCR4 targeting	Reversed age-related trabecular bone loss	Preclinical (Animal)	**Cost**: Extremely High **Reg**: Exosome-Liposome Hybrid Biologic	[76]
CH6-LNP-siNLRP3 + siNLRP3	**Active**: Osteoblast-specific CH6 aptamer	Enhanced osteogenic differentiation, reduced ROS	Preclinical (Animal)	**Cost**: Very High **Reg**: Aptamer-Targeted RNAi Formulation	[77]
PA@TLipo + Pomolic acid (PA)	**Active**: ALN-PEG functionalization	Restored BMD, enhanced osteoblast activity	Preclinical (Animal)	**Cost**: Moderate to High **Reg**: Targeted Botanical Combination	[5]
(DSS)6-Lipo + Quercetin	**Active**: (AspSerSer)6 peptide targeting	Enhanced targeted accumulation, increased bone volume	Preclinical (Animal)	**Cost**: Moderate to High **Reg**: Peptide-Targeted Drug Formulation	[78]

Note: In vivo efficacy metrics generally represent findings from preclinical rodent models unless otherwise specified.

Abbreviations: ALN, alendronate; AM, alendronate-modified methotrexate liposomes; AE, alendronate-modified estradiol liposomes; BMD, bone mineral density; CXCR4, C-X-C chemokine receptor type 4; DSS, aspartate-serine-serine peptide sequence; E2, estradiol; EXO, exosome; GFP, green fluorescent protein; Lipo, liposome; LNP, lipid nanoparticle; MSC, mesenchymal stem cell; MTX, methotrexate; NPs, nanoparticles; OPC, osteoclast precursor cell; PA, pomolic acid; PEG, polyethylene glycol; pOCm, pre-osteoclast membrane; Reg, regulatory pathway; RNAi, RNA interference; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor 1; siRNA, small interfering RNA; ZEB1, zinc finger E-box-binding homeobox 1.

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progenitors, and endosomal escape in sequence. The efficiency losses at each step of this cascade are rarely quantified in the reviewed studies, making the true bone-cell delivery fraction largely unknown.

Cell membrane–coated and hybrid liposomal systems represent a further advance in targeting precision. The Na_2HPO_4@Lipo-pOCm system neutralized intracellular pH specifically within osteoclasts, thereby inhibiting their resorptive activity and improving bone quality in OVX models in vivo.[73] Osteopontin (OPN)-guided DSPE-PEG-ALN LNPs designed for the delivery of methotrexate or estradiol achieved threefold higher drug accumulation in bone tissue relative to unmodified liposomes, improving bone repair in both osteosarcoma and OVX mouse models in vivo, as evidenced by a 30% increase in BV/TV and a 25% increase in trabecular thickness (Tb.Th).[74] In models of disuse osteopenia—relevant to bedridden patients or astronauts experiencing microgravity-induced bone loss—$(AspSerSer)_6$–cationic liposomes encapsulating anti–miRNA-132-3p mitigated BMSC osteogenic suppression in vivo by restoring RUNX2 acetylation, improving BV/TV by 29.5% and Tb.Th by 18.2% in hindlimb-unloading mice.[75] $CXCR4^+$ exosome–liposome hybrids delivering anti–miR-188 to BMSCs inhibited adipogenic differentiation while promoting osteogenesis in 18-month-old mice in vivo, achieving this through coordinated downregulation of PPARγ and upregulation of RUNX2, SP7, and Bglap, resulting in improved trabecular number (Tb.N) and reduced cortical porosity.[76]

The cell membrane-coated and hybrid liposomal systems achieve impressive targeting specificity in rodent models, but a critical and underacknowledged limitation is the significant donor-source variability inherent to biological membrane preparations. The surface proteome of BMSC or platelet membranes varies substantially with donor age, health status, passage number, and culture conditions—heterogeneity that may translate to inconsistent targeting efficiency and therapeutic response across individual patients, posing formidable quality control challenges for clinical manufacturing under GMP standards. Furthermore, the reported improvements in BV/TV (18–29%) and Tb.Th derive exclusively from OVX or hindlimb-unloading mouse models; neither model adequately replicates the cortical thinning and intracortical remodeling patterns that predominate in elderly human osteoporosis, limiting the generalizability of these structural outcome data to the clinical target population.

Inflammation-targeted liposomal strategies address the immunological microenvironment nodes outlined in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes. CH6 aptamer–modified LNPs—composed of DOTAP, DSPC, DSPE-PEG-CH6, and cholesterol—were loaded with NLRP3-targeting siRNA to selectively engage osteoblasts in postmenopausal osteoporosis (PMOP) rats in vivo. Silencing of NLRP3 suppressed the NF-κB pathway while upregulating interferon-related genes (eg, Oas1b), reducing pro-inflammatory cytokines (IL-1β, IL-18) and enhancing osteogenic markers (RUNX2, ALP, OCN). This intervention produced substantial in vivo improvements in bone microarchitecture: BMD increased by 28.5%, BV/TV by 43.2%, and Tb.Th by 37.1%—among the most pronounced structural benefits reported for any liposomal platform in this review.[77]

The CH6 aptamer-modified LNP system warrants particular critical scrutiny precisely because of its exceptional reported outcomes. BMD increases of 28.5% and BV/TV improvements of 43.2% substantially exceed magnitudes reported for most established clinical pharmacotherapies, raising questions about the baseline severity of OVX-induced osteoporosis, the treatment duration, and the specific quantification methodology employed. Exceptional efficacy claims in rodent models have historically demonstrated poor predictive validity for human trials, particularly when derived from single-laboratory studies without independent replication or confirmation in a second model system. The absence of dose-response characterization, off-target organ toxicity profiling, and large-animal pharmacokinetic validation must be explicitly acknowledged as essential preconditions for any translational advancement of this system, regardless of the magnitude of effects observed in the OVX rat.

Osteoclast-targeted liposomal formulations have demonstrated complementary therapeutic value. A DSPC/cholesterol/DSPE-PEG_{3400}–ALN formulation encapsulating pomolic acid (PA; loading efficiency 13%) achieved bone-specific delivery through its ALN surface modification. The delivered PA inhibited osteoclast differentiation by modulating the NF-κB/ERK/NFATc1 pathway in vivo, producing significant improvements in BV/TV, Tb.N, and trabecular separation (Tb.Sp) in OVX mice while reducing systemic toxicity relative to free PA administration.[5]

The ALN-functionalized liposomal delivery of pomolic acid highlights a fundamental design tension inherent to bisphosphonate-mediated bone targeting: ALN's high affinity for hydroxyapatite is non-discriminatory with respect to bone remodeling state, directing accumulation indiscriminately to both actively resorbing and quiescent bone surfaces.

This limitation means drug release is spatially decoupled from osteoclast activity, potentially resulting in therapeutic delivery to sites requiring no intervention while failing to achieve adequate concentrations at high-turnover resorption lacunae where intervention is most needed. The pomolic acid loading efficiency of 13% also raises a practical concern: the majority of the liposomal carrier mass constitutes inactive excipient, raising the administered dose of lipid components required to achieve therapeutic drug concentrations—a consideration with direct implications for infusion volume, lipid-related toxicity, and cost of goods in chronic administration settings.

Innovative applications of LNPs are further expanding the therapeutic scope of this class beyond conventional osteoblast/osteoclast targeting. DSPE-PEG_{2000}-$(DSS)_6$ peptide–modified liposomes encapsulating the senolytic agent quercetin were engineered to target low-crystallinity hydroxyapatite, enabling the selective elimination of senescent BMSCs—a distinct cellular node implicated in age-related bone deterioration—without compromising healthy cells. In both doxorubicin-induced osteoporosis and naturally aged (24-month-old) mouse models in vivo, this system upregulated osteogenic markers (OCN, RUNX2) and enhanced mineralization rates, highlighting a fundamentally different therapeutic modality—targeting cellular senescence rather than simply delivering an established drug through a novel carrier.[78]

Liposomal platforms possess a distinct and largely unmatched capability for encapsulating and systemically delivering fragile nucleic acid therapeutics—including siRNAs and anti-miRNAs—a functional niche that inorganic carriers and simple polymeric systems struggle to occupy. In this sense, they occupy a strategically important position bridging synthetic carriers such as PLGA and fully biological vectors such as exosomes, combining favorable biocompatibility with the manufacturing scalability and mature clinical translation precedent demonstrated by LNP-based mRNA vaccines. Nevertheless, their application to the chronic, long-term treatment demands of osteoporosis remains constrained by three primary liabilities: intrinsic in vivo instability, susceptibility to rapid immune-mediated clearance, and premature drug leakage prior to reaching the target site. Advanced engineering strategies—including PEGylation, bone-homing surface functionalization (ALN, peptides, aptamers), and exosome–liposome hybridization—have partially mitigated these vulnerabilities, but their in vivo robustness in large-animal models and human physiology requires further validation before clinical translation can be meaningfully pursued.

