Mesenchymal stem cells in drug/gene delivery: implications for cell therapy.

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Source
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Abstract
Stem cells have been therapeutically utilized in replacement of hematopoetic cells for decades. This is in contrast to the recent emergence of adult stem cells as, perhaps, safe and beneficial therapeutics for multiple diseases and disorders. In particular, mesenchymal stem cells (MSCs) are currently used in multiple human clinical trials. Although MSCs are ubiquitous, bone marrow, umbilical cord and adipose tissue are the sources where MSCs are isolated for research and clinical application. MSCs were thought to be mesodermal due to the initial reports showing their differentiation into specialized mesodermal cells such as chondrocytes. However, it now appears that MSCs might be neuroectodermal in origin. Thus far, there is no evidence of in vivo transformation of MSCs. However, it is too early to prove or disprove that MSCs can be transformed in vivo in clinical trials. MSCs display immunosuppressive properties when placed in a milieu of inflammatory mediators. This phenotype makes MSCs easily available for therapies as 'off-the-shelf cells. Additionally, MSCs express chemotactic receptors, thereby allowing them to migrate to sites of tissue injury. This latter property has proven useful in the embodiment of MSCs as cellular vehicles to deliver targeted therapeutics to precise regions. The MSCs would typically harbor a prodrug or ectopically express a therapeutic gene to be delivered at a targeted site. This approach has been utilized in a number of different indications requiring precise therapeutic delivery, specifically cancer, cardiovascular disorders and neurodegenerative diseases. Combined with their immune-privileged status, safe clinical profile and low tumorigenicity, MSCs offer vast potential to benefit patients with serious diseases, for which limited treatment options exist.

Decreased pool of mesenchymal stem cells is associated with altered chemokines serum levels in atrophic nonunion fractures.


Source
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Abstract
Nonunion fractures can cause severe dysfunction and are often difficult to treat mainly due to a poor understanding of their physiopathology. Although many aspects of impaired fracture healing have been extensively studied, little is known about the cellular and molecular mechanisms leading to atrophic nonunion. Therefore, the aim of the present study was to assess the pools and biological functions of bone marrow-derived mesenchymal stem cells (hMSCs) and circulating endothelial progenitor cells (EPCs) in atrophic nonunion patients compared to healthy subjects, and the systemic levels of growth factors involved in the recruitment, proliferation and differentiation of these cells. In nonunions, the pool of hMSCs was decreased and their proliferation delayed. However, once committed, hMSCs from nonunions were able to proliferate, differentiate into
osteoblastic cells and mineralize in vitro as efficiently as hMSCs from healthy subjects. In parallel, we found altered serum levels of chemokines and growth factors involved in the chemotaxis and proliferation of hMSCs such as leptin, interleukin-6 (IL-6) and its soluble receptor, platelet-derived growth factor-BB (PDGF-BB), stem cell factor (SCF) and insulin-like growth factor-1 (IGF-1). Moreover, we showed that the number of EPCs and their regulating growth factors were not affected in nonunion patients. If nonunion is generally attributed to a vascular defect, our results also support a role for a systemic mesenchymal and osteogenic cell pool defect that might be related to alterations in systemic levels of factors implicated in their chemotaxis and proliferation.


Dexamethasone-Induced Lipolysis Increases the Adverse Effect of Adipocytes on Osteoblasts Using Cells Derived from Human Mesenchymal Stem Cells.

