

**Mini Review Article**

Copyright © All rights are reserved by Paula V Messina

# Nano-solutions: Transforming Bone Tissue Engineering

**Paula V Messina\* and Paula S Rivero***INQUISUR – CONICET, Department of Chemistry, Universidad Nacional del Sur, B8000CPB, Bahía Blanca, Argentina***Corresponding author:** Paula V Messina, INQUISUR – CONICET, Department of Chemistry, Universidad Nacional del Sur, B8000CPB, Bahía Blanca, Argentina.**Received Date:** July 15, 2024**Published Date:** August 13, 2024**Abstract**

Nanotechnology is vital in bone tissue regeneration, using nanoscale materials to mimic the natural bone matrix, enhance cellular functions, and support stem cell differentiation. It improves scaffold biocompatibility and mechanical properties, accelerating bone healing. This technology offers innovative solutions for treating bone defects and diseases effectively.

**Introduction**

Nanotechnology is at the forefront of modern biomedical research, providing groundbreaking solutions to some of the most pressing challenges in medicine and biology. One of the most exciting applications of nanotechnology is in bone tissue regeneration, a critical area in orthopedics, dentistry, and trauma surgery. The complex structure and dynamic physiological properties of bone tissue necessitate advanced materials and methodologies for effective repair and regeneration. By manipulating materials at the nanoscale, researchers are developing innovative strategies that not only enhance bone healing but also promote cell attachment and facilitate the intricate processes involved in bone tissue regeneration.

**Understanding Bone Tissue and Its Regeneration**

Before delving into the specifics of nanotechnology applications, it is essential to understand the structure and biology of bone tissue. Bone is a dynamic organ composed of a mineralized matrix predominantly made of hydroxyapatite, collagen fibers, and

various cells, including osteoblasts, osteocytes, and osteoclasts. The continuous remodeling of bone tissue involves a delicate balance between bone formation and resorption, making it critical for maintaining skeletal integrity and function [1]. In cases of bone injuries, fractures, or diseases such as osteoporosis, the body's natural repair mechanisms may be insufficient, necessitating external interventions. Traditional bone grafts, both autografts and allografts, have limitations, such as donor site morbidity and potential for disease transmission. Thus, there is an urgent need for innovative biomaterials and techniques that can enhance bone regeneration and healing processes [2].

**Nanotechnology in Bone Regeneration****The Role of Nanotechnology**

Nanotechnology, defined as the manipulation of matter at dimensions typically ranging from 1 to 100 nanometers, can profoundly impact bone tissue engineering [2,3]. By fabricating materials at the nanoscale, researchers can exploit unique physical

and chemical properties that are not observed in bulk materials. This nanoscale manipulation has led to the development of various advanced biomaterials that can significantly improve bone regeneration outcomes [3].

## Key Nanostructures in Bone Regeneration

### Nanoparticles

Nanoparticles are minute particles that possess unique characteristics due to their small size and high surface area. Various types of nanoparticles, such as titanium dioxide, zinc oxide, and silver nanoparticles, have been extensively researched for their applications in bone regeneration [4,5]. These nanoparticles can enhance the mechanical strength and bioactivity of bone scaffolds while also imparting antibacterial properties, which are crucial for preventing infection at the site of implantation [6-8].

**Titanium Dioxide Nanoparticles:** Known for their excellent biocompatibility and ability to promote osteoblast differentiation, titanium dioxide nanoparticles have shown promise in enhancing the mechanical properties of bone scaffolds [9-11].

**Zinc Oxide Nanoparticles:** These nanoparticles not only exhibit antimicrobial activity but also promote osteogenic differentiation, making them valuable in the context of bone tissue engineering [12].

**Silver Nanoparticles:** Renowned for their potent antibacterial properties, silver nanoparticles can reduce the risk of postoperative infections, thereby increasing the success rate of bone regeneration procedures [13,14].

### Nanofibers

Electrospinning techniques have enabled the production of nanofibrous scaffolds that closely mimic the extracellular matrix (ECM) of natural bone tissue. These nanofibers provide a suitable microenvironment for cell attachment, proliferation, and differentiation, which are essential for effective bone regeneration [15,16].

