**ML 13-20 (01/04/2020)**

Stem Cells Transl Med. 2020 Mar 26. doi: 10.1002/sctm.19-0333. [Epub ahead of print]

# The mesenchymal stromal cell secretome impairs methicillin-resistant Staphylococcus aureus biofilms via cysteine protease activity in the equine model.

Marx C[1], Gardner S[1], Harman RM[1], Van de Walle GR[1].
**Author information**

**Abstract**

Mesenchymal stromal cells (MSCs) from various species, such as humans, mice, and horses, were recently found to effectively inhibit the growth of various bacteria associated with chronic infections, such as nonhealing cutaneous wounds, via secretion of antimicrobial peptides. These MSC antimicrobial properties have primarily been studied in the context of the planktonic phenotype, and thus, information on the effects on bacteria in biofilms is largely lacking. The objectives of this study were to evaluate the in vitro efficacy of the MSC secretome against various biofilm-forming wound pathogens, including the methicillin-resistant Staphylococcus aureus (MRSA), and to explore the mechanisms that affect bacterial biofilms. To this end, we used equine MSC, because the horse represents a physiologically relevant model for human wound healing and offers a readily translatable model for MSC therapies in humans. Our salient findings were that the equine MSC secretome inhibits biofilm formation and mature biofilms of various bacteria, such as Pseudomonas aeruginosa, S. aureus, and Staphylococcus epidermidis. Furthermore, we demonstrated that equine MSC secrete cysteine proteases that destabilize MRSA biofilms, thereby increasing the efficacy of antibiotics that were previously tolerated by the biofilms. In light of the rise of antibiotic-resistant bacterial strains as an increasing global health threat, our results provide the rationale for using the MSC secretome as a complementary treatment for bacterial skin infections in both humans and horses.

Stem Cells Int. 2020 Mar 7;2020:2560174. doi: 10.1155/2020/2560174. eCollection 2020.

# Recent Advance in Source, Property, Differentiation, and Applications of Infrapatellar Fat Pad Adipose-Derived Stem Cells.

Zhong YC[1,2], Wang SC[1,2], Han YH[1], Wen Y[1].
**Author information**

**Abstract**

Infrapatellar fat pad (IPFP) can be easily obtained during knee surgery, which avoids the damage to patients for obtaining IPFP. Infrapatellar fat pad adipose-derived stem cells (IPFP-ASCs) are also called infrapatellar fat pad mesenchymal stem cells (IPFP-MSCs) because the morphology of IPFP-ASCs is similar to that of bone marrow mesenchymal stem cells (BM-MSCs). IPFP-ASCs are attracting more and more attention due to their characteristics suitable to regenerative medicine such as strong proliferation and differentiation, anti-inflammation, antiaging, secreting cytokines, multipotential

capacity, and 3D culture. IPFP-ASCs can repair articular cartilage and relieve the pain caused by osteoarthritis, so most of IPFP-related review articles focus on osteoarthritis. This article reviews the anatomy and function of IPFP, as well as the discovery, amplification, multipotential capacity, and application of IPFP-ASCs in order to explain why IPFP-ASC is a superior stem cell source in regenerative medicine.

Stem Cells Int. 2020 Mar 7;2020:1031985. doi: 10.1155/2020/1031985. eCollection 2020.

# A Chemically Defined Serum-Free Culture System for Spontaneous Human Mesenchymal Stem Cell Spheroid Formation.

Zhao Y[1], Xiao E[1], Lv W[1], Dong X[1], He L[2], Wang Y[3], Zhang Y[1].
Author information

**Abstract**

Mesenchymal stem cells (MSCs) possess promising potential in tissue engineering and regenerative medicine. Previous studies demonstrated that spheroid formation of MSCs exhibited improved stemness maintenance and therapeutic potential compared with monolayer culture. To date, various spheroid culture systems have been developed but most of them required low adhesion conditions or special equipment. In this study, we demonstrated that inoculation of dissociated MSCs in TeSR-E8 medium could induce self-assemble spheroid formation in conventional tissue culture polystyrene dishes. Compared with monolayer culture, adipose-derived stem cell (ADSC) spheroids enhanced the proliferation and osteogenic capability of ADSCs compared with monolayer culture. When reseeded in normal serum-containing medium, the expression level of stemness biomarkers was even higher in spheroid-derived ADSCs than monolayer culture. Importantly, spheroid ADSCs could effectively promote the M2 polarization of macrophages both *in vitro* and *in vivo*. After transplantation into mouse, spheroid ADSCs improved the survival rate and significantly decreased serum levels of proinflammatory factors IL-1*β* and TNF-*α* following LPS challenge. In summary, we developed a 3D spheroid culture system through TeSR-E8 medium without the involvement of low adhesion conditions and special equipment, which provided a practical and convenient method for spheroid formation of MSCs with great potential for stem cell clinical therapy.