Biomimetic and Cell-Derived Nanoplatforms

To dynamically modulate the highly interconnected signaling networks and osteoimmune microenvironment described in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes—including PI3K/Akt, Wnt/β-catenin, NF-κB, and m6A epitranscriptomic axes—biomimetic platforms, particularly exosomes and cell-derived vesicles, offer biological advantages that synthetic carriers fundamentally cannot replicate. These nanoscale vesicles (30–150 nm in diameter) can be categorized into two functionally distinct classes: natural or endogenous exosomes, which harness their inherent biological tropism and intrinsic cargo (miRNAs, proteins, lipids) to exert cell-type-specific therapeutic effects; and engineered or functionally enhanced exosomes, which are chemically or genetically modified with synthetic ligands (eg, SDSSD bone-targeting peptides, aptamers) to achieve strict precision targeting and programmable payload delivery, detailed in Table 5. Recent studies have demonstrated their collective capacity to promote osteogenesis, inhibit osteoclastogenesis, and remodel the bone microenvironment across a diverse spectrum of osteoporosis etiologies.

Natural endogenous exosomes leverage biological tropism and intrinsic cargo to engage the anabolic and anti-catabolic nodes of bone remodeling. Plasma exosomes derived from young adults stimulated osteogenic differentiation and prevented bone loss in OVX rats in vivo, an effect mediated by miR-142-5p targeting ZFPM2 to enhance osteoblast activity and inhibit osteoclast differentiation—demonstrating superior anti-osteoporotic efficacy compared to aged-donor exosomes and underscoring the age-dependent therapeutic potency of endogenous exosomal cargo.[85] Bone marrow MSC-derived exosomes promoted M2 macrophage polarization in OVX mice in vivo by upregulating TRIM25, which directed TREM1 degradation to enhance osteogenesis and reduce bone loss—directly engaging the osteoimmune axis identified in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes.[86] Oyster mantle-derived exosomes (OMEs), enriched in phospholipids and osteogenic proteins, promoted bone homeostasis in OVX mice in vivo by simultaneously activating the PI3K/Akt/β-catenin pathway to drive osteogenesis and inhibiting NF-κB signaling to suppress osteoclast activity, with the additional clinical advantages of oral tolerability and the absence of systemic toxicity.[81] Exosomes derived from mechanically stressed C2C12 myofibroblasts attenuated glucocorticoid-

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Table 5 Exosome-Based Nanoplatforms for Osteoporosis Therapy: Targeting Strategies, in vivo Efficacy, Clinical Status, Cost, and Regulatory Pathways

Nanoplatform (Source) and Cargos	Targeting Strategy	In vivo Efficacy Metrics	Clinical Trial Status	Est. Manufacturing Cost & Regulatory Pathway	Ref.
FNDC5/Irisin-exosomes (Skeletal muscle) + Irisin, AA, DHA	**Intrinsic**: Clathrin-mediated endocytosis to osteoblasts	Enhanced bone formation and improved trabecular mass	Preclinical (Animal)	**Cost**: High (Isolation) **Reg**: Cell-Derived Biologic	[79]
hUCMSC-EXOs (Umbilical cord MSCs) + Endogenous signals	**Intrinsic**: PI3K/AKT activation, ferroptosis inhibition	Reduced bone loss, promoted osteogenic differentiation	Preclinical (Animal)	**Cost**: High (Cell culture) **Reg**: Cell-Derived Biologic	[80]
Oyster mantle exosomes (Oyster tissue) + Phospholipids, minerals	**Intrinsic**: Mineral/protein-enriched bone affinity	Increased bone mineral density and promoted defect healing	Preclinical (Animal)	**Cost**: Moderate to High **Reg**: Natural Product Biologic	[81]
RRP serum exosomes (Paeonia-treated serum) + miR-29a-3p	**Intrinsic**: Wnt pathway regulation via NFIA	Restored trabecular microarchitecture in OVX models	Preclinical (Animal)	**Cost**: High **Reg**: Botanical/Animal Biologic	[82]
Epimedium nanovesicles (Epimedium herb) + Flavonoids, miRNAs	**Intrinsic**: Hydroxyapatite synergy, PI3K/Akt/mTOR	Enhanced osteogenesis, prevented systemic bone loss	Preclinical (Animal)	**Cost**: Moderate **Reg**: Botanical Nanomedicine	[83]
C2C12-exosomes (Stressed myoblasts) + miR-92a-3p	**Intrinsic**: PTEN/AKT signaling modulation	Promoted targeted osteoblast differentiation	Preclinical (Animal)	**Cost**: High **Reg**: Cell-Derived Biologic	[84]
Young plasma exosomes (Human plasma) + miRNAs, DNA, proteins	**Intrinsic**: Rejuvenation of osteogenic pathways	Reversed age-related bone deterioration and fragility	Preclinical (Animal)	**Cost**: Very High (Donor dependent) **Reg**: Blood-Derived Biologic	[85]
BMSC-derived exosomes (Bone marrow MSCs) + TRIM25 regulators	**Intrinsic**: Macrophage polarization (M2 pathway)	Reduced local inflammation, stimulated bone repair	Preclinical (Animal)	**Cost**: High **Reg**: Cell-Derived Biologic	[86]
Osteoclast exosomes (Osteoclasts) + lncRNA AW011738	**Intrinsic**: TREM1 axis regulation	Inhibited excessive osteoclastogenesis and resorption	Preclinical (Animal)	**Cost**: High **Reg**: Cell-Derived Biologic	[87]
BGN + BMSC-EVs (BMSCs) + lncRNA NRON	**Passive/Intrinsic**: Endocytosis by pre-osteoclasts	Suppressed osteoclast maturation and bone resorption	Preclinical (Animal)	**Cost**: High **Reg**: Cell-Derived Biologic	[88]
RAW-Exos (Macrophage RAW264.7) + miR-3102-5p	**Active**: Engineered alox15 targeting to osteoblasts	Improved bone microenvironment and structural integrity	Preclinical (Animal)	**Cost**: Very High **Reg**: Engineered Cell Biologic	[89]
PS-EMs (Exosome mimetics) + CXCR3 antagonist (AMG487)	**Active**: PS receptor-mediated osteoclast targeting	Suppressed osteoclast activity, preserved BMD	Preclinical (Animal)	**Cost**: High **Reg**: Biomimetic Combination	[90]
BT-Exo (Induced MSCs) + siRNA (Shn3)	**Active**: SDSSD peptide-mediated bone targeting	Promoted targeted bone formation at skeletal sites	Preclinical (Animal)	**Cost**: Extremely High **Reg**: Peptide-Targeted RNAi Biologic	[91]
MC3T3-Exo (MC3T3-E1 osteoblasts) + METTL14	**Active**: EphA2-engineered osteoclast targeting	Modulated osteoclast differentiation, reduced bone loss	Preclinical (Animal)	**Cost**: Very High **Reg**: Engineered Cell Biologic	[92]
hBMSC-Exo (Human BMSCs) + METTL3 mRNA	**Active**: SDSSD peptide-modified bone targeting	Enhanced local osteoblast activity and increased BMD	Preclinical (Animal)	**Cost**: Extremely High **Reg**: Targeted Gene Therapy	[93]
PL-exo-ALN (Platelets) + Growth factors (PDGF, VEGF, TGF-beta)	**Active**: ALN-functionalized hydroxyapatite binding	Synergistic enhancement of bone vascularization and repair	Preclinical (Animal)	**Cost**: Very High **Reg**: Targeted Blood Biologic	[94]

Notes: In vivo efficacy metrics generally represent findings from preclinical rodent models of osteoporosis unless otherwise specified. Endogenous nanoplatforms typically utilize intrinsic homing capabilities, whereas engineered nanoplatforms utilize active surface modifications.

