Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.60.009448

The Application and Prospects of Cell Therapy in ONFH

Junming Zhang[1], Dawei Zhang[2], Lijun Sun[3], Jiang Peng[3]*

[1]*Postgraduate Training Base, Jinzhou Medical University (960 Hospital of the Chinese PLA), China*

[2]*Department of Orthopedics, 960 Hospital of PLA, China*

[3]*Institute of Orthopedics, Chinese PLA General Hospital, China*

***Corresponding author:** Jiang Peng, Institute of Orthopedics, The Fourth Medical Center, Chinese PLA General Hospital, Beijing, China

ARTICLE INFO

Received: December 18, 2024

Published: January 30, 2025

Citation: Junming Zhang, Dawei Zhang, Lijun Sun, Jiang Peng. The Application and Prospects of Cell Therapy in ONFH. Biomed J Sci & Tech Res 60(3)-2025. BJSTR. MS.ID.009448.

ABSTRACT

Osteonecrosis of the femoral head is a serious condition that severely affects joint function and causes pain. Traditional treatment methods, such as medication and surgical interventions, often have limited effectiveness. Therefore, exploring new treatment options is crucial. In recent years, cell-based therapies have emerged as an innovative treatment approach, attracting significant attention from researchers and clinicians. This paper aims to review the current status of cell therapy in the treatment of osteonecrosis of the femoral head, focusing on the effects and mechanisms of different cell types, evaluating the progress of related clinical studies, and exploring future directions for development. By conducting a comprehensive analysis of existing literature, this review seeks to provide valuable insights for clinical practice, while also highlighting the potential challenges and advantages of cell therapy in real-world applications.

Keywords: Cell Therapy; Osteonecrosis of the Femoral Head; Stem Cells; Clinical Research; Treatment Effect

Abbreviations: ONFH: Osteonecrosis of the Femoral Head; BMSCs: Bone Marrow Mesenchymal Stem Cells; ADSCs: Adipose-Derived Stem Cells; ESCs: Embryonic Stem Cells; EPCs: Endothelial Progenitor Cells; PLA: Polylactic Acid; HA: Hydroxyapatite; IPSCs: Induced Pluripotent Stem Cells; RA: Retinoic Acid; NAC: N-Acetylcysteine; MSC: Mesenchymal Stem Cells; PDGF: Platelet-Derived Growth Factor

Introduction

Osteonecrosis of the femoral head (ONFH) is a pathological condition characterized by the death of bone tissue due to insufficient blood supply, which typically leads to the degradation of the femoral head's structure and function. The disease mechanism is complex, and it commonly affects individuals between the ages of 30 and 50, with particularly high incidence rates among military personnel and other high-risk populations [1]. Epidemiological studies estimate that there are approximately 8.12 million cases of ONFH in China, and various risk factors, such as age, race, and occupation, significantly influence its occurrence in specific populations [2]. While traditional treatments, such as medication and surgical interventions, can alleviate symptoms, they often fail to reverse the underlying damage and come with a risk of complications [3]. Therefore, finding more effective treatment strategies has become a critical task in the field of orthopaedics. In recent years, cell therapy has emerged as a promising treatment modality, demonstrating significant potential in bone tissue repair. Cell therapy not only promotes the regeneration of damaged tissues but also helps to improve the bone healing process by modulating the microenvironment [4]. The application of cell therapy in ONFH has gained increasing attention, particularly the use of stem cell technology to improve the healing of bone defects, which has become a new focus of research.

Introduction to Cell Therapy

Basic Concepts of Cell Therapy

Definition and Classification of Cell Therapy: Cell therapy refers to the medical technique of introducing living cells into a patient's body to treat or prevent diseases. Depending on the source of the cells, cell therapy can be classified into autologous and allogeneic cell therapies. Autologous cell therapy involves using the patient's own cells for treatment, which carries a lower risk of immune rejection. On the other hand, allogeneic cell therapy uses cells from a donor, potentially offering higher efficacy but also increasing the risk of immune

rejection [5]. In the field of orthopedics, stem cell therapy has gained significant attention due to the ability of stem cells to self-renew and differentiate into various cell types, which can aid in the healing of bone tissue after injury [6].