Pain Physician. 2020 Mar;23(2):E85-E131.

# Bone Marrow Concentrate (BMC) Therapy in Musculoskeletal Disorders: Evidence-Based Policy Position Statement of American Society of Interventional Pain Physicians (ASIPP).

Manchikanti L, Centeno CJ[1], Atluri S[2], Albers SL[3], Shapiro S[4], Malanga GA[5], Abd-Elsayed A[6], Jerome M[7], Hirsch JA[8], Kaye AD[9], Aydin SM[10], Beall D[11], Buford D[12], Borg-Stein J[13], Buenaventura RM[14], Cabaret JA[15], Calodney AK[16], Candido KD[17], Cartier C[18], Latchaw R[3], Diwan S[19], Dodson E[20], Fausel Z[1], Fredericson M[21], Gharibo CG[22], Gupta M[23], Kaye AM, Knezevic NN[24], Kosanovic R[25], Lucas M[25], Manchikanti MV[26], Mason RA[27], Mautner K[28], Murala

S[25], Navani A[29], Pampati V[30], Pastoriza S[1], Pasupuleti R[31], Philip C[32], Sanapati MR[33], Sand T[34], Shah RV, Soin A[35], Stemper I[36], Wargo BW[37], Hernigou P[38].

**Author information**

## Abstract

*BACKGROUND:*

The use of bone marrow concentrate (BMC) for treatment of musculoskeletal disorders has become increasingly popular over the last several years, as technology has improved along with the need for better solutions for these pathologies. The use of cellular tissue raises a number of issues regarding the US Food and Drug Administration's (FDA) regulation in classifying these treatments as a drug versus just autologous tissue transplantation. In the case of BMC in musculoskeletal and spine care, this determination will likely hinge on whether BMC is homologous to the musculoskeletal system and spine.

*OBJECTIVES:*

The aim of this review is to describe the current regulatory guidelines set in place by the FDA, specifically the terminology around "minimal manipulation" and "homologous use" within Regulation 21 CFR Part 1271, and specifically how this applies to the use of BMC in interventional musculoskeletal medicine.

*METHODS:*

The methodology utilized here is similar to the methodology utilized in preparation of multiple guidelines employing the experience of a panel of experts from various medical specialties and subspecialties from differing regions of the world. The collaborators who developed these position statements have submitted their appropriate disclosures of conflicts of interest. Trustworthy standards were employed in the creation of these position statements. The literature pertaining to BMC, its effectiveness, adverse consequences, FDA regulations, criteria for meeting the standards of minimal manipulation, and homologous use were comprehensively reviewed using a best evidence synthesis of the available and relevant literature.RESULTS/Summary of Evidence: In conjunction with evidence-based medicine principles, the following position statements were developed: Statement 1: Based on a review of the literature in discussing the preparation of BMC using accepted methodologies, there is strong evidence of minimal manipulation in its preparation, and moderate evidence for homologous utility for various musculoskeletal and spinal conditions qualifies for the same surgical exemption. Statement 2: Assessment of clinical effectiveness based on extensive literature shows emerging evidence for multiple musculoskeletal and spinal conditions.• The evidence is highest for knee osteoarthritis with level II evidence based on relevant systematic reviews, randomized controlled trials and nonrandomized studies. There is level III evidence for knee cartilage conditions. • Based on the relevant systematic reviews, randomized trials, and nonrandomized studies, the evidence for disc injections is level III.• Based on the available literature without appropriate systematic reviews or randomized controlled trials, the evidence for all other conditions is level IV or limited for BMC injections. Statement 3: Based on an extensive review of the literature, there is strong evidence for the safety of BMC when