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Abstract
The increased bone marrow lipid deposition in steroid-associated bone loss diseases indicates that abnormalities in fat metabolism are associated with disease development. Recent studies have suggested that bone marrow adipocytes are secretory cells and that they may release substances that have an inhibitory effect on the differentiation and function of osteoblasts. We hypothesized that exposure of bone-marrow-derived adipocytes to corticosteroids exacerbates their deleterious effects on osteoblast metabolism and function. Adipocytes and osteoblasts derived from a human mesenchymal stem cell line (240L) were co-cultured in the absence of direct cell contact with or without dexamethasone treatment. After 6 days of co-culture, adipocytes to corticosteroids exacerbated their deleterious effects on osteoblast metabolism and function. Adipocytes and osteoblasts derived from a human mesenchymal stem cell line (240L) were co-cultured in the absence of direct cell contact with or without dexamethasone treatment. After 6 days of co-culture, osteoblasts demonstrated significantly lower levels of function based on lower mineralization, alkaline phosphatase activity and expression of osteogenic (Runx2, osteocalcin) mRNA marker. Dexamethasone treatment resulted in significantly lower levels of osteoblastic function compared with co-cultured cells without dexamethasone. Furthermore, conditioned media from dexamethasone-treated adipocytes induced a similar toxic effect and increased apoptosis involving activation of caspases 3/7 compared with conditioned media without dexamethasone treatment. Within the conditioned media, a substantial increase in the levels of leptin and two saturated fatty acids (FAs; stearate and palmitate) was observed after dexamethasone treatment. Although leptin supplementation failed to induce the inhibitory effect on osteoblasts, similar toxic results were produced with stearate and palmitate treatment, and an increase in intracellular reactive oxygen species was observed. Stearate- and palmitate-induced apoptosis was blocked by a reactive oxygen species scavenger pyrrolidine dithiocarbamate. These data show that saturated FAs secreted from adipocytes induce lipotoxic effects via mechanisms that may involve reactive oxygen species accumulation in osteoblasts. Our results suggest that inhibition of saturated FA secretion would protect osteoblasts against adipocytes in corticosteroid-associated bone loss diseases.


Cytotoxicity of local anesthetics on human mesenchymal stem cells.
Rahnama R, Wang M, Dang AC, Kim HT, Kuo AC.

Source
Abstract

BACKGROUND:
Local anesthetics are frequently delivered intra-articularly to provide perioperative pain control. Previous studies have shown that the commonly used drugs lidocaine, ropivacaine, and bupivacaine can be toxic to human chondrocytes. The present study was conducted to determine whether the toxic effects of local anesthetics on human chondrocytes also extend to human mesenchymal stem cells.

METHODS:
Human mesenchymal stem cells from three healthy donors were grown in tissue culture and exposed to the following anesthetic treatments for sixty minutes: (1) 1% lidocaine, (2) 2% lidocaine, (3) 0.25% bupivacaine, (4) 0.5% bupivacaine, (5) 0.2% ropivacaine, and (6) 0.5% ropivacaine. The cells were then allowed to recover for twenty-four hours in regular growth media, and viability was measured with use of fluorescent staining for live cells or a luminescence assay for ATP content.

RESULTS:
The live cell counts and ATP content were correlated ($r^2 = 0.79$), and 2% lidocaine was found to be significantly more toxic than all doses of bupivacaine and ropivacaine. Treatment with 1% lidocaine resulted in significantly fewer live cells (49%) compared with the control, and the live cell count was also significantly less than that for the other anesthetics. However, the ATP level in the 1% lidocaine group was not significantly lower than those in the other groups. Bupivacaine and ropivacaine did not exhibit significant differences in toxicity compared with the control or with each other.

CONCLUSIONS:
Ropivacaine and bupivacaine had limited toxicity in human mesenchymal stem cells. However, lidocaine could significantly decrease mesenchymal stem cell viability. Since other studies have shown ropivacaine to be less toxic to chondrocytes than bupivacaine, ropivacaine may be a safer intra-articular anesthetic.

CLINICAL RELEVANCE:
Mesenchymal stem cells likely play a key role in healing following surgical procedures such as microfracture and ligament reconstruction. If local anesthetics are used following joint surgery, selection of an agent with low toxicity toward mesenchymal stem cells, such as ropivacaine, may maximize tissue healing potential.