The Role of Cell Therapy in Bone Tissue Repair: The role of cell therapy in bone tissue repair is primarily reflected in the following aspects: First, stem cells can differentiate into osteoblasts, directly participating in the formation and reconstruction of bone tissue. Second, stem cells secrete growth factors and cytokines, regulating the local microenvironment, promoting angiogenesis, and facilitating tissue repair [7]. In addition, cell therapy can also reduce inflammation and accelerate the bone healing process through its immunomodulatory effects [8]. A study by Oliveira CS et al. showed that the use of bone marrow-derived stem cells or adipose-derived stem cells for treatment can significantly improve the healing of bone defects, achieving favorable results in clinical applications [9]. In summary, cell therapy provides new approaches and methods for the clinical treatment of ONFH, offering more effective treatment options to improve patients' quality of life.

Cell Types and their Application in ONFH

ONFH is a complex pathological process involving the interaction and functional changes of various cell types. Recent studies have shown that stem cells play a crucial role in the occurrence and treatment of ONFH. Different types of stem cells, such as bone marrow mesenchymal stem cells (BMSCs), adipose-derived stem cells (ADSCs), as well as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), each have distinct potential applications in the repair and regeneration of ONFH.

Bone Marrow Mesenchymal Stem Cells, BMSCs: BMSCs are a type of adult stem cell with multipotent differentiation potential, capable of differentiating into osteoblasts, adipocytes, chondrocytes, and other cell types. In animal experiments, BMSCs have shown promising application prospects as an important component of bone tissue engineering. For example, Xu H et al. combined 3D-printed polyester (PCL) scaffolds with BMSCs to create a composite scaffold for the treatment of cranial defects in mice. The experimental results demonstrated that the PCL scaffold seeded with BMSCs significantly promoted bone regeneration and neovascularization, highlighting the effectiveness of BMSCs in bone defect repair [10]. In addition, another study involving rabbits showed that co-cultured endothelial progenitor cells (EPCs) and BMSCs grew well on a bio-scaffold, promoting the formation of blood vessels and bone, and accelerating the repair of bone defects [11]. The results of these animal experiments indicate that BMSCs not only promote bone tissue regeneration but also enhance the repair effect through synergistic interactions with other cell types. In clinical research, the application of BMSCs in bone tissue engineering has attracted widespread attention, primarily because they not only promote bone tissue regeneration but also possess strong immunomodulatory functions, which can reduce the risk of rejection following transplantation [12].

A study by Haleem A et al. demonstrated that BMSCs play a crucial role in bone defect repair. They not only directly participate in bone formation but also promote the proliferation and differentiation of surrounding cells by secreting growth factors and cytokines, thereby accelerating the bone healing process. Furthermore, BMSCs are relatively abundant and easy to obtain, making them an ideal source of cells for regenerative medicine [13]. Studies have shown that BMSCs play an important role in the treatment of ONFH by promoting bone regeneration and angiogenesis, thus improving the healing of the necrotic area. In a study by Zhao J et al., BMSCs were used to treat steroid-induced ONFH. The results showed that BMSCs significantly increased bone density and promoted the regeneration of bone tissue [14]. Research has shown that combining BMSCs with biomaterials can effectively improve the healing of bone defects. Clinical trial results indicate that patients treated with BMSCs show significantly better bone healing outcomes compared to traditional treatment methods [15]. In addition, Teng C et al. explored a therapeutic strategy combining BMSCs with bone morphogenetic protein (BMP9). The results showed that this combination significantly enhanced bone regenerative capacity, demonstrating the potential of BMSCs in clinical bone tissue engineering applications.

In addition, Teng C et al. explored a therapeutic strategy combining BMSCs with BMP9. The results showed that this combination significantly enhanced bone regenerative capacity, demonstrating the potential of BMSCs in clinical bone tissue engineering applications [16]. Furthermore, BMSCs improve the microenvironment by secreting growth factors and cytokines, promoting the functional recovery of surrounding cells. This mechanism provides a theoretical basis for their application in the treatment of ONFH [17]. These studies provide strong evidence for the clinical application of BMSCs, driving their development in bone tissue engineering.

Adipose-Derived Stem Cells, ADSCs: ADSCs have gained widespread attention due to their excellent immunomodulatory properties, tissue regeneration capabilities, and multipotent differentiation potential. ADSCs are primarily sourced from adipose tissue, particularly subcutaneous fat in the abdomen and inner thighs. Compared to stem cells from other sources, adipose tissue is relatively easy to harvest with minimal trauma, offers a higher cell concentration, and presents fewer ethical concerns [18]. ADSCs play a crucial role in bone tissue engineering, with their mechanism of promoting osteogenesis primarily involving the regulation of multiple signaling pathways. Studies have shown that signaling pathways such as Wnt/β-catenin, BMPs and transforming growth factor-beta (TGF-β) are key players in the differentiation of ADSCs into osteoblasts. The Wnt signalling pathway, in particular, regulates the stability of intracellular β-catenin, activating the expression of osteogenesis-related genes such as Runx2 and Osterix, thereby promoting bone formation [19]. In addition, the

BMP signaling pathway regulates osteoblast proliferation and differentiation by activating Smad proteins, thereby enhancing the ability to form bone. This pathway plays a crucial role in the osteogenic potential of ADSCs, further supporting their application in bone tissue engineering [20]. The TGF-β signaling pathway also plays a crucial role in regulating the interaction between osteoblasts and osteoclasts.

