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# Facilitated recruitment of mesenchymal stromal cells by bone marrow concentrate and platelet rich plasma.

Holmes HL[1], Wilson B[1], Goerger JP[2], Silverberg JL[3], Cohen I[3], Zipfel WR[2], Fortier LA[1].
**Author information**

## Abstract

**BACKGROUND:**

Biologics containing growth factors are frequently used to enhance healing after musculoskeletal injuries. One mechanism of action is thought to be though the ability of biologics to induce homing and migration of endogenous mesenchymal stromal cells (MSCs) to a target tissue. However, the ability of biologics to stimulate chemotaxis (directed migration of cells) and chemokinesis (increase rate of cell migration) of MSCs is unknown.

**HYPOTHESIS/PURPOSE:**

The aim of this study was to directly compare the ability of biologics including platelet rich plasma (PRP) and bone marrow concentrate (BMC) to induce MSC migration. The hypothesis was that leukocyte-low platelet rich plasma (Llo PRP) would induce migration to a greater extent than leukocyte-high platelet rich plasma (Lhi PRP) or BMC.

**METHODS:**

Bone marrow-derived MSCs were isolated from 8 horses. Migration of MSCs toward a biologic (BMC, Llo PRP, and Lhi PRP) or the positive control platelet derived growth factor (PDGF) was continuously traced and measured for 24hrs using time-lapse microscopy and a microfluidics device. Cell migration, chemotaxis and chemokinesis were determined by measurements of displacement, number of cells migrated, and cell flux.

**RESULTS:**

All biologics resulted in a significantly greater percentage of MSCs migrated compared to the positive control (PDGF). MSCs migrated further toward BMC compared to Llo PRP. Cell migration, measured as cell flux, was greater toward BMC and Lhi PRP than Llo PRP.

**CONCLUSION:**

The biologics BMC and Lhi PRP elicit greater chemotaxis and chemokinesis of MSCs than Llo PRP. However, all biologics recruited the same number of MSCs suggesting that differences in other regenerative effects, such as growth factor concentration, between biologics should be strongly considered when choosing a biologic for treatment of musculoskeletal injuries. The results of this study have the potential to reduce the need, risks, and costs associated with MSC culture and delivery.

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# Cell-sheet-derived ECM coatings and their effects on BMSCs responses.

Wang X, Chen Z, Zhou B, Duan X, Weng WJ, Cheng K, Wang H, Lin J.

**Abstract**

Extracellular matrix (ECM) provides a dynamic and complex environment to determine the fate of stem cells. In this work, in vitro cultured cell sheets were treated with paraformaldehyde or ethanol and eventually become ECM. Such ECM was then immobilized on titanium substrates via polydopamine chemistry. Their effects on bone marrow mesenchymal stromal cells (BMSCs) behaviors were investigated. It was found that paraformaldehyde treated ECM coatings (PT-ECM) showed well-maintained microstructure, whereas that of ethanol treated (ET-ECM) were completely changed. As a result, different amide structures and distributions of ECM components, such as laminin and collagen I, were exhibited. Alkaline phosphatase activity, osteocalcin secretion, related gene expression and mineral deposition were evaluated for BMSCs cultured on both ECM coatings. PT-ECM was demonstrated to promote osteogenic differentiation much more efficiently than ET-ECM. That is ascribed to the preservation of native ECM milieu of PT-ECM. Such ECM acquirement and immobilization method could establish surfaces being able to direct stem cell responses on various materials. That shows promising potential in bone tissue engineering and other related biomedical applications.

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# Manufacturing human mesenchymal stem cells at clinical scale: process and regulatory challenges.

Jossen V[1], van den Bos C[2], Eibl R[3], Eibl D[3].

**Author information**

**Abstract**

Human mesenchymal stem cell (hMSC)-based therapies are of increasing interest in the field of regenerative medicine. As economic considerations have shown, allogeneic therapy seems to be the most cost-effective method. Standardized procedures based on instrumented single-use bioreactors have been shown to provide billion of cells with consistent product quality and to be superior to traditional expansions in planar cultivation systems. Furthermore, under consideration of the complex nature and requirements of allogeneic hMSC-therapeutics, a new equipment for downstream processing (DSP) was successfully evaluated. This mini-review summarizes both the current state of the hMSC production process and the challenges which have to be taken into account when efficiently producing hMSCs for the clinical scale. Special emphasis is placed on the upstream processing (USP) and DSP operations which cover expansion, harvesting, detachment, separation, washing and concentration steps, and the regulatory demands.

Cell Transplant. 2018 Jan;27(1):117-129. doi: 10.1177/0963689717737089.

