Chapter 2
Mesenchymal Stem Cells in Clinical Applications

Phuc Van Pham

2.1 Introduction

Mesenchymal stem cells (MSCs) are multipotent stem cells that can differentiate into a variety of cell types, e.g., osteoblasts (bone cells), chondrocytes (cartilage cells), and adipocytes (fat cells). MSCs were first discovered by Alexander Maximow, who identified a cell type within the mesenchyme with potential to develop into various types of blood cells. McCulloch and James later revealed the clonal nature of marrow cells in 1963 (Becker et al. 1963; Siminovitch et al. 1963). An ex vivo assay for examining the potential of multipotent marrow clonogenic cells was reported in the 1970s by Friedenstein and colleagues (Friedenstein et al. 1974, 1976). MSCs were determined based on three common characteristics: ability to adhere to culture vessels with a fibroblast-like shape; expression of characteristic markers Stro-1, CD133, CD29, CD44, CD90, CD105 (SH2), SH3, SH4 (CD73), c-kit, CD71, and CD106; and ability to differentiate into specialized cells, e.g., the bone, cartilage, and fat. To easily determine which stem cells are MSCs, in 2006 the International Society of Cellular Therapy defined MSCs with some minimal criteria (Dominici et al. 2006), including:

1. MSCs must be adherent to plastic under standard tissue culture conditions.
2. MSCs must express some specific markers such as CD73, CD90, and CD150 and lack expression of CD14, CD34, CD45 or CD11b, CD79 alpha or CD19, and HLA-DR.
3. MSCs must successfully differentiate into osteoblasts, adipocytes, and chondroblasts under in vitro conditions.

P. V. Pham (✉)
Laboratory of Stem Cell Research and Application, University of Science, Vietnam National University, Ho Chi Minh City, Vietnam
e-mail: pvphuc@hcmuns.edu.vn

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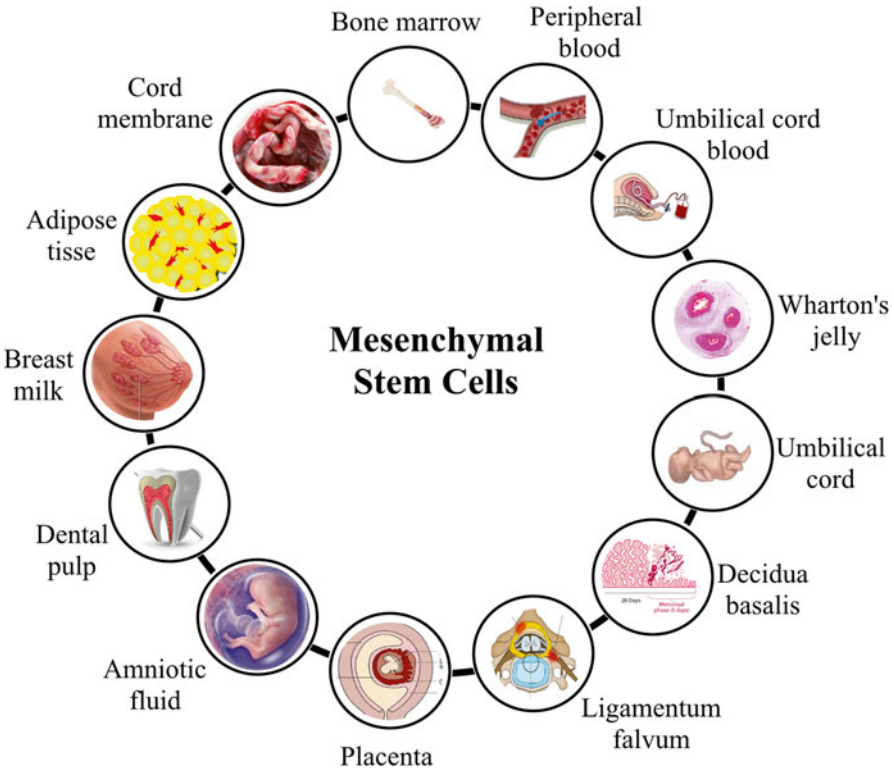

Fig. 2.1 Sources of MSCs. MSCs can be derived from several tissues in the adult or infant human body

The first identified source of MSCs was bone marrow. MSCs are currently isolated from many different tissues in the body, such as the adipose tissue, peripheral blood, umbilical cord blood, banked umbilical cord blood, umbilical cord, umbilical cord membrane, umbilical cord vein, Wharton's jelly of the umbilical cord, placenta, decidua basalis, ligamentum flavum, amniotic fluid, amniotic membrane, dental pulp, chorionic villi of the human placenta, fetal membranes, menstrual blood, breast milk, and urine (Fig. 2.1, Table 2.1).