Abbreviations: AA, arachidonic acid; ALN, alendronate; BGN, bioactive glass nanoparticles; BMD, bone mineral density; BMSC, bone mesenchymal stem cell; DHA, docosahexaenoic acid; EphA2, ephrin type-A receptor 2; EV, extracellular vesicle; FNDC5, fibronectin type III domain-containing protein 5; hUCMSC, human umbilical cord mesenchymal stem cell; lncRNA, long non-coding RNA; METTL, methyltransferase-like; miRNA, microRNA; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; NFIA, nuclear factor I A; OVX, ovariectomized; PDGF, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; PL, platelet; PS, phosphatidylserine; PS-EM, phosphatidylserine-exosome mimetic; PTEN, phosphatase and tensin homolog; Reg, regulatory pathway; RRP, radix paeoniae rubra; SDSSD, serine-aspartate-serine-serine-aspartate peptide sequence; siRNA, small interfering RNA; TGF-beta, transforming growth factor beta; TREM1, triggering receptor expressed on myeloid cells 1; VEGF, vascular endothelial growth factor.

induced osteoporosis (GIOP) in mice in vivo and enhanced BMSC proliferation and differentiation by delivering miR-92a-3p, which modulated the PTEN/AKT signaling axis.[84] Epimedium-derived extracellular nanovesicles (EELNs) combined with hydroxyapatite nanowhiskers promoted alveolar bone regeneration in OVX rats in vivo by activating the PI3K/Akt/mTOR-RUNX2 pathway, offering a locally effective strategy with minimal systemic exposure.[83]

A fundamental challenge common to all natural endogenous exosome studies reviewed here is the significant donor-source variability that complicates both mechanistic interpretation and clinical standardization. The therapeutic superiority of young-donor versus aged-donor plasma exosomes—while mechanistically compelling—raises an immediate practical concern: establishing a clinical supply chain for young-donor-derived exosomes at therapeutic scale involves complex logistical, ethical, and quality control challenges that are not addressed in the reviewed literature. More critically, the reviewed in vivo studies rely predominantly on single-dose or short-course administration in young OVX rodents—a model that does not adequately represent the aged, systemically compromised host environment of the target clinical population, in whom exosome biodistribution, cellular uptake efficiency, and endosomal escape capacity may differ substantially. The co-administration of heterogeneous exosomal cargo—encompassing hundreds of miRNA species and proteins simultaneously—also raises safety concerns that systematic cargo profiling in the reviewed studies does not sufficiently address.

Exosomes sourced from skeletal muscle and enriched with FNDC5/irisin promoted osteoblast proliferation in vitro through activation of the Cav1-AMPKα-Nrf2 pathway, manifesting as an elevated proportion of cells in the S and G2 phases and accompanied by inhibition of ferroptosis. Oral administration of recombinant irisin recapitulated these effects in vivo, proposing a compelling "exercise mimetic" therapeutic strategy for patients with limited mobility for whom conventional physical activity is impractical or contraindicated.[79] Traditional Chinese medicine-derived exosome platforms have also been investigated: Zhuang-Gu-Fang (ZGF)—a herbal compound incorporating Epimedium and Astragalus—enhanced BMSC osteogenic differentiation and regulated bone metabolism via myofibroblast-derived exosomes in vivo, demonstrating a capacity to delay senile osteoporosis (SOP) progression through an endogenous secretome-mediated mechanism.[95]

The traditional Chinese medicine-derived and muscle exosome platforms reviewed here represent therapeutically creative but analytically challenging systems whose complex, incompletely characterized cargo makes causal mechanistic attribution extremely difficult. The simultaneous delivery of hundreds of miRNA species, proteins, and lipids—each with independent biological activities—prevents confident attribution of observed therapeutic effects to specific molecular mediators, a level of mechanistic clarity that regulatory agencies require for Investigational New Drug (IND) filing. The "black box" nature of cargo composition also raises legitimate safety concerns: potentially beneficial miRNAs may co-segregate with oncogenic or immunostimulatory species that are not systematically screened in the reviewed studies, representing an uncharacterized safety liability that must be resolved before any clinical advancement.

Engineered exosomes advance beyond natural tropism by integrating synthetic targeting elements and programmable therapeutic payloads to achieve precision modulation of specific molecular nodes. An exosome platform modified with the SDSSD bone-targeting peptide and loaded with Shn3-targeting siRNA enhanced osteogenesis and angiogenesis via the Wnt/ERK/RUNX2 pathway while concurrently inhibiting osteoclastogenesis in OVX mice in vivo—exemplifying the multi-nodal, cell-transplantation-free approach enabled by engineered exosomal delivery.[91] Human umbilical cord MSC-derived exosomes (hUCMSC-EXOs) modified to counteract glucocorticoid-induced ferroptosis reversed the suppressive effect of glucocorticoids on osteoblast activity and improved bone microarchitecture in a GIOP model in vivo via the PI3K/AKT pathway.[80] Exosomes from Rehmanniae Radix Praeparata extracts upregulated miR-29a-3p to activate the Wnt/β-catenin pathway in OVX rats in vivo, improving bone microarchitecture through a systemic delivery route.[82] Engineered exosomes carrying METTL14 inhibited osteoclast activity in OVX mice in vivo by suppressing m6A methylation of NFATC1—a transcription factor central to osteoclastogenesis—providing a potential alternative strategy for patients at risk of bisphosphonate-associated osteonecrosis of the jaw.[92] Complementarily, exosomes delivering the METTL3 enzyme to BMSCs simultaneously promoted osteoblast differentiation and inhibited adipogenic lineage commitment in vivo, addressing the pathological osteoblast-to-adipocyte lineage shift characteristic of postmenopausal osteoporosis.[93]

Engineered exosomes represent the most scientifically sophisticated tools in the nanoplatform landscape, but their translational trajectory is substantially constrained by manufacturing realities that are systematically underreported in the primary literature. The genetic engineering of source cells to overexpress METTL14, METTL3, or bone-targeting peptides requires viral transduction or CRISPR-based modification—processes subject to stringent biosafety regulations and introducing the risk of insertional mutagenesis in producer cells, with attendant implications for the safety profile of harvested vesicles. Furthermore, the quantity of functionally engineered exosomes obtainable per producer cell passage is severely limited by intrinsic cellular secretion capacity, rendering current production yields incompatible with the multi-dose treatment regimens required for chronic osteoporosis management—without orders-of-magnitude improvements in production technology, scalability remains the Achilles' heel of this otherwise highly promising platform.

Osteoclast-targeted strategies using cell-derived vesicles further expand this platform's therapeutic scope. Phosphatidylserine fusion exosome mimics encapsulating the CXCR3 antagonist AMG487 reduced osteoclast recruitment and increased BMD in OVX mice in vivo.[90] Conversely, osteoclast-derived exosomes naturally carrying the lncRNA AW011738 were found to exacerbate bone loss through activation of the TREM1/NLRP3 pathway in vivo—a finding that reveals the dual role of endogenous exosomes in osteoporosis pathogenesis and validates AW011738 knockdown as a therapeutic counter-strategy.[87] BGN-guided bone marrow MSC-derived exosomes inhibited osteoclastogenesis and reversed bone loss in OVX mice via the lncRNA NRON.[88] lncRNA-mediated osteoclast suppression via NRON represents an emerging but mechanistically undercharacterized approach; the upstream regulatory factors controlling NRON expression in the osteoporotic bone microenvironment remain poorly defined, and the off-target transcriptional consequences of NRON modulation across non-skeletal tissues have not been systematically evaluated—a safety gap that must be resolved before lncRNA-based exosomal therapies can be meaningfully advanced toward clinical investigation.

The finding that osteoclast-derived exosomes carrying lncRNA AW011738 exacerbate bone loss underscores a critical safety consideration frequently overlooked in therapeutic exosome literature: endogenous exosomes are bidirectional mediators of intercellular communication, and their roles in disease pathogenesis are profoundly cell-type- and context-dependent. This duality implies that any therapeutic strategy relying on systemic administration of cell-derived vesicles must rigorously profile the complete cargo composition to exclude pathogenic species—a characterization standard that the majority of reviewed studies do not meet, relying instead on limited miRNA panels rather than comprehensive small RNA sequencing, proteomics, and lipidomics. Until such comprehensive safety characterization becomes standard practice in the field, the risk-benefit assessment for systemically administered therapeutic exosomes remains insufficiently defined to support confident clinical translation.

