Clinical applications of mesenchymal stem cells

Nayoun Kim[1] and Seok-Goo Cho[1,2]

[1]Laboratory of Immune Regulation, Convergent Research Consortium for Immunologic Disease, [2]Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

**Correspondence to
Seok-Goo Cho, M.D.**
Laboratory of Immune Regulation, Convergent Research Consortium for Immunologic Disease, and Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Korea
Tel: +82-2-2258-6052
Fax: +82-2-599-3589
E-mail: chosg@catholic.ac.kr

Mesenchymal stem cells (MSCs) are self-renewing, multipotent progenitor cells with multilineage potential to differentiate into cell types of mesodermal origin, such as adipocytes, osteocytes, and chondrocytes. In addition, MSCs can migrate to sites of inflammation and exert potent immunosuppressive and anti-inflammatory effects through interactions between lymphocytes associated with both the innate and adaptive immune system. Along with these unique therapeutic properties, their ease of accessibility and expansion suggest that use of MSCs may be a useful therapeutic approach for various disorders. In the clinical setting, MSCs are being explored in trials of various conditions, including orthopedic injuries, graft versus host disease following bone marrow transplantation, cardiovascular diseases, autoimmune diseases, and liver diseases. Furthermore, genetic modification of MSCs to overexpress antitumor genes has provided prospects for clinical use as anticancer therapy. Here, we highlight the currently reported uses of MSCs in clinical trials and discuss their efficacy as well as their limitations.

Keywords: Clinical trial; Tissue therapy; Graft vs host disease; Mesenchymal stromal cells

INTRODUCTION

Mesenchymal stem cells (MSCs) are self-renewing, multipotent progenitor cells with multilineage potential to differentiate into cell types of mesodermal origin, such as adipocytes, osteocytes, and chondrocytes [1]. While MSCs are most commonly isolated from bone marrow [2], they are also isolated from other tissues including adipose tissue [3,4], placenta [5], amniotic fluid [6], and umbilical cord blood [7,8]. Due to their accessibility and convenient expansion protocols, MSCs have been recognized as promising candidates for cellular therapy. However, growing interest in MSCs has led to

questioning the equivalence of MSCs isolated from different sources and expanded from various protocols. To address this issue, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy developed the minimal criteria to universally define human MSCs [9]. The criteria include adherence to plastic, specific surface antigen expression ($CD73^+$ $CD90^+$ $CD105^+$ $CD34^-$ $CD45^-$ $CD11b^-$ $CD14^-$ $CD19^-$ $CD79a^-$ $HLA-DR^-$) as well as multipotent differential potential under standard *in vitro* differentiation conditions (Table 1).

In addition to their ease of isolation and *ex vivo* expansion, MSCs possess unique characteristics that

Table 1. Minimal criteria of mesenchymal stem cells

Surface markers	Differentiation potential	Other characteristics
CD73$^+$	Osteogenic	Adherence to plastic
CD90$^+$	Adipogenic	Spindle-shape morphology
CD105$^+$	Chondrogenic	
CD34$^-$		
CD45$^-$		
CD11b$^-$		
CD14$^-$		
CD19$^-$		
CD79a$^-$		
HLA-DR$^-$		

make them attractive therapeutic agents for treatment of various diseases. First, MSCs have the ability to differentiate across various lineages beyond the conventional mesodermal lineages. The multipotency of MSCs has led to their application in regenerative medicine and tissue repair. Second, recent studies have indicated that MSCs can provide therapeutic benefit through the secretion of soluble factors to induce an immunomodulatory environment. Third, MSCs have the capacity to migrate toward sites of injury and tumor microenvironments. Although the mechanisms are not fully understood, this unique tropism has allowed MSCs to serve as delivery vehicles for targeted therapy.

The potential of MSC therapy involving their unique characteristics has been demonstrated in various *in vivo* disease models and has shown encouraging results for possible clinical use. In a clinical setting, MSCs are now being explored in trials for various conditions, including orthopedic injuries, graft versus host disease (GVHD) following bone marrow transplantation (BMT), cardiovascular diseases, autoimmune diseases, and liver diseases. Furthermore, genetic modification of MSCs to overexpress antitumor genes has provided prospects for use as anticancer therapy in clinical settings. This review focuses on the currently reported uses of MSC therapy in clinical settings and highlights their therapeutic potential and limitations.

THERAPEUTIC PROPERTIES OF MSCs

Recent studies involving MSC therapy have focused on their unique biological properties and functions, which may contribute to their therapeutic potential in clinic settings.

Differentiation and regenerative potential

MSCs are characterized by their ability to self-renew and to differentiate into cells of the mesenchymal lineage, including adipocytes, osteoblasts, chondrocytes, tenocytes, skeletal myocytes, and cells of the visceral mesoderm [2,10,11]. In addition, some studies suggested that the differentiation potential of MSCs extends beyond the conventional mesodermal lineage and that they can also differentiate into cells of ectodermal and endodermal origin, such as hepatocytes [12,13], neurons [14,15], and cardiomyocytes [16,17]. The multilineage differential potential of MSCs is commonly examined by *in vitro* functional assays using specific differentiation media, and these *in vitro* data encouraged further investigation of MSCs as a potential source of tissue repair. However, due to the lack of specific MSC markers, there is little information on the *in vivo* differentiation of MSCs, as compared to *in vitro* characterization. Studies have suggested MSC engraftment and transdifferentiation *in vivo* in various models of damaged or mutated bone, cartilage [18], myocardial [19,20], neural [21,22], and hepatic tissues [13], but whether the observed therapeutic effects are due to paracrine interactions or true differentiation capacity remains to be elucidated. In one study, MSCs labeled with green fluorescent protein (GFP) were injected intravenously and examined for engraftment and differentiation potential [23]. GFP-labeled MSCs were initially located in the lungs and, subsequently, MSCs were detected in other tissues at low frequencies, such as bronchiolar epithelial cells, hepatocytes, and renal tubular cells. Importantly, there was no evidence of clonal expansion and the mechanism of differentiation was not determined, suggesting that the observation of MSCs in various tissues could have been due to simple fusion events. Overall, the therapeutic potential of MSCs has been observed in various injury models, but *in vivo* data supporting the true differentiation and regenerative potential of MSCs are still lacking.

Immune modulation

MSCs have significant clinical implications as they exert potent immunosuppressive and anti-inflammatory effects through the interactions between the lymphocytes associated with both the innate and adaptive immune systems. MSCs suppress T cell proliferation [24-26], B cell functions [25,27,28], natural killer cell proliferation and cytokine production [29], and prevent the differentiation, maturation, and activation of dendritic cells [30-37]. Importantly, MSCs can suppress cells independently of the major histocompatibility complex (MHC) identity between donor and recipient due to their low expression of MHC-II and other costimulatory molecules [38]. While MSCs can exert immunosuppressive effects by direct cell to cell contact, their primary mechanism is production of soluble factors, including transforming growth factor-β [39], hepatocyte growth factor (HGF) [26], nitric oxide [40], and indoleamine 2,3-dioxygenase (IDO) [41]. Furthermore, through cell to cell contact and the production of soluble factors, MSCs induce an immunosuppressive environment by generating regulatory T cells (Tregs). The ability of MSCs to induce Tregs has been observed both *in vitro* [42,43] and *in vivo* in various models [44-49]. In addition, MSCs can induce plasmacytoid dendritic cells to produce interleukin (IL)-10 [50], which may also support the development of Tregs *in vivo*. These observations suggest that MSCs are key regulators of immune modulation by directly suppressing activated immune cells and indirectly recruiting Tregs.