2.2 How MSCs Can Treat Diseases?

Different than other stem cells, MSCs can be used to treat diseases by two different mechanisms, including tissue repair and immune modulation. While tissue repair is related to the differentiation of multipotent MSCs, immune modulation is a particular property of MSCs. Over the last decades, MSCs have been considered as a feasible source of stem cells for tissue regeneration. It hopes to open the new era of

Table 2.1 Human MSC sources, cell surface markers, and expansion media with serum supplements

Source	Method of isolation	Media	Serum supplement	Cell surface markers		References
				Positive	Negative	
Bone marrow	Ficoll density gradient method	DMEM	FBS	CD73, CD90, CD105, STRO-1	CD14, CD34, CD45, HLA-DR	Mamidi et al. (2012), Otsuru et al. (2013) and Stewart et al. (1999)
	Novel marrow filter device	DMEM-F12				
		ADMEM				
Adipose tissue	Digestion method	DMEM	FBS	CD73, CD090, CD29, CD44, CD71, CD105, CD13, CD166, STRO-1	CD14, CD31, CD34, CD45	Castrechini et al. (2012), El-Kheir et al. (2014) and Gronthos et al. (2001)
	Membrane filtration method	DMEM-LG	FCS			
Amniotic fluid and membrane	Density gradient method	α-MEM	FBS	CD29, CD44, CD90, CD105, CD, SH2, SH3, HLA-DR	CD10, CD14,CD34, HLA-DR	Cai et al. (2010), In 't Anker et al. (2003) and Tsai et al. (2004)
	Digestion method	DMEM/F12				
Dental tissues	Digestion method	α-MEM	FCS	CD29, CD44, CD90, CD105	CD14, CD34, CD45	Huang et al. (2009), Kadar et al. (2009) and Seifrtova et al. (2012)
		MEM	FBS			
Endometrium	Digestion method	DMEM-F12	FCS	CD73, CD90, CD105, CD146	CD34, CD45	Schuring et al. (2011)
Limb bud	Digestion method	DMEM-LG	FBS	CD13, CD29,CD90, CD105, CD106	CD3, CD4, CD14, CD15, CD34, CD45, HLA-DR	Jiao et al. (2012)
Peripheral blood	Ficoll density gradient	α-MEM	NBCS	CD44, CD90, CD105, HLA-ABC	CD45, CD133	Ab Kadir et al. (2012)
Placenta and fetal membrane	Digestion method	DMEM-LG	FBS	CD29, CD73, CD90, CD105	CD34, CD45	Raynaud et al. (2012)
Salivary gland	Digestion method (Ringer solution)	DMEM	FCS	CD13, CD29, CD44, CD90, STRO-1	CD34, CD45	Rotter et al. (2008)
Skin and foreskin	Digestion method	DMEM-HG DMEM DMEM-F12	FBS	CD44, CD73, CD90, CD105, CD166, SSEA-4, vimentin	CD34, CD45, HLA-DR	Bartsch et al. (2005) and Riekstina et al. (2008)

(continued)

Table 2.1 (continued)