**Biopolymer-based Nanofibers:** Materials such as poly(lactic acid) (PLA), polycaprolactone (PCL), and gelatin have been employed to create nanofibrous scaffolds that promote osteogenic differentiation and enhance cellular activities [17,18].

**Hybrid Nanofibers:** By combining natural and synthetic polymers, researchers can engineer nanofibrous scaffolds that exhibit enhanced mechanical properties and bioactivity, facilitating better bone tissue integration [16,19].

### Nanospheres and Nanocapsules

Nanospheres and nanocapsules serve as effective carriers for delivering growth factors or therapeutic agents directly to the site of bone injury. By controlling the release profiles of these agents, nanocarriers can enhance cellular responses and promote tissue regeneration [20].

**Controlled Drug Delivery:** Utilizing nanotechnology for drug

delivery allows for sustained release of bioactive molecules, such as BMP-2 (Bone Morphogenetic Protein-2), directly to the bone defect site, significantly improving healing outcomes [21,22].

**Targeted Delivery Systems:** By functionalizing nanocarriers with specific ligands, researchers can achieve targeted delivery to osteogenic cells, enhancing the efficacy of regenerative treatments [23,24].

## Hydroxyapatite: A Cornerstone of Bone Regeneration

Hydroxyapatite (HA) is a naturally occurring mineral form of calcium apatite and a primary component of bone tissue. Due to its excellent biocompatibility, osteoconductivity, and ability to promote bone in-growth, HA is widely utilized in various bone regeneration applications. Recent advances in nanotechnology have led to the development of nanostructured hydroxyapatite (nHA), which exhibits superior properties compared to its micron-sized counterparts [7,8,17-19,21,25,26].

### Properties of Nanostructured Hydroxyapatite

**Enhanced Surface Area and Reactivity:** Nanostructured hydroxyapatite has a significantly higher surface area, which increases its reactivity and interaction with biological systems. This property promotes better integration with surrounding tissues and supports the proliferation and differentiation of osteogenic cells.

**Bioactivity:** The increased surface area and unique morphology of nHA enhance its bioactivity, facilitating the adsorption of proteins and other biomolecules that are crucial for cell adhesion and proliferation.

**Mechanical Properties:** nHA can be combined with various polymers to create composite materials that exhibit tailored mechanical properties suitable for load-bearing applications in bone tissue engineering.

**Composite Materials:** The combination of nHA with polymers or other inorganic materials has led to the development of composite scaffolds that offer a balance of mechanical strength, biodegradability, and bioactivity. These composites can significantly enhance the overall performance of bone graft materials.

**Polymer-Hydroxyapatite Composites:** By integrating nHA with biocompatible polymers such as PLA or PCL, researchers can create scaffolds that not only support cell growth but also mimic the natural bone matrix [8,17-19].

**Ceramic-Polymer Composites:** Combining nHA with other ceramic materials can result in scaffolds that exhibit superior mechanical properties and biological performance, making them ideal candidates for bone regeneration applications [25-27].

**Bioactive Coatings:** Applying nHA coatings on metallic implants, such as titanium alloys, can significantly improve their osteointegration. These coatings facilitate bone apposition and minimize the risk of implant failure due to loosening or infection [28-30].

**Surface Modification:** By coating metallic implants with nHA, the surface properties are enhanced, promoting better cell adhesion and bone growth around the implant [29].

**Long-term Stability:** HA coatings can improve the long-term stability of implants in the biological environment, reducing the incidence of implant-related complications [30].

## Applications and Implications of Nanotechnology in Bone Tissue Engineering

The integration of nanotechnology in bone tissue engineering has led to numerous applications that significantly impact clinical practice. These advancements not only improve the efficacy of bone regeneration strategies but also pave the way for more personalized and effective treatment options.

### Scaffold Development

The creation of multifunctional scaffolds that not only provide structural support but also release bioactive molecules, thus promoting angiogenesis and osteogenesis, is one of the most critical applications of nanotechnology in bone regeneration. **Angiogenesis Promotion:** Scaffolds incorporating growth factors or nanoparticles can stimulate the formation of new blood vessels, crucial for the successful integration of bone grafts and scaffolds [31,32].

- **Cellular Interaction:** The nanoscale features of scaffolds enhance the interaction between cells and the scaffold, leading to improved cellular responses and tissue regeneration [33].