performed by trained physicians with the appropriate precautions under image guidance utilizing a sterile technique.Statement 4: Musculoskeletal disorders and spinal disorders with related disability for economic and human toll, despite advancements with a wide array of treatment modalities.Statement 5: The 21st Century Cures Act was enacted in December 2016 with provisions to accelerate the development and translation of promising new therapies into clinical evaluation and use. Statement 6: Development of cell-based therapies is rapidly proliferating in a number of disease areas, including musculoskeletal disorders and spine. With mixed results, these therapies are greatly outpacing the evidence. The reckless publicity with unsubstantiated claims of beneficial outcomes having putative potential, and has led the FDA Federal Trade Commission (FTC) to issue multiple warnings. Thus the US FDA is considering the appropriateness of using various therapies, including BMC, for homologous use.Statement 7: Since the 1980's and the description of mesenchymal stem cells by Caplan et al, (now called medicinal signaling cells), the use of BMC in musculoskeletal and spinal disorders has been increasing in the management of pain and promoting tissue healing. Statement 8: The Public Health Service Act (PHSA) of the FDA requires minimal manipulation under same surgical procedure exemption. Homologous use of BMC in musculoskeletal and spinal disorders is provided by preclinical and clinical evidence. Statement 9: If the FDA does not accept BMC as homologous, then it will require an Investigational New Drug (IND) classification with FDA (351) cellular drug approval for use. Statement 10: This literature review and these position statements establish compliance with the FDA's intent and corroborates its present description of BMC as homologous with same surgical exemption, and exempt from IND, for use of BMC for treatment of musculoskeletal tissues, such as cartilage, bones, ligaments, muscles, tendons, and spinal discs.

*CONCLUSIONS:*

Based on the review of all available and pertinent literature, multiple position statements have been developed showing that BMC in musculoskeletal disorders meets the criteria of minimal manipulation and homologous use.

Pain Physician. 2020 Mar;23(2):E85-E131.

# Bone Marrow Concentrate (BMC) Therapy in Musculoskeletal Disorders: Evidence-Based Policy Position Statement of American Society of Interventional Pain Physicians (ASIPP).

Manchikanti L, Centeno CJ[1], Atluri S[2], Albers SL[3], Shapiro S[4], Malanga GA[5], Abd-Elsayed A[6], Jerome M[7], Hirsch JA[8], Kaye AD[9], Aydin SM[10], Beall D[11], Buford D[12], Borg-Stein J[13], Buenaventura RM[14], Cabaret JA[15], Calodney AK[16], Candido KD[17], Cartier C[18], Latchaw R[3], Diwan S[19], Dodson E[20], Fausel Z[1], Fredericson M[21], Gharibo CG[22], Gupta M[23], Kaye AM, Knezevic NN[24], Kosanovic R[25], Lucas M[25], Manchikanti MV[26], Mason RA[27], Mautner K[28], Murala S[25], Navani A[29], Pampati V[30], Pastoriza S[1], Pasupuleti R[31], Philip C[32], Sanapati MR[33], Sand T[34], Shah RV, Soin A[35], Stemper I[36], Wargo BW[37], Hernigou P[38].

**Author information**

**Abstract**

*BACKGROUND:*

The use of bone marrow concentrate (BMC) for treatment of musculoskeletal disorders has become increasingly popular over the last several years, as technology has improved along with the need for better solutions for these pathologies. The use of cellular tissue raises a number of issues regarding the US Food and Drug Administration's (FDA) regulation in classifying these treatments as a drug versus just autologous tissue transplantation. In the case of BMC in musculoskeletal and spine care, this determination will likely hinge on whether BMC is homologous to the musculoskeletal system and spine.

*OBJECTIVES:*

The aim of this review is to describe the current regulatory guidelines set in place by the FDA, specifically the terminology around "minimal manipulation" and "homologous use" within Regulation 21 CFR Part 1271, and specifically how this applies to the use of BMC in interventional musculoskeletal medicine.