Source	Method of isolation	Media	Serum supplement	Cell surface markers		References
				Positive	Negative	
Sub-amniotic umbilical cord lining membrane	Digestion method	DMEM-HG	FBS	CD29, CD44, CD73, CD90, CD105	CD34, CD45	Kita et al. (2010) and Moretti et al. (2010)
		DMEM				
		CMRL1660				
Synovial fluid	Ficoll density gradient method	α-MEM	FBS	CD44, CD90, CD105, CD147, STRO-1	CD31, CD34, CD45, CD106	Morito et al. (2008)
Wharton's jelly	Enzymatic digestion method	DMEM	FBS	CD73, CD90, CD105	CD14, CD34, CD45, CD79, HLA-DR	Hou et al. (2009)
Menstrual blood	Density gradient centrifugations	*α*-MEM	FBS	CD56, CD73, CD90, CD105 and CD146	CD14, CD45, HLA-DR	Rossignoli et al. (2013)
Human milk	Centrifugations	DMEM	UCBS	CD44, CD29, SCA-1	CD33, CD34, CD45, CD73	Patki et al. (2010)

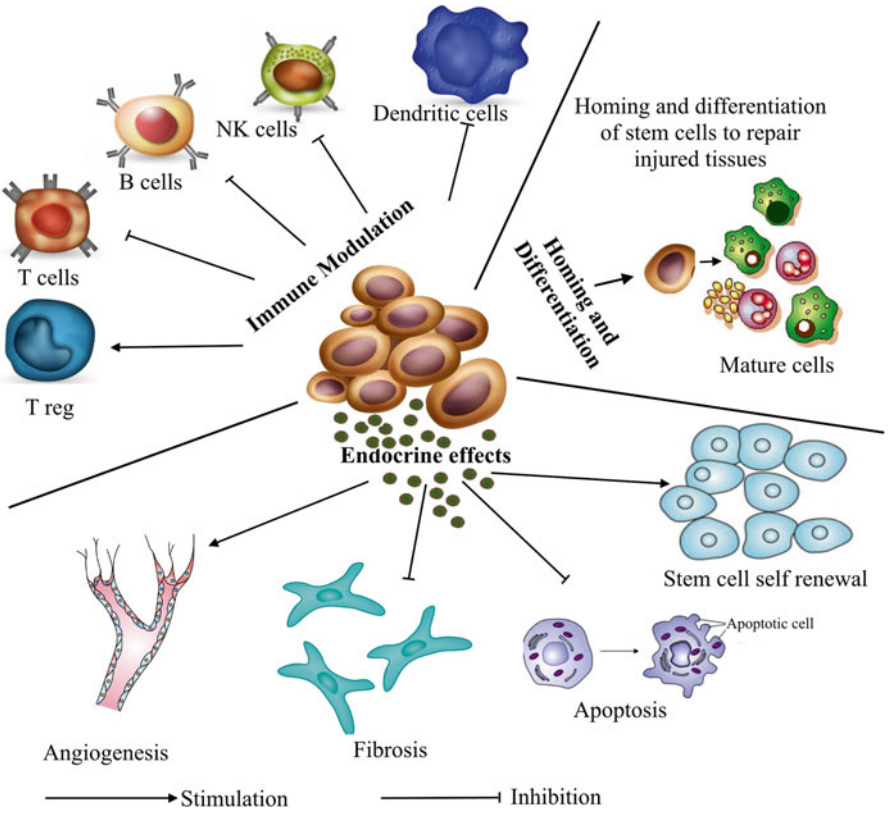

Fig. 2.2 Some mechanisms of MSCs in therapeutic application. MSCs are multipotent stem cells; therefore, they can differentiate into some specific cells that can replace some injured cells/damaged adult cells. In another strategy, MSCs can modulate the immune response via some cytokines

stem cell therapy for degenerative diseases. However, the immune modulation capacity of MSCs has been the subject of recent interest over the past several years. The first MSC drug, Prochymal produced by Osiris Therapeutics, was approved in 2012 and is used for immune modulation in graft-versus-host disease (GVHD) treatment (Fig. 2.2).