Microenvironment-regulatory and vascular coupling strategies address the broader osteoimmune and angiogenic nodes identified in Molecular Signaling Pathways Governing Bone Remodeling: Focus on Therapeutic Nodes. Macrophage-derived exosomes co-loaded with miR-3102-5p inhibited lipid peroxidation and inflammation by targeting Alox15 in OVX mice in vivo, exerting concurrent osteoprotective and anti-inflammatory effects.[89] ALN-modified platelet lysate exosomes enhanced bone-vascular coupling in GIOP rats in vivo by delivering PDGF-BB and VEGF, significantly increasing both BMD and microvessel volume.[94] In smoking-related osteoporosis (SROP)—a clinically underappreciated etiology—cigarette smoke extract (CSE) exposure was shown to activate ferroptosis and ROS pathways that impair BMSC function in vivo. Engineered exosomes delivering the ferroptosis inhibitor Fer-1, further augmented with bone-targeting peptides, effectively restored BMSC osteogenic capacity and ameliorated bone loss in vivo, offering a mechanistically grounded strategy specifically tailored to this patient population.[96]

The microenvironment-regulatory and vascular coupling strategies reviewed in this subsection, while representing some of the most clinically nuanced approaches in the exosome literature, share a set of translational vulnerabilities that deserve explicit acknowledgment. The macrophage-derived exosome system co-loaded with miR-3102-5p addresses a genuinely important therapeutic node—the osteoimmune microenvironment—but macrophage-derived vesicles carry a heterogeneous inflammatory cargo whose composition shifts substantially depending on the polarization state of the source macrophage population at the time of harvest; without stringent and standardized polarization protocols, batch-to-batch consistency of the anti-inflammatory payload cannot be guaranteed, and pro-inflammatory cargo contamination remains a latent risk. The ALN-modified platelet lysate exosome system presents a complementary concern: platelet

lysates are inherently donor-variable biological materials containing growth factors, coagulation proteins, and immunomodulatory lipids beyond the intended PDGF-BB and VEGF payload, making precise dose-response characterization of the therapeutic components difficult and raising the possibility that non-target biological activities of the lysate contribute to—or confound—the reported skeletal and vascular outcomes. The smoking-related osteoporosis (SROP) ferroptosis-targeting strategy is mechanistically innovative and addresses an underserved patient population, but its translational relevance is constrained by the absence of chronic smoking exposure models; the acute CSE exposure paradigm employed does not adequately recapitulate the cumulative oxidative burden, systemic inflammatory milieu, and compromised pulmonary pharmacokinetics characteristic of long-term smokers, in whom the biodistribution and therapeutic efficacy of systemically administered engineered exosomes may differ substantially from the acute model predictions.

In comparative terms, biomimetic and cell-derived platforms—exosomes in particular—represent the most biologically intelligent carriers in the nanoplatform landscape, possessing the highest intrinsic biocompatibility, the lowest immunogenicity, and the unique capacity to deliver complex biomolecular cocktails (miRNAs, proteins, lncRNAs) for sophisticated, multinodal modulation of bone remodeling pathways. Natural exosomes exploit endogenous biological tropism, while engineered variants layer synthetic precision targeting atop this biological foundation. However, this very biological complexity constitutes their Achilles' heel for clinical translation. Severe bottlenecks in large-scale GMP-compliant manufacturing, ultra-low extraction yields from source cells, significant batch-to-batch inconsistency arising from donor cell state variability, and incompletely characterized in vivo biodistribution collectively place exosome therapies furthest from immediate clinical deployment relative to synthetic LNPs or biodegradable PLGA systems, both of which benefit from established manufacturing infrastructure and regulatory precedent. Engineered exosomes partially address specificity limitations by grafting synthetic targeting ligands, but this further compounds manufacturing complexity and quality control demands. Consequently, while exosomes remain among the most conceptually advanced tools in osteoporosis research, their path to the clinic is substantially longer and more challenging than that of any other nanoplatform class reviewed herein. Future priorities must include the development of scalable isolation and engineering protocols, standardized characterization frameworks, and rigorous large-animal pharmacokinetic and immunogenicity profiling.

Comparative Assessment of Clinical Translatability

Beyond their mechanistic distinctions, the four nanoplatform classes diverge markedly in their translational readiness—a dimension that fundamentally dictates real-world clinical impact yet is frequently underweighted in preclinical discourse. To render this comparison both rigorous and actionable, we evaluated each platform across four translationally relevant axes: GMP-compliant scalability, cost-effectiveness, active targeting efficiency, and biocompatibility (Figure 4).

The resulting radar profiles reveal a clear hierarchical structure rather than a simple binary trade-off. Polymeric nanoparticles emerge as the most comprehensively balanced platform, with their polygonal profile fully enclosing that of liposomes across all four evaluated dimensions—a visual representation of their dominant composite translational score. This superiority stems from the exceptional tunability of polymer chemistry, which affords simultaneous optimization of drug encapsulation, surface functionalization, and degradation kinetics, all within manufacturing frameworks that are both GMP-amenable and cost-competitive. Liposomal systems, while closely trailing polymeric NPs and demonstrating strong scores in scalability and cost-effectiveness—underpinned by well-established industrial processes and multiple FDA-approved precedents—are nonetheless circumscribed within the polymeric NP profile, indicating a uniformly lower composite performance across the benchmarking criteria.

At the opposing translational pole, biomimetic platforms (exemplified by exosomes) register the highest targeting efficiency score in the entire dataset, a direct consequence of their endogenous membrane proteome and inherent tissue-homing capacity. This biological distinction, however, is offset by the lowest scores in scalability and cost-effectiveness, consistent with the field-wide recognition that standardized GMP-compliant exosome manufacturing remains a largely unsolved engineering challenge. Inorganic nanoparticles occupy an intermediate position, with moderate manufacturing feasibility tempered by persistent biocompatibility concerns arising from long-term biopersistence—a consideration that continues to complicate their regulatory pathway.

Taken together, this multi-dimensional benchmarking supports a stage-stratified translational roadmap: polymeric nanoparticles currently represent the most comprehensively viable platform for near-term clinical advancement, with

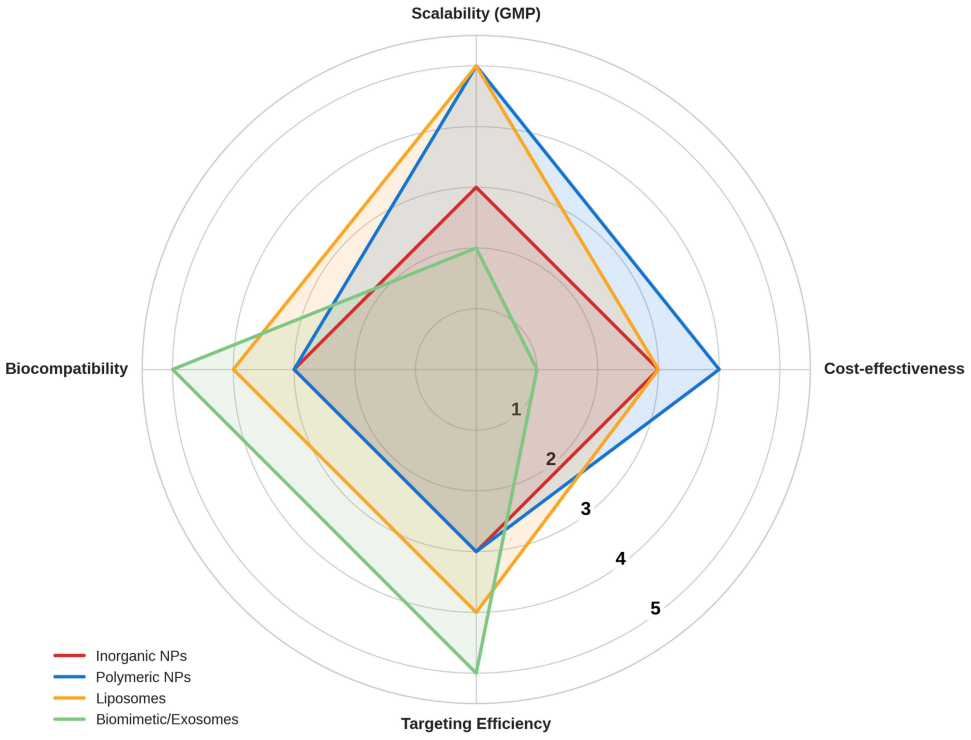

Figure 4 Radar chart assessment of the clinical translational potential of four major bone-targeted nanoplatform classes. Four nanoplatform categories—Inorganic NPs, Polymeric NPs, Liposomes, and Biomimetic/Exosomes—are benchmarked across four translational dimensions: Scalability (GMP-compliant manufacturing feasibility), Cost-effectiveness, Targeting Efficiency, and Biocompatibility (scored 1–5; 5 = optimal). Liposomes and Polymeric NPs exhibit the most balanced translational profiles, achieving high scores across all four axes, particularly in scalability and cost-effectiveness. Inorganic NPs demonstrate moderate performance with relative weakness in targeting efficiency. Biomimetic platforms (exosomes) attain peak scores for biocompatibility and targeting efficiency, but are critically constrained by poor scalability and prohibitively high production costs, limiting near-term clinical deployment.[5] Copyright 2024, Dovepress.

liposomal systems offering a well-validated complementary option; biomimetic platforms, despite unmatched biological fidelity, require fundamental breakthroughs in scalable manufacturing before their translational potential can be realized.