*METHODS:*

The methodology utilized here is similar to the methodology utilized in preparation of multiple guidelines employing the experience of a panel of experts from various medical specialties and subspecialties from differing regions of the world. The collaborators who developed these position statements have submitted their appropriate disclosures of conflicts of interest. Trustworthy standards were employed in the creation of these position statements. The literature pertaining to BMC, its effectiveness, adverse consequences, FDA regulations, criteria for meeting the standards of minimal manipulation, and homologous use were comprehensively reviewed using a best evidence synthesis of the available and relevant literature.RESULTS/Summary of Evidence: In conjunction with evidence-based medicine principles, the following position statements were developed: Statement 1: Based on a review of the literature in discussing the preparation of BMC using accepted methodologies, there is strong evidence of minimal manipulation in its preparation, and moderate evidence for homologous utility for various musculoskeletal and spinal conditions qualifies for the same surgical exemption. Statement 2: Assessment of clinical effectiveness based on extensive literature shows emerging evidence for multiple musculoskeletal and spinal conditions.• The evidence is highest for knee osteoarthritis with level II evidence based on relevant systematic reviews, randomized controlled trials and nonrandomized studies. There is level III evidence for knee cartilage conditions. • Based on the relevant systematic reviews, randomized trials, and nonrandomized studies, the evidence for disc injections is level III.• Based on the available literature without appropriate systematic reviews or randomized controlled trials, the evidence for all other conditions is level IV or limited for BMC injections. Statement 3: Based on an extensive review of the literature, there is strong evidence for the safety of BMC when performed by trained physicians with the appropriate precautions under image guidance utilizing a sterile technique.Statement 4: Musculoskeletal disorders and spinal disorders with related disability for economic and human toll, despite advancements with a wide array of treatment modalities.Statement 5: The 21st Century Cures Act was enacted in December 2016 with provisions to accelerate the

development and translation of promising new therapies into clinical evaluation and use. Statement 6: Development of cell-based therapies is rapidly proliferating in a number of disease areas, including musculoskeletal disorders and spine. With mixed results, these therapies are greatly outpacing the evidence. The reckless publicity with unsubstantiated claims of beneficial outcomes having putative potential, and has led the FDA Federal Trade Commission (FTC) to issue multiple warnings. Thus the US FDA is considering the appropriateness of using various therapies, including BMC, for homologous use.Statement 7: Since the 1980's and the description of mesenchymal stem cells by Caplan et al, (now called medicinal signaling cells), the use of BMC in musculoskeletal and spinal disorders has been increasing in the management of pain and promoting tissue healing. Statement 8: The Public Health Service Act (PHSA) of the FDA requires minimal manipulation under same surgical procedure exemption. Homologous use of BMC in musculoskeletal and spinal disorders is provided by preclinical and clinical evidence. Statement 9: If the FDA does not accept BMC as homologous, then it will require an Investigational New Drug (IND) classification with FDA (351) cellular drug approval for use. Statement 10: This literature review and these position statements establish compliance with the FDA's intent and corroborates its present description of BMC as homologous with same surgical exemption, and exempt from IND, for use of BMC for treatment of musculoskeletal tissues, such as cartilage, bones, ligaments, muscles, tendons, and spinal discs.

*CONCLUSIONS:*

Based on the review of all available and pertinent literature, multiple position statements have been developed showing that BMC in musculoskeletal disorders meets the criteria of minimal manipulation and homologous use.

Stem Cell Res Ther. 2020 Mar 25;11(1):134. doi: 10.1186/s13287-020-01630-w.

# A model study for the manufacture and validation of clinical-grade deciduous dental pulp stem cells for chronic liver fibrosis treatment.

Iwanaka T[1], Yamaza T[2], Sonoda S[3], Yoshimaru K[1], Matsuura T[1], Yamaza H[4], Ohga S[5], Oda Y[6], Taguchi T[1].

**Author information**

## Abstract

*BACKGROUND:*

Human deciduous pulp stem cells (hDPSCs) have remarkable stem cell potency associated with cell proliferation, mesenchymal multipotency, and immunosuppressive function and have shown beneficial effects in a variety of animal disease models. Recent studies demonstrated that hDPSCs exhibited in vivo anti-fibrotic and anti-inflammatory action and in vivo hepatogenic-associated liver regeneration, suggesting that hDPSCs may offer a promising source with great clinical demand for treating liver diseases. However, how to manufacture ex vivo large-scale clinical-grade hDPSCs with the appropriate quality, safety, and preclinical efficacy assurances remains unclear.

*METHODS:*

We isolated hDPSCs from human deciduous dental pulp tissues formed by the colony-forming unit-fibroblast (CFU-F) method and expanded them under a xenogeneic-free and serum-free (XF/SF) condition; hDPSC products were subsequently stored by two-step banking including a master cell bank (MCB) and a working cell bank (WCB). The final products were directly thawed hDPSCs from the WCB. We tested the safety and quality check, stem cell properties, and preclinical potentials of final hDPSC products and hDPSC products in the MCB and WCB.