### Bone Regeneration in Critical Defects

For large bone defects or non-union fractures, nanostructured materials can provide a conducive environment for bone regeneration, potentially reducing healing time and improving outcomes [34].

**Critical Size Defects:** Nanotechnology enables the design of scaffolds that can effectively fill critical-sized bone defects, offering mechanical support while promoting new bone formation [35].

**Non-union Fractures:** By utilizing nanostructured materials, the healing of non-union fractures can be facilitated, addressing a common challenge in orthopedic practice [36,37].

### Personalized Medicine

Advancements in nanotechnology allow for the customization of scaffolds and implants based on patient-specific needs, enhancing the effectiveness of regenerative treatments [38].

**Patient-specific Scaffolds:** Utilizing 3D printing and bioprinting techniques, personalized scaffolds can be developed that match the anatomical and mechanical requirements of individual patients [38,39].

**Tailored Drug Delivery Systems:** Personalized nanocarriers can be designed to release specific growth factors or drugs based on the patient's unique healing profile [39-41].

The future of nanotechnology in bone tissue regeneration is

bright, with ongoing research focused on several key areas that promise to advance the field further. The development of smart nanomaterials that can respond to physiological stimuli (e.g., pH, temperature) to release therapeutic agents in a controlled manner holds significant promise for optimizing healing processes.

**Stimuli-responsive Systems:** By engineering nanocarriers that can respond to changes in the local environment, researchers can achieve targeted and controlled release of bioactive agents, enhancing the efficacy of bone regeneration therapies [10,41-43].

**Real-time Monitoring:** Smart materials may also allow for real-time monitoring of the healing process, providing valuable feedback on the efficacy of the treatment [44,45].

The use of advanced manufacturing techniques, such as 3D printing and bioprinting, to create personalized scaffolds with complex architectures that mimic the native bone structure is a rapidly evolving area in bone tissue engineering [38,39,46].

**Complex Geometries:** 3D printing technologies enable the fabrication of scaffolds with intricate designs that can enhance mechanical stability and biological performance [47].

**Scaffold Customization:** Bioprinting allows for the inclusion of living cells within the scaffold, creating a more biologically relevant environment that promotes effective tissue regeneration [48,49].

## Regulatory and Safety Considerations

As nanomaterials advance toward clinical application, it is crucial to establish safety regulations and guidelines to ensure their biocompatibility and minimize potential risks associated with their use [3,50,51].

**Standardization of Testing:** There is a need for standardized protocols to assess the safety and efficacy of nanomaterials in bone regeneration applications [52].

**Long-term Biocompatibility:** Ensuring the long-term safety and biocompatibility of nanostructured materials is essential to prevent adverse effects in patients [53].

## Conclusion

Nanotechnology holds transformative potential for the field of bone tissue regeneration. By leveraging novel nanostructures, particularly hydroxyapatite, researchers are developing advanced materials that significantly enhance the biological performance and effectiveness of bone regeneration strategies. The integration of nanotechnology into scaffold design, drug delivery systems, and surface modifications has led to significant advancements in the field, paving the way for innovative solutions to complex clinical challenges. Continued innovation and interdisciplinary collaboration in this field are essential to overcome current challenges and pave the way for successful clinical applications, ultimately improving patient outcomes in orthopedic and dental medicine. The future landscape of bone tissue engineering promises to be dynamic and impactful, driven by the continued exploration of nanotechnology's vast potential.

## Acknowledgments

The authors acknowledge the financial support of Universidad Nacional del Sur (UNS, PGI 24/Q131], Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, PIP 11220210100126CO]. and Agencia Nacional de Promoción Científica y Tecnológica [ANPCyT, PICT-2021-I-A-00108]. PSR has a fellowship of UNS and P.V.M. is a Principal researcher of CONICET.

## Conflict of Interest

No Conflict of interest.