The interactions between these signaling pathways form a complex signaling network that ensures the proper formation and repair of bone tissue. This network is essential for maintaining the balance between bone formation and resorption, which is vital for normal bone homeostasis and effective bone tissue regeneration [21,22]. ADSCs can promote the repair and regeneration of damaged tissues through the secretion of cytokines and exosomes [23]. This demonstrates the potential of ADSCs in tissue regeneration. Their role in promoting bone regeneration has also been validated, as they enhance the differentiation and mineralization of osteoblasts, thereby improving the healing of bone defects. Through these mechanisms, ADSCs contribute to both the formation of new bone tissue and the restoration of bone structure, making them a promising tool in bone tissue engineering and repair [24]. Recent studies have shown that ADSCs can undergo osteogenic differentiation on appropriate biomaterial scaffolds, promoting bone regeneration. By combining with various biomaterials, ADSCs not only enhance the regenerative capacity at bone defect sites but also improve the speed and quality of bone healing [25]. For example, using composite scaffolds made of polylactic acid (PLA) and hydroxyapatite (HA), Steijvers E et al. found that ADSCs could effectively promote bone mineralization and the expression of osteogenesis-related genes, thereby accelerating the bone regeneration process [26]. ADSCs can not only differentiate into adipocytes but also transform into various other cell types, such as osteoblasts and chondrocytes. This multipotency gives ADSCs broad application potential in the treatment of ONFH and demonstrates promising prospects for their use in regenerative medicine.

Embryonic Stem Cells, ESCs: ESCs are a type of cell with self-renewal and multipotent differentiation abilities, and they have attracted significant attention in regenerative medicine in recent years. ESCs can differentiate into various cell types, including osteoblasts, playing a crucial role in bone tissue engineering. Due to their powerful pluripotency, ESCs can differentiate into osteocytes under appropriate conditions, providing a rich source of cells for bone tissue regeneration [27]. A study by Hao J et al. demonstrated that combining ESCs with biomaterial scaffolds not only enhances the efficiency of bone regeneration but also improves the quality of the regenerated bone. In recent years, many studies have focused on optimizing the differentiation conditions of ESCs to improve their differentiation efficiency into osteoblasts. For example, by adjusting the composition of the culture medium and adding specific growth factors, the osteogenic potential of ESCs can be significantly enhanced [28]. At the same time, with a deeper understanding of the biological properties of ESCs, researchers have increasingly recognized their potential applications in bone tissue engineering, particularly in addressing clinical issues such as bone defects and fractures. The promising prospects of ESCs in these areas highlight their potential to revolutionize the treatment of bone-related conditions [29]. Therefore, understanding the differentiation mechanisms of ESCs in the osteogenic process not only provides new insights for the regeneration of skeletal injuries but also lays the foundation for the development of novel bone repair materials. This makes ESCs potentially valuable in the treatment of ONFH [30].

Overall, ESCs have demonstrated broad application potential in the treatment of ONFH. Through mechanisms such as promoting bone regeneration, improving the microenvironment, and regulating immune responses, ESCs offer new approaches and methods for the clinical treatment of ONFH. Future research will further elucidate the specific mechanisms of these stem cells in the treatment of ONFH, providing a more solid foundation for clinical applications.