2.2.1 Tissue Regeneration

MSCs were shown to have differentiation potential into mesenchymal cells as well as endoderm and ectoderm cells. Based on this capacity, MSCs were considered as a suitable cell source for tissue regeneration from the bone, cartilage, adipose tissue, heart,

muscle, and skin. Using in vitro assays, MSCs have been successfully differentiated into osteoblasts (Castren et al. 2015; Glueck et al. 2015; Wang et al. 2015), chondroblasts (Ibrahim et al. 2015; Moghadam et al. 2014; Pustlauk et al. 2015), adipocytes (Li et al. 2015b; Mohammadi et al. 2015), neurons (Bagher et al. 2015; Kim et al. 2015; Nan et al. 2015), insulin-producing cells (Allahverdi et al. 2015; Balici et al. 2016; Ngoc et al. 2011; Van Pham et al. 2014), skeletal muscle (Xu et al. 2015), endothelial progenitor cells (Ikhapoh et al. 2015), cardiac progenitor cells (Li et al. 2015a; Pham et al. 2014; Yang et al. 2015c), and hepatocytes (Han et al. 2015; Sawitza et al. 2015; Ye et al. 2015).

Animal models showed that transplanted MSCs could differentiate in vivo into functional cells at injected sites and contribute to recovering tissue functions. In the minipig model with injured cartilage, Ha et al. (2015) showed that injected human umbilical cord blood-derived MSCs (UC-MSCs) could differentiate and regenerate the cartilage (Ha et al. 2015). Similarly, MSCs can also successfully differentiate into functional insulin-producing cells in vivo in diabetic mice (Yang et al. 2015b), hepatic cells (Hu and Li 2015; Zhong et al. 2015), and neurons (Taran et al. 2014). In animal models, MSCs from the bone marrow, umbilical cord blood, umbilical cord, and peripheral blood have been successfully used to treat several diseases, such as injured cartilage (Punwar and Khan 2011; Song et al. 2014), osteoarthritis (Ozeki et al. 2015; Wolfstadt et al. 2015; Xia et al. 2015), myocardial infarction (MI) (Chen et al. 2015), cornea damage (Guo et al. 2006; Ma et al. 2006), wound healing (Li et al. 2015d; Pelizzo et al. 2015), brain and spinal cord injury (Mannoji et al. 2014; Wu et al. 2015), lung failure (Liu et al. 2014a; Matthay et al. 2010), liver cirrhosis (Tang et al. 2015; Yang et al. 2015a), bone healing (Dehghan et al. 2015; Li et al. 2015c), and diabetes mellitus (DM) (Hao et al. 2013; Kong et al. 2014; Lian et al. 2014; Yaochite et al. 2015).

Based on these studies, MSCs have been clinically applied in disease treatment, especially for tissue injury and degenerative medicine. One popular application of MSCs in degenerative disease is in osteoarthritis as well as injured cartilage. Bornes et al. (2014) showed that MSC transplantation shows positive functional outcomes at 12–48 months postimplantation (Bornes et al. 2014). The first reported use of MSCs to repair cartilage damage in humans was conducted by Wakitani et al. in 1998 (Wakitani et al. 2004). To date, approximately 15 publications have reported the application of MSCs in cartilage regeneration (Bornes et al. 2014). The first MSC-based product (allogeneic umbilical cord blood MSC or CARTISTEM) was approved to treat injured cartilage in Korea in 2014. MSCs have also been clinically used in the treatment of wound healing (Falanga et al. 2007; Rasulov et al. 2005; Ravari et al. 2011; Vojtassak et al. 2006).

2.2.2 Immune Modulation

In comparison to other stem cells, MSCs exhibit a powerful capacity of regulating immune responses. Many studies showed that MSCs could regulate immune responses both in vitro and in vivo. The effects of MSCs on immune cells are summarized in Tables 2.2 and 2.3. MSCs can affect all kinds of immune cells including

Table 2.2 Immunomodulatory effects of MSCs on immune cells

Immune cell type	MSCs' effects
T lymphocyte	Suppress T-cell proliferation induced by cellular or nonspecific mitogenic stimuli (Di Nicola et al. 2002)
	Alter the cytokine secretion profile of naive and effector T cells (Aggarwal and Pittenger 2005)
	Promote the expansion and function of Treg cells losh (English et al. 2009)
B lymphocyte	Inhibit proliferation of B lymphocyte (Augello et al. 2005)
	Affect the chemotactic properties of B cells (Corcione et al. 2006)
	Suppress B-cell terminal differentiation (Asari et al. 2009)
NK cell	Alter the phenotype of NK cells and suppress proliferation, cytokine secretion, and cytotoxicity against HLA class I-expressing targets (Sotiropoulou et al. 2006; Spaggiari et al. 2006)
Dendritic cells (DCs)	Influence differentiation, maturation, and function of monocyte-derived dendritic cells (Zhang et al. 2004)
	Suppress dendritic cell migration, maturation, and antigen presentation (Chen et al. 2007)
	Induce mature DCs into a novel Jagged-2-dependent regulatory DC population (Zhang et al. 2009)

