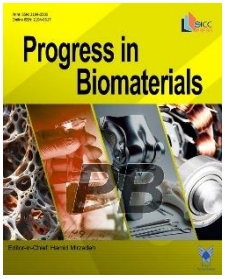

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Stem Cell–Biomaterial Interactions in Bone Tissue Engineering: From Molecular Mechanisms to Translational Challenges

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Abstract

The growing incidence of trauma-induced bone defects, tumors, malformations, and age-related degenerative conditions presents a substantial clinical and socioeconomic challenge. Traditional treatments, such as autografts and implants, have significant limitations, including donor-site morbidity and immune rejection. Emerging bone tissue engineering (BTE) leverages mesenchymal stem cells (MSCs) and induced pluripotent stem cell (iPSC)-derived osteoprogenitors to create a regenerative microenvironment. Advances in biomaterials, including osteoconductive ceramics and bioresorbable polymers, enhance scaffold design, enabling the creation of hierarchical architectures that mimic the natural properties of bone. Innovations like smart scaffolds are poised to improve regeneration through controlled release of growth factors and responsiveness to external cues. However, the transition from promising preclinical results to routine clinical application faces challenges, including variability in stem cell sources, scalability issues in scaffold production, and regulatory hurdles. This review synthesizes research on stem cell-biomaterial interactions, which are vital for bone regeneration, focusing on molecular processes, scaffold design principles, osteogenic promotion strategies, and existing preclinical and clinical evidence. The findings aim to guide researchers and clinicians in developing effective bone-regenerative therapies.

Keywords: Bone tissue engineering (BTE), Mesenchymal stem cells (MSCs), Scaffold design, Osteogenesis, Regenerative therapies

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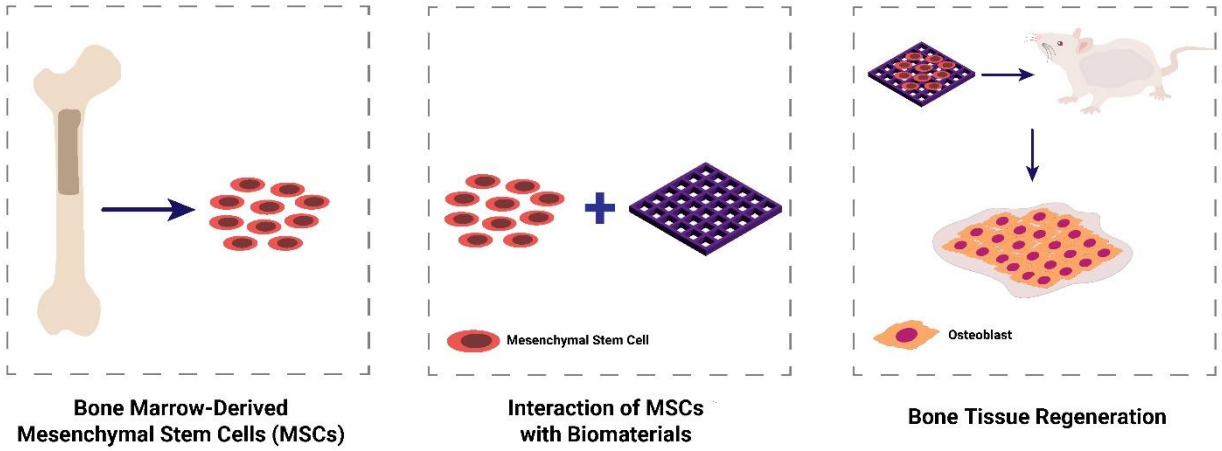

1. Introduction

Trauma-induced bone defects, tumor excision, malformations, and degenerative diseases with age constitute a significant clinical and socioeconomic burden in the world [1, 2]. The traditional options of autografts, allografts, metallic, or ceramic implants are still considered the clinical gold standards, but they have significant drawbacks, including donor-site morbidity, insufficient tissue supply, immune rejection, disease transmission, and mechanical mismatches that can worsen long-term performance [3-5]. It is against this backdrop that bone tissue engineering (BTE) has emerged as an interdisciplinary approach combining cells, biomaterials, and bioactive cues to reestablish a pro-regenerative microenvironment [6-11]. Mesenchymal stem cells (MSCs), specifically and prominently, induced pluripotent stem cell (iPSC)-derived osteoprogenitors are desirable due to their multipotential, trophic/paracrine effects, and immunomodulatory functions, which can expedite osteogenesis and regulate inflammation within the defect niche [6, 12].

In the past, the field has evolved from basic forms of grafting to more complex biomaterials and scaffold systems. The gold standard of autologous bone grafting applies to numerous clinical situations, but its limitations have prompted the development of synthetic and biologic alternatives. Initial synthetic bone implants are based on osteoconductive ceramics (e.g., hydroxyapatite, β-tricalcium phosphate) and bioresorbable polymers, which can be used to fill defects and allow bone to grow [13]. The development of micro- and nanofabrication, electrospinning, and additive manufacturing (e.g., 3D printing) enabled scaffold design to progress toward hierarchical architectures that replicate the multiscale porosity and mechanical anisotropy of bone [14-17]. The concept of a smart or stimulus-responsive scaffold, which can release growth factors in a controlled manner, produce mechanical or biochemical signals on demand, or detect local cues, has emerged as a promising future direction for achieving spatiotemporal control over regeneration [3, 18-20].

A network of adhesive receptors, signaling cascades, and mechanotransduction pathways mediates the interactions between stem cells and biomaterials at the molecular level. Integrin interaction and focal adhesion assembly are modulated by surface chemistry and topography, stimulating intracellular kinases and transcriptional programs (e.g., MAPK, PI3K/AKT, Wnt/β-catenin) to induce osteogenic commitment [6]. Nuclear mechanosensors (YAP/TAZ), cytoskeletal tension, and epigenetic states are influenced by the mechanical properties of the substrate and loading, and consequently, mechanical cues are linked to gene expression [13].

Despite encouraging in vitro and numerous promising preclinical in vivo outcomes, a transition to routine clinical application is challenging. The significant challenges include variability in the sources and activity of stem cells, the scalability and reproducibility of scaffold production, controllable biodegradation equivalent to that of new bone formation, vascularization of large constructs, regulatory complexity, the cost of manufacture, and control of long-term safety [3]; Theodosaki et al. [21] published a systematic review of human clinical trials, which, however, is heterogeneous in terms of study design and mixed outcomes.

The present review attempts to summarize existing research on stem cell-biomaterial interactions within the framework of bone regeneration, which includes the

molecular processes (adhesion, signaling, mechanotransduction), principles of materials and scaffold design (chemistry, architecture, degradability), the approaches to promote osteogenesis (growth-factor delivery, biofunctionalization, co-culture and vascularization strategies), and the preclinical and clinical evidence-base. This review provides a roadmap for researchers and clinicians to develop clinically useful, biologically relevant bone-regenerative therapeutic approaches. Figure 1 indicates an example of stem cell-biomaterial interaction for BTE. In the present study, we have retrieved relevant studies from Google Scholar with no search strategy since we had not considered a systematic protocol for this work. The inclusion criteria were all research articles with accessible full-texts published in English, and the exclusion criteria were all review papers, letter to editors, commentaries, conference abstracts, etc.