Induced Pluripotent Stem Cells, iPSCs: Compared to embryonic stem cells, induced pluripotent stem cells (iPSCs) offer several advantages. First, iPSCs have a wide range of sources and can be obtained from various somatic cells, including skin fibroblasts, blood cells, and more. This makes their acquisition relatively simple and free from ethical concerns, as they do not involve the use of embryos [31]. Additionally, iPSCs exhibit strong proliferative ability in vitro and, under appropriate conditions, can differentiate into various cell types, demonstrating properties similar to those of embryonic stem cells [32]. However, iPSCs still face challenges regarding genomic stability and differentiation potential. These issues, such as the risk of genetic mutations and incomplete differentiation, need to be addressed in future research to fully harness the therapeutic potential of iPSCs and ensure their safety and efficacy in clinical applications [33]. The application of iPSCs in bone regeneration has been validated in various animal models. For example, a study by Yu L et al. demonstrated that using retinoic acid (RA) to induce iPSCs for rapid osteogenesis resulted in the formation of osteoblasts within just 10 days. In the experiment, the researchers created a 5-mm mandibular bone defect in rats and used 3D-printed Ti6Al4V scaffolds combined with iPSC-induced osteoblasts for repair. The results showed that the rapidly induced iPSCs significantly enhanced bone regeneration and bone integration, indicating that using iPSCs for bone defect repair is a safe, effective, and reproducible method [34].

In addition, another study using a mouse model investigated the role of vascular networks generated by iPSC-derived endothelial cells in bone regeneration. The study found that these vascular networks could integrate with the host's blood vessels. Although the promoting effect on bone regeneration was limited, the findings offer new insights for future bone regeneration strategies, highlighting the potential of iPSC-derived endothelial cells in improving vascularization and supporting bone tissue repair [35]. These studies indicate that the application of iPSCs in animal models offers new potential and di-

rections for bone regeneration. In preclinical studies, the application of iPSCs has demonstrated significant potential in bone regeneration therapy. Research shows that iPSCs can effectively differentiate into osteoblasts and exhibit strong regenerative capabilities in bone defect models. For instance, Kato H et al. used iPSCs derived from peripheral blood mononuclear cells, successfully inducing osteoblasts and transplanting them into a rat bone defect model. The results revealed that the transplanted group showed significantly better bone formation compared to the control group. This highlights the promising therapeutic potential of iPSCs in bone defect repair [36]. In addition, iPSCs can accelerate differentiation into the chondrogenic lineage through three-dimensional (3D) rotating culture systems, thereby promoting bone regeneration [37]. The progress of these preclinical studies not only validates the application potential of iPSCs in bone regeneration but also lays a solid foundation for their future clinical translation. The combination of iPSCs with biomaterials has shown promising prospects in bone regeneration research. By combining iPSCs with various biomaterials, more ideal scaffolds can be created to promote bone tissue regeneration. For example, researchers have developed a biomimetic nanofiber scaffold loaded with N-acetylcysteine (NAC).

This scaffold not only improves mechanical properties but also effectively promotes osteogenic differentiation of iPSC-derived mesenchymal stem cells. Such advancements highlight the potential of biomaterial-enhanced iPSC therapies for more effective bone repair and regeneration [35]. In addition, electrospun synthetic nanofiber scaffolds have also been shown to support the osteogenic differentiation of iPSCs, thereby enhancing bone regeneration [38]. These composite application studies indicate that the combination of iPSCs with biomaterials not only improves the effectiveness of bone regeneration but also provides new strategies and approaches for bone tissue engineering. Therefore, a deeper exploration of the potential applications of iPSCs in bone tissue engineering offers new insights and approaches for the clinical treatment of ONFH.

Mechanisms of Cell Therapy

The Biological Mechanisms that Promote Bone Regeneration: Bone tissue has the ability to regenerate itself, but in certain cases, such as trauma or disease, this regenerative capacity may be impaired. Cell-based therapies promote bone regeneration through various biological mechanisms. First and foremost, mesenchymal stem cells (MSCs) play a key role in bone regeneration. Studies have shown that MSCs can secrete a variety of growth factors and cytokines, which stimulate the proliferation and differentiation of surrounding cells, thereby accelerating the bone repair and regeneration process. These factors not only enhance the healing of bone defects but also contribute to the remodeling of damaged bone tissue, making MSC-based therapies a promising approach for treating bone injuries and disorders [39]. In addition, MSCs can regulate the local microenvironment by reducing inflammation and promoting angiogenesis, both of which are crucial for bone regeneration [40]. In recent years, advances in bone tissue engineering have made it possible to enhance bone regeneration through the combination of biomaterials and cells. Researchers have developed various scaffold materials that not only provide a foundation for cell attachment and growth but also promote the activity of bone cells through mechanical and biochemical signals. For example, the application of 3D printing technology has enabled more precise design of scaffolds, allowing for better simulation of the natural structure and function of bone tissue. This enhanced design improves the regeneration outcomes by providing a more favorable environment for cell growth, differentiation, and integration, ultimately promoting more effective bone healing and repair [41]. In addition, the construction of bone organoids has provided a new platform for studying the mechanisms of bone regeneration. These organoids can mimic the complex biological functions of bone tissue in vitro, offering a more realistic model to investigate the cellular and molecular processes involved in bone formation, remodeling, and repair [42].