However, MSCs are not constitutively inhibitory. MSCs are highly dependent on environmental inflammatory conditions. Under acute inflammatory conditions polarized by M1 macrophages and helper T lymphocyte (Th)-type-1 cytokines, especially the proinflammatory cytokine interferon (IFN)-γ, the immunosuppressive capacity of MSCs is enhanced through increased production of ICAM-1, CXCL-10, CCL-8, and IDO [51-53]. On the other hand, under chronic inflammatory conditions when MSCs are polarized by M2 macrophages and Th2 cytokines, MSCs can be recruited into the fibrotic process [51]. Thus, the therapeutic effects of MSCs depend on the inflammatory microenvironment, which should be taken into consideration when used for therapy.

Migratory capacity

A number of studies have suggested that MSCs have the capacity to migrate to sites of inflammation and tumor microenvironments. Although the exact mechanisms underlying MSC migration remain to be elucidated, studies have shown that MSC migration is dependent on various chemokine and receptor interactions, such as stromal cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4) [54,55], stem cell factor/c-kit, HGF/c-Met [56], vascular endothelial growth factor (VEGF)/VEGF receptor [57], platelet-derived growth factor (PDGF)/PDGF receptor [54,58], monocyte chemoattractant protein-1 (MCP-1)/C-C chemokine receptor type 2 [59], and high mobility group box 1/receptor for advanced glycation endproducts [60,61] as well as other cell adhesion molecules [55,62]. These cytokine and chemokine receptor pairs play important roles in leukocytes that respond to injury and inflammation or hematopoietic stem cells (HSC) and are thought to function similarly in MSCs. Furthermore, the tumor microenvironment closely resembles an unhealed wound that continuously produces inflammatory mediators, including cytokines, chemokines, and other chemoattractant molecules [63]. This constant inflammatory signaling may become a target for MSC migration. Among the chemokine receptor pairs, SDF-1 and CXCR4 are important mediators of stem cell recruitment to tumors [54]. In addition, many tumor microenvironments exhibit hypoxia that results in expression of proangiogenic molecules. The hypoxia-induced transcription factor HIF-1α activates the transcription of genes, including VEGF, macrophage migration inhibitor factor, tumor necrosis factors, and numerous proinflammatory cytokines [64], inducing the generation of chemokines, such as MCP-1, involved in migration of MSCs toward tumors [59]. Many different chemokine factors and receptors have been implicated in the migration of MSCs and further studies that exploit additional chemokine/receptor interactions are needed to develop targeted MSC therapies to inflammatory and tumor sites.

CLINICAL APPLICATIONS OF MSCs

MSCs have attracted attention due to their unique ther-

apeutic properties. In this review, we summarize some of the clinical trials of MSC therapy in various fields (Table 2).

Bone and cartilage diseases

The ability of MSCs to differentiate into osteoblasts, tenocytes, and chondrocytes has attracted interest for their use in orthopedic settings. First, MSCs have been shown to be beneficial in treating bone disorders, such as osteogenesis imperfecta (OI) and hypophosphatasia. OI is characterized by skeletal fragility and connective tissue alterations caused by alteration of type I collagen production by osteoblasts. Pediatric patients with OI underwent allogeneic hematopoietic stem cell transplantation (HSCT) and the transplanted bone marrow cells engrafted and generated functional osteoblasts leading to improvement in bone structure and function [65]. Although, only a low level of engraftment was achieved, a follow-up study demonstrated continued improvements in patients for 18 to 36 months post-transplantation [66]. It is important to note that these

patients were transplanted with whole bone marrow instead of MSCs alone. In another follow-up study, patients who received HSCT were infused with the same donor MSCs [67]. The additional infusion of MSCs showed further benefit, but this was limited in duration. Furthermore, a fetus diagnosed with severe OI underwent *in utero* MSC transplantation [68]. After birth, psychomotor development and growth were normal. Hypophosphatasia is a genetic disorder of mesenchymal origin with mutation in tissue nonspecific alkaline phosphatase. Although the numbers of clinical studies are limited, pediatric patients who received BMT showed significant clinical improvements [69,70]. Administration of MSCs alone in hypophosphatasia has not yet been studied; some authors have suggested that cultured MSCs may fail to engraft after intravenous infusion due to loss of adhesion molecules and loss of self-renewal ability [71,72]. However, even patients receiving whole bone marrow did not reveal significant donor MSC engraftment despite clinical improvements [69].

Table 2. Clinical trials of mesenchymal stem cell therapy

Reference	Disease	Phase	No. of patients	MSC source	Route	Outcome
Horwitz et al. [65]	OI	I	3	Allo-BM	IV	Improved
Horwitz et al. [67]	OI	I	6	Allo-BM	IV	Improved
Le Blanc et al. [68]	OI	I	1	Allo-fetal	*In utero* transplantation	Improved
Wakitani et al. [73]	Cartilage defects	I	2	Allo-BM	Intra-articular cartilage	Improved
Wakitani et al. [74]	Cartilage defects	I	12	Allo-BM	Intra-articular cartilage	Improved
Wakitani et al. [75]	Cartilage defects	I	24	Allo-BM	Intra-articular cartilage	Improved
Kuroda et al. [76]	Cartilage defects	I	1	Allo-BM	Intra-articular cartilage	Improved
Baron et al. [78]	HSCT	I	20	Allo-BM	Cotransplantation	Improved
Lazarus et al. [79]	HSCT	I	46	Allo-BM	Cotransplantation	Improved
Ning et al. [80]	HSCT	I	10	Allo-BM	Cotransplantation	Improved but higher recurrence rate of hematologic malignancy
Bernardo et al. [82]	HSCT	I	13	Allo-BM	Cotransplantation	Did not support engraftment but abrogated GVHD
Macmillan et al. [83]	HSCT	I/II	15	Allo-BM	Cotransplantation	Improved
Le Blanc et al. [84]	aGVHD	I	1	Allo-BM	IV	Improved
Fang et al. [85]	aGVHD	I	6	Allo-adipose tissue	IV	Improved

