Cell Transplantation, Vol. 25, pp. 829–848, 2016

0963-6897/16 $90.00 + .00
DOI: http://dx.doi.org/10.3727/096368915X689622
E-ISSN 1555-3892
www.cognizantcommunication.com

Review

Clinical Trials With Mesenchymal Stem Cells: An Update

Tiziana Squillaro,*† Gianfranco Peluso,† and Umberto Galderisi*‡§

*Department of Experimental Medicine, Biotechnology and Molecular Biology Section, Second University of Naples, Naples, Italy
†Institute of Bioscience and Bioresources, National Research Council CNR, Naples, Italy
‡Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, Temple University, Philadelphia, PA, USA
§Genome and Stem Cell Center (GENKOK), Erciyes University, Kayseri, Turkey

In the last year, the promising features of mesenchymal stem cells (MSCs), including their regenerative properties and ability to differentiate into diverse cell lineages, have generated great interest among researchers whose work has offered intriguing perspectives on cell-based therapies for various diseases. Currently the most commonly used adult stem cells in regenerative medicine, MSCs, can be isolated from several tissues, exhibit a strong capacity for replication in vitro, and can differentiate into osteoblasts, chondrocytes, and adipocytes. However, heterogeneous procedures for isolating and cultivating MSCs among laboratories have prompted the International Society for Cellular Therapy (ISCT) to issue criteria for identifying unique populations of these cells. Consequently, the isolation of MSCs according to ISCT criteria has produced heterogeneous, nonclonal cultures of stromal cells containing stem cells with different multipotent properties, committed progenitors, and differentiated cells. Though the nature and functions of MSCs remain unclear, nonclonal stromal cultures obtained from bone marrow and other tissues currently serve as sources of putative MSCs for therapeutic purposes, and several findings underscore their effectiveness in treating different diseases. To date, 493 MSC-based clinical trials, either complete or ongoing, appear in the database of the US National Institutes of Health. In the present article, we provide a comprehensive review of MSC-based clinical trials conducted worldwide that scrutinizes biological properties of MSCs, elucidates recent clinical findings and clinical trial phases of investigation, highlights therapeutic effects of MSCs, and identifies principal criticisms of the use of these cells. In particular, we analyze clinical trials using MSCs for representative diseases, including hematological disease, graft-versus-host disease, organ transplantation, diabetes, inflammatory diseases, and diseases in the liver, kidney, and lung, as well as cardiovascular, bone and cartilage, neurological, and autoimmune diseases.

Key words: Mesenchymal stem cells (MSCs); Clinical trials; Immunomodulation; Differentiation; Secretome; Paracrine effects

INTRODUCTION

The promising features of stem cells, including their regenerative properties and ability to give rise to cells of various lineages, have generated great interest in these cells that has paved the way for numerous studies offering intriguing perspectives on cell-based therapies for various diseases. It is widely accepted that stem cells can be split into two major groups: embryonic and nonembryonic stem cells. Embryonic stem cells (ESCs) derive from the inner cell mass of blastocysts and can differentiate into cells of all three germ layers. To date, the interest of researchers and clinicians in these cells remains limited, however, due to both teratoma formation and controversies over the ethics of using stem cells. As such, results of trials using non-ESCs, mostly adult stem cells, are highly attractive in the scientific community. Despite the limited differentiation potential of adult stem cells, they can be isolated from several tissues and are currently the most

Received July 10, 2015; final acceptance February 3, 2016. Online prepub date: September 29, 2015.
Address correspondence to Umberto Galderisi, Department of Experimental Medicine, Second University of Naples, via Costantinopoli, 16, 80128, Naples, Italy. Tel: +39 081 566-7585; Fax: +39 081 566-7547; E-mail: umberto.galderisi@unina2.it *or* Gianfranco Peluso, Institute of Bioscience and Bioresources, CNR, via Pietro Castellino 111, 80131 Naples, Italy. Tel: +39 081 613-2280; E-mail: gianfranco.peluso@ibbr.cnr.it

commonly used cells in regenerative medicine (132,133). These findings, along with the rapid development of cellular therapy during the last decade, have contributed to an increased use of these cells in preclinical research and clinical trials.

Among adult stem cells, mesenchymal stem cells (MSCs) represent a highly investigated population given their unique biological properties (132). MSCs were first described in 1967 by Friedenstein et al., who from bone marrow (BM) isolated adherent, fibroblast-like clonogenic cells called colony-forming unit-fibroblasts (CFU-F). These cells showed a strong capacity for replication in vitro, could differentiate into osteoblasts, chondrocytes, adipocytes, and supported hematopoietic stroma when a single CFU-F was retransplanted in vivo (33).

Following these pioneering studies, several scientists isolated and cultivated the entire population of BM stromal cells identified as cultures of MSCs (35). However, the heterogeneity of isolation and cultivation procedures among laboratories prompted the International Society for Cellular Therapy (ISCT) to establish criteria for identifying unique populations of MSCs. In 2006, the ICST defined MSCs according to the following criteria:

i. MSCs must be purified from the BM stromal population based on plastic adherence under standard culture conditions.
ii. MSCs must be positive for CD105, CD90, and CD73, express low levels of MHC-I, and be negative for MHC-II, CD11b, CD14, CD34, CD45, and CD31.
iii. MSCs must differentiate in vitro into osteocytes, chondrocytes, and adipocytes (24).

Yet these criteria do not support the purification of homogenous MSC populations. In fact, the isolation of MSCs according to ISCT criteria produces heterogeneous, nonclonal cultures of stromal cells containing stem cells with different multipotential properties, committed progenitors, and differentiated cells. Although the nature and functions of MSCs remain unclear, nonclonal stromal cultures obtained from BM and other tissues that contain a subpopulation of stem cells are currently serving as sources of putative MSCs for therapeutic purposes, largely due to findings that they might be effective in the treatment of several diseases (35).

MSCs have been isolated from multiple tissues other than BM, including skeletal muscle tissue (138), adipose tissue (49), synovial membranes (46), saphenous veins (17), dental pulp (99), periodontal ligaments (111), cervical tissue (89), Wharton's jelly (93), umbilical cords (106), umbilical cord blood (28), amniotic fluid (29), placentae (84), lung tissue (42,79), liver tissue (49,138), and dermal tissue (138). Added to the unique properties of MSCs, including their multilineage differentiation potential, their ready availability, and their extensive capacity for in vitro expansion, the secretion of trophic factors that favor tissue remodeling and immunoregulatory properties have made these cells suitable candidates for an array of applications for treating various congenital and acquired diseases (7,131).

Twenty years ago, Lazarus conducted the first clinical trial using BM cell injection in patients with hematologic malignancies (64). Since then, numerous clinical trials have been conducted to test the feasibility and efficacy of MSC-based therapy, and more than 2,000 patients have been administered with allogeneic or autologous MSCs for the treatment of various diseases, including graft-versus-host disease (GVHD), hematologic malignancies, organ transplantation, cardiovascular diseases, neurological diseases, and autoimmune diseases, as well as in organ transplantations, to heal refractory wounds and to counteract defects in the bones and cartilage (55,63,132). According to data reported by the US National Institutes of Health (http://www.clinicaltrial.gov/), as of June 2015, 493 MSC-based clinical trials either have been completed or remain ongoing.

In the present article, we provide a comprehensive review of MSC-based clinical trials worldwide that scrutinizes the biological properties of MSCs, elucidates recent clinical findings and clinical trial phases of investigation, highlights therapeutic effects of MSCs, and identifies principal criticisms of the use of these cells.

MSCs AND CELL THERAPY: BIOLOGICAL PROPERTIES SUPPORTING CLINICAL USE

MSCs show tremendous potential for the treatment of many diseases, including both immunological and non-immunological disorders. Though a uniform mechanism governing MSC-based therapy has not yet been discovered, available data have revealed several working models that promote the beneficial effects of MSCs (133). The therapeutic potential of these cells stems from several properties, including their ability to i) differentiate into various cell lineages, ii) secrete soluble factors crucial for cell survival and proliferation, iii) modulate immune response, and iv) migrate to the exact site of injury (Fig. 1).

Differentiation Potential

As multipotent stem cells, MSCs can differentiate, both in vitro and in vivo, into various mesenchymal tissues, including those of bones, cartilage, fat, muscles, tendons, and BM. Furthermore, MSCs exhibit remarkable plasticity given their ability to transdifferentiate, or undergo an abrupt alteration in phenotype, thereby giving rise to cells possessing the characteristics of different lineages. It has been documented that MSCs in vitro can transdifferentiate into non-mesoderm-like cells, including neuron-like cells, hepatocytes, and pancreatic islet-like cells. Chen et al. first reported the ability of these

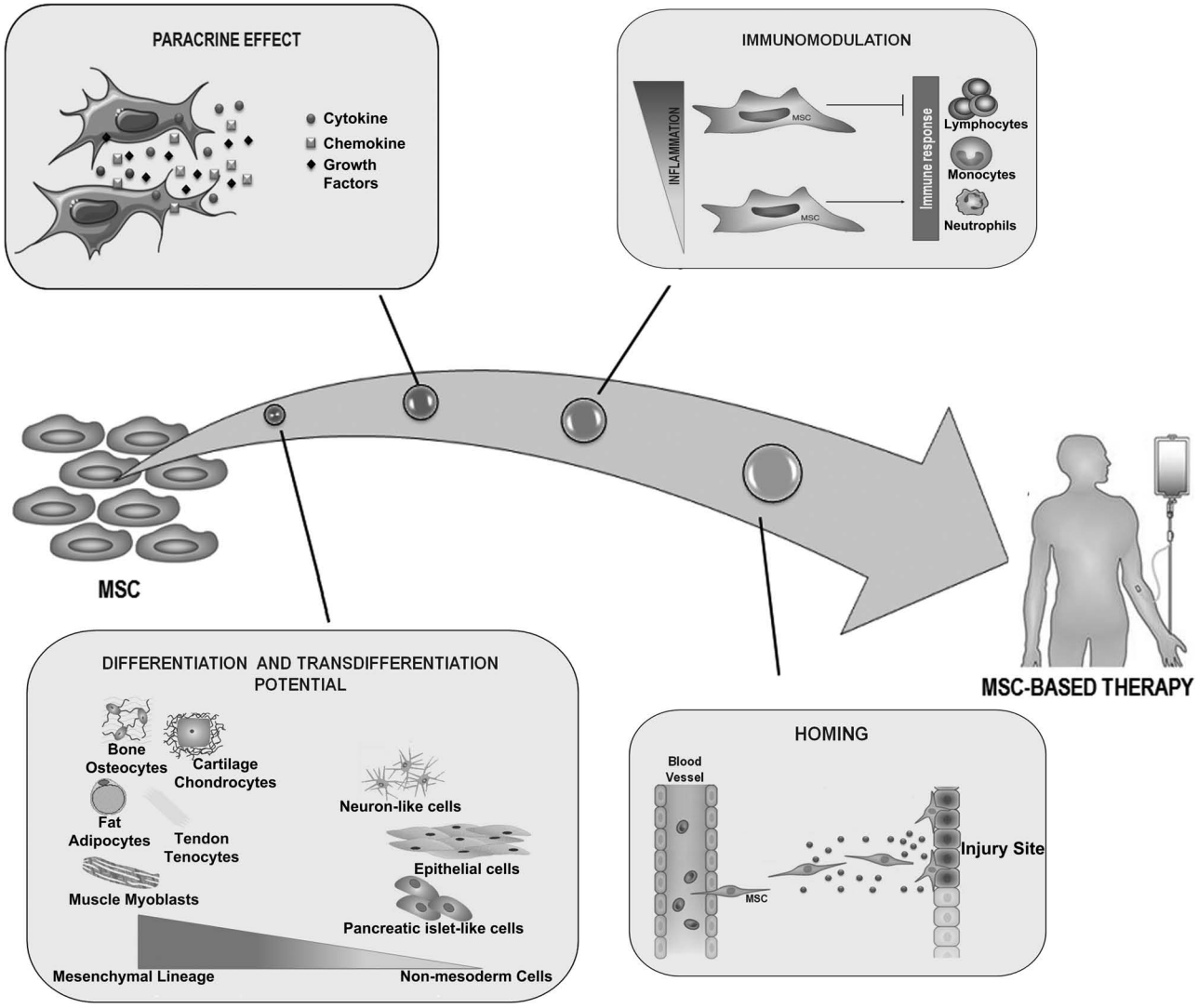


Figure 1. Biological properties supporting MSC clinical use. The therapeutic potential of MSCs relies on their unique properties as i) the capacity to differentiate into various cell lineage (bottom, left), ii) the ability to secrete soluble factors that are crucial for cell survival and proliferation (top, left), iii) the ability to modulate immune response (top, right), iv) the ability to migrate to the exact site of injury (bottom, right).

cells to differentiate into pancreatic islet cells (11). Their seminal findings were confirmed by other studies demonstrating that MSCs transdifferentiate into islet-like clusters expressing insulin and glucagon (9).