The Role of Cytokines and Growth Factors: Cytokines and growth factors play a crucial role in bone regeneration. They directly influence the repair and regeneration of bone tissue by regulating cell proliferation, differentiation, and migration. Growth factors such as BMPs, transforming growth factor-beta (TGF-β), and platelet-derived growth factor (PDGF) are particularly effective in promoting bone formation and healing [43]. These factors promote bone homeostasis and regeneration by activating specific cellular signaling pathways, which not only stimulate the differentiation of osteoblasts (bone-forming cells) but also inhibit the activity of osteoclasts (bone-resorbing cells). This balanced regulation is crucial for effective bone repair and regeneration [39]. In addition, cytokines such as IL-6 and IL-10 also play regulatory roles in bone regeneration. They are not only involved in the inflammatory response but also influence the function of immune cells, thereby indirectly promoting bone repair [40]. By regulating cytokines and growth factors, researchers aim to optimize the microenvironment for bone regeneration, enhancing the effectiveness and safety of treatments. In clinical applications, combining cell therapy with the use of these factors could pave the way for new therapeutic strategies to address clinical challenges such as bone defects and nonunion fractures [41].

Future Directions and Challenges

Technological Advancements and Innovations

With the rapid development of the biomedical field, technological advancements and innovations are playing an increasingly important role in future medical practices. Particularly in the areas of precision medicine and cell therapy, continuous technological progress is making personalized treatment possible. For example, advances in genomics have enabled us to analyze patients' genetic information, allowing for the development of more precise treatment plans, thereby improving both the effectiveness and safety of treatments

[44]. In addition, the application of artificial intelligence and big data analytics has provided new insights into early disease diagnosis and personalized treatment. By analyzing large volumes of data, doctors can gain a better understanding of a patient's condition and optimize treatment plans accordingly [45]. However, the application of these technologies also brings new challenges, such as data privacy and security concerns, the accessibility of technology, and the training of healthcare professionals. These issues need to be addressed in future developments to ensure that these advancements can be effectively integrated into healthcare systems while safeguarding patient rights and ensuring equitable access to high-quality care [46].

Ethical Issues and Regulatory Challenges

As biotechnological and medical advancements continue to progress, ethical issues and regulatory challenges are becoming increasingly prominent. For example, in the application of cell therapy and gene editing technologies, ensuring informed consent from patients, protecting their privacy, and providing comprehensive information about potential risks have become urgent issues that need to be addressed [47]. In addition, the varying applicability of bioethical frameworks across different countries and regions presents challenges for international collaboration. To address these issues, researchers suggest establishing more comprehensive ethical review mechanisms and regulatory frameworks to ensure the safety and efficacy of new technologies while facilitating their clinical application [48]. For example, in the case of research involving human embryo models, the related ethical and legal issues must be addressed through systematic evaluation and regulation to ensure the sustainable development of scientific research [48].

Cell Therapy in Personalized and Precision Medicine

The concept of personalized and precision medicine has gained widespread attention in cell therapy. By analyzing multi-omics data, including the genome, metabolome, and microbiome of patients, personalized treatment plans can be developed for each individual. This approach allows for more targeted therapies, improving treatment efficacy by considering the unique biological makeup of each patient, thereby enhancing the precision and effectiveness of medical interventions [44]. For example, in cancer treatment, personalized immunotherapy targeting tumor-specific antigens has gradually become a research focus. This approach tailors the treatment strategy to each patient's specific condition, selecting the most appropriate therapy based on the individual characteristics of the tumor. By doing so, it aims to improve survival rates and quality of life for patients, offering a more precise and effective treatment option [49]. However, the implementation of personalized treatment still faces many challenges, including high costs, the technical expertise required from clinicians, and the standardization of treatment plans. In the future, as technology advances and costs decrease, personalized and precision medicine is expected to be applied in a broader range of fields, making it more accessible and effective for a larger number of patients [50].