Table 2. Continued

Reference	Disease	Phase	No. of patients	MSC source	Route	Outcome
Le Blanc et al. [86]	aGVHD	II	55	Allo-BM	IV	Improved
Lucchini et al. [87]	aGVHD, cGVHD	I	16	Allo-BM	IV	Improved (greater in aGVHD)
Muller et al. [88]	aGVHD, cGVHD	I	5	Allo-BM	IV	Improved (greater in aGVHD)
Prasad et al. [89]	aGVHD	I	12	Allo-BM	IV	Improved
Ringden et al. [90]	aGVHD	I	8	Allo-BM	IV	Improved
von Bonin et al. [91]	aGVHD	I	13	Allo-BM	IV	Improved
Wu et al. [92]	aGVHD	I	2	Allo-UCB	IV	Improved
Zhou et al. [93]	cGVHD	I	4	Allo-BM	Intra-BM	Improved
Kebriaei et al. [94]	aGVHD	II	32	Allo-BM	IV	Improved
Weng et al. [95]	cGVHD	I	19	Allo-BM	IV	Improved
Kuzmina et al. [96]	aGVHD, cGVHD	II	37	Allo-BM	IV	Improved
Chen et al. [100]	MI	I	69	Allo-BM	Intracoronary	Improved
Chen et al. [101]	MI	I	46	Allo-BM	Intracoronary	Improved
Katritsis et al. [102]	MI	I	22	Allo-BM	Intracoronary	Improved
Katritsis et al. [103]	MI	I	5	Allo-BM	Intracoronary	Improved
Yang et al. [104]	MI	I	16	Allo-BM	Intracoronary	Improved
Zeinaloo et al. [105]	MI	I	1	Allo-BM	Intracoronary	Improved
Hare et al. [106]	MI	I	53	Allo-BM	IV	Improved
Ichim et al. [107]	MI	I	1	Allo-placental	IV	Improved
Garcia-Olmo et al. [109]	Crohn disease	I	10	Allo-BM	Intrafistula	Improved
Garcia-Olmo et al. [110]	Crohn disease	II	14	Auto adipose-tissue	Intrafistula	Improved
Mohyeddin Bonab et al. [111]	Multiple sclerosis	I	10	Allo-BM	Intrathecal	Mixed
Yamout et al. [112]	Multiple sclerosis	I	10	Allo-BM	IV	Mixed
Karussis et al. [113]	Multiple sclerosis	I/II	15	Allo-BM	Intrathecal	Mixed
Riordan et al. [114]	Multiple sclerosis	I	3	Auto/allo adipose-tissue	IV and Intrathecal	Mixed
Liang et al. [116]	SLE	I	15	Allo-BM	IV	Improved
Sun et al. [117]	SLE	I	16	Allo-UCB	IV	Improved
Liang et al. [118]	SLE	I	1	Allo-UCB	IV	Improved
Carrion et al. [119]	SLE	I	2	Allo-BM	IV	No change
Mohamadnejad et al. [125]	Liver cirrhosis	I	4	Allo-BM	IV	Improved
Kharaziha et al. [126]	Liver cirrhosis	I/II	8	Allo-BM	IV	Improved

MSC, mesenchymal stem cell; OI, osteogenesis imperfecta; Allo, allogeneic; BM, bone marrow; IV, intravenous; HSCT, hematopoietic stem cell transplantation; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease; UCB, umbilical cord blood; MI, myocardial infarction; Auto, autologous; SLE, systemic lupus erythematosus.

Similar to studies on genetic bone disorders, there have been limited reports demonstrating the efficacy of MSCs in promoting cartilage repair in which MSCs embedded in collagen gel were transplanted into the knee joints of patients with articular cartilage defects [73-76]. MSC transplantation has been shown to produce significant clinical improvements with cartilage repair; however, the mechanisms underlying cartilage regeneration are still unknown. The transplanted MSCs may have differentiated into chondrocytes, but it is also possible that MSCs produce soluble factors to induce other cells of the microenvironment to differentiate into cartilage.

BMT and GVHD

HSCT has been widely used over the past several decades to treat patients with various malignant and nonmalignant diseases. However, the procedure remains complicated by regimen-related toxicity, engraftment failure, and GVHD [77]. Preconditioning regimens, such as chemotherapy and/or radiotherapy, may damage the bone marrow and lead to a diminished engraftment of stem cells. MSCs are an attractive therapeutic approach during or after transplantation as their transplantation can minimize the toxicity of the conditioning regimens while inducing hematopoietic engraftment and decrease the incidence and severity of GHVD. In several studies, MSCs were cotransplanted with HSCs to facilitate engraftment [78-83] but their efficacy remains unclear. Similarly, the infusion of third-party haploidentical MSCs during pediatric umbilical cord blood transplantation was shown to induce prompt hematopoietic recovery [83]. On the other hand, some studies have suggested that cotransplantation of MSCs does not affect the kinetics of engraftment [82]. While there have been no trials of MSCs for hematopoiesis, the best studied therapeutic application of MSC is GVHD.

GVHD is a severe inflammatory condition that results from immune-mediated attack of recipient tissues by donor T cells during BMT. The clinical efficacy of MSCs in acute GVHD (aGVHD) was first observed in a 9-year-old boy with steroid-resistant grade IV aGVHD [84]. The patient, who was unresponsive to other therapies, showed a complete response after receiving haploidentical third-party MSCs. Following this pilot study, MSC treatment has been studied extensively in steroid-refractory GVHD [84-92]. In 2006, six of eight patients with steroid-resistant grade III to IV GVHD showed complete remission to MSC treatment [90]. The European Group for Blood and Marrow Transplantation then led a multicenter phase II study in which both pediatric and adult patients with steroid-resistant GVHD were treated with MSCs derived from various sources, including HLA-identical and haploidentical sibling donor bone marrow or third-party mismatched donor bone marrow [86]. Sixty-eight percent of these patients showed complete responses with a significantly reduced transplantation-related mortality rate. Not only did this multicenter study confirm that MSCs are a powerful therapeutic tool it also reduced concerns regarding HLA disparity between the MSC donor and recipient through extensive use of third-party-derived MSCs. Based on these properties, MSCs have been further developed into an FDA-approved commercialized "off-the-shelf" product known as Prochymal (Osiris Therapeutics Inc., Columbia, MD, USA), which is derived from the bone marrow of healthy adult donors [93]. Prochymal was used in a randomized prospective study to treat patients directly after diagnosis of GVHD [94]. Ninety-four percent of the patients had an initial response and showed no infusional toxicities or ectopic tissue formation. In a multicenter trial, a higher response rate was seen in children (84%), as compared to adults (60%) [86]. Therefore, Prochymal was used to specifically treat pediatric patients less than 18 years old with severe steroid-resistant grade III and IV aGVHD [89]. Overall, seven of 12 patients showed complete responses suggesting that pediatric patients may respond better to MSC treatment.

While studies on the use of MSCs for treatment of aGVHD have yielded promising results, the therapeutic efficacy of MSCs in chronic GVHD (cGVHD) is less clear because of the paucity of studies. While some studies indicated efficacy of MSCs, even in cGVHD [93], others suggested that MSCs are less effective in cGVHD than aGVHD [87,88,95]. In studies of MSC therapy in both aGVHD and cGVHD patients, the response rates were higher in aGVHD than cGVHD patients [96]. In addition, the infusion of MSCs following HSCT could prevent the development of aGVHD, while the development cGVHD remained unaffected. Thus, specific pa-

tient recruitment and study designs may allow critical analysis of the effects of MSC treatment in GVHD patients in the future.

Cardiovascular diseases

Despite improvements in medical and surgical therapies, heart disease and heart failure continue to show high morbidity and mortality rates. MSC therapy is an attractive candidate for cardiovascular repair due to its regenerative and immunomodulatory properties. In preclinical studies, MSCs were shown to engraft and improve cardiac repair after administration [97-99]. Clinical trials using MSCs to improve cardiac function have also yielded encouraging results. In a pilot study, 69 patients with acute myocardial infarction received percutaneous coronary injection, and were randomized to receive intracoronary injection of autologous MSCs or standard saline as controls [100]. There were no serious adverse events following MSC administration and the MSC-treated group showed significant improvements in cardiac function, as compared to the control group. This was also the first study to follow and detect the viability of MSCs and cardiac function with cardiac electromechanical mapping. The results indicated that MSCs were still viable 3 months after transplantation. Following this study, MSCs have been used to treat acute and chronic myocardial infarction patients, with significant improvements in heart functions [101-105]. In addition to autologous MSCs, the efficacy of allogeneic MSCs has also been reported. The commercial bone marrow-derived MSC product Prochymal was administered to reperfused myocardial infarction patients in a double blind, placebo-controlled dose-range safety trial [106]. Allogeneic MSCs were well tolerated with a significant increase in left ventricular ejection fraction and lower incidences of arrhythmia and chest pain, as compared to the placebo group. Allogeneic MSCs derived from the placenta also resulted in significant clinical improvements [107]. Thus, the availability of an off-the-shelf MSC product shows promise with regard to the development of cardiac therapy.