The differentiation and transdifferentiation potential of MSCs has contributed to increasing interest in these cells and, in turn, promoted new clinical perspectives on their function. Promising evidence that MSCs can differentiate into epithelial-like cells has posed an intriguing scenario for tissue engineering and cell therapy. Sasaki et al. demonstrated that these cells give rise to keratinocytes and multiple skin cell types, thereby contributing to wound repair procedures (109). By using a mouse model with ischemia and reperfused kidneys, Li et al. furthermore reported that infused MSCs could transdifferentiate toward renal tubular epithelium, which contributes to maintaining tissue structural integrity and tissue recovery (72). Overall, these reports have sustained the idea that MSC infusion might benefit organ and tissue repair given the ability of these cells to differentiate into cells of the targeted tissue and replace damaged resident cells. Nevertheless, a body of evidence sustains that following systemic injection most MSCs are trapped in capillary beds of various tissues, especially the lungs, thus suggesting that their local administration is the preferred method of administration to take advantage of their differentiation potential (35,70,115). Despite the considerable body of evidence supporting the usefulness of

MSCs, controversy about using stem cells persists, fueled by the chief criticism that most results confirming any MSC-related hypotheses have been inferred by being documented in in vitro studies only. Nevertheless, mounting in vivo evidence suggests that the benefits of MSCs in treating diseases are not limited to their differentiation potential only, since that aspect is only part of the total mechanism underlying their therapeutic effects.

Paracrine Effects

It has recently come to light that the benefits of MSC transplants are attributable to the capacity of MSCs to secrete a wide variety of cytokines, chemokines, and growth factors. Several findings suggest that the key role of MSCs in interacting with their microenvironments involves their release of dozens of active biological factors that exert profound effects on local cellular dynamics (35). It has also been demonstrated that these released factors may prevent adjacent cells from undergoing apoptosis and stimulate their proliferation, thereby promoting the regeneration of injured tissue (131).

In regenerative medicine, the paracrine effect exerted by MSCs has been hypothesized to sustain the observation of many scientists reporting that the number of implanted MSCs detected in target tissue was too low to explain tissue recovery or wound healing (131). Further evidence has clearly demonstrated that infused MSCs, once in damaged tissue sites ripe for repair, interacted closely with local stimuli, including inflammatory cytokines, ligands of toll-like receptors, and hypoxia, which seemed, in turn, to stimulate the cells to show several growth factors that perform multiple functions in tissue regeneration (6,18). Though a thorough in vivo examination of the MSC secretome and of strategies to modulate the secretion of molecules by MSCs has yet to be performed, current techniques have been useful for identifying factors released by MSCs at high levels, such as proteins involved in immune system signaling [i.e., interleukin-6 (IL-6), IL-8, monocyte chemoattractant protein-1 (MCP-1), and transforming growth factor-β (TGF-β)], extracellular matrix remodelers [i.e., TIMP metallopeptidase inhibitor 2 (TIMP-2), fibronectin, periostin, collagen, decorin, and metalloproteinase inhibitors], and growth factors and their regulators [i.e., vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), bone morphogenetic protein 2 (BMP-2), basic fibroblast growth factor (bFGF), and insulin-like growth factor-binding protein 3 (IGFBP3), IGFBP4, IGFBP7] (35).

Although not well characterized, the benefits of MSC-conditioned media are clearly supported by numerous experimental findings sustaining the theory of paracrine effects. Indeed, it has been demonstrated that MSC-conditioned media may act as chemoattractants for recruiting macrophages and endothelial cells into the wound, thereby enhancing the healing process (10). Takahashi et al. have also reported that MSC-conditioned media infused into acutely infarcted hearts improved cardiac function in terms of control by increasing capillary density and decreasing infarct size (120).

Immunomodulation

Since the ability of MSCs to modulate the immune system was first demonstrated in 2000, a body of related literature has revealed that these cells were effective in treating various immune disorders in both human and animal models (75,133). Though the mechanism by which these cells exert their immunomodulatory function is not fully understood, the most accredited theory posits cell-to-cell contact and/or the release of soluble immunosuppressive factors. Both in vitro and in vivo studies have reported that MSCs interacted with a wide range of immune cells and displayed an ability to suppress the excessive response of T cells, B cells, dendritic cells, macrophages, and natural killer cells (47,128). MSCs can also induce regulatory T cells (Tregs) and maintain the capability of Tregs to suppress self-reactive T-effector responses. It has been proposed that Tregs generated in vivo in the presence of MSCs would persist and expand (39,43,123). Given that injection of exogenous, short-lived MSCs could act as catalysts in expanding long-lasting antigen-specific Tregs, it would have important implications for their immunoregulatory potential (123).

This evidence has contributed to uphold MSCs as suitable candidates in the treatment of autoimmune diseases and GVHD. For instance, donor-derived MSCs have been shown to induce long-term allograft acceptance in a rat model of heart transplantation (101). Furthermore, given that inflammation-causative tissue damage is a key process triggered in response to injury and disease, MSCs could become the gold standard for the treatment of any tissue or organ damage associated with intense inflammatory activity (e.g., rheumatoid arthritis, kidney failure, heart injury). According to these findings, it has been proposed that MSCs could play a positive role in promoting tissue repair (4).

An emerging body of evidence clarifies that the immunomodulatory property of MSCs is not strictly related to immunosuppression. More specifically, it has been proposed that MSCs interact with their environments both by negatively regulating the immune response in the case of major inflammation and by stimulating the immune system by releasing proinflammatory molecules if the level of inflammatory cytokines is low (4,35).

Homing Mechanism

The homing mechanism of MSCs lies in their ability to reach damaged tissue in response to a correct combination

of signaling molecules from the injured tissue and corresponding receptors on the MSCs themselves. Most evidence of migration and homing mechanisms has derived from studies evaluating leucocyte migration (91) into inflamed tissues. Despite a considerable body of literature reporting the mechanism of MSC migration toward injured tissue and the role of surface receptors and molecules that drive this migration, the mechanisms by which MSCs are recruited are not fully understood.

Studies performed both in human and animal models demonstrated that MSCs migrate specifically to damaged tissue sites exhibiting inflammation (32,50,78), although most became trapped in the microvasculature of the lung. MSC homing involves several important cell trafficking-related molecules such as chemokines, adhesion molecules, and matrix metalloproteinases (MMPs) (130). Among them, the most important signalers are stromal-derived factor 1 (SDF-1), C-X-C chemokine receptor type 4 (CXCR4), and hepatocyte growth factor (HGF)-MET proto-oncogene, receptor tyrosine kinase (c-MET) axes (95,112,116). The migration process is highly dependent on the chemokine receptor CXCR4 and its binding partner, the SDF-1 CXCL12, which was previously linked to the homing of hematopoietic stem cells (HSCs) (115). Wynn et al. have demonstrated that CXCR4 can appear in subpopulations of MSCs, which aids in CXCL12-dependent migration and homing (135). Aside from CXCR4, BM-MSCs express CCR1, CCR4, CCR7, CCR10, CCR9, CXCR5, and CXCR6, which are also involved in MSC migration (115). To reach the injured tissue, MSCs first adhere to vascular endothelial cells and cross the endothelial barrier in a process known as transendothelial migration (110). Studies investigating the mechanisms of adhesion between MSCs and microvascular endothelium indicate that MSCs display coordinated rolling and adhesion behavior on endothelial cells mediated by the very late antigen-4/vascular cell adhesion molecule-1 (VLA-4/VCAM-1) (107,131).

In addition to chemokines and adhesion molecules, several MMPs such as MMP-2 and membrane type 1 MMP (MT1-MMP) have proven to be essential to the invasiveness of MSCs (23,104). Notably, homing-related molecules in general can be upregulated by inflammatory cytokines such as tumor necrosis factor (TNF) and IL-1 (103), suggesting that different inflammation statuses might promote distinct MSC engraftment and therapeutic efficiencies (133).

MSC-BASED CELL THERAPY: CLINICAL TRIALS

Accumulating evidence of the remarkable potential of MSC-based therapy in the treatment of numerous diseases has been used to address their translation from the bench to the bedside. According to the official database of the US National Institutes of Health, 493 MSC-based clinical trials have been reported as of June 15, 2015; most were performed to evaluate the biomedical potential of MSCs in treating hematological diseases, GVHD, diabetes, inflammatory diseases, and diseases in the liver, kidneys, and lungs, as well as cardiovascular, bone and cartilage, neurological, and autoimmune diseases (Fig. 2A).

An important parameter used to describe the status of a clinical trial is its *phase of investigation* described by the US Food and Drug Administration (FDA). According to FDA guidelines, of the total five phases, phase 0 clinical trials encompass exploratory trials involving very limited human exposure and no therapeutic or diagnostic intent; phase I trials include safety studies that elucidate the most frequent and serious adverse events related to drug administration; phase II trials consist of studies that gather preliminary data on effectiveness in human patients; phase III trials encompass studies about the safety and effectiveness of newer treatments compared to standard and/or most well-known treatments; and phase IV trials are studies of FDA-approved drugs that delineate additional information including the drugs' risks, benefits, and optimal usage. Notably, phase I/II and phase II/III are mixtures of their respective phases.

Figure 3 reports the phases of investigation of the 493 MSC-based clinical trials (Fig. 3A) and the most representative treated pathologies (Fig. 3B). According to these data, most clinical trials occur in an early phase (phase I, I/II, or II), demonstrating that the therapeutic effectiveness of MSCs needs to be investigated. Furthermore, the long-term safety of MSC-based therapies remains poorly established and continues to pose a major limitation to translating MSCs into clinical practice.

MSCs IN HEMATOLOGICAL PATHOLOGIES AND GVHD

Although allogenic HSC transplantation is an effective therapy for several hematological pathologies (e.g., lymphoma, myeloma, and some leukemias), the major issues limiting its efficacy continue to be infections, bleeding, engraftment failure, and GVHD (41,119). In particular, GVHD is a form of rejection characterized by the attack of cells transplanted to host tissues and organs (e.g., the digestive tract, skin, and liver) and is associated with high morbidity and mortality (30). It has been acknowledged that acute GVHD (aGVHD) occurs in 30–80% of recipients depending on the extent of HLA-identical sibling and donor sources (138). Currently, corticosteroids are the gold standard for the initial treatment of aGVHD given their response rate of 50–80%. However, patients whose initial therapy failed showed only a 10–30% chance of long-term survival (21,140).

It is well documented that MSCs possess great immunosuppressive capacities and produce cytokines that can

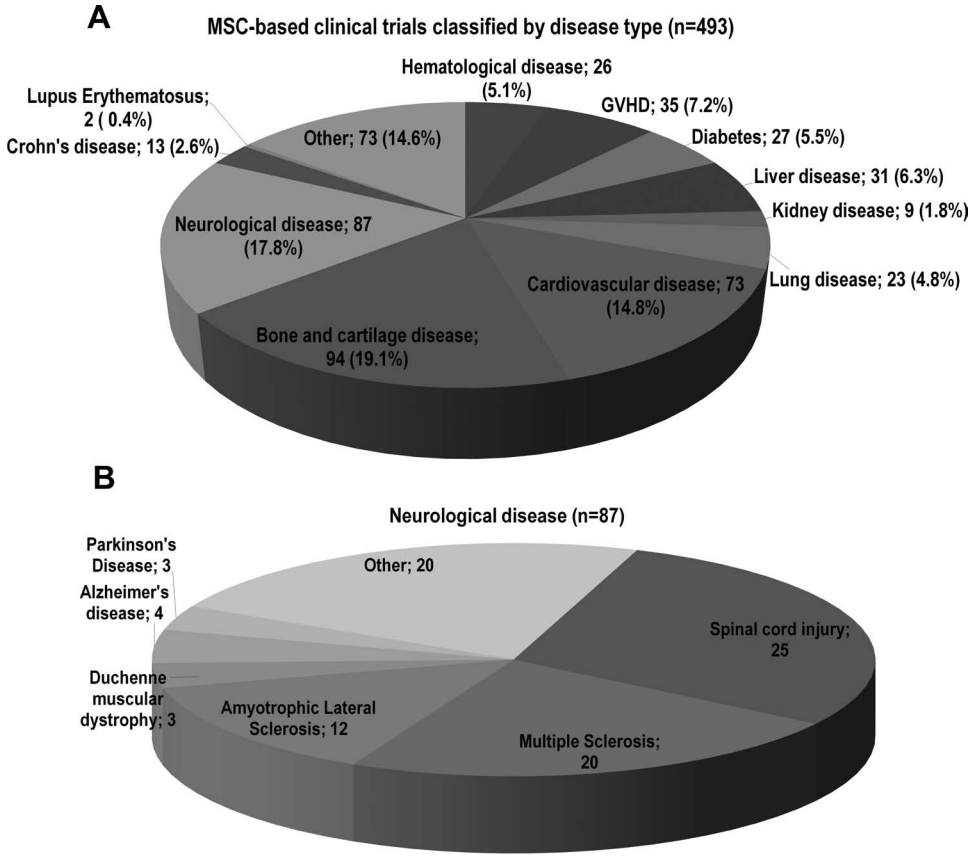
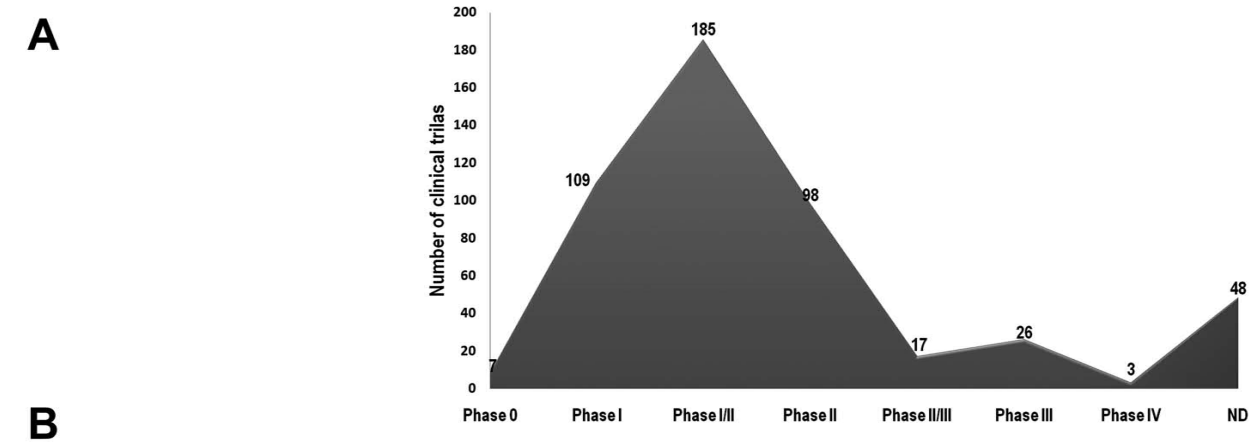


Figure 2. (A) The number and percentage of MSC-based clinical trials classified by disease type. (B) A subclassification of MSC-based clinical trials for neurological disease. Data from www.clinicaltrial.gov.