# Wharton's Jelly Mesenchymal Stromal Cells Support the Expansion of Cord Blood-derived CD34+ Cells Mimicking a

# Hematopoietic Niche in a Direct Cell-cell Contact Culture System.

Lo Iacono M[1], Russo E[2], Anzalone R[3,4], Baiamonte E[1], Alberti G[3], Gerbino A[2], Maggio A[1], La Rocca G[2,3], Acuto S[1].
**Author information**

**Abstract**

Wharton's jelly mesenchymal stromal cells (WJ-MSCs) have been recently exploited as a feeder layer in coculture systems to expand umbilical cord blood-hematopoietic stem/progenitor cells (UCB-HSPCs). Here, we investigated the role of WJ-MSCs in supporting ex vivo UCB-HSPC expansion either when cultured in direct contact (DC) with WJ-MSCs or separated by a transwell system or in the presence of WJ-MSC-conditioned medium. We found, in short-term culture, a greater degree of expansion of UCB-$CD34^+$ cells in a DC system (15.7 ± 4.1-fold increase) with respect to the other conditions. Moreover, in DC, we evidenced two different $CD34^+$ cell populations (one floating and one adherent to WJ-MSCs) with different phenotypic and functional characteristics. Both multipotent $CD34^+/CD38^-$ and lineage-committed $CD34^+/CD38^+$ hematopoietic progenitors were expanded in a DC system. The former were significantly more represented in the adherent cell fraction than in the floating one (18.7 ± 11.2% vs. 9.7 ± 7.9% over the total $CD34^+$ cells). Short-term colony forming unit (CFU) assays showed that HSPCs adherent to the stromal layer were able to generate a higher frequency of immature colonies (CFU-granulocyte/macrophage and burst-forming unit erythroid/large colonies) with respect to the floating cells. In the attempt to identify molecules that may play a role in supporting the observed ex vivo HSPC growth, we performed secretome analyses. We found a number of proteins involved in the HSPC homing, self-renewal, and differentiation in all tested conditions. It is important to note that a set of sixteen proteins, which are only in part reported to be expressed in any hematopoietic niche, were exclusively found in the DC system secretome. In conclusion, WJ-MSCs allowed a significant ex vivo expansion of multipotent as well as committed HSPCs. This may be relevant for future clinical applications.

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# Reporting of Mesenchymal Stem Cell Preparation Protocols and Composition: A Systematic Review of the Clinical Orthopaedic Literature.

Robinson PG[1], Murray IR[1,2], West CC[2], Goudie EB[1], Yong LY[2], White TO[1], LaPrade RF[3].
**Author information**

**Abstract**

**BACKGROUND:**

Mesenchymal stem cells (MSCs) are increasingly being used in the treatment of a wide variety of sports-related conditions. Despite this enthusiasm, the biological properties of MSCs and their effects on musculoskeletal tissue healing remain poorly understood. MSC-based strategies encompass cell populations with heterogeneous phenotypes isolated from multiple tissues and using different methods.

Therefore, comprehensive reporting of the source, preparation methods, and characteristics of MSC strategies is essential to enable interpretation of results.

**PURPOSE:**

To perform a systematic review of levels of reporting of key variables in MSC preparation and composition for clinical studies evaluating MSC-based therapies in the treatment of musculoskeletal conditions.

**STUDY DESIGN:**

Systematic review.

**METHODS:**

A systematic review of the clinical orthopaedic and sports medicine literature from 2002 to 2017 was performed. The following inclusion criteria were used: human clinical trials, published in the English language, involving the administration of MSC-based therapies for orthopaedic or sports medicine applications. In vitro or ex vivo studies, editorials, letters to the editor, and studies relating to cosmetic, neurological, or dental applications were excluded.

**RESULTS:**

Of the 1259 studies identified on the initial search, 36 studies were found to satisfy the inclusion criteria for analysis on comprehensive review. Fifty-seven percent of studies evaluated bone marrow-derived MSCs, 41% evaluated adipose-derived MSCs, and 2% evaluated synovium-derived MSCs. Considerable deficiencies in the reporting of key variables, including the details of stem cell processing, culture conditions, and the characteristics of cell populations delivered, were noted. Overall, studies reported only 52% (range, 30%-80%) of variables that may critically influence outcome. No study provided adequate information relating to all of these variables.

**CONCLUSION:**

All existing clinical studies evaluating MSCs for orthopaedic or sports medicine applications are limited by inadequate reporting of both preparation protocols and composition. Deficient reporting of the variables that may critically influence outcome precludes interpretation, prevents others from reproducing experimental conditions, and makes comparisons across studies difficult. We encourage the adoption of emerging minimum reporting standards for clinical studies evaluating the use of MSCs in orthopaedics.