Strengths, Limitations, and Translational Challenges of Bone-Targeted Nanotherapies

The potential of bone-targeted nanotherapies lies in their ability to overcome the limitations of conventional medicine. Advanced surface functionalization allows these therapies to achieve precise targeting. They can effectively "home" to bone tissue and differentiate between the microenvironments of bone formation and resorption, enabling direct delivery to osteoblasts or osteoclasts. This specificity optimizes the drug's biodistribution and pharmacokinetics, facilitating efficient accumulation at the pathological site and enhancing therapeutic efficacy even at reduced dosages. A key advantage is the improved safety profile; by directing the drug to the skeleton, exposure to healthy organs is minimized, reducing systemic toxicity.

However, achieving this potential presents significant scientific challenges. The complexity of nanoparticle design is a major obstacle. A functional nanocarrier is a sophisticated assembly of various molecules, making its synthesis and quality control demanding. Once produced, these nanocarriers must navigate intricate biological barriers in vivo. From injection into the bloodstream to reaching the target cell, they must evade immune clearance by organs like the liver and spleen and efficiently cross the vascular endothelium. Additionally, target heterogeneity within the disease microenvironment complicates matters, as the expression of target receptors can vary between patients and disease stages, leading to unpredictable efficacy.

Therapeutic Strengths of Bone-Targeted Nanotherapies

Bone-targeted nanotherapies offer a fundamentally different therapeutic paradigm for osteoporosis management, one that addresses several intrinsic limitations of conventional systemic pharmacology through a combination of spatial precision and functional versatility. Surface functionalization of diverse carrier platforms—including exosomes, PLGA nanoparticles, mesoporous silica nanoparticles (MSNs), and bisphosphonate- or peptide-decorated nanosystems—enables preferential accumulation at hydroxyapatite-rich bone remodeling surfaces or selective engagement of osteotropic receptors, thereby concentrating therapeutic payloads at sites of pathological activity while substantially curtailing off-target tissue exposure. A defining strength of these platforms lies in their cargo promiscuity: the same nanocarrier architecture can be adapted to deliver small molecules, recombinant proteins, growth factors, or nucleic acid therapeutics such as siRNA, enabling direct pharmacological intervention at key signaling nodes including the Wnt/β-catenin and RANKL–RANK axes that are otherwise difficult to modulate with conventional agents.

Controlled-release kinetics, engineered through biodegradable polymeric matrices, further improve systemic pharmacokinetics by sustaining therapeutic concentrations over extended intervals, reducing dosing frequency, and attenuating systemic immunogenicity. Beyond single-modality therapy, multifunctional nanocarrier designs permit the co-delivery of osteogenic and anti-resorptive cargos within a unified platform, theoretically enabling simultaneous stimulation of bone formation and suppression of osteoclastogenesis—a combinatorial effect that no currently approved single-agent therapy can replicate. The additional integration of diagnostic contrast agents within such constructs opens avenues for image-guided, personalized treatment monitoring. Finally, the engineering of stimuli-responsive release mechanisms—triggered by local pH gradients, bone-specific enzymatic activity, or hypoxic cues within the remodeling microenvironment—introduces a further dimension of therapeutic precision that is entirely absent from conventional pharmacology. Against the backdrop of globally escalating osteoporosis burden, the public health imperative for scalable and effective nanosolutions has never been more pressing.[2]

Scientific and Technical Challenges

Despite these advantages, major scientific and translational challenges limit clinical adoption. First, nanoparticle instability and batch variability compromise biodistribution, cellular uptake, and potency, complicating dose optimization and study comparability. Second, interactions with serum proteins and immune cells lead to the immediate formation of a "protein corona". This biological coating can completely mask painstakingly engineered targeting ligands (eg, peptides), leading to off-target effects, loss of targeting efficiency, and rapid clearance by the mononuclear phagocyte system. Third, the bone microenvironment is highly complex; variable perfusion, dense mineral matrix, hypoxia, and inflammation can impair nanoparticle transport, retention, and cargo release, thereby reducing therapeutic efficacy.[97] Fourth, a fundamental contradiction exists between the chronic nature of osteoporosis and the long-term toxicity of carriers. Because osteoporosis requires long-term, potentially lifelong administration, chemically stable inorganic nanoparticles (eg, MSNs, gold NPs) that inevitably accumulate in the liver, spleen, or kidneys pose unacceptable long-term biopersistence risks.

Barriers to Clinical Translation

Clinical translation remains restricted by multiple regulatory and logistical hurdles. Moving beyond the laboratory—where milligram-scale synthesis and centrifugation are relatively simple—to kilogram-scale continuous production under strictly controlled environments imposes massive technical and financial pressures. Biological variability of cell-derived products, especially exosomes, leads to batch-to-batch differences in cargo composition and bioactivity, reducing reproducibility. Standardization of donor selection, culture conditions, and isolation methods is therefore essential to ensure consistent quality.

Furthermore, regulatory agencies (such as the FDA and EMA) often classify complex, actively targeted, drug-loaded nanoplatforms as "combination products" (drug-device or drug-biologic combinations). This classification subjects them to exceptionally stringent regulatory pathways. Agencies require comprehensive biodistribution and long-term safety data that demonstrate preferential accumulation in bone tissue, limited off-target distribution, and acceptable clearance. In

addition, validated manufacturing controls and release assays are necessary. Quality-by-design principles, detailed physicochemical and functional characterization, and strict adherence to current good manufacturing practice (cGMP) are prerequisites for approval, but these add to development costs and complexity.

Further barriers include intellectual property issues, uncertain reimbursement pathways, and the need for interdisciplinary collaboration across materials science, pharmacology, and clinical medicine. To accelerate translation, several strategies have been proposed: (1) engineering biomimetic synthetic exosomes to minimize biological heterogeneity; (2) employing microfluidic and continuous-flow manufacturing to improve reproducibility; (3) optimizing stealth coatings to reduce immune clearance; and (4) designing stimuli-responsive release systems tailored to the bone microenvironment.

Finally, reliable potency assays, physiologically relevant animal models, and long-term biodistribution and toxicity studies are required to de-risk development programs. Early engagement with regulatory authorities, coupled with economic and cost-effectiveness analyses, will be essential to identify patient subgroups most likely to benefit and to support equitable clinical implementation of bone-targeted nanotherapies.

Critical Comparison with Clinical "Gold Standard" Therapies

Despite the promise of nanotherapeutics, their true translational value must be compared against clinical "gold standard" therapies, such as oral bisphosphonates (like alendronate) and injectable biologics (like denosumab).

- Addressing Specific Clinical Problems: Oral bisphosphonates suffer from extremely low bioavailability (<1%) and are associated with severe gastrointestinal (GI) side effects. Bone-targeting nanosystems[5,57] that encapsulate bisphosphonates for intravenous injection directly address both problems, eliminating GI toxicity while potentially lowering the systemic dose.
- Improving Efficacy: Denosumab (a RANKL antibody), while highly effective, is expensive and can lead to rebound fractures upon discontinuation. Nanosystems delivering anti-RANKL siRNA or modulating other pathways such as Wnt[39,91] may offer a more durable effect or achieve multi-pathway regulation lacking in biologics. For instance, systems that simultaneously inhibit osteoclasts and promote osteoblasts (dual-action)[45] are theoretically superior to purely anti-resorptive denosumab.
- Cost-Effectiveness and Regulatory Hurdles: While conventional biologics face their own regulatory pathways, complex nanomedicines face dual scrutiny. However, their ultimate clinical and commercial value lies in serving as a viable delivery platform for highly potent but fragile novel biologics (including siRNA, miRNAs, or peptides) that otherwise lack an effective systemic delivery mechanism, thereby justifying the higher developmental costs.

Current Clinical Trial Landscape: Devices Lead, Therapeutics Follow

To honestly gauge where bone-targeted nanomedicine actually stands, as opposed to where the academic literature suggests it should be, one must look beyond preclinical publications and examine the clinical trial record directly. A survey of the ClinicalTrials.gov registry, summarized in Table 6, provides valuable insight the gap between what is being published and what is being tested in patients remains stubbornly wide.