Discussion

In recent years, cell therapy has emerged as an innovative treatment approach, gradually revealing its potential advantages in the management of ONFH. Through a comprehensive analysis of various studies, it has been found that cell therapy not only helps improve clinical symptoms and restore joint function but also promotes the regeneration and repair of bone tissue to some extent. These benefits make cell therapy an important complement to traditional treatment methods. However, despite the promising potential of cell therapy in the treatment of ONFH, existing research results show a certain degree of variability. These discrepancies primarily stem from factors such as treatment methods, cell sources, patient individual differences, and follow-up durations. To address this, future research needs to focus on standardization to better compare the effectiveness of different treatment approaches. Additionally, conducting larger-scale clinical trials will help validate the long-term effects of cell therapy in ONFH and provide strong evidence to support its integration into routine clinical practice. Future research should also focus on exploring the mechanisms of cell therapy to uncover the biological foundations of its effects, thereby providing a theoretical basis for optimizing treatment strategies. Additionally, establishing multidisciplinary collaborative platforms to promote the integration of basic research with clinical applications will create favorable conditions for the rapid development of cell therapy. Overall, the application of cell therapy in ONFH is still evolving. Although current research offers hope, further exploration and validation are needed. With continued efforts, we are hopeful that more effective and safer treatment options will be available for patients with ONFH in the future.

References

1. Gun BK, Rachel MF, Ryan WG, Julia OB, Nicholas K, et al. (2020) Non-modifiable Risk Factors Associated with Avascular Necrosis in the US Military. Mil Med 185(1-2): e178-e182.
2. Zhao DW, Yu M, Hu K, Wei W, Lei Y, et al. (2015) Prevalence of Nontraumatic Osteonecrosis of the Femoral Head and its Associated Risk Factors in the Chinese Population: Results from a Nationally Representative Survey. Chin Med J (Engl) 128(21): 2843-2850.
3. Pavelka T, M Salasek, P Barta, F Fridrich, V Dzupa, et al. (2019) Avascular Necrosis of Femoral Head and Coxarthrosis Progression after Acetabular Fractures. Acta Chir Orthop Traumatol Cech 86(6): 381-389.
4. Chinnadurai S, Balaji C, Bhuvanesh M, Vignesh M, Balameena S, et al. (2020) Clinical profile of osteonecrosis in systemic lupus erythematosus - Experience from a tertiary care centre in South India. J Family Med Prim Care 9(8): 4363-4367.
5. Itami J, Kenya K, Taisuke M, Yoshitaka H, Yuko K, et al. (2022) Non-Robustness of Ang's Risk Classification in Human Papillomavirus-Related Oropharyngeal Squamous Cell Carcinoma in Japanese Patients. Cancers (Basel) 14(10): 2442.
6. Ohori Morita Y, Kunimichi N, Phoonsuk L, Praphawi N, Xichao M, et al. (2022) Novel Mesenchymal Stem Cell Spheroids with Enhanced Stem Cell Characteristics and Bone Regeneration Ability. Stem Cells Transl Med 11(4): 434-449.