*RESULTS:*

We optimized manufacturing procedures to isolate and expand hDPSC products under a XF/SF culture condition and established the MCB and the WCB. The final hDPSC products and hDPSC products in the MCB and WCB were validated the safety and quality including population doubling ability, chromosome stability, microorganism safety, and stem cell properties including morphology, cell surface marker expression, and multipotency. We also evaluated the in vivo immunogenicity and tumorigenicity and validated in vivo therapeutic efficacy for liver regeneration in a $CCl_4$-induced chronic liver fibrosis mouse model in the final hDPSC products and hDPSC products in the WCB.

*CONCLUSION:*

The manufacture and quality control results indicated that the present procedure could produce sufficient numbers of clinical-grade hDPSC products from a tiny deciduous dental pulp tissue to enhance clinical application of hDPSC products in chronic liver fibrosis.

Asian Pac J Cancer Prev. 2020 Mar 1;21(3):837-843. doi: 10.31557/APJCP.2020.21.3.837.

# Candida albicans Beta-Glucan Induce Anti- Cancer Activity of Mesenchymal Stem Cells against Lung Cancer Cell Line: An In-Vitro Experimental Study.

Peymaeei F[1], Sadeghi F[1], Safari E[2,3], Khorrami S[2], Falahati M[1], Roudbar Mohammadi S[4], Roudbary M[1].

**Author information**

## Abstract

*OBJECTIVE:*

β-glucan, glucopyranosyl polymers of fungi cell wall, represent an immune stimulating effects with potential anti-cancer activity. Mesenchymal stem cells (MSC) have immunomodulating properties in cancer microenvironment. The aim of this study was to investigate the anti-cancer effect of Candida albicans (C. albicans) beta-glucan on MSCs supernatant for apoptosis assay of lung cancer cells in vitro.

*METHODS:*

Beta-glucan was extracted from cell wall of C.albicans. MSC isolated from adipose tissue of patients and confirmed using specific surface markers expression which examined by flow cytometry. MSCs treated with various concentrations of β-glucans for 48 hours. Cytotoxic effect of β-glucans was

evaluated using MTT assay. MSC and lung cancer line cocultured and treated with β-glucans and apoptosis assay was done by flow cytometry.

*RESULTS:*

Cytotoxicity findings showed a significant decrease in MSC viability during 48h, however it was dose-dependent (P<0.05). According to the obtained findings, supernatant of mesenchymal stem cells treated with β-glucans increased cancer cells apoptosis (P<0.05).

*CONCLUSION:*

Beta glucan may highlight a potential and novel promising candidate in future strategies to cause apoptosis of cancer cells and consider as therapeutic  agent against tumor growth as well. Definitely, more in vitro and in vivo studies are required to understand its functions.

Cell Biol Toxicol. 2020 Mar 23. doi: 10.1007/s10565-020-09521-9. [Epub ahead of print]

# The use of large animals to facilitate the process of MSC going from laboratory to patient-'bench to bedside'.

Hotham WE[1], Henson FMD[2,3].
**Author information**

**Abstract**

Large animal models have been widely used to facilitate the translation of mesenchymal stem cells (MSC) from the laboratory to patient. MSC, with their multi-potent capacity, have been proposed to have therapeutic benefits in a number of pathological conditions. Laboratory studies allow the investigation of cellular and molecular interactions, while small animal models allow initial 'proof of concept' experiments. Large animals (dogs, pigs, sheep, goats and horses) are more similar physiologically and structurally to man. These models have allowed clinically relevant assessments of safety, efficacy and dosing of different MSC sources prior to clinical trials. In this review, we recapitulate the use of large animal models to facilitate the use of MSC to treat myocardial infarction-an example of one large animal model being considered the 'gold standard' for research and osteoarthritis-an example of the complexities of using different large animal models in a multifactorial disease. These examples show how large animals can provide a research platform that can be used to evaluate the value of cell-based therapies and facilitate the process of 'bench to bedside'.

J Mater Sci Mater Med. 2020 Mar 23;31(4):37. doi: 10.1007/s10856-020-06373-x.

# A comparative in vitro study of the effect of biospecific integrin recognition processes and substrate nanostructure on stem cell 3D spheroid formation.