2. Osteogenic Potential and Stem Cell Biology

The outstanding multipotency of MSCs, particularly their ability to differentiate into osteoblasts, has been a focus of BTE [22]. Regenerative therapies require this differentiation capability, but it can be highly variable, thereby representing a persistent problem in clinical translation. Recent breakthroughs in high-resolution analytical methods, including single-cell multiomic analysis, have begun to reveal the hidden complexity of MSC biology. Research has shown that MSCs derived from various donors exhibit variability. In particular, they are based on differences in chromatin-accessible regulatory elements [22]. These readily accessible chromatin regions are dynamic regulatory switches, and their specialized arrangement within the population of donor MSCs directly determines the differentiation potential of these cells. The single-cell level of understanding of this donor heterogeneity is critical towards predicting cell performance and enhancing donor selection strategy within clinical BTE.

Among others, bone marrow mesenchymal stem cells (BMSCs) are considered the most promising source for effective bone regeneration [23]. This is because they are effective across a variety of in vitro and in vivo studies. However, the exact molecular mechanisms that enable them to outperform other sources (e.g., adipose-derived MSCs) are currently under intensive investigation.

The discipline is changing fast as a result of the incorporation of new research methods such as single-cell sequencing. These technologies are providing a deeper understanding of the intricate gene regulatory systems that control stem cell differentiation as never before [24]. Researchers are identifying essential molecular checkpoints by mapping transcriptomic, epigenomic, and proteomic responses in individual cells as they develop through the osteogenic pathway. This specific insight is expected to advance regenerative medicine toward more targeted solutions, enabling genetic or pharmacological control of MSCs to promote bone development before implantation.

3. Design Principles of Biomaterials to Regenerate Bones

In BTE, biomaterial design has been found to play a critical role in enabling stem cell interactions, osteogenic differentiation, and effective bone regeneration [25-27]. These materials should recapitulate the extracellular matrix (ECM) of native bone to facilitate the adhesion, proliferation, migration, and differentiation of stem cells and to provide biocompatibility and degradation upon handling [28, 29]. The main design principles are biocompatibility, mechanical properties, porosity, and osteoinductive and osteoconductive properties, as well as biomimetic or smart features, where the products are responsive to environmental stimuli [30]. In terms of mechanical properties, some simulation techniques can also be used to predict the properties of the selected biomaterials. Finite element method (FEM), representative volume element (RVE), computational fluid dynamics (CFD), and continuum damage mechanics (CDM) are among the modeling and computational methods used to investigate the properties of BTE structures and biomaterials [9, 31-37].

Biodegradability and biocompatibility are the backbone that enable the biomaterial to be integrated into the tissues of the host organism without causing adverse host defense responses and to break down at a pace similar to new bone development. This enables the scaffold to be filled with stem cells, including MSCs, and promotes regeneration [38, 39]. The mechanical properties must be similar to those of natural bone, providing structural support while exhibiting viscoelasticity and porosity to resist physiological loads and facilitate cellular penetration [38, 40, 41].

Porosity and pore size are important factors that promote stem cell migration, nutrient diffusion, vascularization, and waste removal. The best designs feature interlinked 3D porous networks with pore sizes ranging from 200 to 350 µm, which enhance the viability of stem cells and facilitate the formation of vascular networks essential for long-term tissue integration [38, 41, 42]. Osteoinduction and osteoconduction provide additional support for stem cell-biomaterial interactions by providing bioactive signals that can promote MSC differentiation into osteoblasts and bone growth. It involves the incorporation of growth factors or signaling

molecules to promote osteogenic and angiogenic reactions [7, 39].

These interactions are augmented by biomimetic and smart properties that mimic the hierarchical organization of bone ECM and include stimuli-responsive functionality (e.g., pH, temperature, electrical, or mechanical responsiveness). These intelligent biomaterials can deliver bioactive molecules in a controlled manner by modulating stem cell activity and adapting to the regenerative microenvironment [7, 19, 41]. Bone regeneration utilizes various types of biomaterials, each with its advantages and disadvantages, which impact their interaction with stem cells (Table 1).

These principles can be applied in both functional and clinical settings where biomaterials are used to immunomodulate the immune system and induce a pro-regenerative environment that supports stem cell activity [19]. Vascularization and innervation are also priorities, facilitating nutrient supply and neural integration and stimulating stem cell-mediated wound healing [42, 44]. With the help of individualized methods, including 3D printing, patient-specific scaffolds achieve optimal matching of stem cell-cell and stem cell-tissue interactions in accordance with anatomical and functional requirements [41, 45].

Overall, the development of biomaterial design into multifunctional, responsive, and personalized systems can address the issue of transnationalization in stem cell-based BTE, enabling more effective and clinically viable regenerative therapies.

4. Molecular Mechanisms of Cell-Material Interactions

The molecular processes that govern interactions between stem cells and biomaterials in BTE are crucial for regulating cellular functions, including adhesion, proliferation, migration, and osteogenic differentiation. These are achieved through a highly sophisticated interplay of physical, chemical, and mechanical signals emanating from the biomaterial surface, which are perceived by the stem cells and converted into cellular signals. Knowledge of these mechanisms enables the design of biomaterials that can replicate the bone ECM, facilitating successful regeneration with minimal adverse reactions [46, 47].

4.1. Physical Interactions

The geometric characteristics of biomaterial surfaces, including topography, roughness, stiffness, surface charge, and nanotopography, have a significant impact on stem cell behavior. For example, surface topography can control stem cell adhesion and focal cytoskeletal organization by altering the number of focal adhesion points and nuclear shape. Mimicking the hierarchical architecture of native bone ECM, Nanoscale patterns can direct MSCs to differentiate into osteogenic lineages, improving cell alignment and differentiation [48-53]. Surface charge and potential also influence protein adsorption and initial cell attachment, which are vital for the subsequent proliferation and development of bone tissue using stem cells [54].

4.2. Chemical Signaling

Chemical cues are those in which bioactive ligands, growth factors, and surface modifications are immobilized to increase interactions with stem cell receptors, thereby signaling. These cues promote MSC proliferation, differentiation, and functional responses, including osteogenesis, through integrin-mediated activation of downstream signaling cascades. For example, osteogenic factors can be released via chemical modification to facilitate ECM deposition and vascularization in bone scaffolds. Additionally, artificial biomaterials can engage in chemical signaling with stem cells, thereby recreating natural intercellular signaling and improving regenerative performance [55-59].

4.3. Mechanical Cues and Mechanotransduction

The mechanical cues within the substrates are transduced by the stem cells through mechanosensitive structures such as integrins, focal adhesions, and the cytoskeleton. This process is known as mechanotransduction, which converts physical forces into biochemical signals that regulate gene expression and protein production, ultimately defining the cell phenotype. Biomaterial stiffness that matches that of normal bone (e.g., high rigidity in cortical bone) in BTE induces MSCs to differentiate into osteoblasts. In contrast, matrices with lower stiffness can induce other differentiation. The responses of stem cells are also dynamic due to changes in the mechanical environment, which promotes bone remodeling and integration [49, 50, 53, 60, 61].