Efficient plasmid-mediated gene transfection of ovine bone marrow mesenchymal stromal cells.
Locatelli P, Olea FD, Hnatiuk A, Sepúlveda D, Pérez Sáez JM, Argüello R, Crottogini A.
Source
Department of Physiology, Favaloro University, Buenos Aires, Argentina.
Abstract

BACKGROUND AIMS:
Given the close similarity between ovine and human cardiomyocytes, sheep models of myocardial infarction and heart failure are increasingly used in studies of stem cell-mediated heart regeneration. In these studies, mesenchymal stromal cells (MSCs) are frequently employed. To enhance the paracrine effects of these MSCs, ex vivo transfection with genes encoding growth factors has been proposed. Although viral vectors exhibit higher transfection efficiency than plasmids, they entail the risks of uncontrolled transgene expression and immune reactions that preclude repeated administration. Our aim was to
optimize the efficiency of plasmid-mediated transfection of ovine MSCs, while preserving cell viability.

**METHODS:**
Varying amounts of diverse cationic lipids were used to obtain the reagent-to-DNA mass ratio showing highest luciferase activity. Transfection efficiency (flow cytometry) was tested on plasmid-green fluorescent protein-transfected MSCs at increasing DNA mass.

**RESULTS:**
Lipofectamine LTX 5 μL and Plus reagent 4 μL with 2 μg of DNA yielded 42.3 ± 4.7% transfection efficiency, while preserving cell viability. Using these transfection conditions, we transfected MSCs with a plasmid encoding human vascular endothelial growth factor (VEGF) and found high VEGF protein concentrations in the culture supernatant from day 2 (1968 ± 324 pg/mL per μg DNA) through at least day 12 (888 ± 386 pg/mL per μg DNA) after transfection.

**CONCLUSIONS:**
Plasmid-mediated transfection of ovine MSCs to over-express paracrine heart-regenerative growth factors is feasible and efficient and overcomes the risks and limitations associated with the use of viral vectors.


**Improved isolation and expansion of bone marrow mesenchymal stromal cells using a novel marrow filter device.**

Otsuru S, Hofmann TJ, Olson TS, Dominici M, Horwitz EM.

**Source**
Division of Oncology/Blood and Marrow Transplantation, The Children's Hospital of Philadelphia and The University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA.

**Abstract**
**BACKGROUND AIMS:**
Mesenchymal stromal cells (MSCs) have been studied as cell therapy to treat a vast array of diseases. In clinical MSC production, the isolated cells must undergo extensive ex vivo expansion to obtain a sufficient dose of MSCs for the investigational treatment. However, extended tissue culture is fraught with potential hazards, including contamination and malignant transformation. Changes of gene expression with prolonged culture may alter the therapeutic potential of the cells. Increasing the recovery of MSCs from the freshly harvested bone marrow allowing for less ex vivo expansion would represent a major advance in MSC therapy.

**METHODS:**
Human bone marrow cells from eight healthy donors were processed using a marrow filter device and, in parallel, using buoyant density centrifugation by two independent investigators. The initial nucleated cell recovery and the final yield, immunophenotype and trilineage differentiation potential of second-passage MSCs were examined.

**RESULTS:**
The marrow filter device generated significantly greater initial cell recovery requiring less investigator time and resulted in approximately 2.5-fold more MSCs after the second passage. The immunophenotype and differentiation potential of MSCs isolated using the two methods were equivalent and consistent with the defining criteria. The two independent investigators generated comparable results.

**CONCLUSIONS:**
This novel filter device is a fast, efficient and reliable system to isolate MSCs and should greatly expedite pre-clinical and clinical investigations of MSC therapy.
Mesenchymal stromal cells: misconceptions and evolving concepts.
Phinney DG, Sensebé L.