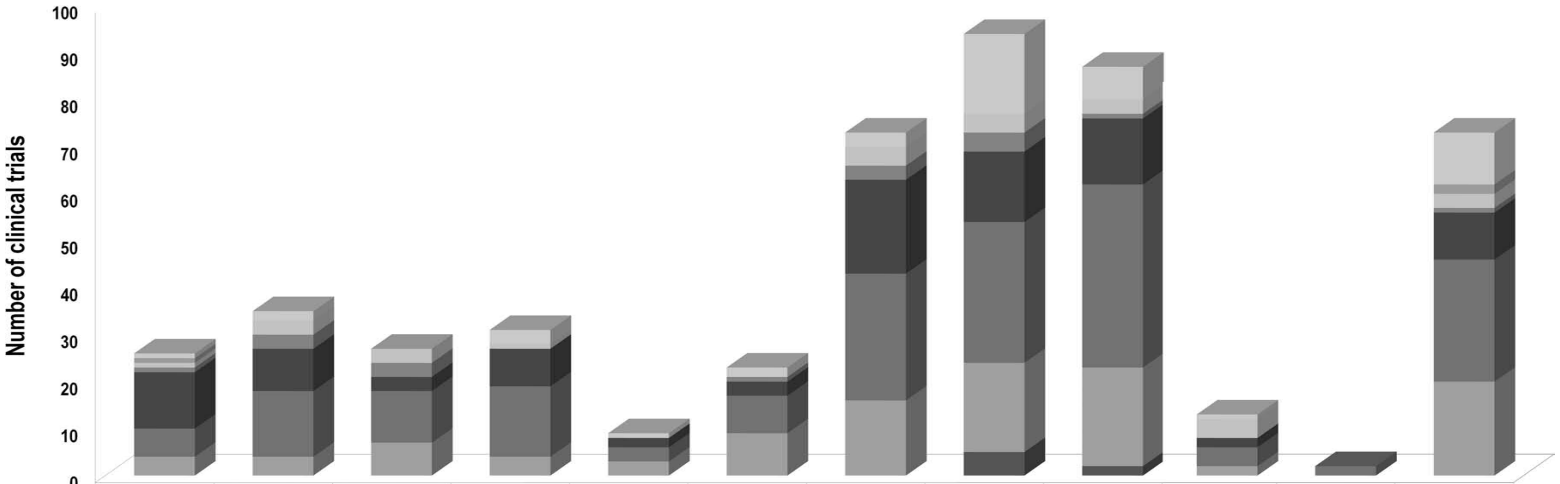
support hematopoiesis and potentially enhance marrow recovery following chemotherapy or radiotherapy (61,67). For these reasons, several researchers have sought to exploit MSCs in order to facilitate the engraftment of HSCs and lessen GVHD severity. Though some results remain controversial, most prospective and retrospective data suggest that MSCs are effective for aGVHD (60,65,69,92). In 2004, Le Blanc et al. first transplanted haploidentical MSCs in a 9-year-old boy receiving severe treatment for resistant grade IV aGVHD of the gut and liver. One-year follow-up observations reported a remarkable clinical response and no complications (68).

An interesting result supporting the effectiveness of MSC-based treatment for hematological malignancies was obtained in a case of a 20-year-old woman suffering from myelogenous leukemia. This patient underwent allogenic HSC and MSC transplantation from her haploidentical father, whose peripheral blood mononuclear cells (PBMNCs) were collected by leukapheresis after pretreatment with granulocyte colony-stimulating factor (GCSF). The products of leukapheresis were further purified to obtain $CD34^+$ HSCs that were infused into the patient. BM aspirate from the iliac crest of the patient's father was collected and plated in a culture to obtain MSCs, which when expanded, were infused following the transplantation of HSCs. As a result, the cells engrafted rapidly, and neither acute nor chronic GVDH were evident in the patient. Thirty-one months after transplantation, the patient exhibited an enduring trilineage hematological response and the complete remission of leukemia, suggesting that MSCs can be used effectively for genetically haploidentical HSC transplantation for acute leukemia (71).

Recently, Zhao et al. treated 47 patients with refractory aGVHD, 28 of whom received MSCs, while the 19 others were infused with saline. MSCs were given at a median dose of 1×10^6 cell/kg weekly until patients achieved complete recovery or had received eight doses of MSCs. After treatment, the overall response rate was 75% in the MSC group, compared with a rate of 42.1% in the vehicle-treated control group. The incidence of infections and tumor relapse did not differ between the groups during aGVHD treatment and follow-up. The authors thus reported that MSC-based treatment might be able to reduce the incidence and severity of chronic GVHD in aGVHD patients, chiefly by improving thymic function without increasing the risk of infection or tumor relapse (140).



B



	Hematological disease	GVHD	Diabetes	Liver disease	Kidney disease	Lung disease	Cardiovascular disease	Bone and cartilage disease	Neurological disease	Crohn's Disease	Lupus Erythematosus	Other
ND	1	2		3	1	2	3	17	7	1		11
Phase IV	1											2
Phase III	1	3	3	1			4	4	3	4		3
Phase II/III	1	3	3			1	3	4	1			1
Phase II	12	9	3	8	2	3	20	15	14	2		10
Phase I/II	6	14	11	15	3	8	27	30	39	4	2	26
Phase I	4	4	7	4	3	9	16	19	21	2		20
Phase 0								5	2			

Figure 3. The 493 MSC-based clinical trials classified according to (A) phase of investigation and (B) phase of investigation and disease type. Data from www.clinicaltrial.gov.

A study conducted by Xiao et al. suggested that treatment with MSCs from a related donor may be a promising therapeutic strategy for patients with refractory aplastic anemia (AA). These authors injected MSCs intravenously into 18 patients, 14 of whom had nonsevere AA, while the four others had severe AA. Though two patients experienced injection-related adverse events, including transient fever and headache, no major adverse events were reported during the follow-up period. After a year, 6 of the 18 patients (33%) had achieved complete or partial recovery to the MSC-based treatment. Moreover, among them, two achieved complete recovery, including the recovery of three hematopoietic cell lines after MSC-based therapy, two patients achieved red cell recovery, and two patients achieved platelet recovery. In the control group, only one patient (5.6%) achieved a partial recovery during the follow-up period (137). The data obtained suggested to the authors that treatment with MSCs from a related donor might represent an effective therapeutic strategy for patients with refractory AA.

Altogether, these results uphold the safety and feasibility of MSC-based therapy for treating hematological diseases and GVHD, as well as align with state-of-the-art clinical trials, mostly of phase I/II or II (Fig. 3A, B).

CARDIOVASCULAR DISEASES

Among MSC-based clinical trials, studies arranged for the treatment of cardiovascular disease represent a substantial proportion (14.8%) (Fig. 2A) and exhibit extremely promising therapeutic significance. Despite the progress of treatment options, ischemic heart diseases and congestive heart failure remain major causes of morbidity and mortality (131). The loss of cardiomyocytes following myocardial infarction induces a contractile dysfunction of the heart, and dead cardiac muscle cells become replaced with fibroblasts to form scar tissue. The transplantation of fetal cardiomyocytes or skeletal myoblasts has been proposed as a promising method for the cardiovascular recovery following myocardial infarction (22,125). Nevertheless, this process remains unfeasible given the difficulty of obtaining donor cells and the percentage of failures associated with attempts to achieve sufficient recovery of physiological function in transplanted hearts (41). Stem cell-based therapy aimed at regenerating damaged myocardium is an emerging treatment modality (79,80). At the same time, a considerable body of evidence from preclinical animal studies and clinical trials has indicated that intracoronary injection of MSCs or a mixed population of BM stem cells could represent a simple, effective approach in the treatment of heart diseases. An interesting study of a treatment for acute myocardial infarction conducted by Chen et al. observed 69 patients over the course of 12 h from the onset of infarction who underwent emergency angiography or angioplasty. After percutaneous coronary intervention (PCI), patients were randomly divided into groups that received either an intracoronary injection of BM-MSCs ($n=34$) or saline ($n=35$) groups. Sixty milliliters of BM from patients undergoing cell therapy was aspirated, and mononuclear cells were cultured for 10 days in order to obtain MSCs. Serial single positron emission computer tomography, cardiac echo, and cardiac electromechanical mapping were applied at designated intervals for 6 months after the transplantation of BM-MSCs or injection of saline. In the MSC therapy group, the percentage of hypokinetic, akinetic, and dyskinetic segments decreased significantly after 3 months; this result was obtained to a lesser extent in the control group. Wall movement velocity over the infarcted area increased significantly in MSC-treated patients, but not in those of the control group. Left ventricular ejection was greater in the cell therapy group than in the control group (12).

A different approach for treating myocardial infarction was presented by Katritsis et al., who acknowledged that the intracoronary transplantation of autologous BM-derived mononuclear cells could improve the contractility of infarcted hearts. However, the authors stated that although the administration of unpurified mononuclear cells avoids problems associated with cell culture expansion, it inevitably consists of a small percentage of pluripotent cells diluted among a massive amount of committed and differentiated cells. They thus hypothesized that a BM population consisting of culture-expanded MSCs along with endothelial progenitor cells (EPCs) also present in marrow stroma could promote both myogenesis by MSCs and angiogenesis by EPCs at the infarcted area of the myocardium (58). Their hypothesis built upon several studies suggesting that cell populations besides HSCs can give rise to ECs. In fact, adult BM-derived stem and progenitor cells distinct from HSCs have also been shown to differentiate into cells of an endothelial lineage (129).

Katritsis et al. enrolled patients who suffered anteroseptal myocardial infarction either recently or in the more distant past. All patients had previously been subjected to angioplasty and the stent implantation of the left anterior descending artery. On the day following PCI, the BM aspirates of some patients ($n=11$) were collected and the mononuclear cells isolated by classical Ficoll separation. Cells were plated in cultures, and after 7 days, the adherent cells were washed, collected, and transferred to the operating room, and the left coronary artery was catheterized for cell transplantation. Two cell suspensions, each containing $1–2\times10^6$ cells, were infused distally to the occluding balloon of the catheter. Both in the transplantation and control groups, an improving trend occurred for the end-diastolic and end-systolic diameter, fraction shortening, ejection fraction, end-diastolic, and end-systolic volume. In 5 of the 11 patients in the transplantation group, myocardial contractility improved at least

one previously nonviable myocardial segment, whereas no participant in the control group showed such improvement. The overall evaluation of results indicated that the positive effect of cell therapy on myocardial contractility occurs primarily in patients who have recently suffered myocardial infarction (58).

In 2011, Friis et al. were the first researchers to evaluate the safety and effectiveness of the intramyocardial injection of an autologous culture of expanded MSCs in patients suffering from stable coronary artery disease (CAD) and refractory angina. The results of the study were quite encouraging; MSC-treated patients showed significant enhancement in left ventricular function and exercise capacity, in addition to an improvement in clinical symptoms and Seattle Angina Questionnaire evaluations (34). Soon after, these positive results were confirmed by Mathiasen et al., who conducted a phase II trial exploiting the intramyocardial delivery of autologous MSCs in patients with chronic ischemic heart failure. A total of 60 patients were randomized in a 2:1 pattern to receive intramyocardial injection of either MSCs or a placebo. A total of 12–15 injections were placed in an ischemically viable region of the myocardium using the electromechanical NOGA-XP system. After 12 months, MSC infusion appeared to have induced the regeneration of damaged myocardial tissue, thereby confirming the safety of the treatment and the improved functional capacity of injured hearts (81).

To evaluate the efficacy of MSCs in therapies for ischemic cardiomyopathy (ICM), Hare et al. performed a noteworthy phase I/II clinical trial involving a randomized dose-finding comparison study (POSEIDON) of allogenic versus autologous MSCs delivered by transendocardial injection in patients with ICM. Both allogenic and autologous cells were found to be safe, and both types demonstrated potential regenerative bioactivity in ICM patients by reducing the infarct size and improving ventricular remodeling as measured by the sphericity index. Most patients who received allografted cells did not mount increased panel-reactive antibodies in response to the therapy (48). An intriguing speculation derived from this study is that the use of allogenic cells as off-the-shelf therapeutic agents can skirt the need for BM aspiration and tissue culture delays before treatment. A possible hypothesis is that the function of autologous MSCs could be impaired in patients with comorbidities or who are of advanced age (48).

Though a considerable number of studies have demonstrated the therapeutic effects of MSC transplantation, the exact underlying mechanism remains unclear. The leading theory is that the potential effects stem from paracrine effects exerted by the release of bioactive molecules by MSCs, which in turn activates resident cells in the heart to grow new blood vessels and cardiomyocytes. The discovery of resident cardiac stem cells supports such a theory (3). Although cardiac stem cells might not be an optimal cell source for clinical trials, for they require myocardial biopsies, there may be an interplay with transplanted MSCs increasing the regenerative potential of the latter cells (81).