Overall, cell-material interactions are the molecular pathways that rely on physical, chemical, and mechanical stimuli to coordinate the responses of the stem cells in BTE. By clarifying these pathways, scholars will be able to develop superior biomaterials that enhance osteogenic potential and overcome the challenges associated with translating them for clinical applications.

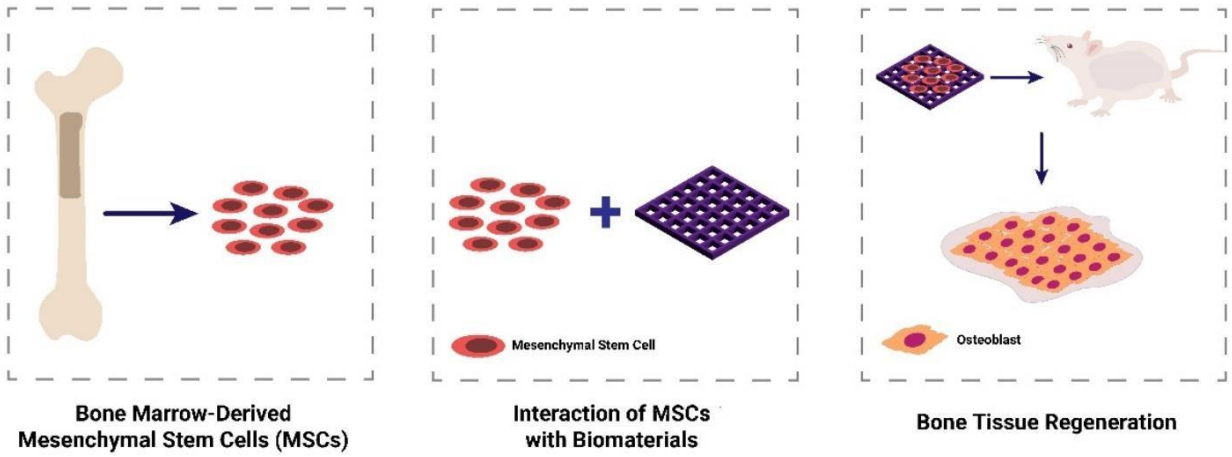

Figure 1. A conceptual schematic of the present review, with an example of a biomaterial (as a scaffold) used to support the in vivo differentiation of MSCs into osteoblasts

Table 1. Advantages and disadvantages of different material types for bone regeneration

Material Type	Advantages	Limitations/Notes	Ref.
Hydroxyapatite	Biomimetic, osteoconductive	Low mechanical strength; often reinforced with composites	[39, 40]
Natural polymers	Biocompatible, cell-friendly	Mechanically weak	[43]
Synthetic polymers	Customizable, controlled degradation	Low biological activity	[39, 43]

Table 2. Important parameters and cellular effects in cell-material interactions

Parameter	Cellular Effect	Ref.
Surface topography	Adhesion, cytoskeleton organization, differentiation	[48, 50-53]
Chemical modification	Signal activation, proliferation, and function	[55, 57]
Mechanical properties	Mechanotransduction, gene expression, phenotype	[53, 60]
Surface charge/potential	Adhesion, protein adsorption, tissue development	[54]

5. Strategies of Enhanced Osteogenesis

Temporarily, the success of BTE depends crucially on the capacity to increase osteogenesis, the mechanism by which MSCs differentiate into the osteoblastic line, lay down mineralized ECM, and ultimately recreate functioning osteoarchitecture [62]. Over the last decade, a complex array of approaches has emerged, including biomaterial design, physical stimulation, genetic/molecular modulation, and cell- and immune-based interventions [63, 64]. The approaches do not work independently; they converge at major signaling crossroads, including BMP/SMAD, PI3K/Akt, ERK1/2, and focal adhesion pathways, to coordinate stem cell fate and tissue-level regeneration. The potential strategies are outlined below, with a particular focus on their interactions with stem cell-biomaterial crosstalk.

5.1. Scaffold and Biomaterial Engineering

The structural, biochemical, and biomechanical signals required to guide osteogenic commitment are provided by biomaterials that serve as scaffolds for delivering stem cells. Some of the most advanced ones are composite scaffolds, which are 3D-printed, combining tunable architecture with bioactive surface functionalization. For instance, collagen-hydroxyapatite-coated polycaprolactone (PCL) scaffolds can dramatically enhance the adhesion, spreading, and osteogenic differentiation of MSCs, presumably by recreating the native organic–inorganic interface of bone and activating integrin-mediated signaling [65].

Nanocomposite strategies also enhance osteoinduction. Graphene oxide (GO) and silica-functionalized GO have been shown to exhibit a strong osteogenic effect by increasing the BMP signaling by upregulating and translocating phosphorylated SMAD1/5 in human MSCs [66]. It is not only a structural but also a signal-amplifying effect, thereby making GO-based materials a bioactive signal enhancer and not a passive substrate.

Magnesium (Mg^{2+})-releasing systems are another interesting class. Mg^{2+} is a dual-activator: it stimulates

PI3K/Akt and increases mitochondrial metabolism in MSCs, although, at the same time, it suppresses angiogenesis by regulating VEGF. In a study by Zhang et al. (2021), a novel type of Mg2+-incorporated dual-crosslinked hydrogel was developed, demonstrating synergistic enhancement of osteogenesis and vascularization in vivo [67]. Similarly, biodegradable Mg alloys enhance bone regeneration kinetics by integrating corrosion-based ion delivery with mechanical assistance [67], highlighting the significance of dynamic cell-biomaterial interactions.

5.2. Mechanical and Physical Stimuli

Mechanical loading remains a fundamental component of bone homeostasis [68]. Tensile strain triggers osteogenic differentiation through bidirectional ephrinB2-EphB4 signaling between osteoblasts and osteoclast precursors in orthodontic and distraction osteogenesis models, which is mediated by ERK1/2 activation [69]. Biomaterials with the desired stiffness or dynamic strain-responsive property (e.g., shape-memory polymers) can thereby be engineered to directly transduce mechanical inputs into pro-osteogenic biochemical signals [70].

5.3. Genetic and Molecular Modulation

Molecular intervention provides high specificity in the precision control of stem cell fate. MicroRNAs (miRNAs) have become key regulators: miR-21 silences PTEN, which, in turn, destabilizes HIF-1alpha even under normoxic conditions, facilitating glycolytic reprogramming and osteoblast differentiation [71]. Likewise, miR-181a/b-1 promotes osteogenesis by targeting PTEN and regulating mitochondrial respiration, thereby connecting metabolic fitness to lineage commitment [72]. Surprisingly, Mg2+ can enhance the low-dose effectiveness of BMP-2 by regulating cellular energy metabolism, indicating that the joint delivery of ions and proteins can help reduce supraphysiological BMP-2 doses used in clinics and decrease the risk of ectopic bone formation and inflammation [73].