## References

- Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS (2015) Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. *BioMed research international*: 421746
- Shaban A, Telegdi J, Vastag G (2022) Chapter 5 - Self-assembling of nanobionics: from theory to applications. In *Fundamentals of Bionanomaterials*, ed. A Barhoum, J Jeevanandam, MK Danquah: 111-38: Elsevier. Number of 111-38 pp.
- Messina P, Luciano B, Placente D (2020) *Tomorrow's Healthcare by Nano-sized Approaches: A Bold Future for Medicine*. CRC Press
- Bozorgi A, Khazaei M, Soleimani M, Jamalpoor Z (2021) Application of nanoparticles in bone tissue engineering; a review on the molecular mechanisms driving osteogenesis. *Biomaterials science* 9: 4541-67
- Rial R, Liu Z, Messina P, Ruso JM (2022) Role of nanostructured materials in hard tissue engineering. *Advances in Colloid and Interface Science* 304: 102682
- Messina PV, Pistonessi BD, Belén F (2023) Nanophase ceramic particles in bone regenerative therapeutics: Theranostic platforms for bone disorders. In *Inorganic Nanosystems*: 437-71: Elsevier. Number of 437-71 pp.
- D'Elía NL, Mathieu C, Hoemann CD, Laiuppa JA, Santillán GE, Messina PV (2015) Bone-repair properties of biodegradable hydroxyapatite nano-rod superstructures. *Nanoscale* 7: 18751-62
- Benedini LA, Moglie Y, Ruso JM, Nardi S, Messina PV (2021) Hydroxyapatite nanoparticle mesogens: morphogenesis of pH-sensitive macromolecular liquid crystals. *Crystal Growth & Design* 21: 2154-66
- Gravina N, Maghni K, Welman M, Mbeh DA, Messina PV (2016) Protective role against hydrogen peroxide and fibroblast stimulation via Ce-doped TiO<sub>2</sub> nanostructured materials. *Biochimica et Biophysica Acta (BBA)-General Subjects* 1860: 452-64
- Zhang J, Zhuang Y, Sheng R, Tomás H, Rodrigues J, et al. (2024) Smart stimuli-responsive strategies for titanium implant functionalization in bone regeneration and therapeutics. *Materials Horizons* 11: 12-36
- de Souza W, Gemini-Piperni S, Grenho L, Rocha LA, Granjeiro JM, et al. (2023) Titanium dioxide nanoparticles affect osteoblast-derived exosome cargos and impair osteogenic differentiation of human mesenchymal stem cells. *Biomaterials Science* 11: 2427-44
- Seo N, Park C, Stahl AM, Cho H, Park S-W, et al. (2021) Effect of zinc oxide nanoparticle addition to polycaprolactone periodontal membranes on antibacterial activity and cell viability. *Journal of Nanoscience and Nanotechnology* 21: 3683-8
- Pistonessi DB, Belén F, Centurion ME, Sica MG, Ruso JM, Messina PV (2023) {111}-Faceted Silver Nanoplates: An Automated and Customized Design for Functionality. *ChemNanoMat* 9: e202300354
- Damle A, Sundaresan R, Rajwade JM, Srivastava P, Naik A (2022) A concise review on implications of silver nanoparticles in bone tissue engineering. *Biomaterials Advances* 141: 213099
- Zhao T, Zhang J, Gao X, Yuan D, Gu Z, Xu Y (2022) Electrospun nanofibers for bone regeneration: from biomimetic composition, structure to function. *Journal of Materials Chemistry B* 10: 6078-106
- Nirwan VP, Kowalczyk T, Bar J, Buzgo M, Filová E, Fahmi A (2022) Advances in electrospun hybrid nanofibers for biomedical applications. *Nanomaterials* 12: 1829
- Benedini LA, Rauschemberger MB, Genovese D, Messina PV (2024) Bio-inspired liquid crystal gel induction via nano-hydroxyapatite mesogens: Viscoelastic and hemostasis regulation under bone remodeling pH and temperature control. *Materials Today Communications* 38: 107989
- Sartuqui J, Gravina AN, Rial R, Benedini LA, Ruso JM, Messina PV (2016) Biomimetic fiber mesh scaffolds based on gelatin and hydroxyapatite nano-rods: Designing intrinsic skills to attain bone repair abilities. *Colloids and Surfaces B: Biointerfaces* 145: 382-91
- Sartuqui J, D'Elía NL, Ercoli D, de Alcazar DS, Cortajarena AL, Messina PV (2019) Mechanical performance of gelatin fiber mesh scaffolds reinforced with nano-hydroxyapatite under bone damage mechanisms. *Materials Today Communications* 19: 140-7
- Wang H, Leeuwenburgh SC, Li Y, Jansen JA (2012) The use of micro-and nanospheres as functional components for bone tissue regeneration. *Tissue Engineering Part B: Reviews* 18: 24-39
- Xia Yj, Wang W, Xia H, Huang Xh, Deng Fp, et al. (2020) Preparation of Coralline Hydroxyapatite Implant with Recombinant Human Bone Morphogenetic Protein-2-Loaded Chitosan Nanospheres and Its Osteogenic Efficacy. *Orthopaedic Surgery* 12: 1947-53
- Sun X, Li X, Qi H, Hou X, Zhao J, et al. (2020) MiR-21 nanocapsules promote early bone repair of osteoporotic fractures by stimulating the osteogenic differentiation of bone marrow mesenchymal stem cells. *Journal of orthopaedic translation* 24: 76-87
- Qi H, Yang L, Li X, Sun X, Zhao J, et al. (2019) Systemic administration of enzyme-responsive growth factor nanocapsules for promoting bone repair. *Biomaterials science* 7: 1675-85
- Khung Y-L, Bastari K, Cho XL, Yee WA, Loo SCJ (2012) Designing calcium phosphate-based bifunctional nanocapsules with bone-targeting properties. *Journal of Nanoparticle Research* 14: 911
- Placente D, Ruso JM, Baldini M, Laiuppa JA, Sieben JM, et al. (2019) Self-fluorescent antibiotic MoO<sub>x</sub>-hydroxyapatite: A nano-theranostic platform for bone infection therapies. *Nanoscale* 11: 17277-92