Perugini V[1], Santin M[2].
**Author information**

**Abstract**

The in vitro study of the properties of the human mesenchymal stem cells as well as their manipulation in culture for clinical purposes depends on the elimination of artefacts caused by the lack of their natural

environment. It is now widely accepted that mesenchymal stem cells should be studied when they are organised as 3D spheroids rather than fibroblast-like colonies. Although this can be achieved with the use of some extracellular matrix proteins or by non-adherent conditions these suffer of significant limitations. The recent development of synthetic substrates resembling the physicochemical and biochemical properties of the adult stem cell niche has prompted questions about the role played by nanotopography and receptor-mediated adhesion. In the present paper, the influence of two types of substrates bearing the same nanostructure, but exposing either a non-specific or an integrin-specific binding motif was studied. Carboxybetaine-tethered hyperbranched poly(ε-lysine) dendrons showed that the hyperbranched structure was fundamental to induce spheroid formation, but these were forming more slowly, were of reduced size and less stable than those growing on substrates based on the same hyperbranched structures that had been functionalised at their uppermost branching generation by a laminin amino acid sequence, i.e. YIGSR. The study shows that both nanostructure and biorecognition need to be combined to achieve a substrate for stem cell spheroid formation as that observed in vivo in the adult stem cell niche.

3 Biotech. 2020 Apr;10(4):161. doi: 10.1007/s13205-020-2134-5. Epub 2020 Mar 6.

# Where is human-based cellular pharmaceutical R&D taking us in cartilage regeneration?

Alkaya D[1], Gurcan C[1], Kilic P[1], Yilmazer A[1,2], Gurman G[1,3].
**Author information**

**Abstract**

Lately, cellular-based cartilage joint therapies have gradually gained more attention, which leads to next generation bioengineering approaches in the development of cell-based medicinal products for human use in cartilage repair. The greatest hurdles of chondrocyte-based cartilage bioengineering are: (i) preferring the cell source; (ii) differentiation and expansion processes; (iii) the time necessary for chondrocyte expansion pre-implantation; and (iv) fixing the chondrocyte count in accordance with the lesion surface area of the patient in question. The chondrocyte presents itself to be the focal starting material for research and development of bioengineered cartilage-based medicinal products which promise the regeneration and restoration of non-orthopedic cartilage joint defects. Even though chondrocytes seem to be the first choice, inevitable complications related to proliferation, dedifferentation and redifferentiation are probable. Detailed studies are a necessity to fully investigate detailed culturing conditions, the chondrogenic strains of well-defined phenotypes and evaluation of the methods to be used in biomaterial production. Despite a majority of the current methods which aid amelioration of joint functionality, they are insufficient in fully restoring the natural structure and composition of the joint cartilage. Hence current studies have trended towards gene therapy, mesenchymal stem cells and tissue engineering practices. There are many studies addressing the outcomes of chondrocytes in the clinical scene, and many vital biomaterials have been developed for structuring the bioengineered cartilage. This study aims to convey to the audience the practical significance of chondrocyte-based clinical applications.

- **at**: Abstract

*Send to*

Int J Mol Sci. 2020 Mar 19;21(6). pii: E2104. doi: 10.3390/ijms21062104.

# Bone Morphogenetic Protein-2 Signaling in the Osteogenic Differentiation of Human Bone Marrow Mesenchymal Stem Cells Induced by Pulsed Electromagnetic Fields.

Martini F[1], Pellati A[2], Mazzoni E[1], Salati S[3], Caruso G[4], Contartese D[1,5], De Mattei M[1].

**Author information**

## Abstract

Pulsed electromagnetic fields (PEMFs) are clinically used with beneficial effects in the treatment of bone fracture healing. This is due to PEMF ability to favor the osteogenic differentiation of mesenchymal stem cells (MSCs). Previous studies suggest that PEMFs enhance the osteogenic activity of bone morphogenetic protein-2 (BMP2) which is used in various therapeutic interventions. This study investigated the molecular events associated to the synergistic activity of PEMFs and BMP2 on osteogenic differentiation. To this aim, human MSCs (hMSCs) were exposed to PEMFs (75 Hz, 1.5 mT) in combination with BMP2, upon detection of the minimal dose able to induce differentiation. Changes in the expression of BMP signaling pathway genes including receptors and ligands, as well as in the phosphorylation of BMP downstream signaling proteins, such as SMAD1/5/8 and MAPK, were analyzed. Results showed the synergistic activity of PEMFs and BMP2 on osteogenic differentiation transcription factors and markers. The PEMF effects were associated to the increase in BMP2, BMP6, and BMP type I receptor gene expression, as well as SMAD1/5/8 and p38 MAPK activation. These results increase knowledge concerning the molecular events involved in PEMF stimulation showing that PEMFs favor hMSCs osteogenic differentiation by the modulation of BMP signaling components.