7. Nasir NJN, Norsyahida A, Khairul BAAN, Norhayati Y (2023) Bone repair and key signalling pathways for cell-based bone regenerative therapy: A review. J Taibah Univ Med Sci 18(6): 1350-1363.
8. Labusca L (2022) Adipose tissue in bone regeneration - stem cell source and beyond. World J Stem Cells 14(6): 372-392.
9. Oliveira CS, Mariana C, Clara RC, Mano JF (2022) The Therapeutic Potential of Hematopoietic Stem Cells in Bone Regeneration. Tissue Eng Part B Rev 28(2): 379-392.
10. Xu H, Chengqiang W, Chun L, Jianjun L, Ziyue P, et al. (2022) Stem Cell-Seeded 3D-Printed Scaffolds Combined with Self-Assembling Peptides for Bone Defect Repair. Tissue Eng Part A 28(3-4): 111-124.
11. Zhao X, Han XS, Zhou QZ, liu BY, Bin Y, et al. (2020) Repair of Bone Defects with Endothelial Progenitor Cells and Bone Marrow-Derived Mesenchymal Stem Cells with Tissue-Engineered Bone in Rabbits. Ann Plast Surg 85(4): 430-436.
12. Boiko AA, VA Malanchuk, MS Myroshnychenko (2024) Reparative osteogenesis in mandible in cases of filling a bone defect with hydroxyapatite-containing osteotropic material and injecting the surrounding soft tissues with thymalin: experimental and morphological study. Wiad Lek 77(1): 68-76.
13. Haleem A, Mohd Javaid, Rizwan HK, Rajiv S (2020) 3D printing applications in bone tissue engineering. J Clin Orthop Trauma11(Suppl 1): S118-S124.
14. Zhao J, Wei H, Hongqing Z, Rui Z, Hao Y, et al. (2022) Bone Regeneration and Angiogenesis by Co-transplantation of Angiotensin II-Pretreated Mesenchymal Stem Cells and Endothelial Cells in Early Steroid-Induced Osteonecrosis of the Femoral Head. Cell Transplant 31: 9636897221086965.
15. Zhou C, Chuan Y, Chen Z, Junyi L, Yuwan L, et al. (2020) A Composite Tissue Engineered Bone Material Consisting of Bone Mesenchymal Stem Cells, Bone Morphogenetic Protein 9 (BMP9) Gene Lentiviral Vector, and P3HB4HB Thermogel (BMSCs-LV-BMP9-P3HB4HB) Repairs Calvarial Skull Defects in Rats by Expression of Osteogenic Factors. Med Sci Monit 26: e924666.
16. Teng C, Zhicheng T, Qiulin H, Huangrong Z, Lu Wang, et al. (2022) Mesenchymal Stem Cells-Hydrogel Microspheres System for Bone Regeneration in Calvarial Defects. Gels 8(5): 275.
17. Fan X, Xin X, Xinjie W, Runzhi X, Fuqiang G, et al. (2022) The protective effect of DNA aptamer on osteonecrosis of the femoral head by alleviating TNF-α-mediated necroptosis via RIP1/RIP3/MLKL pathway. J Orthop Translat 36: 44-51.
18. Alstrup T, Marco E, Mette EB, Niels HH, Bjarne KM, et al. (2020) Measured Levels of Human Adipose Tissue-Derived Stem Cells in Adipose Tissue Is Strongly Dependent on Harvesting Method and Stem Cell Isolation Technique. Plast Reconstr Surg 145(1): 142-150.
19. Zhu S, Wei C, Alasdair M, Yi Ping Li (2024) Cell signaling and transcriptional regulation of osteoblast lineage commitment, differentiation, bone formation, and homeostasis. Cell Discov 10(1): 71.
20. Zou ML, Zhong HC, Ying T, Si Yu L, Yuan J, et al. (2021) The Smad Dependent TGF-β and BMP Signaling Pathway in Bone Remodeling and Therapies. Front Mol Biosci 8: 593310.
21. Zhou CC, ZP Wu, SJ Zou (2020) The Study of Signal Pathway Regulating the Osteogenic Differentiation of Bone Marrow Mesenchymal Stem Cells. Sichuan Da Xue Xue Bao Yi Xue Ban 51(6): 777-782.
22. Li G, Yin Z, Jiezhou W, Renhao Y, Qi S, et al. (2023) Adipose stem cells-derived exosomes modified gelatin sponge promotes bone regeneration. Front Bioeng Biotechnol 11: 1096390.
23. Lin Z, Yoichiro S, Yukiko I, Junya O, Masahiro S, et al. (2023) Therapeutic Potential of Adipose-Derived Stem Cell-Conditioned Medium and Extracellular Vesicles in an *In Vitro* Radiation-Induced Skin Injury Model. Int J Mol Sci 24(24): 17214.
24. Arif F, MF Rahman, CF Khan (2023) Adipose derived stem cells for the peripheral nerve regeneration: review of techniques and clinical implications. J Pak Med Assoc 73(S1)(2): p. S148-S154.
25. Zhang W, Naiguo W, Ming Y, Tianze S, Jing Z, et al. (2022) Periosteum and development of the tissue-engineered periosteum for guided bone regeneration. J Orthop Translat 33: 41-54.
26. Steijvers E, A Ghei, Z Xia (2022) Manufacturing artificial bone allografts: a perspective. Biomater Transl 3(1): 65-80.
27. Ferreira MJS, Fabrizio EM, Paul AH, Leona O, Michael B, et al. (2022) Pluripotent stem cells for skeletal tissue engineering. Crit Rev Biotechnol 42(5): 774-793.
28. Hao J, Cao J, Lei W, Aijin M, Si C, et al. Requirements for human embryonic stem cells. Cell Prolif 53(12): e12925.
29. Liu J, Lili Y, Liu K, Feng G (2023) Hydrogel scaffolds in bone regeneration: Their promising roles in angiogenesis. Front Pharmacol 14: 1050954.
30. Junyent S, Clare LG, James LAS, Shukry JH (2020) Specialized cytonemes induce self-organization of stem cells. Proc Natl Acad Sci USA 117(13): 7236-7244.
31. Aksoy ZB, KC Akcali (2024) Generation of Induced Pluripotent Stem Cells from Erythroid Progenitor Cells. Methods Mol Biol 2835: 99-110.
32. Tetè G, B Dorto, M Nagni, M Agostinacchio, E Polizzi, et al. (2020) Role of induced pluripotent stem cells (IPSCS) in bone tissue regeneration in dentistry: a narrative review. J Biol Regul Homeost Agents 34(6 S3): 1-10.
33. Hasaart KAL, Freek M, Joske U, Mark V, Markus J van R, et al. (2022) Human induced pluripotent stem cells display a similar mutation burden as embryonic pluripotent cells *in vivo*. I Science 25(2): 103736.
34. Yu L, Yong Y, Bin Z, Bai X, Qi F, et al. (2020) Rapid human-derived iPSC osteogenesis combined with three-dimensionally printed Ti6Al4V scaffolds for the repair of bone defects. J Cell Physiol 235(12): 9763-9772.
35. Li X, Feng X, Shuguang W, Zhoujun Z, Dai J, et al. (2021) N-Acetyl-Cysteine-Loaded Biomimetic Nanofibrous Scaffold for Osteogenesis of Induced-Pluripotent-Stem-Cell-Derived Mesenchymal Stem Cells and Bone Regeneration. Front Bioeng Biotechnol 9: 767641.
36. Kato H, Katsuhito W, Akiko S, Shoko O, Azuma T, et al. (2022) Bone regeneration of induced pluripotent stem cells derived from peripheral blood cells in collagen sponge scaffolds. J Appl Oral Sci 30: e20210491.
37. Zhang M, Junfeng S, Ming X, Jin W, Kunimichi N, et al. (2020) Recapitulation of cartilage/bone formation using iPSCs via biomimetic 3D rotary culture approach for developmental engineering. Biomaterials 260: 120334.
38. Azari Matin A, Khashayar F, Sahand SM, Reza T, Seyed AH, et al. (2022) Synthetic electrospun nanofibers as a supportive matrix in osteogenic differentiation of induced pluripotent stem cells. J Biomater Sci Polym Ed 33(11): 1469-1493.
39. Jaber M, Hofbauer LC, Christine H, Georg ND, Sara C, et al. (2023) Reduced Bone Regeneration in Rats with Type 2 Diabetes Mellitus as a Result of Impaired Stromal Cell and Osteoblast Function-A Computer Modeling Study. JBMR Plus 7(11): e10809.
40. Chen S, Xiao C, Zhen G, Jiacan S (2022) The horizon of bone organoid: A perspective on construction and application. Bioact Mater 18: 15-25.
41. Perier Metz C, GN Duda, S Checa (2021) Initial mechanical conditions within an optimized bone scaffold do not ensure bone regeneration - an in-silico analysis. Biomech Model Mechanobiol 20(5): 1723-1731.