5.4. Cell-Based and Immunomodulatory Strategies.

Immune cells and stem cells jointly contribute to the formation of the regenerative microenvironment [74]. MSC transplantation has never been replaced; however, recent studies suggest that paracrine dominance may be a key factor. Functionally engineered extracellular vesicles (EVs) from MSCs, when functionalized to recruit endogenous progenitors and osteoprogenitors sequentially, have demonstrated improved repair of aged bone, where traditional MSC engraftment often fails [75, 76].

It is also noteworthy that macrophage plasticity has been identified as a factor influencing bone healing. The initial response is that of pro-inflammatory (M1) macrophages, which must change to pro-regenerative (M2) phenotypes to enable MSC osteogenesis. This polarization can be actively directed by biomaterial surface topography, ion release (e.g., Sr 2 +, Mg 2 +), and cytokine-loaded scaffolds. As shown by Niu et al. [77], M2-skewed macrophages produce OSM (oncostatin M) and BMP-2, which directly stimulate MSCs-STAT3 and SMAD1/5, which is a fundamental design principle of immunosteogenic coupling.

6. Preclinical and Clinical Evidence

Numerous preclinical investigations have shown that a strategic combination of stem cells and biomaterial scaffolds is highly effective in stimulating bone regeneration, especially in critical-size defect models. Nanostructured calcium phosphate (CaP)-based biomaterials are used not only as structural scaffolds but also as bioactive signaling platforms that facilitate adhesion, growth, and osteogenic differentiation of stem cells. Scaffolds containing stem cells are superior to the cell-free control in rodent and large-animal models for bridging defects, accelerating bone formation, and restoring biomechanical properties [78-80]. For example, human gingival mesenchymal stem cells (hGMSCs) cultured on CaP bio-ceramics developed stable cellular bridges at the cell-material interface, promoting rapid incorporation and new bone formation [80].

Clinical translation is a challenging exercise, notwithstanding encouraging preclinical results. Strategies to overcome the mincluder challenges include maintaining in vivo cell viability after addressing implantation and host immune responses (particularly with allogeneic or xenogeneic constituents), as well as addressing potential risks such as ectopic mineralization and tumor formation resulting from uncontrolled stem cell proliferation [79, 81]. The further difficulty in meeting regulatory approval and standardizing biomaterials is due to biomaterial-related complications, such as an inflammatory response to degradation byproducts, a lack of mechanical strength during load-bearing conditions, and variability in product batches.

So far, few stem cell-biomaterial combinations have advanced to late-stage clinical trials, and most approved products (e.g., MACI-inspired bone analogs [82]) are based on autologous MSCs and soluble ceramic scaffolds. Although trials in the early stages of human

trials have shown better outcomes in non-union fractures and spinal fusion, limited data on functional outcomes and scaffold resorption kinetics have been reported in long-term follow-ups. Therefore, despite solid proof of concept in preclinical models, efficient clinical validation requires harmonized protocols, strict biomarker tracking (e.g., osteocalcin, ALP, micro-CT measurements), and multicenter trials to assess efficacy and safety across multiple patient populations.

7. Future Trends and Technologies

There is a paradigm shift in the BTE field, driven by the convergence of advances in materials science, stem cell biology, and bioengineering. The next-generation technologies and new trends are rewriting the interactions between the stem cell and biomaterials to be used to induce osteogenesis, vascularization, immune modulation, and functional integration- the way to move the promise of the stem cell in vitro and the induction of the same effect in vivo. The future of this discipline is shaped by four key technological frontiers, as follows.

7.1. Intelligent and Biomimetic Scaffolds

Innovations in 3D bioprinting and biofabrication have enabled the control of scaffold architecture, composition, and cellular placement at spatiotemporal scales, creating patient-specific implants with anisotropy and hierarchy similar to those of native bone [7, 83]. Most importantly, bioinspired materials, in particular nanostructured CaP, collagen-hydroxyapatite complexes, and mineralized silk fibroin, mimic the physicochemical cues of the natural ECM, thereby promoting MSCs adhesion, proliferation, and osteogenic commitment [78, 84].

Still more radical are smart (stimuli-responsive) scaffolds, which can detect and respond to biological signals (e.g., pH, enzyme activity, mechanical strain, or inflammatory cytokines). These bio-responsive systems may be able to release growth factors (e.g., BMP-2, VEGF) on demand, alter stiffness to suit the needs of each healing stage, or dynamically adjust surface topography in response to the changing stages of bone repair, thus coordinating scaffold activity with bone repair dynamics [7]. These stimuli-responsive biomaterials are a step towards autonomous regenerative implants [85].

7.2. Exosome-Integrated Platforms: Extracellular Vesicles (EVs)

Cell-free regenerative therapies are gaining popularity as safer and more scalable alternatives to whole-cell therapies. Bioactive cargo (miRNAs, proteins, lipids) is transported by EVs, especially MSC-derived exosomes, dental pulp stem cell-derived exosomes, or iPSC-derived exosomes. It controls osteoinduction, angiogenesis, and immunomodulation without the risks of tumorigenicity, ectopic development, or immune depression [86].

One of the most significant technological advances is a strategic combination of EVs with biomaterials: the scaffold functionalized with EV-binding motifs (e.g., heparin, CD63-affinity peptides), as well as the scaffold engineered with controlled-release matrices (e.g., thermosensitive hydrogels, layer-by-layer coverages), is effective to obtain sustained, localized delivery, which improves bioavailability and therapeutic efficacy. Recent developments include exosome-mimetic nanovesicles and engineered EVs expressing osteogenic miRNAs (e.g., miR29b, miR148 b), which further optimize regenerative specificity [87-90].

7.3. Biologically Directed Molecularly Engineered Biomaterials

Greater insight into stem cell mechanotransduction is guiding the rational design of nanoscale biomaterials. Surface topography (e.g., nanogratings, nanopits), stiffness gradients (~1040 kPa simulating osteogenic niches), and ligand patterning (e.g., RGD density, spatial clustering) can now be systematically varied to stimulate integrin-mediated FAK signaling, RhoA/ROCK cytoskeletal remodeling, and downstream osteogenic transcription factors (e.g., Runx2, Osterix) [91-94]. Biomaterials are also being co-functionalized with bioactive motifs that crosstalk with canonical signaling pathways: Wnt-activating peptides (e.g., GSK3b inhibitors), Notch ligand mimetics (e.g., Jagged-1 coatings), or BMP-mimetic sequences can be used to modulate a pathway selectively without supraphysiological doses of cytokine- biomimetic cytokines- reducing off-target effects and maximizing regenerative fidelity [95-97].

7.4. Multimodal Integration and the Digital-Physical Convergence

The future of convergence is in multifunctional, multi-stimuli platforms that integrate structural support, biological instruction, sensing, and actuation. 4D-printed scaffolds are structures that change shape after implantation (e.g., self-folding scaffolds that change to the shape of the defect geometry) [98, 99]. Conductive polymer-ceramic composites that allow the passage of the electric current to stimulate osteogenesis (e.g., polypyrrole-2T) [100-102]. Smart implants equipped

with IoT-built biosensors (e.g., pH, strain, and cytokine detectors) enable real-time monitoring of the healing process and adjust therapy based on remote feedback [7, 103]. Recently, AI and ML algorithms and methods have been used in various biomedicine-related fields [104-110]. Smart implants, coupled with AI-based design (e.g., generative adversarial networks to optimize scaffolds) and digital twins to plan surgery on a patient-by-patient basis, will support a novel generation of predictive, customized, and precision bone regeneration [111, 112].