Preclinical evidence reporting the infusion of in vitro predifferentiated MSCs represented an intriguing hypothesis to enhance the recovery of cardiac tissue following injury. Despite the beneficial effect exerted by predifferentiated MSCs on cardiac function, some criticisms arose from their long-lasting effect; indeed, it has been demonstrated to be short lived and disappear within 1 month, unlike undifferentiated MSCs, which were immune privileged and have been shown to survive long term in allogeneic myocardium, resulting in a significant improvement on cardiac function (54,90,136).

NEUROLOGICAL DISEASES

Cellular therapies represent a new frontier in the treatment of neurological diseases. In this context, MSCs factor into promising new approaches in neurological clinical work due to their ability to dampen inflammation, inhibit pathogenic immune responses, and release neuroprotective factors (127). Preclinical data show that MSC trophic properties and bioactive substances seem to effectively suppress neuroinflammation, decrease local lesions, and reduce the symptoms of neurological functional deficits (25,126).

To date, most clinical trials have focused chiefly on the long-term safety and efficacy of MSC-based therapies, as made clear by the abundance of phase I, I/II, and II clinical trials (Fig. 3A, B). However, MSCs also play roles in promising approaches for treating neurological diseases. Notably, most of the 88 MSC-based clinical trials involving the treatment of neurological disease targeted multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and spinal cord injury (Fig. 2B). MS is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that leads to cumulative and irreversible CNS damage (57,105). Over time, therapeutic approaches to MS have sought to suppress the immune system's control of the inflammatory process that causes demyelination and axonal damage (27,117). However, currently available treatments for MS are only partially effective, especially in the progressive phases of the disease (57).

Connick et al. conducted an interesting phase IIA study of autologous MSCs in secondary progressive MS in which they evaluated the safety and effectiveness of a cell-based treatment. Ten patients were infused with autologous MSCs administered intravenously at a dose of $1–2 \times 10^6$ cells/kg, after which they were monitored clinically for evidence of adverse reactions for a minimum of 4 h. Immediate adverse events consistent with type 1 hypersensitivity (e.g., pruritus, rash, and fever) were reported in only approximately 10% of patients following the intravenous administration of autologous or allogeneic MSCs.

Despite these promising preliminary results in determining the safety and feasibility of the intervention, the authors concluded that a longer follow-up period might be necessary to achieve sufficient power, and they remained committed to follow up with patients monthly (16).

Of note is another intriguing report by Karussis et al., in which both MS and ALS patients were infused with MSCs (57). ALS is a neurodegenerative disease that selectively affects motor neurons in the brain and spinal cord, thereby leading to bulbar, respiratory, and limb weakness (108). Previous efforts using various neuroprotective agents in both progressive MS and ALS patients did not yield successful results. On the basis of preclinical experience and data from clinical studies (82,83,87,106), Karussis et al. initiated an exploratory trial with autologous BM-MSC in 34 patients with intractable MS or progressive ALS. After culture, MSCs were injected either intrathecally ($n=34$) or intravenously ($n=14$) into 15 MS and 19 ALS patients. The 6–25 months of follow-up did not reveal any significant immediate or late adverse effects, yet indicated clinical stabilization and even improvement in some patients. Magnetic resonance imaging indicated the possible dissemination of MSCs from the lumbar site of transplantation to the occipital horns, meninges, spinal roots, and spinal cord parenchyma. An immunological analysis of lymphocyte subsets and cytokine production performed in 12 patients demonstrated the immediate immunomodulating effects of MSCs in vivo, starting as early as 4 h following MSC transplantation and including both an increase in $CD4^+$ $CD25^+$ regulatory cells and a reduction in the proportion of activated dendritic cells and lymphocytes, as well as of lymphocyte proliferation. Overall, these data clearly illustrate the feasibility and acceptable safety profile of the transplantation of autologous BM-MSCs in MS and ALS patients. The data obtained also demonstrated for the first time in human neurological diseases the systemic immunomodulatory effects of MSCs in vivo previously described in animal studies (57). The finding of early clinical stabilization or even improvement in some patients could be related to these immunomodulating effects. The possibility of neuroprotection and neuroregeneration via the transdifferentiation of MSCs into cells of neuronal or glial lineage, albeit theoretically viable, has yet to be proven by neuroimaging studies. Further controlled trials are thus warranted to evaluate the long-term safety and potential clinical efficacy of MSC transplantation.

Spinal cord injury (SCI) can cause devastating motor and sensory functional impairment, neurological deficits, and permanent paralysis. Despite various available methods for treating SCI, the prognosis often remains poor, and the recovery process is slow and inefficient (62,132). Yet one promising approach is an MSC-based treatment. Numerous preclinical studies have demonstrated that MSCs can improve anatomical and functional recovery in animal models of SCI (15,97,114,121). In a phase I clinical trial, Ra et al. intravenously infused eight male patients who had suffered SCI with autologous adipose MSCs (4×10^8 cells). At the 3-month follow-up, the safety of MSCs was demonstrated when no serious adverse events were detected. MSC system transplantation, moreover, did not induce tumor development (102). A few years later, Mendonça et al. conducted a phase I trial involving 14 patients of both genders with chronic traumatic SCI. A fixed cell number (5×10^6 cells/cm^3) was locally injected per lesion volume. Added to data supporting the general safety of the procedure and its tolerability, all patients remarkably displayed various improvements in tactile sensitivity, and eight patients in particular showed gains in lower limb motor function. Statistically significant correlations among improvements in neurological function and both injury size and level were also apparent (85).

Altogether, these studies have reported that autologous MSCs in treatments for MS, ALS, and SCI were safe and feasible and could promote neurological improvements. This evidence supports general data reporting an increase in MSC-based clinical trials for neurological disease in the last 3 years (132).

BONE AND CARTILAGE DISEASE

Since their first isolation, MSCs have been firmly associated with bone physiology given their pivotal role in the growth and lifelong turnover of tissues and in their native regenerative capacities. Moreover, this association has resounded with greater force in the age of regenerative medicine. The intrinsic ability of MSCs to differentiate into osteocytes and chondrocytes both in vitro and in vivo make them highly suitable candidates for the treatment of bone and cartilage disease. Indeed, most clinical trials (94 of 493) registered on the official database of US National Institutes of Health assessed this topic (Fig. 2A).

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a genetic disorder caused by dominant mutations in the type 1 collagen genes COL1A1 and COL1A2 characterized by osteopenia and multiple fractures, severe bone deformities, and considerably shortened stature. Given the lack of an effective cure for OI, promising results obtained with MSC-based therapies contributed to revealing an intriguing scenario to both researchers and clinicians (77). The first clinical trials in this context were performed by Horwitz et al., who demonstrated the feasibility of combined allogenic BM and MSC transplantation for children with severe OI (51). This preliminary study showed that mesenchymal progenitors in transplanted marrow could migrate to bone, thereby giving rise to osteoblasts that determined the improvement of bone structure. Consequently, the

authors confirmed these promising results by increasing the number of children treated with an MSC population isolated and purified from BM (50,52).

In 2005, Le Blanc et al. reported a novel clinical trial using in utero MSC allogenic transplantation in a female fetus with severe OI. After birth, the infant showed no immunoreactivity against the donor, and during the first 2 years, only three fractures were revealed. At follow-up, both normal psychomotor development and correct growth tendencies were observed (66). The long-term clinical course of the same patients submitted to a secondary transplantation of the same donor of MSCs at 8 years of age was further described in 2014; these results showed a low-level engraftment in bone and improved linear growth, mobility, and fracture incidence. These findings in turn provided further insights into the safety of fetal MSC engraftment, its likely clinical benefits, and the feasibility of retransplantation with the same donor cells. However, the authors concluded that further studies are required since the limited study could not produce any conclusive results (45).

Osteoarthritis (OA) is a form of arthritis characterized by the degeneration of articular cartilage accompanied by subchondral bone sclerosis and synovial inflammation (40). Its clinical manifestation includes joint pain and impaired movement that affects the surrounding tissue with local inflammation. OA is the most prevalent of chronic diseases affecting most of the population aged more than 65 years (77). Despite its prevalence and high morbidity, no treatment is yet available to improve or reverse the disease's process. In this sense, MSCs demonstrate promising prospects in their clinical application in OA patients. Considerable preclinical studies have demonstrated the potential of BM-MSCs to stimulate the regeneration of cartilage and halt the progressive destruction of joints (77).

In a fascinating pilot study, Orozco et al. administered the intra-articular injection of autologous BM-MSCs to treat 12 patients affected by chronic knee pain that was unresponsive to conservative treatments and showed radiological evidence of OA. Besides evidence of the treatments' feasibility and safety, follow-up at 1 year indicated its clinical efficacy. Indeed, patients showed a rapid, progressive improvement according to algofunctional indices, along with a decrease in poor cartilage area and an enhancement in cartilage quality (96). Taken together, these findings contribute to highlight the efficacy of MSC-based therapies for the treatment of chronic knee OA. Analogously intriguing were the results obtained by Wong et al., who reported a prospective randomized controlled clinical trial with a 2-year follow-up period. They analyzed the results of using intra-articular autologous BM-MSC injections in 28 patients undergoing high tibial osteotomy (HTO) and microfracture for knees with various cartilage defects. The results showed effective improvement in both the short-term clinical and 1-year postoperative outcomes in repaired cartilage tissue observed with magnetic resonance technology (134).

Despite these promising results, the clinical application of MSCs in OA and OI remains immature, and its effects need to be further investigated, as demonstrated by the prevalence of clinical trials of phases I/II and II (Fig. 3A, B).

LIVER, LUNG, AND KIDNEY INJURY

Given their abilities to immunomodulate, differentiate, and release bioactive molecules, MSCs have been shown to be effective in the treatment of many organ diseases triggered by tissue injury and/or degeneration. Clinical observations reported the efficacy of these cells, once infused, in ameliorating tissue damage and/or improving function after lung injury (20), kidney disease (1), and liver injury (56,84). Indeed, from 2012 onward, the number of MSC-based clinical trials conducted for the treatment of these pathologies has increased (Fig. 2A) (132,133).

The lungs are highly susceptible to edema and endothelial permeability caused by traumatic injury and represent good targets for MSC-based cell therapy, given the ability of MSCs to preserve and restore pulmonary endothelium and decrease inflammation (73). Recent clinical trials have clearly assessed the safety and feasibility of using MSCs intravenously administrated for the treatment of patients affected by moderate or severe acute respiratory distress syndrome and idiopathic pulmonary fibrosis (8,88).

MSCs seem to pose great promise for the treatment of impaired livers, especially those affected by advanced fibrosis. Zhang et al. examined the safety and efficacy of umbilical cord-derived MSC (UC-MSC) transfusion in patients affected by liver cirrhosis. Clinical parameters detected during a 1-year follow-up period showed significantly improved liver function in patients who received UC-MSCs, as well as no significant side effects or complications (139). Similarly encouraging results were obtained by Shi et al., who assessed the efficacy of UC-MSCs for treating acute-on-chronic liver failure (ACLF), a severe, life-threatening condition affecting chronic hepatitis B patients. These authors demonstrated that UC-MSC transfusions significantly increased the survival rates of ACLF patients, reduced the model for end-stage liver disease scores, and increased liver function (113). In sum, these data demonstrate that UC-MSC transfusions are safe and may serve as a novel therapeutic approach for liver diseases.

Given their complex pathophysiology, acute and chronic kidney injuries after transplantation have been considered to pose problems in clinical work, yet also to

have paved the way for the clinical introduction of MSC-based cell therapies. Despite promising preclinical results obtained with animal models that indicated the effectiveness of MSCs in reducing acute and chronic kidney injuries, clinical trials remain in the early phases and largely aim to investigate the safety and efficacy of allogenic MSC infusion (38,88). Preliminary data described by Gooch et al. indicate that the infusion of allogenic MSCs seemed to prevent all complications in patients with post-cardiopulmonary bypass-induced acute kidney injury (AKI) and promote kidney recovery. Their data demonstrated that MSC infusion also prevented all postoperative renal failure (0% vs. 20% AKI incidence compared with the case control) and thus abbreviated hospitalization (44). Analogously, Togel and Westenfelder reported a clinical study of 16 patients undergoing on-pump cardiac surgery, all of whom were identified as being at high risk of postoperative AKI. They demonstrated that MSC infusions were safe in all tested dosages and offered evidence of the protective effect of these cells on kidney function and abbreviated hospitalization length compared with historical case controls (124).

As shown in Figure 3A and B, though most aforementioned clinical trials have been of early phases (e.g., phase I/II), their increase in the last 3 years and their promising preliminary results offer proof of the wide range of applications of MSCs in clinic practice.

CHRONIC INFLAMMATORY AND AUTOIMMUNE DISEASES

MSCs have also shown promise in playing an immediate anti-inflammatory, immunomodulatory role in some autoimmune diseases with little evidence of toxicity (131). Preclinical studies have demonstrated that MSCs are effective in the treatment of autoimmune diseases such as systemic lupus erythematosus (SLE), a chronic autoimmune disease with significant morbidity and mortality characterized by highly diverse clinical manifestations that can affect any organs in the body (130). The conventional treatment of SLE relies primarily on high doses of corticosteroids, cyclophosphamides, and other immunosuppressive and biological agents. Although these drugs have prompted markedly improved outcomes in SLE patients (19), a subset of patients may suffer severe side effects, including infection, ovarian failure, and secondary malignancy (53,59,94), which remain the important causes of mortality in SLE patients. Therefore, more effective, less toxic treatments are needed. Clinical studies of MSC-based treatments conducted in refractory and severe SLE patients resulted in the induction of clinical remission and improvements in serological markers of organ dysfunction (74,118,130). To date, two clinical trials with MSCs for SLE in an unknown status are available in an online database (www.clinicaltrials.gov).