Source
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Abstract
Nearly half a century has passed since the publication of the first articles describing plastic-adherent cells from bone marrow, referred to initially as colony-forming unit fibroblasts, then marrow stromal cells, mesenchymal stem cells and most recently multipotent mesenchymal stromal cells (MSCs). As expected, our understanding of the nature and biologic functions of MSCs has undergone major paradigm shifts over this time. Despite significant advances made in deciphering their complex biology and therapeutic potential in both experimental animal models and human clinical trials, numerous misconceptions regarding the nature and function of MSCs have persisted in the field. Continued propagation of these misconceptions in some cases may significantly impede the advancement of MSC-based therapies in clinical medicine. We have identified six prevalent misconceptions about MSCs that we believe affect the field, and we attempt to rectify them based on current available data.

Concise review: adipose-derived stromal vascular fraction cells and platelet-rich plasma: basic and clinical implications for tissue engineering therapies in regenerative surgery.
Gentile P, Orlandi A, Scioli MG, Di Pasquali C, Bocchini I, Cervelli V.

Source
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Abstract
Cell-based therapy and regenerative medicine offer a paradigm shift in regard to various diseases causing loss of substance or volume and tissue or organ damage. Recently, many authors have focused their attention on mesenchymal stem cells for their capacity to differentiate into many cell lineages. The most widely studied types are bone marrow mesenchymal stem cells and adipose-derived stem cells (ADSCs), which display similar results. Based on the literature, we believe that the ADSCs offer advantages because of lower morbidity during the harvesting procedure. Additionally, platelet-rich plasma can be used in this field for its ability to stimulate tissue regeneration. The aims of this article are to describe ADSC preparation and isolation procedures, preparation of platelet-rich plasma, and the application of ADSCs in regenerative plastic surgery. We also discuss the mechanisms and future role of ADSCs in cell-based therapy and tissue engineering.

Current status of mesenchymal stem cell therapy and bone marrow transplantation in IBD.
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Source
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Abstract
Cellular therapy is a promising new approach to address unmet medical needs in patients with IBD, mainly Crohn's disease (CD). Two series have reported autologous
hematopoietic stem cell transplantation (HSCT) for CD. The largest one is a phase I study from Chicago including 24 patients with active CD refractory to conventional therapies. All patients went into remission with a CD Activity Index (CDAI) <150. The percentage of clinical relapse-free survival was 91% at 1 year, 63% at 2 years, 57% at 3 years, 39% at 4 years and 19% at 5 years. The percentage of patients in remission (CDAI <150), steroid-free or medication-free at any post-transplantation evaluation interval remained ≥70, ≥80 and ≥60%, respectively. In Europe and Canada, a currently ongoing randomized trial hopes to answer the question of whether autologous HSCT adds any benefit to the effect of immunosuppression used during mobilization. Although promising, HSCT for CD is still experimental and its toxicity leaves this option for a considerably reduced number of refractory patients in whom the disease is not amenable to surgical resection. A more recently developed, less aggressive approach involves the use of mesenchymal stem cells (MSCs). Successful pre-clinical studies using MSCs in models of autoimmunity, inflammation or tissue damage have paved the way for clinical trials. Two phase I studies on autologous bone marrow-derived MSCs for the treatment of active refractory CD have been published recently; one using systemic administration in patients with luminal CD and the other assessing the effects of local injection of MSCs for the treatment of fistulizing CD, showing that application of autologous MSCs is feasible, well tolerated and might produce clinical benefits.


Chemokines and adult bone marrow stem cells.

Rankin SM.

Source
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Abstract
The adult bone contains a number of distinct populations of stem cells, including haematopoietic stem cells, mesenchymal stem cells, endothelial progenitor cells and fibrocytes. While haematopoietic stem cells are required to provide a lifelong supply of blood cells it is thought that the other populations of stem cells play a role in tissue regeneration and potentially disease. The chemokine CXCL12 is produced constitutively in the bone marrow and, acting via CXCR4, is critical in maintaining HSPCs in a quiescent state and retaining all subsets of stem and progenitor cells in the bone marrow environment. The cytokine G-CSF, used clinically to mobilize haematopoietic stem cells for bone marrow transplants, activates the sympathetic nervous system and bone marrow macrophages to reduce the expression of CXCL12 by bone marrow stromal cells, thereby promoting the exit of haematopoietic stem cells from the bone marrow. Understanding the molecular mechanisms underlying G-CSF stimulated mobilization has led to development of CXCR4 antagonists as fast acting mobilizing agents for haematopoietic stem cells. Evidence now suggests that CXCR4 antagonists can similarly mobilize distinct subsets of progenitor cells, namely the endothelial progenitor cells and mesenchymal stem cells, but this requires conditioning of the bone marrow with VEGF rather than G-CSF.