Autoimmune diseases

Autoimmune diseases result from an inappropriate immune response of the body against normal cells and tissues. Based on their ability to modulate immune responses, MSCs have also been proposed as a treatment for autoimmune diseases. Patients suffering from severe autoimmune diseases do not respond to standard therapy and often require autologous or allogeneic HSCT [108]. However, HSCT presents many additional complications as well as risks such as toxicity and the incidence of GVHD. Autologous HSCT has often been criticized as identical autoimmune immune cells are being returned back to the patient. Thus, the administration of MSCs may be a safer and more feasible method of treatment. First, the therapeutic role of MSCs has been investigated in patients with Crohn disease. Crohn disease, also known as inflammatory bowel disease, is a chronic inflammatory disorder in which the immune system attacks the gastrointestinal tract. Five patients with Crohn disease were treated with autologous adipose tissue-derived MSCs [109]. The patients were given intralesional treatment of MSCs mixed with fibrin glue. Two patients showed normal healing of the infiltrated area and 75% of treated fistulas had closed and showed signs of significant repair 8 weeks after treatment. These promising results led to a phase II clinical trial [110]. Second, on the basis of preclinical studies, there have been clinical reports on the therapeutic role of MSCs in multiple sclerosis, a chronic inflammatory demyelinating disease of the central nervous system that leads to irreversible damage. Therapeutic approaches have aimed to control the immune response; however, there are still no effective treatments available. In a pilot study, 10 patients with multiple sclerosis received intrathecal injection of culture-expanded MSCs [111]. While administration of MSCs is feasible and safe, the clinical improvements are less clear. During functional assessments, six patients showed some degree of improvement in their sensory, pyramidal, and cerebellar functions, while others showed no improvement or deterioration. Furthermore, the majority of patients showed no differences in MRI assessments after 12 months, indicating that MSC therapy may have less efficacy in multiple sclerosis. Subsequent trials similarly showed mixed results [112-114]. Third, the role of MSCs has also been documented in systemic lupus erythematosus (SLE), an autoimmune inflammatory disease with multiorgan involvement including the kidney, brain, lung, and hematopoietic systems. The most widely

used immunosuppressive therapy is corticosteroid administration; however, steroid-based therapies are associated with significant side effects. While MSCs seem to be an attractive therapeutic approach, a recent study suggested that MSCs derived from SLE patients show functional abnormalities [115] and, thus, MSC transplantation may be more effective, as compared to autologous MSCs. In a pilot study determining the safety and efficacy of MSC transplantation in refractory SLE patients, allogeneic MSC transplantation ameliorated disease activity, improved serological markers, and stabilized renal functions [116]. Umbilical cord-derived MSCs have also shown therapeutic potential in SLE patients [117,118]. On the other hand, the use of autologous MSCs was safe, but did not induce significant changes in disease activity [119].

Finally, rheumatoid arthritis (RA) is a T cell-mediated autoimmune disease characterized by cartilage and bone destruction. Their anti-inflammatory properties and regenerative potential indicate that MSCs could offer a novel therapeutic approach to treat RA. However, the role of MSCs in RA has not yet been reported in clinical trials. The therapeutic potential of MSCs is controversial in preclinical studies, which may have delayed their application in clinical trials. While some studies have suggested the efficacy of MSC therapy in collagen-induced arthritis (CIA) models [120,121], many others have suggested that MSCs alone do not suppress the development of Th17-mediated joint inflammation [122,123]. We have also observed that MSCs are ineffective for treatment of CIA [124]. Thus, MSCs have attracted attention as a therapeutic approach for rheumatic diseases, but the immunomodulatory mechanisms must be clarified to ensure further applications in autoimmune diseases.

Liver diseases

MSCs have been used to treat cirrhosis in a limited number of trials. Cirrhosis is a chronic liver disease characterized by progressive hepatic fibrosis and loss of hepatic structure with formation of regenerative nodules. Liver transplantation is often the only option in advanced stage patients; however, it is limited by lack of donors, surgical complications, and rejection. MSCs have the potential to be used for the treatment of liver diseases due to their regenerative potential and immu-

nomodulatory properties. Furthermore, MSC therapy could provide minimally invasive procedures with relatively few complications, as compared to liver transplantation. In a phase I trial, four patients suffering from end-stage liver cirrhosis were treated with autologous MSCs and showed improved quality of life with no side effects during follow-up [125]. In another phase I to II clinical trial, eight patients with end-stage liver diseases received autologous MSCs. MSC administration was well tolerated and improved liver functions [126]. Thus, MSC therapy is safe, feasible, and applicable in end-stage liver disease.

Cancer

MSCs are emerging as vehicles for cancer gene therapy due to their inherent migratory abilities toward tumors [127]. Whether MSCs themselves have antitumor effects is still controversial as some studies have suggested that even unmodified MSCs inhibit tumor growth and angiogenesis [128-130], while others report that MSCs promote tumorigenesis and metastasis [131-133]. Nonetheless, MSCs have been genetically modified to overexpress various anticancer genes, such as ILs [134-138], IFNs [139-141], prodrugs [142,143], oncolytic viruses [144-147], antiangiogenic agents [148], proapoptotic proteins [149,150], and growth factor antagonists [151], for targeted treatment of different cancer types. While preclinical models using gene-modified MSCs for the treatment of cancer have been well studied, clinical trials utilizing engineered MSCs for cancer therapy have not yet been reported. The safety of MSC administration remains a concern even though MSC administration has not yet shown any major adverse events. Their potential to transform malignantly [152,153] and weaken graft versus leukemia effects following HSCT [80] are major issues with regard to guaranteeing the safety of MSC therapy. Engineered MSCs that overexpress potentially hostile molecules may pose serious problems in addition to these concerns. The lack of safety mechanisms following MSC administration has delayed the application of engineered MSCs in clinical settings. Recently, a safety system to allow control of the growth and survival of MSCs has been developed. The safety mechanism is a suicide system based on an inducible caspase-9 protein that is activated using a specific chemical inducer of dimerization (CID) [154]. Exposure

to CID induced directed MSC killing within 24 hours. The development of such safety mechanisms and their incorporation into MSC therapy may allow extensive use of genetically engineered MSCs to treat cancer patients in clinical settings.

CONCLUSIONS

With their ability to differentiate into multiple lineages, secrete factors related to immune regulation, and migrate toward sites of inflammation, MSCs have many clinical implications. The results of multiple clinical trials using MSCs have been promising but also highlight the critical challenges that must be addressed in the future. More research is needed to determine the mechanisms and biological properties of MSCs to enhance their therapeutic efficacy in various diseases. Furthermore, the heterogeneity of the MSC population presents a challenge for generalized findings. Therefore, it is important to standardize the generation protocols, including cell culture conditions, source, passage, and cell density, as they may impact MSC phenotype as well as functions. Further randomized, controlled, multicenter clinical trials are necessary to determine the optimal conditions for MSC therapy. With further advances, MSCs will play an important role in managing many disorders that lack effective standard treatment.

Conflict of interest
No potential conflict of interest relevant to this article is reported.

REFERENCES

1. Kim EJ, Kim N, Cho SG. The potential use of mesenchymal stem cells in hematopoietic stem cell transplantation. Exp Mol Med 2013;45:e2.

2. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143-147.

3. Izadpanah R, Trygg C, Patel B, et al. Biologic properties of mesenchymal stem cells derived from bone marrow and adipose tissue. J Cell Biochem 2006;99:1285-1297.

4. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng 2001;7:211-228.

5. Zhang Y, Li C, Jiang X, et al. Human placenta-derived mesenchymal progenitor cells support culture expansion of long-term culture-initiating cells from cord blood CD34+ cells. Exp Hematol 2004;32:657-664.

6. Roubelakis MG, Pappa KI, Bitsika V, et al. Molecular and proteomic characterization of human mesenchymal stem cells derived from amniotic fluid: comparison to bone marrow mesenchymal stem cells. Stem Cells Dev 2007;16:931-952.

7. Bieback K, Kern S, Kluter H, Eichler H. Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood. Stem Cells 2004;22:625-634.

8. Erices A, Conget P, Minguell JJ. Mesenchymal progenitor cells in human umbilical cord blood. Br J Haematol 2000;109:235-242.

9. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells: the International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315-317.

10. Jiang Y, Jahagirdar BN, Reinhardt RL, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 2002;418:41-49.

11. Tremain N, Korkko J, Ibberson D, Kopen GC, DiGirolamo C, Phinney DG. MicroSAGE analysis of 2,353 expressed genes in a single cell-derived colony of undifferentiated human mesenchymal stem cells reveals mRNAs of multiple cell lineages. Stem Cells 2001;19:408-418.

12. Petersen BE, Bowen WC, Patrene KD, et al. Bone marrow as a potential source of hepatic oval cells. Science 1999;284:1168-1170.

13. Schwartz RE, Reyes M, Koodie L, et al. Multipotent adult progenitor cells from bone marrow differentiate into functional hepatocyte-like cells. J Clin Invest 2002;109:1291-1302.

14. Tropel P, Platet N, Platel JC, et al. Functional neuronal differentiation of bone marrow-derived mesenchymal stem cells. Stem Cells 2006;24:2868-2876.

15. Cogle CR, Yachnis AT, Laywell ED, et al. Bone marrow transdifferentiation in brain after transplantation: a retrospective study. Lancet 2004;363:1432-1437.

16. Rose RA, Keating A, Backx PH. Do mesenchymal stromal cells transdifferentiate into functional cardiomyocytes? Circ Res 2008;103:e120.

17. Pijnappels DA, Schalij MJ, Ramkisoensing AA, et al. Forced alignment of mesenchymal stem cells undergoing cardiomyogenic differentiation affects functional integration with cardiomyocyte cultures. Circ Res 2008;103:167-176.

18. Pereira RF, Halford KW, O'Hara MD, et al. Cultured adherent cells from marrow can serve as long-lasting precursor cells for bone, cartilage, and lung in irradiated mice. Proc Natl Acad Sci USA 1995;92:4857-4861.

19. Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation 2002;105:93-98.

20. Dai W, Hale SL, Martin BJ, et al. Allogeneic mesenchymal stem cell transplantation in postinfarcted rat myocardium: short- and long-term effects. Circulation 2005;112:214-223.

21. Satake K, Lou J, Lenke LG. Migration of mesenchymal stem cells through cerebrospinal fluid into injured spinal cord tissue. Spine (Phila Pa 1976) 2004;29:1971-1979.

22. Bae JS, Han HS, Youn DH, et al. Bone marrow-derived mesenchymal stem cells promote neuronal networks with functional synaptic transmission after transplantation into mice with neurodegeneration. Stem Cells 2007;25:1307-1316.

23. Anjos-Afonso F, Siapati EK, Bonnet D. In vivo contribution of murine mesenchymal stem cells into multiple cell-types under minimal damage conditions. J Cell Sci 2004;117(Pt 23):5655-5664.

24. English K, Ryan JM, Tobin L, Murphy MJ, Barry FP, Mahon BP. Cell contact, prostaglandin E(2) and transforming growth factor beta 1 play non-redundant roles in human mesenchymal stem cell induction of CD4+CD25(High) forkhead box P3+ regulatory T cells. Clin Exp Immunol 2009;156:149-160.

25. Glennie S, Soeiro I, Dyson PJ, Lam EW, Dazzi F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood 2005;105:2821-2827.

26. Di Nicola M, Carlo-Stella C, Magni M, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 2002;99:3838-3843.

27. Augello A, Tasso R, Negrini SM, et al. Bone marrow mesenchymal progenitor cells inhibit lymphocyte proliferation by activation of the programmed death 1 pathway. Eur J Immunol 2005;35:1482-1490.

28. Corcione A, Benvenuto F, Ferretti E, et al. Human mesenchymal stem cells modulate B-cell functions. Blood 2006;107:367-372.

29. Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, Moretta L. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. Blood 2008;111:1327-1333.

30. Jiang XX, Zhang Y, Liu B, et al. Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. Blood 2005;105:4120-4126.

31. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105:1815-1822.

32. Maccario R, Podesta M, Moretta A, et al. Interaction of human mesenchymal stem cells with cells involved in alloantigen-specific immune response favors the differentiation of CD4+ T-cell subsets expressing a regulatory/suppressive phenotype. Haematologica 2005;90:516-525.

33. Groh ME, Maitra B, Szekely E, Koc ON. Human mesenchymal stem cells require monocyte-mediated activation to suppress alloreactive T cells. Exp Hematol 2005;33:928-934.

34. Beyth S, Borovsky Z, Mevorach D, et al. Human mesenchymal stem cells alter antigen-presenting cell maturation and induce T-cell unresponsiveness. Blood 2005;105:2214-2219.

35. Zhang W, Ge W, Li C, et al. Effects of mesenchymal stem cells on differentiation, maturation, and function of human monocyte-derived dendritic cells. Stem Cells Dev 2004;13:263-271.

36. Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, Dazzi F. Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. Transplantation 2007;83:71-76.

37. Nauta AJ, Kruisselbrink AB, Lurvink E, Willemze R, Fibbe WE. Mesenchymal stem cells inhibit generation and function of both CD34+-derived and monocyte-derived dendritic cells. J Immunol 2006;177:2080-2087.

38. Stagg J, Pommey S, Eliopoulos N, Galipeau J. Interferon-gamma-stimulated marrow stromal cells: a new type of nonhematopoietic antigen-presenting cell. Blood 2006;107:2570-2577.

39. Keating A. How do mesenchymal stromal cells suppress T cells? Cell Stem Cell 2008;2:106-108.

40. Ren G, Zhang L, Zhao X, et al. Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell 2008;2:141-150.

41. Meisel R, Zibert A, Laryea M, Gobel U, Daubener W, Dilloo D. Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation. Blood 2004;103:4619-4621.

42. Ye Z, Wang Y, Xie HY, Zheng SS. Immunosuppressive effects of rat mesenchymal stem cells: involvement of CD4+CD25+ regulatory T cells. Hepatobiliary Pancreat Dis Int 2008;7:608-614.

43. Di Ianni M, Del Papa B, De Ioanni M, et al. Mesenchymal cells recruit and regulate T regulatory cells. Exp Hematol 2008;36:309-318.

44. Joo SY, Cho KA, Jung YJ, et al. Mesenchymal stromal cells inhibit graft-versus-host disease of mice in a dose-dependent manner. Cytotherapy 2010;12:361-370.

45. Zappia E, Casazza S, Pedemonte E, et al. Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. Blood 2005;106:1755-1761.