The clinical translations that have genuinely reached human investigation tend to fall into three practical categories: lipid-based carriers used to improve the oral absorption of nutritional supplements, nanostructured mineral formulations that work through ion exchange to alter the local bone metabolic environment, and nanocrystalline bone grafts or implant coatings that mimic native bone architecture to support osseointegration. These are, by and large, incremental refinements of existing clinical tools rather than the precision-targeted nanotherapeutics that dominate the research literature.

The near-total absence of actively targeted nano-biologic therapies from late-stage trials, with siRNA-loaded polymeric nanoparticles being the most conspicuous example, is telling. It reflects not a failure of scientific imagination but the weight of hard practical constraints: GMP scale-up processes that remain unsolved at the engineering level, protein corona effects that silently dismantle targeting functionality in vivo, and a long-term safety dataset that regulatory agencies reasonably require but the field has not yet generated. Closing this gap will take more than incremental technical progress. It will require manufacturing engineers, regulatory scientists, and clinicians working from a genuinely shared roadmap, a degree of coordinated and sustained investment that the field, for all its scientific creativity, has yet to fully commit to.

Table 6 Representative Ongoing and Completed Clinical Trials of Bone-Targeted Nanosystems

NCT Identifier	Intervention	Nanotechnology & Mechanism	Regulatory Category	Trial Status
NCT06372158	Liposomal Calcium	**Lipid Nanocarrier**: Enhances gastrointestinal stability and calcium absorption via membrane fusion or M-cell uptake, overcoming the low bioavailability of traditional supplements.	Nutritional Intervention	Recruiting
NCT06249906	Micro-structured Bioceramic	**Surface Engineering**: Evaluates the osseointegration efficiency of bioceramic implants with hierarchical micro/nano-structures in treating osteoarthritis and bone loss.	Medical Device	Recruiting
NCT06651502	Nano-HA Coated Implant	**Biomimetic Coating**: Employs a nano-hydroxyapatite coating on implants to mimic natural bone mineral structure, enhancing osseointegration in the jawbones of osteoporotic patients.	Medical Device	Recruiting
NCT07059065	FIBERGRAFT Aeridyan Matrix	**Nanofiber Scaffold**: A synthetic bone graft substitute composed of bioactive glass microfibers and nanofibers, providing a biomimetic extracellular matrix to promote bone fusion.	Medical Device	Active, not recruiting
NCT05178719	PMA-Zeolite (Clinoptilolite)	**Microporous Mineral**: Long-term (5-year) evaluation of tribomechanically activated zeolite in protecting bone density by adsorbing heavy metals and releasing osteogenic silicon.	Dietary Supplement	Active, not recruiting
NCT03901989	PMA-Zeolite	**Microporous Mineral**: Randomized, double-blind controlled trial evaluating the 12-month effect of activated zeolite on bone remodeling markers (eg, CTX) and bone mineral density.	Dietary Supplement	Completed
NCT04615260	NanoBone Synthetic Bone Graft	**Nanocrystalline Technology**: Composed of nanocrystalline hydroxyapatite embedded in a highly porous silica matrix, mimicking autologous bone structure for bone regeneration.	Medical Device	Completed

Notes: Data were retrieved from the ClinicalTrials.gov registry. This landscape highlights that current clinical translations are predominantly limited to medical devices, macroscopic implant coatings, and nutritional supplements, underscoring the severe translational bottlenecks for actively targeted nano-biotherapeutics.
Abbreviations: CTX, C-terminal telopeptide of type I collagen; HA, hydroxyapatite; NCT, National Clinical Trial; PMA, Panaceo Micro Activation (a tribomechanical activation process for zeolites).

Future Research Directions and Strategies

The potential of bone-targeted nanotherapies lies in their ability to overcome the limitations of conventional medicine. Advanced surface functionalization (Figure 5A) allows these therapies to achieve precise targeting. They can effectively "home" to bone tissue (Figure 5B) and differentiate between the microenvironments of bone formation and resorption, enabling direct delivery to osteoblasts or osteoclasts (Figure 5C and D). This specificity optimizes the drug's biodistribution and pharmacokinetics, facilitating efficient accumulation at the pathological site and enhancing therapeutic efficacy even at reduced dosages. A key advantage is the improved safety profile; by directing the drug to the skeleton, exposure to healthy organs is minimized, reducing systemic toxicity.

However, achieving this potential presents significant scientific challenges. The complexity of nanoparticle design is a major obstacle. A functional nanocarrier is a sophisticated assembly of various molecules, making its synthesis and quality control demanding. Once produced, these nanocarriers must navigate intricate biological barriers in vivo. From injection into the bloodstream to reaching the target cell, they must evade immune clearance by organs like the liver and spleen and efficiently cross the vascular endothelium. Additionally, target heterogeneity within the disease microenvironment complicates matters, as the expression of target receptors can vary between patients and disease stages, leading to unpredictable efficacy.

Beyond research challenges, there are significant obstacles to clinical translation. Chief among these is scalable manufacturing. Transitioning from laboratory-grade, milligram-scale synthesis to kilogram-scale production for clinical use under Good Manufacturing Practice (GMP) standards imposes considerable technical and financial pressures. Long-term safety is also a critical prerequisite for clinical application; the metabolic fate of the nanomaterials must be understood to mitigate the risk of long-term toxicity due to bioaccumulation. Finally, the success of the development pipeline heavily relies on the predictive power of preclinical animal models. The "translational gap" between these models and the human physiological environment remains a critical factor, often contributing to the failure of promising nanomedicines in human clinical trials.

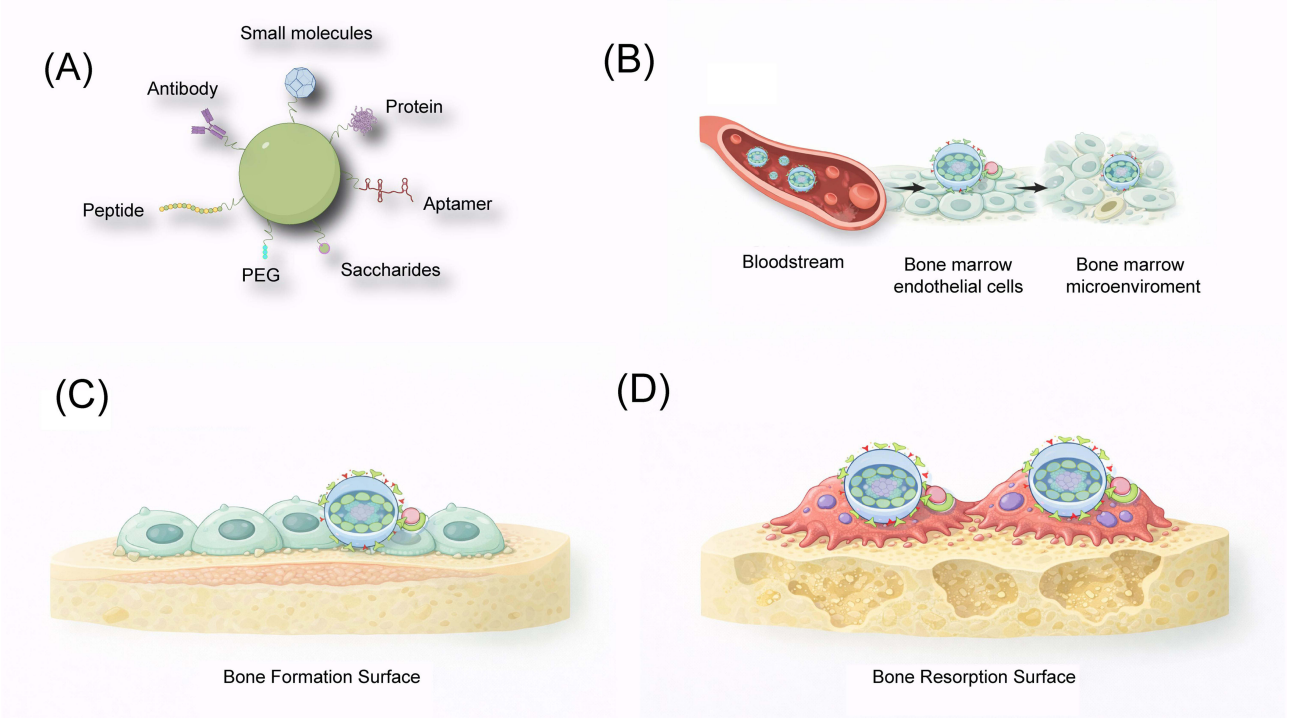

Figure 5 Schematic overview of bone-targeting strategies and sequential cellular interactions of functionalized nanocarriers. (**A**) Surface functionalization strategies for nanocarriers. Nanocarriers can be modified with diverse ligands, including antibodies, peptides, PEG, saccharides, aptamers, proteins, and small molecules, to improve cell- and tissue-selective targeting. (**B**) Bone marrow homing process of functionalized nanocarriers. Following systemic administration, nanocarriers circulate in the bloodstream, interact with bone marrow endothelial cells, and subsequently extravasate into the bone marrow microenvironment through target-mediated recognition. (**C**) Targeting at the bone formation surface. Nanocarriers preferentially localize to osteoblast-lined bone formation surfaces, where osteoblasts are arranged along a newly formed osteoid-rich matrix. (**D**) Targeting at the bone resorption surface. Nanocarriers preferentially localize to osteoclast-associated bone resorption surfaces, characterized by irregular resorptive contours and active osteoclastic interaction.