Multipotent mesenchymal stromal cells and the innate immune system.

Le Blanc K, Mougiakakos D.

Source
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Abstract
Multipotent mesenchymal stromal cells (MSCs) have unique immunoregulatory and regenerative properties that make them an attractive tool for the cellular treatment of autoimmunity and inflammation. Their underlying molecular mechanisms of action together with their clinical benefit - for example, in autoimmunity - are being revealed by an increasing number of clinical trials and preclinical studies of MSCs. However, autoimmunity and therapy-related alloimmunity are not only triggered and sustained by responses of the adaptive immune system; there is growing evidence that components of the innate immune system also have a key role. It is therefore important to study the crosstalk between MSCs and innate immunity, which ranges from the bone marrow niche to injured tissue.

**J Cell Biochem.** 2012 Sep;113(9):2806-12. doi: 10.1002/jcb.24166.

**Functional heterogeneity of mesenchymal stem cells: implications for cell therapy.**

**Phinney DG.**

**Source**
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**Abstract**
The term mesenchymal stem cell (MSCs) was adopted in the 1990s to describe a population of bone-marrow-derived cells that demonstrated the capacity for tri-lineage differentiation at a clonal level. Research conducted during the ensuing decades has demonstrated that MSCs fulfill many functions in addition to connective tissue progenitors including contributing to the HSC niche and regulating the function of immune effector cells of both the innate and adaptive immune system. Despite these advances, fundamental aspects of MSC biology remain indeterminate. For example, the embryonic origin of MSCs and their niche in vivo remains a highly debated topic. More importantly, the mechanisms that regulate self-renewal and lineage specification have also been largely unexplored. The later is significant in that MSC population’s exhibit considerable donor-to-donor and intra-population heterogeneity but knowledge regarding how different functional attributes of MSCs are specified at the population level is unknown. This poses significant obstacles in research and in efforts to develop clinical manufacturing protocols that reproducibly generate functionally equivalent MSC populations. Herein, I discuss data demonstrating that MSC populations are intrinsically heterogeneous, elaborate on the molecular basis for this heterogeneity, and discuss how heterogeneity impacts clinical manufacturing and the therapeutic potency of MSCs.


**Stem cells combined with bone graft substitutes in skeletal tissue engineering.**


**Source**
Newcastle University, Institute of Cellular Medicine, Musculoskeletal Research group, Newcastle upon Tyne, Tyne and Wear NE17RU, UK.

**Abstract**
INTRODUCTION:
Bone grafting is used to repair large bone defects and autograft is recognised as producing the best clinical outcome, which is partly due to its cellular component. When autograft is unavailable, allograft and bone graft substitutes can be used; however, they rely on the host bed to provide cellular osteogenic activity.
AREAS COVERED:
Bone graft substitutes have the potential to benefit from the addition of stem cells aimed at enhancing the rate and quality of defect repair. Mesenchymal stem cells (MSCs) can be isolated from bone marrow or periosteum and culture expanded. Other sources of primary cells include muscle, adipose tissue, human umbilical cord and the pluripotent embryonic stem cells (ESCs).