42. Wu J, Yang Z, BinBin Y, Hongxing H (2023) The Application of Organoids in the Research of Skeletal Diseases: Current Status and Prospects. Stud Health Technol Inform 308: 597-604.

43. Cui Y, Hairui L, Lixia M (2022) Novel insights into nanomaterials for immunomodulatory bone regeneration. Nanoscale Adv 4(2): 334-352.

44. Kiyotani K, Y Toyoshima, Y Nakamura (2021) Personalized immunotherapy in cancer precision medicine. Cancer Biol Med 18(4): 955-965.

45. Posa A, Barbieri P, Mazza G, Alessandro T, Luigi N, et al. (2023) Technological Advancements in Interventional Oncology. Diagnostics (Basel) 13(2): 228.

46. Wang L, F Wang, W Zhang (2021) Bioethics in China's Biosecurity Law: forms, effects, and unsettled issues. J Law Biosci 8(1): lsab019.

47. Mollaki V (2021) Ethical Challenges in Organoid Use. BioTech (Basel) 10(3): 12.

48. Iltis AS, Grace K, Emily R, Kirstin RWM (2023) Ethical, legal, regulatory, and policy issues concerning embryoids: a systematic review of the literature. Stem Cell Res Ther 14(1): 209.

49. Micheletti C, G Bonetti, G Madeo, M Gadler, S Benedetti, et al. (2023) Omics sciences and precision medicine in glioblastoma. Clin Ter 174(Suppl 2(6)): 77-84.

50. Didiasova M, A Banning, R Tikkanen (2024) Development of precision therapies for rare inborn errors of metabolism: Functional investigations in cell culture models. J Inherit Metab Dis 47(3): 509-516.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.60.009448

Jiang Peng. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php