Recently, investigators also sought to use MSCs to treat Crohn's disease, a chronic inflammatory disorder of the gastrointestinal tract. Refractory patients have not responded to conventional treatments involving steroids or immunosuppressive agents or anti-TNF therapy (131). Following a pilot study, Duijvestein et al. reported that autologous BM-MSC injection in patients with refractory Crohn's disease was an encouraging therapy. In five of eight MSC-treated patients, Crohn's disease activity index scores improved, and clinical responses were observed in the other three patients (26). In 2011, another pilot study was performed with 10 patients with fistulizing Crohn's disease. MSCs were injected into both the lumen and wall of the fistula tracts. After 12 months, sustained complete closure was achieved in seven cases and incomplete closure in three cases, all of the fistula tracts with a parallel reduction of Crohn's disease, of the perianal disease activity index, and of rectal mucosal healing (13). The same authors assessed the long-term outcomes of the same patients from 2007 to 2014 and confirmed the previous encouraging results (14).

ORGAN TRANSPLANTATION

Given their immunological characteristics, such as low immunogenicity and immunoregulatory properties, MSCs may also offer therapeutic opportunities in organ transplantation. Preclinical studies evidenced the effectiveness of MSCs in regulating the invoked immune response in settings such as tissue injury, transplantation, and autoimmunity, and paved the way for their use in treating GVHD induced by solid organ transplantation as well as repairing damaged tissue(s) (122). Ding and colleagues demonstrated the role played by MSCs in preventing rejection and leading to long-term normoglycemia in a mouse pancreatic-islet allograft model (23). Regardless of the encouraging results of preclinical studies, key issues need to be addressed before MSC-based therapies become a safe option for clinical studies (31).

The main clinical trials on the matter are still ongoing (11 of 493, grouped in the section "Other") (Fig. 2A) and focus on MSC administration following kidney and liver transplantation. Despite the promising results about the safety of the procedure and beneficial effects, cautious optimism has to be addressed in the immediate future (100). In 2013, Peng and colleagues carried out a non-randomized trial to assess safety and efficacy of donor BM-MSC in living-donor kidney transplant (LDKT) recipients. They demonstrated that direct MSC injection into the renal artery, along with standard immunosuppressive therapy, was safe as well as MSC recipients maintained stable graft function during 1-year follow-up and displayed higher numbers of peripheral B-memory ($CD27^+$) cells at 3 months (98).

Table 1. Status of MSC-Based Clinical Trials

	Open Studies		Closed Studies						Open/Closed Studies
Pathology	Recruiting	Not Yet Recruiting	Completed	Terminated	Active Not Recruiting	Enrolling by Invitation	Withdrawn	Suspended	Unknown
Overall	184	31	104	8	49	16	6	3	92
Hematological disease	12	3	4	1	0	2	0	0	4
GVHD	15	0	7	0	3	1	0	0	9
Diabetes	9	2	3	0	3	1	0	0	9
Liver disease	8	1	3	1	2	2	0	0	14
Kidney disease	2	1	1	2	0	0	0	0	3
Lung disease	13	1	4	1	2	0	0	0	2
Cardiovascular disease	30	7	19	1	8	1	1	1	5
Bone and cartilage disease	30	3	29	1	15	3	1	0	14
Neurological disease	29	6	20	1	8	5	2	2	14
Crohn's disease	6	0	4	0	2	0	0	0	1
Lupus erythematosus	0	0	0	0	0	0	0	0	2
Other	31	7	10	0	6	1	2	0	16

The table reports the 493 MSC-based clinical trials (overall) classified by status and disease type. *Recruiting*: The study is currently recruiting participants. *Not yet recruiting:* The study has not started recruiting participants. *Completed:* The study has ended normally, and participants are no longer being examined or treated (i.e., the "last subject, last visit" has occurred). *Terminated:* The study has stopped recruiting or enrolling participants early and will not start again. Participants are no longer being examined or treated. *Active, not recruiting:* The study is ongoing (i.e., participants are receiving an intervention or being examined), but potential participants are not currently being recruited or enrolled. *Enrolling by invitation:* A study that selects its participants from a population or group of people decided on in advance by the researchers. These studies are not open to everyone who meets the eligibility criteria, but only to people in that particular population who are specifically invited to participate. *Withdrawn:* The study stopped early, before enrolling its first participant. *Suspended:* The study has stopped recruiting or enrolling participants early, but may start again. *Unknown:* A study in ClinicalTrials.gov with a status of Recruiting, Not yet recruiting, or Active, not recruiting and whose status has not been verified within the past 2 years. Studies with an Unknown recruitment status are considered open studies or closed studies, depending on their last known recruitment status. Data from www.ClinicalTrials.gov.

Table 2. MSC-Based Clinical Trials in a Completed Status

Pathology	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	ND
Overall	31	40	15	3	4	1	10
Hematological disease	1	2	1	0	0	0	0
GVHD	0	4	2	0	1	0	0
Diabetes	1	1	0	0	0	0	1
Liver disease	0	3	0	0	0	0	0
Kidney disease	0	0	0	0	0	0	1
Lung disease	3	0	1	0	0	0	0
Cardiovascular disease	2	11	4	1	0	0	1
Bone and cartilage disease	12	8	3	1	2	0	3
Neurological disease	9	8	2	0	0	0	1
Crohn's disease	0	1	1	1	0	0	1
Lupus erythematosus	0	0	0	0	0	0	0
Other	3	2	1	0	1	1	2

The table reports the completed MSC-based clinical trials classified by phase of investigation and disease type. Data from www.ClinicalTrials.gov.

An interesting clinical trial, still ongoing, aims at evaluating the safety and tolerability of MSC administration after liver or kidney organ transplantation. Ten patients undergoing liver transplantation and 10 patients undergoing kidney transplantation have been selected to receive a single infusion of MSCs (www.clinicaltrials.gov; #NCT01429038). Their results will provide further insights about the clinical use of MSC in organ transplantation.

MSC-BASED CLINICAL TRIALS: EVIDENCE AND CRITICISM

In this review, we offer evidence showing that in the last 3 years, the number of MSC-based clinical trials has nearly doubled, surpassing the 206 studies described by Wang et al. in 2012 (132) to the current tally of 493 (Fig. 2A). Most clinical trials are phase I ($n=109$), phase I/II ($n=185$), and phase II ($n=98$) trials; only a few are of phase II/III ($n=17$) or phase III ($n=26$) (Fig. 3A). Interestingly, this stratification is observed even considering the phases of investigation of single disease trials (Fig. 3B). Notably, a high number of the 493 reported trials are ongoing; 184 are in recruiting status versus the 104 that have been completed (Tables 1 and 2). These studies' conclusions will be extremely informative in terms of providing evidence that MSC infusion and administration seem to be well tolerated, as well as support preliminary observations underscoring that the efficacy of MSC-based therapy is primarily restricted to GVHD and hematological, bone, and cartilage diseases.

These findings seem to highlight that the beneficial effect of MSC-based treatment could be principally due by the immunomodulation and regenerative potential of these cells. Indeed, it has to be pointed out that the inflammation-causing tissue damage triggered in response to injury and disease is a key aspect of many pathologies, so the beneficial effect of MSCs could be ascribed to both immunomodulatory and regenerative properties. This joint action may contribute to MSC therapeutic potential for the treatment of any tissue or organ damage associated with intense inflammatory activity (e.g., rheumatoid arthritis, kidney failure, heart injury, multiple sclerosis) (3,33). Indeed, it has been demonstrated that MSC-based therapy seemed to modulate aberrant immune responses causing demyelination and axonal injury associated with MS, as well as to repair and restore damaged CNS tissue and cells (2).

Overall, these data indicate that much work remains to be done before MSCs can pass from the bench to the bedside. Issues such as donor heterogeneity, ex vivo expansion, immunogenicity, and cryopreservation can be considered the Achilles's heel of MSC-based therapies (35,37).

According to the minimal criteria suggested by ISCT, current procedures for MSCs isolation, expansion, and use in therapy are standardized toward isolating and cultivating a nonclonal population of stromal cells. Nevertheless, every nonclonal population of MSCs may contain a different percentage of stem cells, which in turn may affect the biological properties of the total population, including its immunoregulatory capacity. Therefore, the percentage of stem and progenitor cells in each batch of MSCs has to be accurately evaluated before being administered to patients. A reliable assay (e.g., CFU-F assay) and the evaluation of the multipotential capacity of each CFU clone may allow the identification of the percentage of stem cells and their multilineage potential in each sample of nonclonal MSCs (36).

Although in vitro expansion is a necessary procedure to guarantee the elevated number of MSCs employed in

each administration, it is also considered to pose important issues. The lack of standardized procedures regulating ex vivo expansion greatly affects MSC properties, and it has been demonstrated that in vitro growth of MSCs can give rise to replicative senescence. Senescent cells are non-functional cells that may affect the activity of surrounding healthy cells by releasing several paracrine factors (5). Senescent cells therefore have to be avoided to preserve the therapeutic potential of any cell batch destined for clinical use. A direct positive link between the early passage of MSCs and clinical outcomes in GVHD has been demonstrated (65). The development of standardized procedures along with the use of reliable methods, including in situ senescence associated with β galactosidase assay and/or a related assay, may allow the identification of the percentage of senescent cells in every MSC sample and contribute to overcoming their adverse effects (36).

Another issue affecting the reliability of MSC-based therapy is the donor heterogeneity. It could be considered as a combination of the aforementioned issues and may affect the biological properties of MSCs even before their ex vivo expansion.

Therefore, introduction of standardized procedures that couple those regulating MSC isolation and ex vivo expansion could contribute to overcoming any divergence in clinical outcome and lead to a faster translation of MSCs into clinical practice.

Overall the evidence presented contributes to fueling the controversy about the clinical use of MSCs; it has been acknowledged that the occurrence, type, and severity of adverse events may vary significantly between different populations and according to different MSC characteristics (e.g., isolation procedure, ex vivo expansion, dose, type) and the nature of the disease being treated (63). Moreover, if no severe side effects have been observed so far, long-term benefits remain uncertain. Indeed, regardless of the kind of pathology and the clinical settings, the median follow-up is still limited in terms of long-term effects, in particular with respect to the evaluation of MSC tumorigenic potential (76,85).

However, most clinical trials are still ongoing, and their conclusions will provide insights on these issues; preclinical data regarding mechanisms of action, long-term safety, and efficacy will also corroborate the evidence supporting the clinical use of MSCs.

CONCLUSION

Looking at both the completed and ongoing clinical trials, MSC-based therapies seem to maintain the promise of safety and to demonstrate that MSC infusion and administration are well tolerated. However, much work remains to be done before MSCs can pass from the bench to the bedside; issues such as donor heterogeneity, ex vivo expansion, immunogenicity, and cryopreservation can be considered the Achilles' heel of MSC-based therapies. Thus, their clinical use must be strictly regulated since it is not possible to claim that every tissue damage or immunological disease may be treated with MSCs. This implies that in the near future the efforts of researchers and clinicians will be addressed to the disclosure of the mechanisms influencing their therapeutic use.

ACKNOWLEDGMENTS: This work was partially supported by grants from the National Operational Program for Research and Competitiveness 2007–2013 (PON) PON01_1802 "Sviluppo di molecole capaci di modulare vie metaboliche intracellulari redox-sensibili per la prevenzione e la cura di patologie infettive, tumorali, neurodegenerative e loro delivery mediante piattaforme nano tecnologiche." The authors declare no conflicts of interest.

REFERENCES

1. Alfarano, C.; Roubeix, C.; Chaaya, R.; Ceccaldi, C.; Calise, D.; Mias, C.; Cussac, D.; Bascands, J. L.; Parini, A. Intraparenchymal injection of bone marrow mesenchymal stem cells reduces kidney fibrosis after ischemia-reperfusion in cyclosporine-immunosuppressed rats. Cell Transplant. 21(9):2009–2019; 2007.
2. Auletta, J. J.; Bartholomew, A. M.; Maziarz, R. T.; Deans, R. J.; Miller, R. H.; Lazarus, H. M.; Cohen, J. A. The potential of mesenchymal stromal cells as a novel cellular therapy for multiple sclerosis. Immunotherapy 4(5):529–547; 2012.
3. Bearzi, C.; Rota, M.; Hosoda, T.; Tillmanns, J.; Nascimbene, A.; De Angelis, A.; Yasuzawa-Amano, S.; Trofimova, I.; Siggins, R. W.; Lecapitaine, N.; Cascapera S.; Beltrami, A. P.; D'Alessandro, D. A.; Zias E.; Quaini, F.; Urbanek, K.; Michler, R. E.; Bolli, R.; Kajstura, J.; Leri A.; Anversa, P. Human cardiac stem cells. Proc. Natl. Acad. Sci. USA 104(35):14068–14073; 2007.
4. Bernardo, M. E.; Fibbe, W. E. Mesenchymal stromal cells: Sensors and switchers of inflammation. Cell Stem Cell 13(4):392–402; 2013.
5. Campisi, J.; d'Adda di Fagagna, F. Cellular senescence: When bad things happen to good cells. Nat. Rev. Mol. Cell Biol. 8(9):729–740; 2007.
6. Caplan, A. I.; Dennis, J. E. Mesenchymal stem cells as trophic mediators. J. Cell. Biochem. 98(5):1076–1084; 2006.
7. Castro-Manrreza, M. E.; Montesinos, J. J. Immunoregulation by mesenchymal stem cells: Biological aspects and clinical applications. J. Immunol. Res. 2015:394917; 2015.
8. Chambers, D. C.; Gellatly, S. L.; Hugenholtz, P.; Hansbro, P. M. JTD special edition 'Hot Topics in COPD'—The microbiome in COPD. J. Thorac. Dis. 6(11):1525–1531; 2014.
9. Chao, K. C.; Chao, K. F.; Fu, Y. S.; Liu, S. H. Islet-like clusters derived from mesenchymal stem cells in Wharton's Jelly of the human umbilical cord for transplantation to control type 1 diabetes. PLoS One 3(1):e1451; 2008.
10. Chen, L.; Tredget, E. E.; Wu, P. Y.; Wu, Y. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. PLoS One 3(4):e1886; 2008.
11. Chen, L. B.; Jiang, X. B.; Yang, L. Differentiation of rat marrow mesenchymal stem cells into pancreatic islet beta-cells. World J. Gastroenterol. 10(20):3016–3020; 2004.
12. Chen, S. L.; Fang, W. W.; Qian, J.; Ye, F.; Liu, Y. H.; Shan, S. J.; Zhang, J. J.; Lin, S.; Liao, L. M.; Zhao, R.