EXPERT OPINION:
MSCs isolated from bone marrow have been the best characterised approach for osteogenic differentiation. Their use with synthetic scaffolds such as hydroxyapatite and tricalcium phosphate has produced promising clinical results. MSCs derived from adipose tissue, muscle or human umbilical cord cells combined with various scaffolds are an attractive option. Further in vivo and clinical investigation of their potential is required. Pluripotent ESCs have a theoretical advantage over MSCs; however, purification, cell-specific differentiation, effective delivery vehicles-scaffolds and teratogenesis control are still under in vitro and in vivo evaluation.

Timeline for development of autologous bone marrow infusion (ABMi) therapy and perspective for future stem cell therapy.

Source
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Abstract
Liver cirrhosis patients generally progress to liver failure. To cure this progressive disease, we developed a novel cell therapy using bone marrow cells; autologous bone marrow cell infusion (ABMi) therapy. We previously described the possible action mechanism of ABMi therapy in the cirrhotic liver, and showed the timeline and results of clinical studies of ABMi therapy. We have also carried out other clinical studies using bone marrow cells and granulocyte colony-stimulating factor. Here, we report a new randomized clinical trial to evaluate the effects of ABMi therapy. However, ABMi therapy may not be possible in patients who are unable to undergo general anesthesia; therefore, we have started to develop a next-generation stem cell therapy using cultured mesenchymal stem cells.

The pro-metastatic role of bone marrow-derived cells: a focus on MSCs and regulatory T cells.
Koh BI, Kang Y.

Source
Department of Molecular Biology, Princeton University, Princeton, New Jersey, USA.

Abstract
Several bone marrow-derived cells have been shown to promote tumour growth and progression. These cells can home to the primary tumour and become active components of the tumour microenvironment. Recent studies have also identified bone marrow-derived cells—such as mesenchymal stem cells and regulatory T cells—as contributors to cancer metastasis. The innate versatility of these cells provides diverse functional aid to promote malignancy, ranging from structural support to signal-mediated suppression of the host
immune response. Here, we review the role of mesenchymal stem cells and regulatory T cells in cancer metastasis. A better understanding of the bipolar nature of these bone marrow-derived cells in physiological and malignant contexts could pave the way for new therapeutics against metastatic disease.


Mesenchymal stromal cells and fibroblasts: a case of mistaken identity?

Hematti P.

Source
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Abstract
The plastic-adherent fibroblast-looking cells that can be isolated and culture-expanded from bone marrow and many other tissues are widely known as mesenchymal stromal cells (MSC). In addition to their fibroblast-like morphology, they are characterized by a panel of cell-surface markers and their potential to differentiate into bone, fat and cartilage. Based on their intriguing immunomodulatory and regenerative properties, MSC are being investigated as cellular therapeutics for a variety of clinical indications. However, many questions regarding the true identity and functionality of these cells in vivo remain unanswered. Fibroblasts, known for a much longer time but still poorly characterized, are also considered to be a ubiquitous stromal element of almost all tissues and are believed to play a role in tissue homeostasis. Despite the presence of MSC and fibroblasts in almost all tissues, similar morphology and other shared characteristics, the exact relationship between MSC and fibroblasts has remained undetermined. In this review, based on recent and old, but often neglected, literature it is suggested that ex vivo culture-expanded MSC and fibroblasts are indistinguishable by morphology, cell-surface markers, differentiation potential and immunologic properties.


Adult bone marrow stem cells in cartilage therapy.

Lubis AM, Lubis VK.

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Abstract
Cartilage defect rarely heals spontaneously since cartilage tissue is poorly vascularized and the lesion usually does not penetrate to subchondral bone, and hence it does not have access to progenitor cells of bone marrow. Severe cartilage damage may lead to osteoarthritis (OA). Current surgical and non-surgical therapeutic interventions in OA are limited to symptom relief and/or repair of focal lesion, and later a total knee replacement is still necessary. Cell therapy with chondrocyte implantation requires healthy cartilage for donor of the cells. Adult mesenchymal stem cells (MSCs) have the ability to differentiate into chondrogenic lineage. They can readily be isolated from bone marrow as well as many other adult tissues and have an extensive proliferation capacity. Therefore, MSCs may offer a great potential to be developed as an alternative for cell-based articular cartilage therapy.