Table 2.3 Important bioactive molecules secreted by MSCs and their functions

Bioactive molecules	Functions
Prostaglandin E2 (PGE2)	Antiproliferative mediators (Bouffi et al. 2010)
	Anti-inflammation (Foraker et al. 2011)
Interleukin-10(IL-10)	Anti-inflammatory (Nemeth et al. 2009)
Transforming growth factorβ-1 (TGFβ1), hepatocyte growth factor (HGF)	Suppress T-lymphocyte proliferation (Di Nicola et al. 2002)
Interleukin-1 receptor antagonist	Anti-inflammatory (Ortiz et al. 2007)
Human leukocyte antigen G isoform (HLA-G5)	Antiproliferative for naive T cells (Selmani et al. 2008)
LL-37	Antimicrobial peptide and reduce inflammation (Krasnodembskaya et al. 2010)
Angiopoietin-1	Restore epithelial protein permeability (Fang et al. 2010)
MMP3, MMP9	Mediating neovascularization (Kim et al. 2007)
Keratinocyte growth factor	Alveolar epithelial fluid transport (Lee et al. 2009)
Endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), placental growth factor (PlGF), and monocyte chemoattractant protein-1 (MCP-1)	Enhance proliferation of endothelial cells and smooth muscle cells (Kinnaird et al. 2004a, b)

T lymphocytes (Aggarwal and Pittenger 2005; Di Nicola et al. 2002; English et al. 2009), B lymphocytes (Asari et al. 2009; Augello et al. 2005; Corcione et al. 2006), natural killer cells (Sotiropoulou et al. 2006; Spaggiari et al. 2006), and dendritic cells (DCs) (Chen et al. 2007; Zhang et al. 2004). MSCs have thus been successfully applied in both preclinical and clinical treatments for some immune disorder-related diseases. For example, MSCs have been used to treat GVHD in patients transplanted with hematopoietic stem cells (Introna and Rambaldi 2015; von Dalowski et al. 2016; Zhao et al. 2015a), systemic lupus erythematosus (Gu et al. 2014; Wang et al. 2014a; Yan et al. 2013), Crohn's disease (Ciccocioppo et al. 2015; Liew et al. 2014), multiple system atrophy (Lee et al. 2012; Sunwoo et al. 2014), multiple sclerosis (Dulamea 2015; Gharibi et al. 2015), and amyotrophic lateral sclerosis (Hajivalili et al. 2016; Lewis and Suzuki 2014; Rushkevich et al. 2015). An allogeneic MSC-based product was approved as drug for GVHD treatment in Canada in 2015 (Prochymal, which is produced by Osiris Therapeutics). This represents the first approved stem cell drug.

2.3 Clinical Applications of MSCs

2.3.1 Approved MSC-Based Products

For the past 5 years, MSCs have been widely used in clinical applications mainly through two main approaches: approved MSC-based products and clinical trials. To date, approximately nine MSC-based products have been approved by several countries for the treatment of different diseases such as degenerative arthritis, post-acute MI, and GVHD (Table 2.4, Fig. 2.3). These products have been used in autologous and allogenous transplantation in several countries and have significantly contributed to the growth of MSC clinical applications.

CARTISTEM®, a combination of human UC-MSCs and sodium hyaluronate, is intended to be used as a single-dose therapeutic agent for cartilage regeneration in humans with cartilage defects of the knee as a result of aging, trauma, or degenerative diseases.

CardioRel® is an autologous product designed for early or planned intervention in patients of MI providing mononuclear and mesenchymal stem cells for cardiac regeneration.