26. Sieben JM, Placente D, Baldini MD, Ruso JM, Laiuppa JA, et al. (2023) Killing Bacteria by Faradaic Processes through Nano-Hydroxyapatite/MoO<sub>x</sub> Platforms. *ACS Applied Materials & Interfaces* 15: 25884-97
27. Adamski R, Siuta D (2021) Mechanical, structural, and biological properties of chitosan/hydroxyapatite/silica composites for bone tissue engineering. *Molecules* 26: 1976
28. Arcos D, Vallet-Regí M (2020) Substituted hydroxyapatite coatings of bone implants. *Journal of Materials Chemistry B* 8: 1781-800
29. Izquierdo-Barba I, Santos-Ruiz L, Becerra J, Feito M, Fernández-Villa D, et al. (2019) Synergistic effect of Si-hydroxyapatite coating and VEGF adsorption on Ti6Al4V-ELI scaffolds for bone regeneration in an osteoporotic bone environment. *Acta Biomaterialia* 83: 456-66
30. Khelifi K, Dhiflaoui H, Ben Rhouma A, Faure J, Benhayoune H, Ben Cheikh Laarbi A (2021) Nanomechanical behavior, adhesion and corrosion resistance of hydroxyapatite coatings for orthopedic implant applications. *Coatings* 11: 477
31. Song Y, Wu H, Gao Y, Li J, Lin K, et al. (2020) Zinc silicate/nano-hydroxyapatite/collagen scaffolds promote angiogenesis and bone regeneration via the p38 MAPK pathway in activated monocytes. *ACS Applied Materials & Interfaces* 12: 16058-75
32. Huang J, Han Q, Cai M, Zhu J, Li L, et al. (2022) Effect of angiogenesis in bone tissue engineering. *Annals of Biomedical Engineering* 50: 898-913
33. Lemos R, Maia FR, Reis RL, Oliveira JM (2022) Engineering of Extracellular Matrix-Like Biomaterials at Nano-and Macroscale toward Fabrication of Hierarchical Scaffolds for Bone Tissue Engineering. *Advanced NanoBiomed Research* 2: 2100116
34. Poh PS, Lingner T, Kalkhof S, Märdian S, Baumbach J, et al. (2022) Enabling technologies towards personalization of scaffolds for large bone defect regeneration. *Current Opinion in Biotechnology* 74: 263-70
35. Bonithon R, Kao AP, Fernández MP, Dunlop JN, Blunn GW, et al. (2021) Multi-scale mechanical and morphological characterisation of sintered porous magnesium-based scaffolds for bone regeneration in critical-sized defects. *Acta Biomaterialia* 127: 338-52
36. Jain Y, Sinha S, Rastogi A, Srivastava PK, Kumar Y, Vivek V (2020) Healing of gap nonunion using autologous cultured osteoblasts impregnated over three-dimensional bio-degradable nanomaterial scaffold: A pilot experiment on rabbits. *Journal of Orthopaedics, Traumatology and Rehabilitation* 12: 86-91
37. Rodríguez-Merchán EC (2022) Bone healing materials in the treatment of recalcitrant nonunions and bone defects. *International Journal of Molecular Sciences* 23: 3352
38. dos Santos J, de Oliveira RS, de Oliveira TV, Velho MC, Konrad MV, et al. (2021) 3D printing and nanotechnology: a multiscale alliance in personalized medicine. *Advanced functional materials* 31: 2009691
39. Hindy OA, Goker M, Yilgor Huri P (2022) Nanoscale agents within 3D-printed constructs: intersection of nanotechnology and personalized bone tissue engineering. *Emergent Materials* 5: 195-205