The technological flow is toward biomaterials that are not only permissive but also instructive, adaptive, and intelligent, that is, they can conduct two-way crosstalk with stem cells and the host microenvironment. However, to be successful in clinical translation, parallel innovation in scalable production, regulatory harmonization, and prolonged safety validation will be needed.

8. Discussion

This review critically analyzes the multidimensional relationships between stem cells and biomaterials in BTE, incorporating molecular processes and material design principles supported by translational evidence. The existing literature suggests that bone regeneration success is not determined by a single factor, but rather by a highly coordinated interaction among the cellular phenotype, the biomaterial's physicochemical properties, and the dynamic host microenvironment.

Among the most vivid lessons that recent research has provided is the high degree of heterogeneity among MSCs, even when obtained from the same tissue source. Recent breakthroughs in single-cell transcriptomics and epigenomics have shown that donor-dependent chromatin accessibility and lineage-priming states are strong predictors of osteogenic potential, and in part, explain the variation in both preclinical and clinical outcomes. It is a significant bottleneck in clinical translation, so it is necessary to implement standardized cell characterization pipelines, predictive biomarkers, and possibly preconditioning strategies before implantation [22].

Scaffolds should now be viewed as evolving beyond passive osteoconductive systems to become instructive and adaptive systems. Integrin-mediated adhesion, focal adhesion assembly, and downstream signaling pathways, including MAPK, PI3K/Akt, and Wnt/-catenin, are all controlled by surface chemistry, nanoscale topography, stiffness differences, and degradation kinetics. Notably, mechanotransduction through YAP/TAZ and cytoskeletal tension is a major controller of the link between material mechanics and nuclear transcriptional programs, supporting the idea that mechanical signals are just as potent as biochemical ones in controlling osteogenesis.

Another paradigm shift is the incorporation of immunomodulation into scaffold construction. Instead of viewing inflammation as a negative, new data show that it predicts regenerative success. Biomaterials with the ability to induce macrophage polarization into a pro-regenerative (M2) phenotype promote osteogenic differentiation of MSCs by paracrine mediators, including oncostatin M and BMP-2. This immune stem cell interaction offers a mechanistic explanation for the development of scaffolds that actively remodel the initial inflammatory niche rather than preventing immune responses.

Although promising in preclinical trials, its application in normal practice has been limited. Among the issues are the lack of vascularization in large constructs, the lack of batch-to-batch consistency in biomaterials, the complexity of the regulatory environment for cell-based products, and unaddressed safety issues that require time, such as the ectopic growth of minerals and uncontrolled cell growth. It is noteworthy that the majority of clinical studies are underpowered, heterogeneous, and lack standardized outcome measures, which prevents them from arriving at definitive conclusions. These concerns underscore the need for harmonized clinical trial designs, GMP-compliant manufacturing plans, and longitudinal follow-up studies with functional and imaging-based endpoints.

New solutions to many of these limitations include emerging approaches, such as EV-based therapies [113], as well as smart and stimulus-responsive scaffolds [114]. Specifically, EV- functionalized scaffolds are an attractive cell-free option that maintain osteogenic and immunomodulatory capabilities while alleviating safety and scalability issues [115]. Together with the new technologies of biofabrication, including 3D and 4D bioprinting [30, 116, 117], these technologies open the path to individually personalized and dynamically versatile bone regenerative treatments.

9. Conclusion

Bone tissue engineering has evolved beyond primitive scaffold-based studies to considerably complex multiscale systems that not only guide stem cell fate but also control host responses. The complex convergence of molecular signals, mechanotransduction, immune modulation, and material-driven biophysical cues is regulated in stem cell-biomaterial interactions, which must be carefully synchronized to achieve functional

bone regeneration. The clinical effectiveness of the future will rely on shifting to constructs designed on a case-by-case basis rather than empirically designed ones aimed at mechanisms, as well as on patient-specific and regulatory-conscious approaches. The most promising directions for overcoming current translational barriers are intelligent biomaterials capable of sensing and responding to a changing regenerative environment, along with cell-free modalities such as EVs and digitally optimized scaffold architectures. Ultimately, the convergence of stem cell biology with materials science, bioengineering, and computational design is revolutionizing the future of bone regeneration. It will require further interdisciplinary work, strict clinical validation, and scalable manufacturing solutions to develop these new, improved biomaterial-stem cell platforms into clinically validated and approvable interventions for treating complex bone defects.

Authors Contribution
All authors have contributed equally to prepare the paper.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflict of interests
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.

References

[1] Pneumaticos, S.G., et al., Segmental bone defects: from cellular and molecular pathways to the development of novel biological treatments. Journal of Cellular and Molecular Medicine, 2010. 14(11): p. 2561-2569.

[2] Migliorini, F., et al., Strategies for large bone defect reconstruction after trauma, infections or tumour excision: a comprehensive review of the literature. European Journal of Medical Research, 2021. 26(1): p. 118.

[3] Zhao, X., et al., Beyond hype: unveiling the Real challenges in clinical translation of 3D printed bone scaffolds and the fresh prospects of bioprinted organoids. Journal of Nanobiotechnology, 2024. 22(1): p. 500.

[4] Ferraz, M.P., Bone Grafts in Dental Medicine: An Overview of Autografts, Allografts and Synthetic Materials. Materials (Basel), 2023. 16(11).

[5] Łuczak, J.W., et al., The Future of Bone Repair: Emerging Technologies and Biomaterials in Bone Regeneration. Int J Mol Sci, 2024. 25(23).

[6] Muniz, T.D.P.T.P., et al., Mesenchymal Stem Cells and Tissue Bioengineering Applications in Sheep as Ideal Model. Stem Cells International, 2024. 2024(1): p. 5176251.

[7] Percival, K.M., V. Paul, and G.A. Husseini, Recent Advancements in Bone Tissue Engineering: Integrating Smart Scaffold Technologies and Bio-Responsive Systems for Enhanced Regeneration. International Journal of Molecular Sciences, 2024. 25(11): p. 6012.

[8] Radhakrishnan, A., et al., Chapter 20 - Emerging strategies in bone tissue engineering, in Tissue Engineering, C.P. Sharma, et al., Editors. 2022, Academic Press. p. 469-492.

[9] Sahbafar, H., Mechanical and biological properties of polylactic acid (PLA)-hardystonite-Fe3O4 scaffolds made by 3D printing for bone tissue engineering. University of Tehran, 2023.

[10] Stamnitz, S. and A. Klimczak, Mesenchymal Stem Cells, Bioactive Factors, and Scaffolds in Bone Repair: From Research Perspectives to Clinical Practice. Cells, 2021. 10(8).

[11] Lumelsky, N., Creating a Pro-Regenerative Tissue Microenvironment: Local Control is the Key. Front Bioeng Biotechnol, 2021. 9: p. 712685.