C. Improvement of cardiac function after transplantation of autologous bone marrow mesenchymal stem cells in patients with acute myocardial infarction. Chin. Med. J. (Engl) 117(10):1443–1448; 2004.
13. Ciccocioppo, R.; Bernardo, M. E.; Sgarella, A.; Maccario, R.; Avanzini, M. A.; Ubezio, C.; Minelli, A.; Alvisi, C.; Vanoli, A.; Calliada, F.; Dionigi, P.; Perotti, C.; Locatelli, F.; Corazza, G. R. Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease. Gut 60(6):788–798; 2011.
14. Ciccocioppo, R.; Gallia, A.; Sgarella, A.; Kruzliak, P.; Gobbi, P. G.; Corazza, G. R. Long-term follow-up of Crohn disease fistulas after local injections of bone marrow-derived mesenchymal stem cells. Mayo Clin. Proc. 90(6):747–755; 2015.
15. Cizkova, D.; Novotna, I.; Slovinska, L.; Vanicky, I.; Jergova, S.; Rosocha, J.; Radonak, J. Repetitive intrathecal catheter delivery of bone marrow mesenchymal stromal cells improves functional recovery in a rat model of contusive spinal cord injury. J. Neurotrauma 28(9):1951–1961; 2011.
16. Connick, P.; Kolappan, M.; Patani, R.; Scott, M. A.; Crawley, C.; He, X. L.; Richardson, K.; Barber, K.; Webber, D. J.; Wheeler-Kingshott, C. A.; Tozer D. J.; Samson R. S.; Thomas D. L.; Du M. Q.; Luan S. L.; Michell A. W.; Altmann D. R.; Thompson A. J.; Miller D. H.; Compston A.; Chandran S. The mesenchymal stem cells in multiple sclerosis (MSCIMS) trial protocol and baseline cohort characteristics: An open-label pre-test:post-test study with blinded outcome assessments. Trials 12:62; 2011.
17. Covas, D. T.; Piccinato, C. E.; Orellana, M. D.; Siufi, J. L.; Silva, W. A., Jr.; Proto-Siqueira, R.; Rizzatti, E. G.; Neder, L.; Silva, A. R.; Rocha, V.; Zago, M. A. Mesenchymal stem cells can be obtained from the human saphena vein. Exp. Cell. Res. 309(2):340–344; 2005.
18. Crisostomo, P. R.; Wang, Y.; Markel, T. A.; Wang, M.; Lahm, T.; Meldrum, D. R. Human mesenchymal stem cells stimulated by TNF-alpha, LPS, or hypoxia produce growth factors by an NF kappa B- but not JNK-dependent mechanism. Am. J. Physiol. Cell Physiol. 294(3):C675–682; 2008.
19. Crow, M. K. Developments in the clinical understanding of lupus. Arthritis Res. Ther. 11(5):245; 2009.
20. Curley, G. F.; Hayes, M.; Ansari, B.; Shaw, G.; Ryan, A.; Barry, F.; O'Brien, T.; O'Toole, D.; Laffey, J. G. Mesenchymal stem cells enhance recovery and repair following ventilator-induced lung injury in the rat. Thorax 67(6):496–501; 2012.
21. Deeg, H. J. How I treat refractory acute GVHD. Blood 109(10):4119–4126; 2007.
22. Delcarpio, J. B.; Claycomb, W. C. Cardiomyocyte transfer into the mammalian heart. Cell-to-cell interactions in vivo and in vitro. Ann. NY Acad. Sci. 752:267–285; 1995.
23. Ding, Y.; Xu, D.; Feng, G.; Bushell, A.; Muschel, R. J.; Wood, K. J. Mesenchymal stem cells prevent the rejection of fully allogenic islet grafts by the immunosuppressive activity of matrix metalloproteinase-2 and -9. Diabetes 58(8):1797–1806; 2009.
24. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.; Krause, D.; Deans, R.; Keating, A.; Prockop, D.; Horwitz, E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8(4):315–317; 2006.
25. Drela, K.; Siedlecka, P.; Sarnowska, A.; Domanska-Janik, K. Human mesenchymal stem cells in the treatment of neurological diseases. Acta Neurobiol. Exp. (Wars) 73(1):38–56; 2013.
26. Duijvestein, M.; Vos, A. C.; Roelofs, H.; Wildenberg, M. E.; Wendrich, B. B.; Verspaget, H. W.; Kooy-Winkelaar, E. M.; Koning, F.; Zwaginga, J. J.; Fidder, H. H.; Verhaar, A. P.; Fibbe W. E.; van den Brink, G. R.; Hommes, D. W. Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: Results of a phase I study. Gut 59(12):1662–1669; 2010.
27. Einstein, O.; Grigoriadis, N.; Mizrachi-Kol, R.; Reinhartz, E.; Polyzoidou, E.; Lavon, I.; Milonas, I.; Karussis, D.; Abramsky, O.; Ben-Hur, T. Transplanted neural precursor cells reduce brain inflammation to attenuate chronic experimental autoimmune encephalomyelitis. Exp. Neurol. 198(2):275–284; 2006.
28. Erices, A.; Conget, P.; Minguell, J. J. Mesenchymal progenitor cells in human umbilical cord blood. Br. J. Haematol. 109(1):235–242; 2000.
29. Fei, X.; Jiang, S.; Zhang, S.; Li, Y.; Ge, J.; He, B.; Goldstein, S.; Ruiz, G. Isolation, culture, and identification of amniotic fluid-derived mesenchymal stem cells. Cell Biochem. Biophys. 67(2):689–694; 2013.
30. Ferrara, J. L.; Reddy, P. Pathophysiology of graft-versus-host disease. Semin. Hematol. 43(1):3–10; 2006.
31. Figliuzzi, M.; Bonandrini, B.; Silvani, S.; Remuzzi, A. Mesenchymal stem cells help pancreatic islet transplantation to control type 1 diabetes. World J. Stem Cells 6(2):163–172; 2014.
32. Forte, A.; Finicelli, M.; Mattia, M.; Berrino, L.; Rossi, F.; De Feo, M.; Cotrufo, M.; Cipollaro, M.; Cascino, A.; Galderisi, U. Mesenchymal stem cells effectively reduce surgically induced stenosis in rat carotids. J. Cell Physiol. 217(3):789–799; 2008.
33. Friedenstein, A. J.; Petrakova, K. V.; Kurolesova, A. I.; Frolova, G. P. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation 6(2):230–247; 1968.
34. Friis, T.; Haack-Sorensen, M.; Mathiasen, A. B.; Ripa, R. S.; Kristoffersen, U. S.; Jorgensen, E.; Hansen, L.; Bindslev, L.; Kjaer, A.; Hesse, B.; Dickmeiss, E.; Kastrup, J. Mesenchymal stromal cell derived endothelial progenitor treatment in patients with refractory angina. Scand. Cardiovasc. J. 45(3):161–168; 2011.
35. Galderisi, U.; Giordano, A. The gap between the physiological and therapeutic roles of mesenchymal stem cells. Med. Res. Rev. 34(5):1100–1126; 2014.
36. Galderisi, U.; Calarco, A.; Melone, M. A. B.; Peluso, G. Is it possible to improve the success rate of cellular therapy based on mesenchymal stem cells? J. Stem Cells Res. Rev. Rep. 1(3):03; 2014.
37. Galipeau, J. The mesenchymal stromal cells dilemma—Does a negative phase III trial of random donor mesenchymal stromal cells in steroid-resistant graft-versus-host disease represent a death knell or a bump in the road? Cytotherapy 15(1):2–8; 2013.
38. Gaspari, F.; Cravedi, P.; Mandala, M.; Perico, N.; de Leon, F. R.; Stucchi, N.; Ferrari, S.; Labianca, R.; Remuzzi, G.; Ruggenenti, P. Predicting cisplatin-induced acute kidney injury by urinary neutrophil gelatinase-associated lipocalin excretion: A pilot prospective case-control study. Nephron. Clin. Pract. 115(2):c154–160; 2010.

39. Ghannam, S.; Pène, J.; Moquet-Torcy, G.; Jorgensen, C.; Yssel, H. Mesenchymal stem cells inhibit human Th17 cell differentiation and function and induce a T regulatory cell phenotype. J. Immunol. 185(1):302–312; 2010.
40. Gharbi, M.; Deberg, M.; Henrotin, Y. Application for proteomic techniques in studying osteoarthritis: A review. Front. Physiol. 2:90; 2011.
41. Giordano, A.; Galderisi, U.; Marino, I. R. From the laboratory bench to the patient's bedside: An update on clinical trials with mesenchymal stem cells. J. Cell Physiol. 211(1):27–35; 2007.
42. Gong, X.; Sun, Z.; Cui, D.; Xu, X.; Zhu, H.; Wang, L.; Qian, W.; Han, X. Isolation and characterization of lung resident mesenchymal stem cells capable of differentiating into alveolar epithelial type II cells. Cell. Biol. Int. 38(4):405–411; 2014.
43. González, M. A.; Gonzalez-Rey, E.; Rico, L.; Büscher, D.; Delgado, M. Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells. Arthritis Rheum. 60(4):1006–1019; 2009.
44. Gooch, A.; Doty, J.; Flores, J.; Swenson, L.; Toegel, F.E.; Reiss, G.R.; Lange, C.; Zander, A.R.; Hu, Z.; Poole, S.; Zhang, P.; Westenfelder, C. Initial report on a phase I clinical trial: Prevention and treatment of post-operative Acute Kidney Injury with allogeneic Mesenchymal Stem Cells in patients who require on-pump cardiac surgery. Cell Ther. Transplant. 1:31–35; 2008.
45. Gotherstrom, C.; Westgren, M.; Shaw, S. W.; Astrom, E.; Biswas, A.; Byers, P. H.; Mattar, C. N.; Graham, G. E.; Taslimi, J.; Ewald, U.; Fisk, N. M.; Yeoh, A. E.; Lin, J. L.; Cheng, P. J.; Choolani, M.; Le Blanc, K.; Chan, J .K. Pre- and postnatal transplantation of fetal mesenchymal stem cells in osteogenesis imperfecta: A two-center experience. Stem Cells Transl. Med. 3(2):255–264; 2014.
46. Gullo, F.; De Bari, C. Prospective purification of a subpopulation of human synovial mesenchymal stem cells with enhanced chondro-osteogenic potency. Rheumatology (Oxford) 52(10):1758–1768; 2013.
47. Han, Z.; Jing, Y.; Zhang, S.; Liu, Y.; Shi, Y.; Wei, L. The role of immunosuppression of mesenchymal stem cells in tissue repair and tumor growth. Cell. Biosci. 2(1):8; 2012.
48. Hare, J. M.; Fishman, J. E.; Gerstenblith, G.; Di Fede Velazquez, D. L.; Zambrano, J. P.; Suncion, V. Y.; Tracy, M.; Ghersin, E.; Johnston, P. V.; Brinker, J. A.; Breton, E.; Davis-Sproul, J.; Schulman, I. H.; Byrnes, J.; Mendizabal, A. M.; Lowery, M. H.; Rouy, D.; Altman, P.; Wong Po Foo, C.; Ruiz, P.; Amador, A.; Da Silva, J.; McNiece, I. K.; Heldman, A. W.; George, R.; Lardo, A. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: The POSEIDON randomized trial. JAMA 308(22):2369–2379; 2012.
49. Heidari, B.; Shirazi, A.; Akhondi, M. M.; Hassanpour, H.; Behzadi, B.; Naderi, M. M.; Sarvari, A.; Borjian, S. Comparison of proliferative and multilineage differentiation potential of sheep mesenchymal stem cells derived from bone marrow, liver, and adipose tissue. Avicenna J. Med. Biotechnol. 5(2):104–117; 2013.
50. Horwitz, E. M.; Gordon, P. L.; Koo, W. K.; Marx, J. C.; Neel, M. D.; McNall, R. Y.; Muul, L.; Hofmann, T. Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: Implications for cell therapy of bone. Proc. Natl. Acad. Sci. USA 99(13):8932–8937; 2002.
51. Horwitz, E. M.; Prockop, D. J.; Fitzpatrick, L. A.; Koo, W. W.; Gordon, P. L.; Neel, M.; Sussman, M.; Orchard, P.; Marx, J. C.; Pyeritz, R. E.; Brenner, M. K. Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. Nat. Med. 5(3):309–313; 1999.
52. Horwitz, E. M.; Prockop, D. J.; Gordon, P. L.; Koo, W. W.; Fitzpatrick, L. A.; Neel, M. D.; McCarville, M. E.; Orchard, P. J.; Pyeritz, R. E.; Brenner, M. K. Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. Blood 97(5):1227–1231; 2001.
53. Houssiau, F. A.; Ginzler, E. M. Current treatment of lupus nephritis. Lupus 17(5):426–430; 2008.
54. Huang, X. P.; Sun, Z.; Miyagi, Y.; McDonald Kinkaid, H.; Zhang, L.; Weisel, R. D.; Li, R. K. Differentiation of allogeneic mesenchymal stem cells induces immunogenicity and limits their long-term benefits for myocardial repair. Circulation 122(23):2419–2429; 2010.
55. Ikebe, C.; Suzuki, K. Mesenchymal stem cells for regenerative therapy: Optimization of cell preparation protocols. Biomed. Res. Int. 2014:951512; 2014.
56. Kanazawa, H.; Fujimoto, Y.; Teratani, T.; Iwasaki, J.; Kasahara, N.; Negishi, K.; Tsuruyama, T.; Uemoto, S.; Kobayashi, E. Bone marrow-derived mesenchymal stem cells ameliorate hepatic ischemia reperfusion injury in a rat model. PLoS One 6(4):e19195; 2011.
57. Karussis, D.; Grigoriadis, S.; Polyzoidou, E.; Grigoriadis, N.; Slavin, S.; Abramsky, O. Neuroprotection in multiple sclerosis. Clin. Neurol. Neurosurg. 108(3):250–254; 2006.
58. Katritsis, D. G.; Sotiropoulou, P. A.; Karvouni, E.; Karabinos, I.; Korovesis, S.; Perez, S. A.; Voridis, E. M.; Papamichail, M. Transcoronary transplantation of autologous mesenchymal stem cells and endothelial progenitors into infarcted human myocardium. Catheter. Cardiovasc. Interv. 65(3):321–329; 2005.
59. Katsifis, G. E.; Tzioufas, A. G. Ovarian failure in systemic lupus erythematosus patients treated with pulsed intravenous cyclophosphamide. Lupus 13(9):673–678; 2004.
60. Kebriaei, P.; Saliba, R.; Rondon, G.; Chiattone, A.; Luthra, R.; Anderlini, P.; Andersson, B.; Shpall, E.; Popat, U.; Jones, R.; Worth, L.; Ravandi, F.; Thomas, D.; O'Brien, S.; Kantarjian, H.; de Lima, M.; Giralt, S.; Champlin, R. Long-term follow-up of allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Impact of tyrosine kinase inhibitors on treatment outcomes. Biol. Blood Marrow Transplant. 18(4):584–592; 2012.
61. Koc, O. N.; Lazarus, H. M. Mesenchymal stem cells: Heading into the clinic. Bone Marrow Transplant. 27(3): 235–239; 2001.
62. Kubinova, S.; Sykova, E. Biomaterials combined with cell therapy for treatment of spinal cord injury. Regen. Med. 7(2):207–224; 2012.
63. Lalu, M. M.; McIntyre, L.; Pugliese, C.; Fergusson, D.; Winston, B. W.; Marshall, J. C.; Granton, J.; Stewart, D. J. Safety of cell therapy with mesenchymal stromal cells (SafeCell): A systematic review and meta-analysis of clinical trials. PLoS One 7(10):e47559; 2012.
64. Lazarus, H. M. Bone marrow transplantation in low-grade non-Hodgkin's lymphoma. Leuk. Lymphoma 17(3–4):199–210; 1995.