Differentiation. 2013 Jan 10;85(1-2):1-10. doi: 10.1016/j.diff.2012.08.004. [Epub ahead of Mesenchymal stem cells and their use in therapy: What has been achieved?]
Abstract
The considerable therapeutic potential of human multipotent mesenchymal stromal cells or mesenchymal stem cells (MSCs) has generated increasing interest in a wide variety of biomedical disciplines. Nevertheless, researchers report studies on MSCs using different methods of isolation and expansion, as well as different approaches to characterize them; therefore, it is increasingly difficult to compare and contrast study outcomes. To begin to address this issue, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed minimal criteria to define human MSCs. First, MSCs must be plastic-adherent when maintained in standard culture conditions (α minimal essential medium plus 20% fetal bovine serum). Second, MSCs must express CD105, CD73 and CD90, and MSCs must lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules. Third, MSCs must differentiate into osteoblasts, adipocytes and chondroblasts in vitro. MSCs are isolated from many adult tissues, in particular from bone marrow and adipose tissue. Along with their capacity to differentiate and transdifferentiate into cells of different lineages, these cells have also generated great interest for their ability to display immunomodulatory capacities. Indeed, a major breakthrough was the finding that MSCs are able to induce peripheral tolerance, suggesting that they may be used as therapeutic tools in immune-mediated disorders. Although no significant adverse events have been reported in clinical trials to date, all interventional therapies have some inherent risks. Potential risks for undesirable events, such as tumor development, that might occur while using these stem cells for therapy must be taken into account and contrasted against the potential benefits to patients.
cellular populations in the human trabecular bone and BM expressing different progenitor cell markers.

**CONCLUSIONS:**
Targeting several multipotency and pluripotency markers, we found that the BM contains identifiable and distinct progenitor cells further justifying their introduction for a wide range of applications in regenerative medicine.


**Duration of in vitro storage affects the key stem cell features of human bone marrow-derived mesenchymal stem cells for clinical transplantation.**

Sohn HS, Heo JS, Kim HS, Choi Y, Kim HO.

Source
Department of Orthopedics, National Medical Center, Seoul, Korea.

Abstract
**BACKGROUND AIMS:**
Mesenchymal stem cells (MSCs) have the ability to self-renew and differentiate into various cell types. Their plasticity and easy availability make them promising candidates for regenerative medicine. However, for successful clinical application, MSCs need to be expanded under a Good Manufacturing Practices-compliant system to obtain a large quantity of these cells. Although the viability and potency of these in vitro-expanded MSCs need to be maintained during preparation and transportation before transplantation, these characteristics have not thoroughly been examined. Our goal in this study was to standardize MSC preparation and storage before their clinical application to ensure reproducible quality and potency for their clinically intended purpose.

**METHODS:**
We examined the viability, self-renewal capacity and differentiation capability of MSCs on short-term in vitro storage in saline or dextrose solution at 4°C and room temperature.

**RESULTS:**
MSCs harvested and suspended in saline for 1-2 h showed >90% viability regardless of storage temperature. However, when cells were stored for >2 h in saline, their viability decreased gradually over time. The viability of cells in dextrose deteriorated rapidly. MSCs lost colony-forming unit and differentiation capacities rapidly as storage time increased. Collectively, we found that a storage period >2 h resulted in a significant decrease in cell viability, cell proliferation capacity and differentiation potency.

**CONCLUSIONS:**
Storage of culture-harvested MSCs for >2 h is likely to result in suboptimal MSC-mediated tissue regeneration because of decreased cell viability and differentiation capacity.


**Species variation in the spontaneous calcification of bone marrow-derived mesenchymal stem cells.**

Huang YZ, Cai JQ, Lv FJ, Xie HL, Yang ZM, Huang YC, Deng L.