[12] Barreca, M.M., P. Cancemi, and F. Geraci, Mesenchymal and Induced Pluripotent Stem Cells-Derived Extracellular Vesicles: The New Frontier for Regenerative Medicine? Cells, 2020. 9(5).

[13] Todd, E.A., et al., Functional Scaffolds for Bone Tissue Regeneration: A Comprehensive Review of Materials, Methods, and Future Directions. Journal of Functional Biomaterials, 2024. 15(10): p. 280.

[14] Ren, Y., et al., Advances in 3D Printing of Highly Bioadaptive Bone Tissue Engineering Scaffolds. ACS Biomaterials Science & Engineering, 2024. 10(1): p. 255-270.

[15] Zhang, Q., et al., 3D printing method for bone tissue engineering scaffold. Medicine in Novel Technology and Devices, 2023. 17: p. 100205.

[16] Wen, Y., et al., 3D printed porous ceramic scaffolds for bone tissue engineering: a review. Biomaterials Science, 2017. 5(9): p. 1690-1698.

[17] Podgórski, R., et al., Fabrication of 3D-Printed Scaffolds with Multiscale Porosity. ACS Omega, 2024. 9(27): p. 29186-29204.

[18] Xue, C., et al., Stimuli-responsive hydrogels for bone tissue engineering. Biomater Transl, 2024. 5(3): p. 257-273.

[19] Wei, H., et al., Recent advances in smart stimuli-responsive biomaterials for bone therapeutics and regeneration. Bone Research, 2022. 10(1): p. 17.

[20] Bagherzadeh, E., et al., Stimuli-responsive piezoelectricity in electrospun polycaprolactone (PCL)/Polyvinylidene fluoride (PVDF) fibrous scaffolds for bone regeneration. Journal of Materials Research and Technology, 2023. 23: p. 379-390.

[21] Theodosaki, A.M., et al., Bone Regeneration with Mesenchymal Stem Cells in Scaffolds: Systematic Review of Human Clinical Trials. Stem Cell Reviews and Reports, 2024. 20(4): p. 938-966.

[22] Chen, D., et al., Osteogenic Differentiation Potential of Mesenchymal Stem Cells Using Single Cell Multiomic Analysis. Genes, 2023. 14(10): p. 1871.

[23] Gholami Farashah, M.S., et al., Bone marrow mesenchymal stem cells' osteogenic potential: superiority or non-superiority

to other sources of mesenchymal stem cells? Cell and Tissue Banking, 2023. 24(3): p. 663-681.

[24] Shen, F. and Y. Shi, Recent Advances in Single-Cell View of Mesenchymal Stem Cell in Osteogenesis. Frontiers in Cell and Developmental Biology, 2022. Volume 9 - 2021.

[25] Rifai, A., et al., Biofabrication of functional bone tissue: defining tissue-engineered scaffolds from nature. Frontiers in Bioengineering and Biotechnology, 2023. Volume 11 - 2023.

[26] Shibli, J.A., et al., Bone Tissue Engineering Using Osteogenic Cells: From the Bench to the Clinical Application. Tissue Engineering Part C: Methods, 2022. 28(5): p. 179-192.

[27] Dec, P., A. Modrzejewski, and A. Pawlik, Existing and Novel Biomaterials for Bone Tissue Engineering. Int J Mol Sci, 2022. 24(1).

[28] Chen, Z., et al., Progress in biomaterials inspired by the extracellular matrix. Giant, 2024. 19: p. 100323.

[29] Cramer, M.C. and S.F. Badylak, Extracellular Matrix-Based Biomaterials and Their Influence Upon Cell Behavior. Ann Biomed Eng, 2020. 48(7): p. 2132-2153.

[30] Noroozi, R., et al., 3D and 4D Bioprinting Technologies: A Game Changer for the Biomedical Sector? Annals of Biomedical Engineering, 2023. 51(8): p. 1683-1712.

[31] Boccaccio, A., et al., Finite element method (FEM), mechanobiology and biomimetic scaffolds in bone tissue engineering. Int J Biol Sci, 2011. 7(1): p. 112-32.

[32] Hendrikson, W.J., et al., The Use of Finite Element Analyses to Design and Fabricate Three-Dimensional Scaffolds for Skeletal Tissue Engineering. Frontiers in Bioengineering and Biotechnology, 2017. Volume 5 - 2017.

[33] Omar, A.M., et al., Geometry-Based Computational Fluid Dynamic Model for Predicting the Biological Behavior of Bone Tissue Engineering Scaffolds. Journal of Functional Biomaterials, 2022. 13(3): p. 104.

[34] E, S.M., et al., Computational fluid dynamics study on three-dimensional polymeric scaffolds to predict wall shear stress using machine learning models for bone tissue engineering applications. Asia-Pacific Journal of Chemical Engineering, 2024. 19(2): p. e3017.

[35] Cronin, D.S., et al., Cortical bone continuum damage mechanics constitutive model with stress triaxiality criterion to predict fracture initiation and pattern. Frontiers in Bioengineering and Biotechnology, 2022. Volume 10 - 2022.

[36] Dimnik, J.M., I.T. Haider, and W.B. Edwards, A continuum damage model of fatigue and failure in whole bone. Journal of the Mechanical Behavior of Biomedical Materials, 2023. 143: p. 105907.

[37] Salehi, S., et al., Application of Continuum Damage Mechanics for Prediction of Wear with Provision for Sequential Speed Operation. Tribology Letters, 2022. 70(4): p. 105.

[38] Battafarano, G., et al., Strategies for Bone Regeneration: From Graft to Tissue Engineering. International Journal of Molecular Sciences, 2021. 22(3): p. 1128.

[39] Tang, G., et al., Recent Trends in the Development of Bone Regenerative Biomaterials. Frontiers in Cell and Developmental Biology, 2021. Volume 9 - 2021.

[40] Ielo, I., et al., Recent Advances in Hydroxyapatite-Based Biocomposites for Bone Tissue Regeneration in Orthopedics. International Journal of Molecular Sciences, 2022. 23(17): p. 9721.

[41] Wang, Z., et al., Pharmaceutical electrospinning and 3D printing scaffold design for bone regeneration. Advanced Drug Delivery Reviews, 2021. 174: p. 504-534.

[42] Dec, P., A. Modrzejewski, and A. Pawlik, Existing and Novel Biomaterials for Bone Tissue Engineering. International Journal of Molecular Sciences, 2023. 24(1): p. 529.

[43] Bharadwaz, A. and A.C. Jayasuriya, Recent trends in the application of widely used natural and synthetic polymer nanocomposites in bone tissue regeneration. Materials Science and Engineering: C, 2020. 110: p. 110698.

[44] Marrella, A., et al., Engineering vascularized and innervated bone biomaterials for improved skeletal tissue regeneration. Materials Today, 2018. 21(4): p. 362-376.

[45] Jia, Z., et al., Design, printing, and engineering of regenerative biomaterials for personalized bone healthcare. Progress in Materials Science, 2023. 134: p. 101072.