Intelligent Design of Multimodal Nanosystems

The integration of nanomedicines with bone tissue-targeting ligands—such as bisphosphonates, Asp/Gla peptides, and CXCR4 ligands—significantly enhances their accumulation in bone and improves overall therapeutic efficacy.[98] For instance, a novel therapeutic agent utilizing liposomal structures as drug reservoirs, along with PA as an antioxidant and ALN as a bone-targeting molecule, has demonstrated promising results in cellular and animal experiments concerning cytotoxicity, bone targeting, and anti-osteoporotic effects.[97,98] Advanced carrier structures can be designed to respond to the bone metabolic microenvironment, employing triggers such as acidic pH or specific enzymatic sites to regulate drug release. These structures can also be simultaneously loaded with multiple therapeutic agents, including anti-osteoclastogenic drugs combined with osteogenic factors or siRNAs, to synergistically enhance bone homeostasis. Additionally, diagnostic functionalities can be incorporated, such as magnetic nanoparticles or fluorophores, to facilitate imaging, tracking, and therapeutic monitoring.[4,98–102] For example, PEGylated polymer nanoparticles can be engineered with surface co-modification of bisphosphonates and CXCR4 ligands, internally loaded with alendronate and BMP-2, releasing the drug in response to low pH environments, and featuring a magnetic core for MRI monitoring of bone density. This multimodal, intelligent nanosystem with targeting capabilities can effectively combine osteogenesis, inhibition of bone resorption, and imaging tracking, offering a novel approach for the precise treatment of osteoporosis.

Direction of Clinical Translation

Currently, most clinically applied nanomedicines focus on cancer treatment, with fewer applications for osteoporosis, especially regarding liposomes, protein particles, nanocrystals, and inorganic nanocarriers.[99] This disparity may stem from the unique characteristics of bone, a dynamic, porous tissue with distinct blood flow distribution compared to other organs. The composition of the bone matrix, primarily hydroxyapatite, and the osteoblast microenvironment present

challenges for effective nanocarrier penetration into bone tissue. Despite using bone-targeting ligands such as bisphosphonates and CXCR4 ligands, their enrichment is often confined to preclinical animal models, as they struggle to overcome barriers like blood flow and immune clearance in humans.

Most bone-targeting nanosystems are still in the animal model or in vitro validation stage. Their clinical translation is hindered by factors such as insufficient collaboration with pharmaceutical companies and regulatory agencies. Additionally, inadequate patient stratification, dosing regimens, and efficacy metrics in clinical design complicate the progression of academic findings into Phase I/II trials.[100] A significant challenge is scaling up laboratory technologies to Good Manufacturing Practice (GMP) production while ensuring batch consistency. This issue is worsened by the lack of high-throughput online testing systems, which delays regulatory approval and commercialization.[101]

A translational gap exists due to the absence of predictive models that closely mimic human physiology, such as large animal models or human organ-on-chip systems, necessary for accurately assessing in vivo behaviors and therapeutic efficacy. Current research often relies heavily on in vitro or small animal models, which may not fully represent human responses.[102]

To address these challenges, strategies from cancer nanomedicine could be adapted. The oncology field frequently utilizes the Enhanced Permeation and Retention (EPR) effect for passive enrichment, often alongside active targeting molecules on the carrier surface. For osteoporosis, a similar "bone EPR" effect could be leveraged in the vascular-rich microenvironment of bone resorption lacunae. This passive accumulation could be enhanced by combining it with bone-targeting ligands like bisphosphonates. Additionally, the resorption site's local environment, characterized by acidic pH or elevated concentrations of osteoclast-secreted Cathepsin K, could trigger targeted drug release, minimizing systemic exposure and side effects.

Optimization of Biological Delivery System

The exosome drug delivery system represents a biomimetic approach, characterized by the encapsulation of nanoparticles within a cell membrane that mimics natural cells. This system emulates biological mechanisms to facilitate precise drug delivery to target sites, thereby enhancing therapeutic efficacy and minimizing drug wastage. Consequently, the delivery system demonstrates high efficiency in drug delivery and therapeutic outcomes. However, further research is necessary to optimize the preparation process and assess the safety of long-term use. To enable efficient production and scaling, it is imperative to develop effective exosome separation and purification techniques, such as the combination of ultracentrifugation and affinity capture, to increase yield and reduce production costs. Additionally, investigating the production methods of engineered exosomes is essential, focusing on enhancing their drug-carrying capacity and targeting abilities through gene editing or chemical modification.[4]

Networked Regulation of Signaling Pathways

Osteoporosis results from an imbalance between osteogenic and osteoclastic activities, regulated by complex signaling networks. Targeting a single pathway is insufficient, as crosstalk between pathways is crucial for bone metabolism regulation. Systems biology and multi-omics approaches are essential for creating dynamic interaction models that identify key nodes like β-catenin and Smad1/5/8, which have varying functions across different cell types and differentiation stages, aiding the development of low-toxicity, high-efficiency therapies.[97]

Nanomaterials offer opportunities for multi-pathway modulation due to their multifunctional modifications, allowing simultaneous targeting of various signaling nodes. For example, zinc-doped hydroxyapatite (ZnHA) enhances osteogenesis through Wnt/β-catenin activation and PI3K/Akt enhancement via GSK-3β inhibition, resulting in a dual pro-osteogenic effect. Gold nanoparticles (GNPs) activate ERK/MAPK signaling to stimulate osteogenesis while inhibiting RANKL signaling to suppress osteoclastogenesis, demonstrating their potential for synergistic regulation.

To conceptualize this networked regulatory strategy, Figure 6 provides a mechanistic model of a co-delivery nanoplatform engineered to simultaneously modulate interconnected bone remodeling pathways. As a representative example, an alendronate-functionalized nanocarrier is co-loaded with a Wnt signaling agonist and RANKL-targeted siRNA (Figure 6A). Upon specific localization to the bone microenvironment and subsequent cellular internalization by osteoblasts, the Wnt agonist drives osteogenesis via β-catenin activation, transcriptionally upregulating osteogenic markers including Runx2, Osterix, and Col1a1 to promote bone formation (Figure 6B). Concurrently, the siRANKL