Source
Laboratory of Stem Cell and Tissue Engineering, Regenerative Medicine Research Center, West China Hospital, Sichuan University, Chengdu, P.R. China.

Abstract
Bone marrow-derived mesenchymal stem cells (BM-MSCs) hold great promise for tissue regeneration. With increasing numbers of clinical trials, the safety of BM-MSCs attracts great interest. Previously, we determined that rat BM-MSCs possessed spontaneous calcification without osteogenic induction after continuous culture. However, it is unclear
whether BM-MSCs from other species share this characteristic. In this study, spontaneous calcification of BM-MSCs from rat, goat, and human specimens was investigated in vitro. BM-MSCs were cultured in complete medium, and calcification was determined by morphologic observation and alizarin red staining. It was demonstrated that rat BM-MSCs possessed a typically spontaneous calcification, whereas goat and human BM-MSCs under the same system proliferated significantly but did not calcify spontaneously. The significant species variation in spontaneous calcification of BM-MSCs described in this study provides useful information regarding evaluation of numerous BM-MSC-based approaches for bone regeneration and the safety of BM-MSCs.


Preclinical and Clinical Studies on the Use of Stem Cells for Bone Repair: A Systematic Review.
Ambikaipalan A, Wong JM, Khan WS.

Source
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Abstract
The management of extensive bone defects in the setting of fracture repair, non-union and revision arthroplasty are challenging problems. The supply of harvestable autologous bone graft is limited, with an associated morbidity, and therefore a need exists for a better solution in large defects. The use of stem cells is an evolving field of research, with different potential applications, ranging from simple injection of cells to tissue engineering using osteogenic cells seeded onto a scaffold. This systematic review aims to collate the published preclinical and clinical studies investigating the potential use of stem cells for bone repair.


Comparison of the effects of human adipose and bone marrow mesenchymal stem cells on T lymphocytes.
Xishan Z, Baoxin H, Xinna Z, Jun R.

Source
Institute of Medical Oncology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, PR China.

Abstract
Mesenchymal stem cells (MSCs) are multipotent cells that can be derived either from the bone marrow (bMSCs) or adipose tissue (aMSCs). We have compared the immune regulatory properties of cells derived from bone marrow and adipose tissue to provide a theoretical basis for the choice of stem cell source for transplantation. The phenotypes of bMSCs and aMSCs are similar, differing only in the expression of CD106. aMSCs proliferate faster than bMSCs, but aMSCs suppressed T-lymphocyte proliferation and activation more poorly than bMSCs. Thus cell origin and abundance are important factors in determining the suitability of MSCs for transplantation. Adipose tissue offers a more promising source of cells for such an application.


Maxillary sinus augmentation with adult mesenchymal stem cells: a review of the current literature.
Mangano FG, Tettamanti L, Sammons RL, Azzi L, Caprioglio A, Macchi A, Mangano C.

Source
Abstract

PURPOSE:
Mesenchymal stem cells (MSCs) have been applied in maxillary sinus augmentation (MSA) with clinically successful results. The purpose of this article was to evaluate the systematically acquired evidence for the effectiveness of cell-based approaches in MSA with various scaffolds, and to narratively assess evidence from additional articles that report effectiveness of cell-based approaches in MSA.

MATERIALS AND METHODS:
Electronic database searches were performed. Inclusion criteria were studies of cell-based approaches in MSA with various scaffolds, in humans, with at least 3 to 4 months of follow-up. Meta-analysis was performed for randomized controlled trials (RCTs) with histologic/histomorphometric evaluation.

RESULTS:
Fifteen studies (4 RCTs) were considered to be eligible for inclusion in the review. The meta-analysis suggested a marginal, nonstatistically significant positive effect of MSCs on the bone regrowth.

CONCLUSIONS:
A number of studies have demonstrated the potential for cell-based approaches in MSA; further RCTs that clearly demonstrate benefits of cell-based approach are needed.