46. Gonzalez MA, Gonzalez-Rey E, Rico L, Buscher D, Delgado M. Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells. Arthritis Rheum 2009;60:1006-1019.

47. Patel SA, Meyer JR, Greco SJ, Corcoran KE, Bryan M, Rameshwar P. Mesenchymal stem cells protect breast cancer cells through regulatory T cells: role of mesenchymal stem cell-derived TGF-beta. J Immunol 2010;184:5885-5894.

48. Nemeth K, Keane-Myers A, Brown JM, et al. Bone marrow stromal cells use TGF-beta to suppress allergic responses in a mouse model of ragweed-induced asthma. Proc Natl Acad Sci U S A 2010;107:5652-5657.

49. Madec AM, Mallone R, Afonso G, et al. Mesenchymal stem cells protect NOD mice from diabetes by inducing regulatory T cells. Diabetologia 2009;52:1391-1399.

50. Choi YS, Jeong JA, Lim DS. Mesenchymal stem cell-mediated immature dendritic cells induce regulatory T cell-based immunosuppressive effect. Immunol Invest 2012;41:214-229.

51. Marigo I, Dazzi F. The immunomodulatory properties of mesenchymal stem cells. Semin Immunopathol 2011;33:593-602.

52. Dazzi F, Marelli-Berg FM. Mesenchymal stem cells for graft-versus-host disease: close encounters with T cells. Eur J Immunol 2008;38:1479-1482.

53. Krampera M, Cosmi L, Angeli R, et al. Role for interferon-gamma in the immunomodulatory activity of human bone marrow mesenchymal stem cells. Stem Cells 2006;24:386-398.

54. Nakamizo A, Marini F, Amano T, et al. Human bone marrow-derived mesenchymal stem cells in the treatment of gliomas. Cancer Res 2005;65:3307-3318.

55. Son BR, Marquez-Curtis LA, Kucia M, et al. 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 2006;24:1254-1264.

56. Forte G, Minieri M, Cossa P, et al. Hepatocyte growth factor effects on mesenchymal stem cells: proliferation, migration, and differentiation. Stem Cells 2006;24:23-33.

57. Ball SG, Shuttleworth CA, Kielty CM. Vascular endothelial growth factor can signal through platelet-derived growth factor receptors. J Cell Biol 2007;177:489-500.

58. Fiedler J, Roderer G, Gunther KP, Brenner RE. BMP-2, BMP-4, and PDGF-bb stimulate chemotactic migration of primary human mesenchymal progenitor cells. J Cell Biochem 2002;87:305-312.

59. Dwyer RM, Potter-Beirne SM, Harrington KA, et al. Monocyte chemotactic protein-1 secreted by primary breast tumors stimulates migration of mesenchymal stem cells. Clin Cancer Res 2007;13:5020-5027.

60. Palumbo R, Galvez BG, Pusterla T, et al. Cells migrating to sites of tissue damage in response to the danger signal HMGB1 require NF-kappaB activation. J Cell Biol 2007;179:33-40.

61. Palumbo R, Bianchi ME. High mobility group box 1 protein, a cue for stem cell recruitment. Biochem Pharmacol 2004;68:1165-1170.

62. Ip JE, Wu Y, Huang J, Zhang L, Pratt RE, Dzau VJ. Mes-

enchymal stem cells use integrin beta1 not CXC chemo-kine receptor 4 for myocardial migration and engraftment. Mol Biol Cell 2007;18:2873-2882.

63. Balkwill F. Cancer and the chemokine network. Nat Rev Cancer 2004;4:540-550.

64. Winner M, Koong AC, Rendon BE, Zundel W, Mitchell RA. Amplification of tumor hypoxic responses by macrophage migration inhibitory factor-dependent hypoxia-inducible factor stabilization. Cancer Res 2007;67:186-193.

65. Horwitz EM, Prockop DJ, Fitzpatrick LA, et al. Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. Nat Med 1999;5:309-313.

66. Horwitz EM, Prockop DJ, Gordon PL, et al. Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. Blood 2001;97:1227-1231.

67. Horwitz EM, Gordon PL, Koo WK, et al. 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 U S A 2002;99:8932-8937.

68. Le Blanc K, Gotherstrom C, Ringden O, et al. Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation 2005;79:1607-1614.

69. Cahill RA, Wenkert D, Perlman SA, et al. Infantile hypophosphatasia: transplantation therapy trial using bone fragments and cultured osteoblasts. J Clin Endocrinol Metab 2007;92:2923-2930.

70. Whyte MP, Kurtzberg J, McAlister WH, et al. Marrow cell transplantation for infantile hypophosphatasia. J Bone Miner Res 2003;18:624-636.

71. Rombouts WJ, Ploemacher RE. Primary murine MSC show highly efficient homing to the bone marrow but lose homing ability following culture. Leukemia 2003;17:160-170.

72. Banfi A, Muraglia A, Dozin B, Mastrogiacomo M, Cancedda R, Quarto R. Proliferation kinetics and differentiation potential of ex vivo expanded human bone marrow stromal cells: implications for their use in cell therapy. Exp Hematol 2000;28:707-715.

73. Wakitani S, Mitsuoka T, Nakamura N, Toritsuka Y, Nakamura Y, Horibe S. Autologous bone marrow stromal cell transplantation for repair of full-thickness articular cartilage defects in human patellae: two case reports. Cell Transplant 2004;13:595-600.

74. Wakitani S, Nawata M, Tensho K, Okabe T, Machida H, Ohgushi H. Repair of articular cartilage defects in the patello-femoral joint with autologous bone marrow mesenchymal cell transplantation: three case reports involving nine defects in five knees. J Tissue Eng Regen Med 2007;1:74-79.

75. Wakitani S, Imoto K, Yamamoto T, Saito M, Murata N, Yoneda M. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. Osteoarthritis Cartilage 2002;10:199-206.

76. Kuroda R, Ishida K, Matsumoto T, et al. Treatment of a full-thickness articular cartilage defect in the femoral condyle of an athlete with autologous bone-marrow stromal cells. Osteoarthritis Cartilage 2007;15:226-231.

77. Tabbara IA, Zimmerman K, Morgan C, Nahleh Z. Allogeneic hematopoietic stem cell transplantation: complications and results. Arch Intern Med 2002;162:1558-1566.

78. Baron F, Lechanteur C, Willems E, et al. Cotransplantation of mesenchymal stem cells might prevent death from graft-versus-host disease (GVHD) without abrogating graft-versus-tumor effects after HLA-mismatched allogeneic transplantation following nonmyeloablative conditioning. Biol Blood Marrow Transplant 2010;16:838-847.

79. Lazarus HM, Koc ON, Devine SM, et al. Cotransplantation of HLA-identical sibling culture-expanded mesenchymal stem cells and hematopoietic stem cells in hematologic malignancy patients. Biol Blood Marrow Transplant 2005;11:389-398.

80. Ning H, Yang F, Jiang M, et al. The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study. Leukemia 2008;22:593-599.

81. Ball LM, Bernardo ME, Roelofs H, et al. Cotransplantation of ex vivo expanded mesenchymal stem cells accelerates lymphocyte recovery and may reduce the risk of graft failure in haploidentical hematopoietic stem-cell transplantation. Blood 2007;110:2764-2767.

82. Bernardo ME, Ball LM, Cometa AM, et al. Co-infusion of ex vivo-expanded, parental MSCs prevents life-threatening acute GVHD, but does not reduce the

risk of graft failure in pediatric patients undergoing allogeneic umbilical cord blood transplantation. Bone Marrow Transplant 2011;46:200-207.