65. Le Blanc, K.; Frassoni, F.; Ball, L.; Locatelli, F.; Roelofs, H.; Lewis, I.; Lanino, E.; Sundberg, B.; Bernardo, M. E.; Remberger, M.; Dini, G.; Egeler, R. M.; Bacigalupo, A.; Fibbe, W.; Ringdén, O. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: A phase II study. Lancet 371(9624):1579–1586; 2008.
66. Le Blanc, K.; Gotherstrom, C.; Ringden, O.; Hassan, M.; McMahon, R.; Horwitz, E.; Anneren, G.; Axelsson, O.; Nunn, J.; Ewald, U.; Nordén-Lindeberg, S.; Jansson, M.; Dalton, A.; Aström, E.; Westgren, M. Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation 79(11):1607–1614; 2005.
67. Le Blanc, K.; Pittenger, M. Mesenchymal stem cells: Progress toward promise. Cytotherapy 7(1):36–45; 2005.
68. Le Blanc, K.; Rasmusson, I.; Sundberg, B.; Gotherstrom, C.; Hassan, M.; Uzunel, M.; Ringden, O. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet 363(9419):1439–1441; 2004.
69. Le Blanc, K.; Ringden, O. Mesenchymal stem cells: Properties and role in clinical bone marrow transplantation. Curr. Opin. Immunol. 18(5):586–591; 2006.
70. Lee, R. H.; Pulin, A. A.; Seo, M. J.; Kota, D. J.; Ylostalo, J.; Larson, B. L.; Semprun-Prieto, L.; Delafontaine, P.; Prockop, D. J. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. Cell Stem Cell 5(1):54–63; 2009.
71. Lee, S. T.; Jang, J. H.; Cheong, J. W.; Kim, J. S.; Maemg, H. Y.; Hahn, J. S.; Ko, Y. W.; Min, Y. H. Treatment of high-risk acute myelogenous leukaemia by myeloablative chemoradiotherapy followed by co-infusion of T cell-depleted haematopoietic stem cells and culture-expanded marrow mesenchymal stem cells from a related donor with one fully mismatched human leucocyte antigen haplotype. Br. J. Haematol. 118(4):1128–1131; 2002.
72. Li, K.; Han, Q.; Yan, X.; Liao, L.; Zhao, R. C. Not a process of simple vicariousness, the differentiation of human adipose-derived mesenchymal stem cells to renal tubular epithelial cells plays an important role in acute kidney injury repairing. Stem Cells Dev. 19(8):1267–1275; 2010.
73. Li, M.; Ikehara, S. Bone-marrow-derived mesenchymal stem cells for organ repair. Stem Cells Int. 2013:132642; 2013.
74. Liang, J.; Zhang, H.; Hua, B.; Wang, H.; Lu, L.; Shi, S.; Hou, Y.; Zeng, X.; Gilkeson, G. S.; Sun, L. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: A pilot clinical study. Ann. Rheum. Dis. 69(8):1423–1429; 2010.
75. Liechty, K. W.; MacKenzie, T. C.; Shaaban, A. F.; Radu, A.; Moseley, A. M.; Deans, R.; Marshak, D. R.; Flake, A. W. Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. Nat. Med. 6(11):1282–1286; 2000.
76. Lin, Y.; Hogan, W. J. Clinical application of mesenchymal stem cells in the treatment and prevention of graft-versus-host disease. Adv. Hematol. 2011:427863; 2011.
77. Liu, Y.; Wu, J.; Zhu, Y.; Han, J. Therapeutic application of mesenchymal stem cells in bone and joint diseases. Clin. Exp. Med. 14(1):13–24; 2014.
78. Mahmood, A.; Lu, D.; Lu, M.; Chopp, M. Treatment of traumatic brain injury in adult rats with intravenous administration of human bone marrow stromal cells. Neurosurgery 53(3):697–702; discussion 702–693; 2003.
79. Martin, J.; Helm, K.; Ruegg, P.; Varella-Garcia, M.; Burnham, E.; Majka, S. Adult lung side population cells have mesenchymal stem cell potential. Cytotherapy 10(2):140–151; 2008.
80. Mathiasen, A. B.; Haack-Sorensen, M.; Kastrup, J. Mesenchymal stromal cells for cardiovascular repair: Current status and future challenges. Future Cardiol. 5(6):605–617; 2009.
81. Mathiasen, A. B.; Jorgensen, E.; Qayyum, A. A.; Haack-Sorensen, M.; Ekblond, A.; Kastrup, J. Rationale and design of the first randomized, double-blind, placebo-controlled trial of intramyocardial injection of autologous bone-marrow derived mesenchymal stromal cells in chronic ischemic heart failure (MSC-HF Trial). Am. Heart J. 164(3):285–291; 2009.
82. Mazzini, L.; Fagioli, F.; Boccaletti, R.; Mareschi, K.; Oliveri, G.; Olivieri, C.; Pastore, I.; Marasso, R.; Madon, E. Stem cell therapy in amyotrophic lateral sclerosis: A methodological approach in humans. Amyotroph. Lateral Scler. Other Motor Neuron Disord. 4(3):158–161; 2003.
83. Mazzini, L.; Ferrero, I.; Luparello, V.; Rustichelli, D.; Gunetti, M.; Mareschi, K.; Testa, L.; Stecco, A.; Tarletti, R.; Miglioretti, M.; Fava, E.; Nasuelli, N.; Cisari, C.; Massara, M.; Vercelli, R., Oggioni, G. D.; Carriero, A.; Cantello, R.; Monaco, F.; Fagioli, F. Mesenchymal stem cell transplantation in amyotrophic lateral sclerosis: A phase I clinical trial. Exp. Neurol. 223(1):229–237; 2010.
84. Meier, R. P.; Müller, Y. D.; Morel, P.; Gonelle-Gispert, C.; Bühler, L. H. Transplantation of mesenchymal stem cells for the treatment of liver diseases, is there enough evidence? Stem Cell Res. 11(3):1348–1364; 2013.
85. Mendonça, M. V.; Larocca, T. F.; de Freitas Souza, B. S.; Villarreal, C. F.; Silva, L. F.; Matos, A. C.; Novaes, M. A.; Bahia, C. M.; de Oliveira Melo Martinez, A. C.; Kaneto, C. M.; Furtado, S. B.; Sampaio, G. P.; Soares, M. B.; dos Santos, R. R. Safety and neurological assessments after autologous transplantation of bone marrow mesenchymal stem cells in subjects with chronic spinal cord injury. Stem Cell Res. Ther. 5(6):126; 2014.
86. Miao, Z.; Jin, J.; Chen, L.; Zhu, J.; Huang, W.; Zhao, J.; Qian, H.; Zhang, X. Isolation of mesenchymal stem cells from human placenta: Comparison with human bone marrow mesenchymal stem cells. Cell Biol. Int. 30(9):681–687; 2006.
87. Mohyeddin Bonab, M.; Yazdanbakhsh, S.; Lotfi, J.; Alimoghaddom, K.; Talebian, F.; Hooshmand, F.; Ghavamzadeh, A.; Nikbin, B. Does mesenchymal stem cell therapy help multiple sclerosis patients? Report of a pilot study. Iran J. Immunol. 4(1):50–57; 2007.
88. Monsel, A.; Zhu, Y. G.; Gennai, S.; Hao, Q.; Liu, J.; Lee, J. W. Cell-based therapy for acute organ injury: Preclinical evidence and ongoing clinical trials using mesenchymal stem cells. Anesthesiology 121(5):1099–1121; 2014.
89. Montesinos, J. J.; Mora-Garcia Mde, L.; Mayani, H.; Flores-Figueroa, E.; Garcia-Rocha, R.; Fajardo-Orduna, G. R.; Castro-Manrreza, M. E.; Weiss-Steider, B.; Monroy-Garcia, A. In vitro evidence of the presence of mesenchymal stromal cells in cervical cancer and their role in protecting cancer cells from cytotoxic T cell activity. Stem Cells Dev. 22(18):2508–2519; 2013.
90. Moscoso, I.; Barallobre, J.; de Ilarduya, O. M.; Añón, P.; Fraga, M.; Calviño, R.; Aldama, G.; Doménech, N. Analysis of different routes of administration of