40. Dayanandan AP, Cho WJ, Kang H, Bello AB, Kim BJ, et al. (2023) Emerging nano-scale delivery systems for the treatment of osteoporosis. *Biomaterials Research* 27: 68
41. Placente D, Benedini LA, Baldini M, Laiuppa JA, Santillán GE, Messina PV (2018) Multi-drug delivery system based on lipid membrane mimetic coated nano-hydroxyapatite formulations. *International Journal of Pharmaceutics* 548: 559-70
42. Wei H, Cui J, Lin K, Xie J, Wang X (2022) Recent advances in smart stimuli-responsive biomaterials for bone therapeutics and regeneration. *Bone research* 10: 17
43. Amirthalingam S, Rajendran AK, Moon YG, Hwang NS (2023) Stimuli-responsive dynamic hydrogels: design, properties and tissue engineering applications. *Materials Horizons* 10: 3325-50
44. Zheng K, Tong Y, Zhang S, He R, Xiao L, et al. (2021) Flexible bichromimetric polyacrylamide/chitosan hydrogels for smart real-time monitoring and promotion of wound healing. *Advanced Functional Materials* 31: 2102599
45. Tang N, Zhang R, Zheng Y, Wang J, Khatib M, et al. (2022) Highly efficient self-healing multifunctional dressing with antibacterial activity for sutureless wound closure and infected wound monitoring. *Advanced Materials* 34: 2106842
46. Collins MN, Ren G, Young K, Pina S, Reis RL, Oliveira JM (2021) Scaffold fabrication technologies and structure/function properties in bone tissue engineering. *Advanced functional materials* 31: 2010609
47. Herath B, Suresh S, Downing D, Cometta S, Tino R, et al. (2021) Mechanical and geometrical study of 3D printed Voronoi scaffold design for large bone defects. *Materials & Design* 212: 110224
48. Montero J, Becerro A, Pardal-Peláez B, Quispe-López N, Blanco J-F, Gómez-Polo C (2021) Main 3D manufacturing techniques for customized bone substitutes. A systematic review. *Materials* 14: 2524
49. Acar AA, Daskalakis E, Bartolo P, Weightman A, Cooper G, et al. (2024) Customized scaffolds for large bone defects using 3D-printed modular blocks from 2D-medical images. *Bio-Design and Manufacturing* 7: 74-87
50. Ghelich P, Kazemzadeh-Narbat M, Hassani Najafabadi A, Samandari M, Memić A, Tamayol A (2022) (Bio) manufactured solutions for treatment of bone defects with an emphasis on US-FDA regulatory science perspective. *Advanced nanobiomed research* 2: 2100073
51. Stanco D, Urbán P, Tirendi S, Ciardelli G, Barrero J (2020) 3D bioprinting for orthopaedic applications: Current advances, challenges and regulatory considerations. *Bioprinting* 20: e00103
52. Ebrahimi M (2020) Standardization and regulation of biomaterials. In *Handbook of Biomaterials Biocompatibility*: 251-65: Elsevier. Number of 251-65 pp.
53. Beheshtizadeh N, Gharibshahian M, Pazhouhnia Z, Rostami M, Zangi AR, et al. (2022) Commercialization and regulation of regenerative medicine products: Promises, advances and challenges. *Biomedicine & Pharmacotherapy* 153: 113431