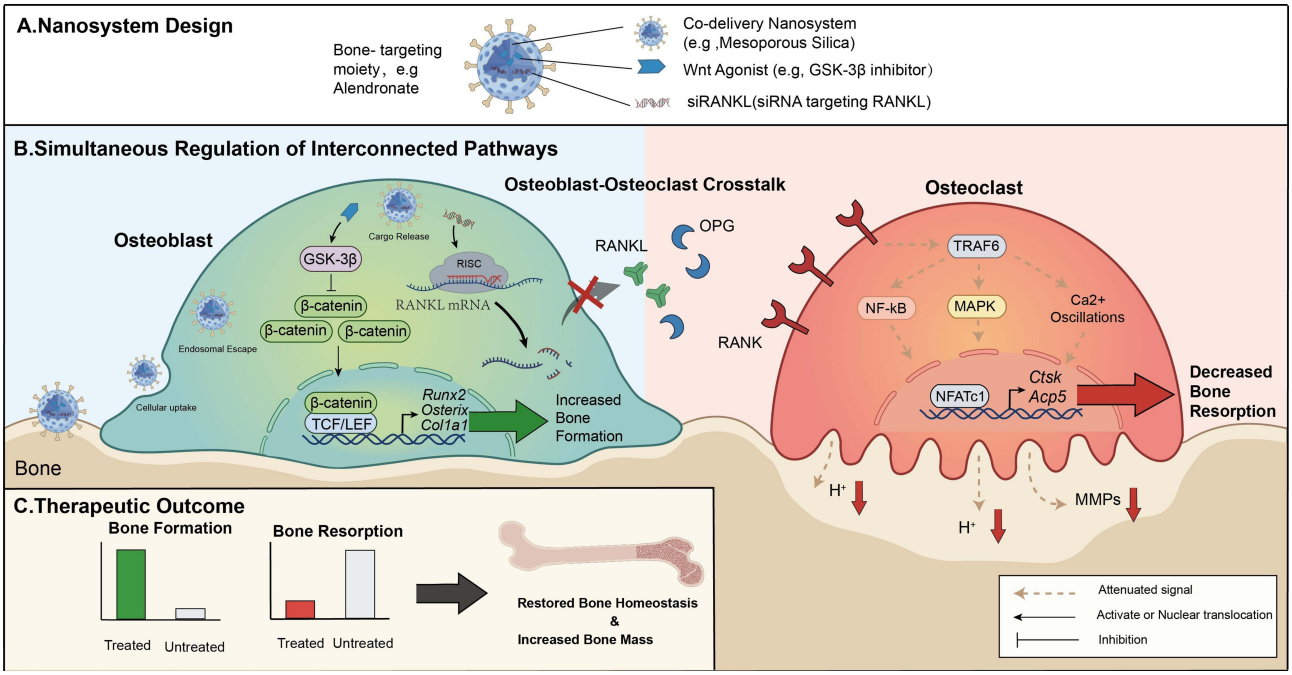

Figure 6 Mechanistic illustration of a co-delivery nanosystem for simultaneous modulation of interconnected bone remodeling pathways. (**A**) Nanosystem Design: A multifunctional nanocarrier (eg, mesoporous silica) surface-functionalized with a bone-targeting moiety (eg, alendronate) is co-loaded with a Wnt pathway agonist (eg, GSK-3β inhibitor) and siRANKL (siRNA targeting RANKL mRNA). (**B**) Simultaneous Networked Pathway Regulation: Following cellular uptake by osteoblasts and endosomal escape, the released GSK-3β inhibitor stabilizes cytoplasmic β-catenin, enabling its nuclear accumulation and TCF/LEF-mediated transcriptional activation of osteogenic genes (Runx2, Osterix, Col1a1) to augment bone formation. Concurrently, the siRANKL cargo is loaded into the RISC complex, triggering sequence-specific RANKL mRNA degradation, thereby reducing RANKL secretion into the extracellular space, diminishing RANK activation on osteoclast precursors, and attenuating downstream TRAF6–NF-κB/MAPK–NFATc1 signaling to suppress osteoclastogenesis and H^+/MMP-mediated bone resorption. (**C**) Therapeutic Outcome: The coordinated dual-action intervention—enhanced bone formation paired with suppressed bone resorption—restores skeletal homeostasis and increases net bone mass. Pointed solid arrows indicate activation or nuclear translocation; blunt-ended lines indicate inhibition; dashed arrows indicate attenuated downstream signaling; the red cross symbol (X) denotes the functional blockade of the RANKL paracrine supply resulting from intracellular RANKL mRNA silencing; and red downward arrows indicate the significantly decreased secretion of bone-resorbing effector molecules (H^+ and MMPs).

cargo is loaded into the RISC complex to silence RANKL expression, abrogating the pro-osteoclastogenic crosstalk between osteoblasts and osteoclasts, and thereby attenuating downstream resorptive signaling cascades—including TRAF6-mediated NF-κB and MAPK activation, NFATc1-driven transcription of Ctsk and Acp5, and the secretion of H^+ and MMPs—ultimately decreasing bone resorption (Figure 6B). This synergistic, dual-action mechanism effectively restores skeletal homeostasis by coupling enhanced bone formation with the suppression of bone resorption, as evidenced by the comparative therapeutic outcome between treated and untreated groups (Figure 6C), exemplifying the future trajectory of precision skeletal nanomedicine.

However, pathway activity is highly dynamic. While β-catenin promotes early osteoblast differentiation, it also enhances mature osteoclast activity, underscoring the need for spatiotemporally specific drug delivery systems to effectively regulate distinct cell types at appropriate stages. High-throughput and CRISPR-based screening can identify critical crosstalk nodes to refine nanomaterial-mediated interventions.

Additionally, the skeletal microenvironment significantly influences signaling interactions. Conditions like hypoxia and inflammation alter pathway dynamics, affecting osteoporosis progression and therapeutic responses. Future research should move from molecular-level analysis to an integrated examination of microenvironmental regulation. Understanding how environmental cues govern signaling crosstalk will support the rational design of next-generation nanosystems with improved therapeutic precision and clinical applicability.

Conclusion

Functional nanomaterials hold significant promise for advancing osteoporosis therapy through targeted drug delivery, controlled release, and precise regulation of bone remodeling pathways. Their tunable physicochemical properties—including

particle size, surface charge, and functional modifications—enable selective accumulation at bone sites rich in hydroxyapatite, thereby enhancing pharmacokinetics and reducing systemic toxicity compared to conventional treatments. With rational design, these nanosystems can simultaneously deliver small molecules, peptides, nucleic acids, and imaging agents, supporting multimodal strategies that promote osteogenesis while inhibiting osteoclastogenesis. However, clinical translation faces ongoing challenges, including limited large-scale reproducibility, stability issues, immunogenicity, and long-term biocompatibility. The complexity and cost of manufacturing, along with batch variability, hinder regulatory approval and commercial viability. Additionally, concerns about nanoparticle persistence, unpredictable degradation, and potential off-target accumulation necessitate thorough safety evaluations. Addressing these limitations requires optimized formulations, standardized production protocols, and comprehensive preclinical-to-clinical validation frameworks. In the future, bone-targeted nanotherapeutics may synergize with gene therapy, regenerative medicine, and artificial intelligence-assisted design to facilitate personalized and effective osteoporosis treatments. Collaboration among researchers, clinicians, and regulatory agencies will be crucial for realizing the full translational potential of these advanced nanoplatforms and delivering safer, more effective therapies that restore skeletal integrity and enhance patient quality of life.

Abbreviations

AI, artificial intelligence; ALN, alendronate; BMD, bone mineral density; BMSCs, bone marrow stromal cells; BMP, Bone Morphogenetic Protein; BV/TV, bone volume fraction; cGMP, current good manufacturing practice; CRP, C-reactive protein; CSE, cigarette smoke extract; DAMPs, damage-associated molecular patterns; Dkk-1, Dickkopf-1; ECM, extracellular matrix; EELNs, Epimedium-derived extracellular nanovesicles; EPR, Enhanced Permeation and Retention; FAK, Focal Adhesion Kinase; GIOP, glucocorticoid-induced osteoporosis; GMP, Good Manufacturing Practice; GNPs, gold nanoparticles; GSK3β, Glycogen Synthase Kinase-3 Beta; HH, Hedgehog; hUCMSC-EXOs, Human umbilical cord mesenchymal stem cell-derived exosomes; JAK, Janus Kinase; LNPs, lipid nanoparticles; MAPK, Mitogen-Activated Protein Kinase; Mincle, macrophage-inducible C-type lectin; ML, Machine learning; MSC, Mesenchymal stem cells; MSNs, mesoporous silica nanoparticles; nHA, nano-hydroxyapatite; OB, Osteoblast; OC, Osteoclast; OGP, osteogenic growth peptide; OMEs, oyster mantle-derived exosomes; OPG, Osteoprotegerin; OPN, osteopontin; OSX, Osterix; OVX, ovariectomized; PDGF-BB, platelet-derived growth factor-BB; PEG, polyethylene glycol; PEI, polyethyleneimine; PLGA, poly(lactic-co-glycolic acid); PMBG/TCP, phosphosilicate mesoporous bioactive glass/tricalcium phosphate; PMOP, postmenopausal osteoporosis; RANKL, Receptor Activator of Nuclear Factor-κB Ligand; ROS, reactive oxygen species; RUNX2, Runt-related transcription factor 2; SASP, Senescence-Associated Secretory Phenotype; SCT-HAP, salmon calcitonin-hydroxyapatite; SII, Systemic Immune-Inflammation Index; SOP, senile osteoporosis; SOST, Sclerostin; SPIO, Superparamagnetic iron oxide; SROP, smoking-related osteoporosis; TAZ, transcriptional coactivator with PDZ-binding motif; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; YAP, Yes-associated protein; ZGF, Zhuang-Gu-Fang; ZnHA, zinc-doped hydroxyapatite.

Data Sharing Statement

As this article is a review paper, no research data were generated.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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