[46] Rodríguez-Merchán, E.C., A Review of Recent Developments in the Molecular Mechanisms of Bone Healing. Int J Mol Sci, 2021. 22(2).

[47] Raggatt, L.J. and N.C. Partridge, Cellular and molecular mechanisms of bone remodeling. J Biol Chem, 2010. 285(33): p. 25103-8.

[48] Luo, J., et al., The influence of nanotopography on cell behaviour through interactions with the extracellular matrix – A review. Bioactive Materials, 2022. 15: p. 145-159.

[49] Janson, I.A. and A.J. Putnam, Extracellular matrix elasticity and topography: Material-based cues that affect cell function via conserved mechanisms. Journal of Biomedical Materials Research Part A, 2015. 103(3): p. 1246-1258.

[50] Ermis, M., E. Antmen, and V. Hasirci, Micro and Nanofabrication methods to control cell-substrate interactions and cell behavior: A review from the tissue engineering perspective. Bioactive Materials, 2018. 3(3): p. 355-369.

[51] Yao, X., R. Peng, and J. Ding, Cell–Material Interactions Revealed Via Material Techniques of Surface Patterning. Advanced Materials, 2013. 25(37): p. 5257-5286.

[52] Di Cio, S. and J.E. Gautrot, Cell sensing of physical properties at the nanoscale: Mechanisms and control of cell adhesion and phenotype. Acta Biomaterialia, 2016. 30: p. 26-48.

[53] Xie, W., et al., Static and Dynamic: Evolving Biomaterial Mechanical Properties to Control Cellular Mechanotransduction. Advanced Science, 2023. 10(9): p. 2204594.

[54] Metwally, S. and U. Stachewicz, Surface potential and charges impact on cell responses on biomaterials interfaces for medical applications. Materials Science and Engineering: C, 2019. 104: p. 109883.

[55] Ventre, M. and P.A. Netti, Engineering Cell Instructive Materials To Control Cell Fate and Functions through Material Cues and Surface Patterning. ACS Applied Materials & Interfaces, 2016. 8(24): p. 14896-14908.

[56] Ficerman, W., M. Wiśniewski, and K. Roszek, Interactions of nanomaterials with cell signalling systems – Focus on purines-mediated pathways. Colloids and Surfaces B: Biointerfaces, 2022. 220: p. 112919.

[57] Mukwaya, V., S. Mann, and H. Dou, Chemical communication at the synthetic cell/living cell interface. Communications Chemistry, 2021. 4(1): p. 161.

[58] Li, S., et al., Chemical Signal Communication between Two Protoorganelles in a Lipid-Based Artificial Cell. Analytical Chemistry, 2019. 91(10): p. 6859-6864.

[59] Zheng, J., et al., Deciphering intercellular signaling complexes by interaction-guided chemical proteomics. Nature Communications, 2023. 14(1): p. 4138.

[60] Brusatin, G., et al., Biomaterials and engineered microenvironments to control YAP/TAZ-dependent cell behaviour. Nature Materials, 2018. 17(12): p. 1063-1075.

[61] Mertgen, A.-S., et al., Multifunctional Biomaterials: Combining Material Modification Strategies for Engineering of Cell-Contacting Surfaces. ACS Applied Materials & Interfaces, 2020. 12(19): p. 21342-21367.

[62] Zha, K., et al., Recent Advances in Enhancement Strategies for Osteogenic Differentiation of Mesenchymal Stem Cells in Bone Tissue Engineering. Front Cell Dev Biol, 2022. 10: p. 824812.

[63] Łuczak, J.W., et al., The Future of Bone Repair: Emerging Technologies and Biomaterials in Bone Regeneration. International Journal of Molecular Sciences, 2024. 25(23): p. 12766.

[64] Lv, B., et al., Functionalized multidimensional biomaterials for bone microenvironment engineering applications: Focus on osteoimmunomodulation. Frontiers in Bioengineering and Biotechnology, 2022. Volume 10 - 2022.

[65] Ebrahimi, Z., et al., Enhanced osteogenic differentiation of stem cells by 3D printed PCL scaffolds coated with collagen and hydroxyapatite. Scientific Reports, 2022. 12(1): p. 12359.

[66] Li, Z., et al., Graphene oxide-functionalized nanocomposites promote osteogenesis of human mesenchymal stem cells via enhancement of BMP-SMAD1/5 signaling pathway. Biomaterials, 2021. 277: p. 121082.

[67] Zhang, X., et al., A novel magnesium ion-incorporating dual-crosslinked hydrogel to improve bone scaffold-mediated osteogenesis and angiogenesis. Materials Science and Engineering: C, 2021. 121: p. 111868.

[68] Gao, F., et al., Mechanical loading-induced change of bone homeostasis is mediated by PGE2-driven hypothalamic interoception. Res Sq, 2023.

[69] Zhao, C., et al., Bidirectional ephrinB2-EphB4 signaling controls bone homeostasis. Cell Metab, 2006. 4(2): p. 111-21.

[70] Li, T., et al., The Current Status, Prospects, and Challenges of Shape Memory Polymers Application in Bone Tissue Engineering. Polymers (Basel), 2023. 15(3).

[71] Yang, C., et al., miRNA-21 promotes osteogenesis via the PTEN/PI3K/Akt/HIF-1α pathway and enhances bone regeneration in critical size defects. Stem Cell Research & Therapy, 2019. 10(1): p. 65.

[72] Zheng, H., et al., MicroRNA-181a/b-1 over-expression enhances osteogenesis by modulating PTEN/PI3K/AKT signaling and mitochondrial metabolism. Bone, 2019. 123: p. 92-102.

[73] Lin, S., et al., Orchestration of energy metabolism and osteogenesis by Mg2+ facilitates low-dose BMP-2-driven regeneration. Bioactive Materials, 2022. 18: p. 116-127.

[74] Aurora, A.B. and E.N. Olson, Immune modulation of stem cells and regeneration. Cell Stem Cell, 2014. 15(1): p. 14-25.

[75] Murali, V.P. and C.A. Holmes, Mesenchymal stromal cell-derived extracellular vesicles for bone regeneration therapy. Bone Rep, 2021. 14: p. 101093.

[76] Yu, T., et al., Harnessing Engineered Extracellular Vesicles from Mesenchymal Stem Cells as Therapeutic Scaffolds for Bone-Related Diseases. Advanced Functional Materials, 2024. 34(38): p. 2402861.

[77] Niu, Y., et al., Modulating macrophage activities to promote endogenous bone regeneration: Biological mechanisms and engineering approaches. Bioactive Materials, 2021. 6(1): p. 244-261.

[78] Wang, P., et al., Bone tissue engineering via nanostructured calcium phosphate biomaterials and stem cells. Bone Research, 2014. 2(1): p. 14017.

[79] Shang, F., et al., Advancing application of mesenchymal stem cell-based bone tissue regeneration. Bioactive Materials, 2021. 6(3): p. 666-683.

[80] Benjumeda Wijnhoven, I., et al., Analysis of cell-biomaterial interaction through cellular bridge formation in the interface between hGMSCs and CaP bioceramics. Scientific Reports, 2020. 10(1): p. 16493.