83. Macmillan ML, Blazar BR, DeFor TE, Wagner JE. Transplantation of ex-vivo culture-expanded parental haploidentical mesenchymal stem cells to promote engraftment in pediatric recipients of unrelated donor umbilical cord blood: results of a phase I-II clinical trial. Bone Marrow Transplant 2009;43:447-454.

84. Le Blanc K, Rasmusson I, Sundberg B, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet 2004;363:1439-1441.

85. Fang B, Song YP, Liao LM, Han Q, Zhao RC. Treatment of severe therapy-resistant acute graft-versus-host disease with human adipose tissue-derived mesenchymal stem cells. Bone Marrow Transplant 2006;38:389-390.

86. Le Blanc K, Frassoni F, Ball L, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 2008;371:1579-1586.

87. Lucchini G, Introna M, Dander E, et al. Platelet-lysate-expanded mesenchymal stromal cells as a salvage therapy for severe resistant graft-versus-host disease in a pediatric population. Biol Blood Marrow Transplant 2010;16:1293-1301.

88. Muller I, Kordowich S, Holzwarth C, et al. Application of multipotent mesenchymal stromal cells in pediatric patients following allogeneic stem cell transplantation. Blood Cells Mol Dis 2008;40:25-32.

89. Prasad VK, Lucas KG, Kleiner GI, et al. Efficacy and safety of ex vivo cultured adult human mesenchymal stem cells (Prochymal) in pediatric patients with severe refractory acute graft-versus-host disease in a compassionate use study. Biol Blood Marrow Transplant 2011;17:534-541.

90. Ringden O, Uzunel M, Rasmusson I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. Transplantation 2006;81:1390-1397.

91. von Bonin M, Stolzel F, Goedecke A, et al. Treatment of refractory acute GVHD with third-party MSC expanded in platelet lysate-containing medium. Bone Marrow Transplant 2009;43:245-251.

92. Wu KH, Chan CK, Tsai C, et al. Effective treatment of severe steroid-resistant acute graft-versus-host disease with umbilical cord-derived mesenchymal stem cells.

Transplantation 2011;91:1412-1416.

93. Zhou H, Guo M, Bian C, et al. Efficacy of bone marrow-derived mesenchymal stem cells in the treatment of sclerodermatous chronic graft-versus-host disease: clinical report. Biol Blood Marrow Transplant 2010;16:403-412.

94. Kebriaei P, Isola L, Bahceci E, et al. Adult human mesenchymal stem cells added to corticosteroid therapy for the treatment of acute graft-versus-host disease. Biol Blood Marrow Transplant 2009;15:804-811.

95. Weng JY, Du X, Geng SX, et al. Mesenchymal stem cell as salvage treatment for refractory chronic GVHD. Bone Marrow Transplant 2010;45:1732-1740.

96. Kuzmina LA, Petinati NA, Parovichnikova EN, et al. Multipotent mesenchymal stromal cells for the prophylaxis of acute graft-versus-host disease: a phase II study. Stem Cells Int 2012;2012:968213.

97. Zhang S, Ge J, Sun A, et al. Comparison of various kinds of bone marrow stem cells for the repair of infarcted myocardium: single clonally purified non-hematopoietic mesenchymal stem cells serve as a superior source. J Cell Biochem 2006;99:1132-1147.

98. Jiang S, Haider H, Idris NM, Salim A, Ashraf M. Supportive interaction between cell survival signaling and angiocompetent factors enhances donor cell survival and promotes angiomyogenesis for cardiac repair. Circ Res 2006;99:776-784.

99. Nagaya N, Kangawa K, Itoh T, et al. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. Circulation 2005;112:1128-1135.

100. Chen SL, Fang WW, Ye F, et al. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. Am J Cardiol 2004;94:92-95.

101. Chen S, Liu Z, Tian N, et al. Intracoronary transplantation of autologous bone marrow mesenchymal stem cells for ischemic cardiomyopathy due to isolated chronic occluded left anterior descending artery. J Invasive Cardiol 2006;18:552-556.

102. Katritsis DG, Sotiropoulou PA, Karvouni E, et al. Transcoronary transplantation of autologous mesenchymal stem cells and endothelial progenitors into infarcted human myocardium. Catheter Cardiovasc Interv 2005;65:321-329.

103. Katritsis DG, Sotiropoulou P, Giazitzoglou E, Karvouni E, Papamichail M. Electrophysiological effects of intracoronary transplantation of autologous mesenchymal and endothelial progenitor cells. Europace 2007;9:167-171.

104. Yang Z, Zhang F, Ma W, et al. A novel approach to transplanting bone marrow stem cells to repair human myocardial infarction: delivery via a noninfarct-relative artery. Cardiovasc Ther 2010;28:380-385.

105. Zeinaloo A, Zanjani KS, Bagheri MM, Mohyeddin-Bonab M, Monajemzadeh M, Arjmandnia MH. Intracoronary administration of autologous mesenchymal stem cells in a critically ill patient with dilated cardiomyopathy. Pediatr Transplant 2011;15:E183-E186.

106. Hare JM, Traverse JH, Henry TD, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. J Am Coll Cardiol 2009;54:2277-2286.

107. Ichim TE, Solano F, Brenes R, et al. Placental mesenchymal and cord blood stem cell therapy for dilated cardiomyopathy. Reprod Biomed Online 2008;16:898-905.

108. Tyndall A. Application of autologous stem cell transplantation in various adult and pediatric rheumatic diseases. Pediatr Res 2012;71(4 Pt 2):433-438.

109. Garcia-Olmo D, Garcia-Arranz M, Herreros D, Pascual I, Peiro C, Rodriguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. Dis Colon Rectum 2005;48:1416-1423.

110. Garcia-Olmo D, Herreros D, Pascual I, et al. Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. Dis Colon Rectum 2009;52:79-86.

111. Mohyeddin Bonab M, Yazdanbakhsh S, Lotfi J, et al. Does mesenchymal stem cell therapy help multiple sclerosis patients? Report of a pilot study. Iran J Immunol 2007;4:50-57.

112. Yamout B, Hourani R, Salti H, et al. Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: a pilot study. J Neuroimmunol 2010;227:185-189.

113. Karussis D, Karageorgiou C, Vaknin-Dembinsky A, et al. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. Arch Neurol 2010;67:1187-1194.

114. Riordan NH, Ichim TE, Min WP, et al. Non-expanded adipose stromal vascular fraction cell therapy for multiple sclerosis. J Transl Med 2009;7:29.

115. Sun LY, Zhang HY, Feng XB, Hou YY, Lu LW, Fan LM. Abnormality of bone marrow-derived mesenchymal stem cells in patients with systemic lupus erythematosus. Lupus 2007;16:121-128.

116. Liang J, Zhang H, Hua B, et al. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. Ann Rheum Dis 2010;69:1423-1429.

117. Sun L, Wang D, Liang J, et al. Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. Arthritis Rheum 2010;62:2467-2475.

118. Liang J, Gu F, Wang H, et al. Mesenchymal stem cell transplantation for diffuse alveolar hemorrhage in SLE. Nat Rev Rheumatol 2010;6:486-489.

119. Carrion F, Nova E, Ruiz C, et al. Autologous mesenchymal stem cell treatment increased T regulatory cells with no effect on disease activity in two systemic lupus erythematosus patients. Lupus 2010;19:317-322.