heterologous 5-azacytidine-treated mesenchymal stem cells in a porcine model of myocardial infarction. Transplant. Proc. 41(6):2273–2275; 2009.
91. Moser, B.; Loetscher, P. Lymphocyte traffic control by chemokines. Nat. Immunol. 2(2):123–128; 2001.
92. Muller, I.; Kordowich, S.; Holzwarth, C.; Isensee, G.; Lang, P.; Neunhoeffer, F.; Dominici, M.; Greil, J.; Handgretinger, R. Application of multipotent mesenchymal stromal cells in pediatric patients following allogeneic stem cell transplantation. Blood Cells Mol. Dis. 40(1):25–32; 2008.
93. Najar, M.; Raicevic, G.; Boufker, H. I.; Fayyad Kazan, H.; De Bruyn, C.; Meuleman, N.; Bron, D.; Toungouz, M.; Lagneaux, L. Mesenchymal stromal cells use PGE2 to modulate activation and proliferation of lymphocyte subsets: Combined comparison of adipose tissue, Wharton's Jelly and bone marrow sources. Cell Immunol. 264(2):171–179; 2010.
94. Navarro-Zarza, J. E.; Alvarez-Hernandez, E.; Casasola-Vargas, J. C.; Estrada-Castro, E.; Burgos-Vargas, R. Prevalence of community-acquired and nosocomial infections in hospitalized patients with systemic lupus erythematosus. Lupus 19(1):43–48; 2010.
95. Neuss, S.; Becher, E.; Woltje, M.; Tietze, L.; Jahnen-Dechent, W. Functional expression of HGF and HGF receptor/c-met in adult human mesenchymal stem cells suggests a role in cell mobilization, tissue repair, and wound healing. Stem Cells 22(3):405–414; 2004.
96. Orozco, L.; Munar, A.; Soler, R.; Alberca, M.; Soler, F.; Huguet, M.; Sentis, J.; Sanchez, A.; Garcia-Sancho, J. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: A pilot study. Transplantation 95(12):1535–1541; 2013.
97. Osaka, M.; Honmou, O.; Murakami, T.; Nonaka, T.; Houkin, K.; Hamada, H.; Kocsis, J. D. Intravenous administration of mesenchymal stem cells derived from bone marrow after contusive spinal cord injury improves functional outcome. Brain Res. 1343:226–235; 2010.
98. Peng, Y.; Ke, M.; Xu, L.; Liu, L.; Chen, X.; Xia, W.; Li, X.; Chen, Z.; Ma, J.; Liao, D.; Li, G.;, Fang, J.; Pan, G.; Xiang, A. P. Donor-derived mesenchymal stem cells combined with low-dose tacrolimus prevent acute rejection after renal transplantation: A clinical pilot study. Transplantation 95(1):161–168; 2013.
99. Perry, B. C.; Zhou, D.; Wu, X.; Yang, F. C.; Byers, M. A.; Chu, T. M.; Hockema, J. J.; Woods, E. J.; Goebel, W. S. Collection, cryopreservation, and characterization of human dental pulp-derived mesenchymal stem cells for banking and clinical use. Tissue Eng. Part C Methods 14(2):149–156; 2008.
100. Pileggi, A.; Xu, X.; Tan, J.; Ricordi, C. Mesenchymal stromal (stem) cells to improve solid organ transplant outcome: Lessons from the initial clinical trials. Curr. Opin. Organ Transplant. 18(6):672–681; 2013.
101. Popp, F. C.; Eggenhofer, E.; Renner, P.; Slowik, P.; Lang, S. A.; Kaspar, H.; Geissler, E. K.; Piso, P.; Schlitt, H. J.; Dahlke, M. H. Mesenchymal stem cells can induce long-term acceptance of solid organ allografts in synergy with low-dose mycophenolate. Transpl. Immunol. 20(1–2): 55–60; 2008.
102. Ra, J. C.; Shin, I. S.; Kim, S. H.; Kang, S. K.; Kang, B. C.; Lee, H. Y.; Kim, Y. J.; Jo, J. Y.; Yoon, E. J.; Choi, H. J.; Kwon E. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. Stem Cells Dev. 20(8):1297–1308; 2011.
103. Ren, G.; Zhao, X.; Zhang, L.; Zhang, J.; L'Huillier, A.; Ling, W.; Roberts, A. I.; Le, A. D.; Shi, S.; Shao, C.; Shi Y. Inflammatory cytokine-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in mesenchymal stem cells are critical for immunosuppression. J. Immunol. 184(5):2321–2328; 2010.
104. Ries, C.; Egea, V.; Karow, M.; Kolb, H.; Jochum, M.; Neth, P. MMP-2, MT1-MMP, and TIMP-2 are essential for the invasive capacity of human mesenchymal stem cells: Differential regulation by inflammatory cytokines. Blood 109(9):4055–4063; 2007.
105. Riordan, N. H.; Ichim, T. E.; Min, W. P.; Wang, H.; Solano, F.; Lara, F.; Alfaro, M.; Rodriguez, J. P.; Harman, R. J.; Patel, A. N.; Murphy M. P.; Lee R. R.; Minev B. Non-expanded adipose stromal vascular fraction cell therapy for multiple sclerosis. J. Transl. Med. 7:29; 2009.
106. Romanov, Y. A.; Svintsitskaya, V. A.; Smirnov, V. N. Searching for alternative sources of postnatal human mesenchymal stem cells: Candidate MSC-like cells from umbilical cord. Stem Cells 21(1):105–110; 2003.
107. Ruster, B.; Gottig, S.; Ludwig, R. J.; Bistrian, R.; Muller, S.; Seifried, E.; Gille, J.; Henschler, R. Mesenchymal stem cells display coordinated rolling and adhesion behavior on endothelial cells. Blood 108(12):3938–3944; 2006.
108. Sabatelli, M.; Madia, F.; Conte, A.; Luigetti, M.; Zollino, M.; Mancuso, I.; Lo Monaco, M.; Lippi, G.; Tonali, P. Natural history of young-adult amyotrophic lateral sclerosis. Neurology 71(12):876–881; 2008.
109. Sasaki, M.; Abe, R.; Fujita, Y.; Ando, S.; Inokuma, D.; Shimizu, H. Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type. J. Immunol. 180(4):2581–2587; 2008.
110. Schmidt, A.; Ladage, D.; Steingen, C.; Brixius, K.; Schinkothe, T.; Klinz, F. J.; Schwinger, R. H.; Mehlhorn, U.; Bloch, W. Mesenchymal stem cells transmigrate over the endothelial barrier. Eur. J. Cell Biol. 85(11):1179–1188; 2006.
111. Seo, B. M.; Miura, M.; Gronthos, S.; Bartold, P. M.; Batouli, S.; Brahim, J.; Young, M.; Robey, P. G.; Wang, C. Y.; Shi, S. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet 364(9429):149–155; 2004.
112. Shi, M.; Li, J.; Liao, L.; Chen, B.; Li, B.; Chen, L.; Jia, H.; Zhao, R. C. Regulation of CXCR4 expression in human mesenchymal stem cells by cytokine treatment: Role in homing efficiency in NOD/SCID mice. Haematologica 92(7):897–904; 2007.
113. Shi, M.; Zhang, Z.; Xu, R.; Lin, H.; Fu, J.; Zou, Z.; Zhang, A.; Shi, J.; Chen, L.; Lv, S.; He, W.; Geng, H.; Jin, L.; Liu, Z.; Wang, F. S. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. Stem Cells Transl. Med. 1(10):725–731; 2012.
114. Shin, D. A.; Pennant, W. A.; Yoon, D. H.; Ha, Y.; Kim, K. N. Co-transplantation of bone marrow-derived mesenchymal stem cells and nanospheres containing FGF-2 improve cell survival and neurological function in the injured rat spinal cord. Acta Neurochir. (Wien) 156(2):297–303; 2014.
115. Sohni, A.; Verfaillie, C. M. Mesenchymal stem cells migration homing and tracking. Stem Cells Int. 2013:130763; 2013.
116. Son, B. R.; Marquez-Curtis, L. A.; Kucia, M.; Wysoczynski, M.; Turner, A. R.; Ratajczak, J.; Ratajczak, M. Z.;

Janowska-Wieczorek, A. Migration of bone marrow and cord blood mesenchymal stem cells in vitro is regulated by stromal-derived factor-1-CXCR4 and hepatocyte growth factor-c-met axes and involves matrix metalloproteinases. Stem Cells 24(5):1254–1264; 2006.
117. Steinman, L. Multiple sclerosis: A two-stage disease. Nat. Immunol. 2(9):762–764; 2001.
118. Sun, L.; Akiyama, K.; Zhang, H.; Yamaza, T.; Hou, Y.; Zhao, S.; Xu, T.; Le, A.; Shi, S. Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans. Stem Cells 27(6):1421–1432; 2009.
119. Tabbara, I. A.; Zimmerman, K.; Morgan, C.; Nahleh, Z. Allogeneic hematopoietic stem cell transplantation: Complications and results. Arch. Intern. Med. 162(14):1558–1566; 2002.
120. Takahashi, M.; Li, T. S.; Suzuki, R.; Kobayashi, T.; Ito, H.; Ikeda, Y.; Matsuzaki, M.; Hamano, K. Cytokines produced by bone marrow cells can contribute to functional improvement of the infarcted heart by protecting cardiomyocytes from ischemic injury. Am. J. Physiol. Heart Circ. Physiol. 291(2):H886–893; 2006.
121. Talac, R.; Friedman, J. A.; Moore, M. J.; Lu, L.; Jabbari, E.; Windebank, A. J.; Currier, B. L.; Yaszemski, M. J. Animal models of spinal cord injury for evaluation of tissue engineering treatment strategies. Biomaterials 25(9):1505–1510; 2004.
122. Tan, J.; Wu, W.; Xu, X.; Liao, L.; Zheng, F.; Messinger, S.; Sun, X.; Chen, J.; Yang, S.; Cai, J.; Gao, X.; Pileggi, A.; Ricordi, C. Induction therapy with autologous mesenchymal stem cells in living-related kidney transplants: A randomized controlled trial. JAMA 307(11):1169–1177; 2012.
123. Tasso, R.; Ilengo, C.; Quarto, R.; Cancedda, R.; Caspi, R. R.; Pennesi, G. Mesenchymal stem cells induce functionally active T-regulatory lymphocytes in a paracrine fashion and ameliorate experimental autoimmune uveitis. Invest. Ophthalmol. Vis. Sci. 53(2):786–793; 2012.
124. Togel, F. E.; Westenfelder, C. Kidney protection and regeneration following acute injury: Progress through stem cell therapy. Am. J. Kidney Dis. 60(6):1012–1022; 2012.
125. Tomita, S.; Li, R. K.; Weisel, R. D.; Mickle, D. A.; Kim, E. J.; Sakai, T.; Jia, Z. Q. Autologous transplantation of bone marrow cells improves damaged heart function. Circulation 100(19 Suppl):II247–256; 1999.
126. Uccelli, A.; Benvenuto, F.; Laroni, A.; Giunti, D. Neuroprotective features of mesenchymal stem cells. Best Pract. Res. Clin. Haematol. 24(1):59–64; 2011.
127. Uccelli, A.; Milanese, M.; Principato, M. C.; Morando, S.; Bonifacino, T.; Vergani, L.; Giunti, D.; Voci, A.; Carminati, E.; Giribaldi, F.; Caponnetto, C.; Bonanno, G. Intravenous mesenchymal stem cells improve survival and motor function in experimental amyotrophic lateral sclerosis. Mol. Med. 18:794–804; 2012.
128. Uccelli, A.; Moretta, L.; Pistoia, V. Mesenchymal stem cells in health and disease. Nat. Rev. Immunol. 8(9):726–736; 2008.
129. Urbich, C.; Dimmeler, S. Endothelial progenitor cells functional characterization. Trends Cardiovasc. Med. 14(8):318–322; 2004.
130. Wang, D.; Zhang, H.; Liang, J.; Li, X.; Feng, X.; Wang, H.; Hua, B.; Liu, B.; Lu, L.; Gilkeson, G. S.; Silver, R. M.; Chen, W.; Shi, S.; Sun, L. Allogeneic mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus: 4 years of experience. Cell Transplant. 22(12):2267–2277; 2013.
131. Wang, J.; Liao, L.; Tan, J. Mesenchymal-stem-cell-based experimental and clinical trials: Current status and open questions. Expert Opin. Biol. Ther. 11(7):893–909; 2011.
132. Wang, S.; Qu, X.; Zhao, R. C. Clinical applications of mesenchymal stem cells. J. Hematol. Oncol. 5:19; 2012.
133. Wei, X.; Yang, X.; Han, Z. P.; Qu, F. F.; Shao, L.; Shi, Y. F. Mesenchymal stem cells: A new trend for cell therapy. Acta Pharmacol. Sin. 34(6):747–754; 2013.
134. Wong, K. L.; Lee, K. B.; Tai, B. C.; Law, P.; Lee, E. H.; Hui, J. H. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: A prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy 29(12):2020–2028; 2013.
135. Wynn, R. F.; Hart, C. A.; Corradi-Perini, C.; O'Neill, L.; Evans, C. A.; Wraith, J. E.; Fairbairn, L. J.; Bellantuono, I. A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. Blood 104(9):2643–2645; 2004.
136. Xia, C.; Cao, J. Imaging the survival and utility of pre-differentiated allogeneic MSC in ischemic heart. Biochem. Biophys. Res. Commun. 438(2):382–387; 2013.
137. Xiao, Y.; Jiang, Z. J.; Pang, Y.; Li, L.; Gao, Y.; Xiao, H. W.; Li, Y. H.; Zhang, H.; Liu, Q. Efficacy and safety of mesenchymal stromal cell treatment from related donors for patients with refractory aplastic anemia. Cytotherapy 15(7):760–766; 2013.
138. Young, H. E.; Steele, T. A.; Bray, R. A.; Hudson, J.; Floyd, J. A.; Hawkins, K.; Thomas, K.; Austin, T.; Edwards, C.; Cuzzourt, J.; Duenzl, M.; Lucas, P. A.; Black, A. C., Jr. Human reserve pluripotent mesenchymal stem cells are present in the connective tissues of skeletal muscle and dermis derived from fetal, adult, and geriatric donors. Anat. Rec. 264(1):51–62; 2001.
139. Zhang, Z.; Lin, H.; Shi, M.; Xu, R.; Fu, J.; Lv, J.; Chen, L.; Lv, S.; Li, Y.; Yu, S.; Geng, H.; Jin, L.; Lau, G. K.; Wang, F. S. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. J. Gastroenterol. Hepatol. 27(Suppl. 2):112–120; 2012.
140. Zhao, K.; Lou, R.; Huang, F.; Peng, Y.; Jiang, Z.; Huang, K.; Wu, X.; Zhang, Y.; Fan, Z.; Zhou, H.; Liu, C.; Xiao, Y.; Sun, J.; Li, Y.; Xiang, P.; Liu, Q. Immunomodulation effects of mesenchymal stromal cells on acute graft-versus-host disease after hematopoietic stem cell transplantation. Biol. Blood Marrow Transplant. 21(1):97–104; 2015.