[81] Augustine, R., et al., Stem Cells in Bone Tissue Engineering: Progress, Promises and Challenges. Stem Cell Reviews and Reports, 2024. 20(7): p. 1692-1731.

[82] Minas, T., MACI Sandwich Technique With Autologous Bone Graft. Video J Sports Med, 2024. 4(1): p. 26350254231188139.

[83] Yang, Z., et al., Stem Cell-Laden Hydrogel-Based 3D Bioprinting for Bone and Cartilage Tissue Engineering. Frontiers in Bioengineering and Biotechnology, 2022. Volume 10 - 2022.

[84] Gao, C., et al., Bone biomaterials and interactions with stem cells. Bone Research, 2017. 5(1): p. 17059.

[85] Yang, K., et al., Unlocking the potential of stimuli-responsive biomaterials for bone regeneration. Frontiers in Pharmacology, 2024. Volume 15 - 2024.

[86] Vig, S. and M.H. Fernandes, Bone Cell Exosomes and Emerging Strategies in Bone Engineering. Biomedicines, 2022. 10(4): p. 767.

[87] Trubiani, O., et al., Human Oral Stem Cells, Biomaterials and Extracellular Vesicles: A Promising Tool in Bone Tissue

Repair. International Journal of Molecular Sciences, 2019. 20(20): p. 4987.

[88] Xie, H., et al., Extracellular Vesicle-functionalized Decalcified Bone Matrix Scaffolds with Enhanced Pro-angiogenic and Pro-bone Regeneration Activities. Scientific Reports, 2017. 7(1): p. 45622.

[89] Liu, F., et al., The potential therapeutic role of extracellular vesicles in critical-size bone defects: Spring of cell-free regenerative medicine is coming. Frontiers in Bioengineering and Biotechnology, 2023. Volume 11 - 2023.

[90] Yu, T., et al., Extracellular vesicle-functionalized bioactive scaffolds for bone regeneration. Asian Journal of Pharmaceutical Sciences, 2024. 19(5): p. 100945.

[91] Zhuo, S., et al., Stem Cell-Biomaterial Interactions for Tissue Engineering. Stem Cells International, 2015. 2015(1): p. 126710.

[92] Karmakar, R., et al., Attributes of Nanomaterials and Nanotopographies for Improved Bone Tissue Engineering and Regeneration. ACS Applied Bio Materials, 2023. 6(10): p. 4020-4041.

[93] Luo, T., et al., A Review on the Design of Hydrogels With Different Stiffness and Their Effects on Tissue Repair. Front Bioeng Biotechnol, 2022. 10: p. 817391.

[94] Hao, D., et al., A bioactive material with dual integrin-targeting ligands regulates specific endogenous cell adhesion and promotes vascularized bone regeneration in adult and fetal bone defects. Bioactive Materials, 2023. 20: p. 179-193.

[95] Nelson, A.L., et al., Therapeutic approaches to activate the canonical Wnt pathway for bone regeneration. J Tissue Eng Regen Med, 2022. 16(11): p. 961-976.

[96] Deng, Y., et al., Biomaterial-Mediated Presentation of Jagged-1 Mimetic Ligand Enhances Cellular Activation of Notch Signaling and Bone Regeneration. ACS Nano, 2022. 16(1): p. 1051-1062.

[97] Cassari, L., et al., Strategies for the Covalent Anchoring of a BMP-2-Mimetic Peptide to PEEK Surface for Bone Tissue Engineering. Materials, 2023. 16(10): p. 3869.

[98] Wang, C., et al., Advanced reconfigurable scaffolds fabricated by 4D printing for treating critical-size bone defects of irregular shapes. Biofabrication, 2020. 12(4): p. 045025.

[99] Zhang, X., et al., Four-Dimensional Printing and Shape Memory Materials in Bone Tissue Engineering. Int J Mol Sci, 2023. 24(1).

[100] Hu, W.W., et al., Electrical stimulation to promote osteogenesis using conductive polypyrrole films. Mater Sci Eng C Mater Biol Appl, 2014. 37: p. 28-36.

[101] Luo, S., et al., Advances in electroactive biomaterials: Through the lens of electrical stimulation promoting bone regeneration strategy. Journal of Orthopaedic Translation, 2024. 47: p. 191-206.

[102] Dixon, D.T., E.N. Landree, and C.T. Gomillion, 3D-Printed Demineralized Bone Matrix-Based Conductive Scaffolds Combined with Electrical Stimulation for Bone Tissue Engineering Applications. ACS Applied Bio Materials, 2024. 7(7): p. 4366-4378.

[103] Nash, K.E., K.G. Ong, and R.E. Guldberg, Implantable biosensors for musculoskeletal health. Connect Tissue Res, 2022. 63(3): p. 228-242.

[104] Basiri, R., et al. Ulcergpt: a multimodal approach leveraging large language and vision models for diabetic foot ulcer image transcription. in International Conference on Pattern Recognition. 2024. Springer.

[105] Wei, Y., et al., A review of algorithm & hardware design for AI-based biomedical applications. IEEE transactions on biomedical circuits and systems, 2020. 14(2): p. 145-163.

[106] Prasad, P.S., et al., Applications of artificial intelligence in biomedical engineering, in Handbook of Artificial Intelligence in Biomedical Engineering. 2021, Apple Academic Press. p. 125-145.

[107] Basiri, R., et al. Synthesizing diabetic foot ulcer images with diffusion model. in Joint European Conference on Machine Learning and Knowledge Discovery in Databases. 2023. Springer.

[108] Strzelecki, M. and P. Badura, Machine learning for biomedical application. 2022, MDPI. p. 2022.

[109] Guo, K., et al., Artificial intelligence-driven biomedical genomics. Knowledge-Based Systems, 2023. 279: p. 110937.

[110] Kolomenskaya, E., et al., Application of Artificial Intelligence at All Stages of Bone Tissue Engineering. Biomedicines, 2024. 12(1): p. 76.

[111] Shah, A.K., et al., Understanding the use of artificial intelligence for implant analysis in total joint arthroplasty: a systematic review. Arthroplasty, 2023. 5(1): p. 54.

[112] Intravaia, J.T., et al., Smart orthopedic biomaterials and implants. Current Opinion in Biomedical Engineering, 2023. 25: p. 100439.

[113] Davies, O.G., Extracellular vesicles: From bone development to regenerative orthopedics. Mol Ther, 2023. 31(5): p. 1251-1274.

[114] Zhu, T., et al., Recent advances of responsive scaffolds in bone tissue engineering. Front Bioeng Biotechnol, 2023. 11: p. 1296881.

[115] Yu, T., et al., Extracellular vesicle-functionalized bioactive scaffolds for bone regeneration. Asian J Pharm Sci, 2024. 19(5): p. 100945.

[116] Kang, X., et al., Bioprinting for bone tissue engineering. Front Bioeng Biotechnol, 2022. 10: p. 1036375.

[117] Prakash, A., et al., 4D printing in dynamic and adaptive bone implants: Progress in bone tissue engineering. Bioprinting, 2024. 44: p. e00373.