Trinity® Evolution™ is an allograft of cancellous bone containing viable adult stem cells and osteoprogenitor cells within the matrix and a demineralized bone component. Trinity Evolution offers an ideal alternative to autograft and other bone grafting options (without their drawbacks).

Osteocel® Plus is an allograft cellular bone matrix that retains its native bone-forming cells, including MSCs and osteoprogenitors. Osteocel® Plus is intended for the repair, replacement, and reconstruction of skeletal defects.

Hearticellgram®-AMI are bone marrow-derived MSCs (BM-MSCs) used to treat acute MI through intracoronary injection. This study assessed the safety and efficacy of intracoronary autologous transplantation of BM-MSCs in patients with

Table 2.4 Allogeneic mesenchymal stem cell-based products approved by several countries

Names of products	Components	For diseases	Kind of transplantation	Company	Country
CARTISTEM	MSCs from umbilical cord blood	Degenerative arthritis	Allo	Medipost	Korea
MPC	Mesenchymal precursor cells	N/A	Allo	Mesoblast	Australia
Cupistem	MSC from adipose tissue	Anal fistula (Crohn's disease)	Auto	Anterogen	South Korea
Prochymal	Mesenchymal stem cells from bone marrow	GVHD	Allo	Osiris Therapeutics	Canada
AlloStem	Bone matrix+BM-MSC	Orthopedics	Allo	AlloSource	USA
Hearticellgram-AMI	BM-MSC	Post-acute myocardial infarction	Auto	FCB Pharmicell	South Korea
Osteocel Plus	BM-MSC	Orthopedics	Allo	NuVasive	USA
Trinity Evolution	Bone matrix with MSC	Orthopedics	Allo	Orthofix	USA
CardioRel	BM-MNC/ MSC	Post-acute myocardial infarction	Auto	Reliance Life Science	India

Fig. 2.3 Some approved MSC-based products in some countries. (**a**) CARTISTEM; (**b**) Trinity Evolution; (**c**) Osteocel; (**d**) Prochymal

acute MI. There were no adverse reactions or major cardiac events. There was an improvement in left ventricular (LV) ejection fraction, already evident 6 h after treatment, in acute myocardial function patients who underwent percutaneous transluminal coronary angiography within 72 h of chest pain onset.

AlloStem is partially demineralized allograft bone combined with adipose-derived MSCs (AD-MSCs). Suitable for general bone grafting applications, AlloStem is similar to autograft bone because it provides the three key properties necessary for bone formation: osteoconductive (partially demineralized allograft bone, the foundation for the AlloStem tissue, provides a natural scaffold for new bone formation), osteoinductive (naturally occurring growth factors present in allograft bone have been shown to encourage osteogenic activity), and osteogenic (AlloStem contains adult MSCs that naturally adhere to the bone substrate and may contribute to the formation of new bone).

Prochymal is the first stem cell therapy approved for use in Canada. It is also the first therapy approved in Canada for acute GVHD. It is an allogeneic stem therapy based on MSCs derived from the bone marrow of adult donors. MSCs are purified from the marrow and cultured and packaged, with up to 10,000 doses derived from a single donor. The doses are stored frozen until needed.

2.3.2 Clinical Trials of MSC-Based Therapy

In addition to approved MSC-based products, MSCs have been used in disease treatment through clinical trials. According to clinicaltrials.gov, approximately 542 registered clinical trials have used MSCs for treatment. The first clinical trial using in vitro expanded MSCs was performed in 1995, in which 15 patients were treated with autologous stem cells (Lazarus et al. 1995). According to clinicaltrials.gov, almost all of the current trials are in phase I, phase II, or phase I/II, and some of these trials are in phase II or phase II/III (Fig. 2.4, Table 2.5).

2.3.2.1 MSCs for Osteoarthritis

MSCs easily differentiate into osteoblasts as well as chondroblasts, and therefore they can be rapidly applied in treating several diseases related to bone and cartilage degeneration. MSCs from various sources have been clinically used in bone and cartilage regeneration (Table 2.6).