120. Mao F, Xu WR, Qian H, et al. Immunosuppressive effects of mesenchymal stem cells in collagen-induced mouse arthritis. Inflamm Res 2010;59:219-225.

121. Zheng ZH, Li XY, Ding J, Jia JF, Zhu P. Allogeneic mesenchymal stem cell and mesenchymal stem cell-differentiated chondrocyte suppress the responses of type II collagen-reactive T cells in rheumatoid arthritis. Rheumatology (Oxford) 2008;47:22-30.

122. Chen B, Hu J, Liao L, et al. Flk-1+ mesenchymal stem cells aggravate collagen-induced arthritis by up-regulating interleukin-6. Clin Exp Immunol 2010;159:292-302.

123. Schurgers E, Kelchtermans H, Mitera T, Geboes L, Matthys P. Discrepancy between the in vitro and in vivo effects of murine mesenchymal stem cells on T-cell proliferation and collagen-induced arthritis. Arthritis Res Ther 2010;12:R31.

124. Park MJ, Park HS, Cho ML, et al. Transforming growth factor beta-transduced mesenchymal stem cells ameliorate experimental autoimmune arthritis through reciprocal regulation of Treg/Th17 cells and osteoclastogenesis. Arthritis Rheum 2011;63:1668-1680.

125. Mohamadnejad M, Alimoghaddam K, Mohyeddin-Bon-

ab M, et al. Phase 1 trial of autologous bone marrow mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis. Arch Iran Med 2007;10:459-466.

126. Kharaziha P, Hellstrom PM, Noorinayer B, et al. Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I-II clinical trial. Eur J Gastroenterol Hepatol 2009;21:1199-1205.

127. Wang H, Cao F, De A, et al. Trafficking mesenchymal stem cell engraftment and differentiation in tumor-bearing mice by bioluminescence imaging. Stem Cells 2009;27:1548-1558.

128. Qiao L, Xu Z, Zhao T, et al. Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model. Cell Res 2008;18:500-507.

129. Khakoo AY, Pati S, Anderson SA, et al. Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma. J Exp Med 2006;203:1235-1247.

130. Otsu K, Das S, Houser SD, Quadri SK, Bhattacharya S, Bhattacharya J. Concentration-dependent inhibition of angiogenesis by mesenchymal stem cells. Blood 2009;113:4197-4205.

131. Djouad F, Plence P, Bony C, et al. Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. Blood 2003;102:3837-3844.

132. Karnoub AE, Dash AB, Vo AP, et al. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature 2007;449:557-563.

133. Zhu W, Xu W, Jiang R, et al. Mesenchymal stem cells derived from bone marrow favor tumor cell growth in vivo. Exp Mol Pathol 2006;80:267-274.

134. Gao P, Ding Q, Wu Z, Jiang H, Fang Z. Therapeutic potential of human mesenchymal stem cells producing IL-12 in a mouse xenograft model of renal cell carcinoma. Cancer Lett 2010;290:157-166.

135. Seo SH, Kim KS, Park SH, et al. The effects of mesenchymal stem cells injected via different routes on modified IL-12-mediated antitumor activity. Gene Ther 2011;18:488-495.

136. Stagg J, Lejeune L, Paquin A, Galipeau J. Marrow stromal cells for interleukin-2 delivery in cancer immunotherapy. Hum Gene Ther 2004;15:597-608.

137. Gunnarsson S, Bexell D, Svensson A, Siesjo P, Darabi A, Bengzon J. Intratumoral IL-7 delivery by mesenchymal stromal cells potentiates IFNgamma-transduced tumor cell immunotherapy of experimental glioma. J Neuroimmunol 2010;218:140-144.

138. Xin H, Kanehira M, Mizuguchi H, et al. Targeted delivery of CX3CL1 to multiple lung tumors by mesenchymal stem cells. Stem Cells 2007;25:1618-1626.

139. Studeny M, Marini FC, Champlin RE, Zompetta C, Fidler IJ, Andreeff M. Bone marrow-derived mesenchymal stem cells as vehicles for interferon-beta delivery into tumors. Cancer Res 2002;62:3603-3608.

140. Ren C, Kumar S, Chanda D, Chen J, Mountz JD, Ponnazhagan S. Therapeutic potential of mesenchymal stem cells producing interferon-alpha in a mouse melanoma lung metastasis model. Stem Cells 2008;26:2332-2338.

141. Ren C, Kumar S, Chanda D, et al. Cancer gene therapy using mesenchymal stem cells expressing interferon-beta in a mouse prostate cancer lung metastasis model. Gene Ther 2008;15:1446-1453.

142. Miletic H, Fischer Y, Litwak S, et al. Bystander killing of malignant glioma by bone marrow-derived tumor-infiltrating progenitor cells expressing a suicide gene. Mol Ther 2007;15:1373-1381.

143. Cavarretta IT, Altanerova V, Matuskova M, Kucerova L, Culig Z, Altaner C. Adipose tissue-derived mesenchymal stem cells expressing prodrug-converting enzyme inhibit human prostate tumor growth. Mol Ther 2010;18:223-231.

144. Komarova S, Kawakami Y, Stoff-Khalili MA, Curiel DT, Pereboeva L. Mesenchymal progenitor cells as cellular vehicles for delivery of oncolytic adenoviruses. Mol Cancer Ther 2006;5:755-766.

145. Stoff-Khalili MA, Rivera AA, Mathis JM, et al. Mesenchymal stem cells as a vehicle for targeted delivery of CRAds to lung metastases of breast carcinoma. Breast Cancer Res Treat 2007;105:157-167.

146. Sonabend AM, Ulasov IV, Tyler MA, Rivera AA, Mathis JM, Lesniak MS. Mesenchymal stem cells effectively deliver an oncolytic adenovirus to intracranial glioma. Stem Cells 2008;26:831-841.

147. Yong RL, Shinojima N, Fueyo J, et al. Human bone marrow-derived mesenchymal stem cells for intravascular delivery of oncolytic adenovirus Delta24-RGD to human gliomas. Cancer Res 2009;69:8932-8940.

148. van Eekelen M, Sasportas LS, Kasmieh R, et al. Human stem cells expressing novel TSP-1 variant have anti-an-

giogenic effect on brain tumors. Oncogene 2010;29:3185-3195.

149. Loebinger MR, Eddaoudi A, Davies D, Janes SM. Mesenchymal stem cell delivery of TRAIL can eliminate metastatic cancer. Cancer Res 2009;69:4134-4142.

150. Mueller LP, Luetzkendorf J, Widder M, Nerger K, Caysa H, Mueller T. TRAIL-transduced multipotent mesenchymal stromal cells (TRAIL-MSC) overcome TRAIL resistance in selected CRC cell lines in vitro and in vivo. Cancer Gene Ther 2011;18:229-239.

151. Kanehira M, Xin H, Hoshino K, et al. Targeted delivery of NK4 to multiple lung tumors by bone marrow-derived mesenchymal stem cells. Cancer Gene Ther 2007;14:894-903.

152. Tolar J, Nauta AJ, Osborn MJ, et al. Sarcoma derived from cultured mesenchymal stem cells. Stem Cells 2007;25:371-379.

153. Wang Y, Huso DL, Harrington J, et al. Outgrowth of a transformed cell population derived from normal human BM mesenchymal stem cell culture. Cytotherapy 2005;7:509-519.

154. Ramos CA, Asgari Z, Liu E, et al. An inducible caspase 9 suicide gene to improve the safety of mesenchymal stromal cell therapies. Stem Cells 2010;28:1107-1115.