Autologous MSCs from bone marrow were used in osteoarthritis with good results (Orozco et al. 2013). Autologous in vitro expanded MSCs were also transplanted in cartilage defects (Wong et al. 2013). Allogeneic expanded MSCs from bone marrow were used to treat chronic knee. Vega et al. (2015) showed that allogeneic MSC therapy is simple, without requirement for surgery, and significantly improves cartilage quality (Vega et al. 2015). ADSCs are also used in cartilage

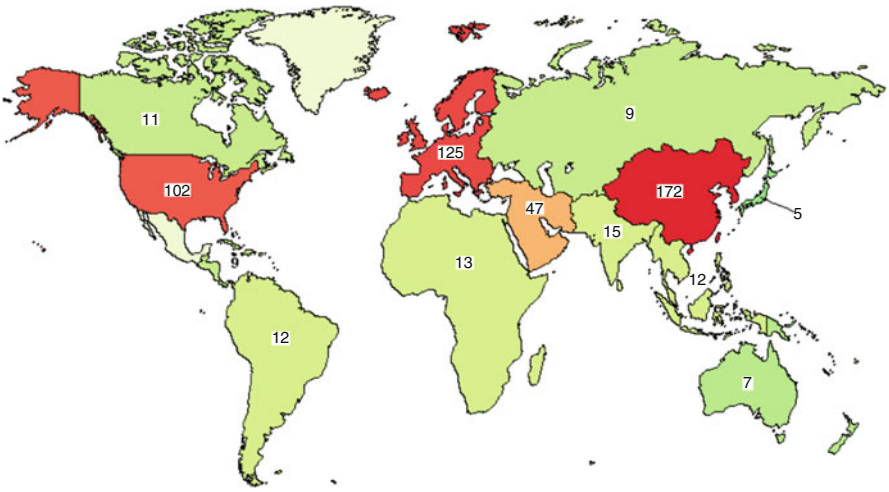

Fig. 2.4 Clinical trials using mesenchymal stem cells

Table 2.5 MSC-based clinical trials in a completed status

Pathology	Clinical status completed						
Overall	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	ND
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	11	1	2
Overall	31	40	15	3	4	1	10

regeneration. Autologous ADSCs have been successfully applied in osteoarthritis treatment. Stromal vascular fraction as non-expanded ADSCs was injected to improve knee osteoarthritis for several years (Bui et al. 2014; Koh et al. 2013; Pak 2011). Almost all studies have shown that ADSC transplantation is safe, with no treatment-related adverse events. Intra-articular injection of ADSCs into the osteoarthritic knee improved function and pain of the knee joint and reduced cartilage

Table 2.6 Clinical trials using MSCs for intra-articular injection of cells

Study name; clinicaltrials.gov identifier	Cell type and source	Indication	Study phase; design
Articular Cartilage Resurfacing With Mesenchymal Stem Cells In Osteoarthritis Of Knee Joint; NCT01207661	MSC, autologous (source unspecified)	Knee OA	Phase I; open label
Adult Stem Cell Therapy for Repairing Articular Cartilage in Gonarthrosis; NCT01227694	MSC, autologous, bone marrow derived	Knee OA	Phase I/II; open label
Side Effects of Autologous Mesenchymal Stem Cell Transplantation in Ankle Joint Osteoarthritis; NCT01436058	MSC, autologous, bone marrow derived	Ankle joint OA	Phase I; open label
Stem Cell Transplantation for the Treatment of Knee Osteoarthritis; NCT00550524	MSC, autologous, bone marrow derived	Knee OA	Phase I; open label
Intra-Articular Autologous Bone Marrow Mesenchymal Stem Cells Transplantation to Treat Mild to Moderate Osteoarthritis; NCT01459640	MSC, autologous, bone marrow derived	Mild-to-moderate knee OA	Phase II; open label, active comparator: hyaluronic acid
Safety and Efficacy of Autologous Bone Marrow Stem Cells for Treating Osteoarthritis; NCT01152125	MSC, autologous, bone marrow derived	OA, KLG III–IV	Phase I/II; open label
Treatment of Knee Osteoarthritis With Autologous Mesenchymal Stem Cells (KDD&MSV); NCT01183728	MSC, autologous, bone marrow derived	Knee OA, KLG II–IV	Phase I/II; open label
Mesenchymal Stem Cell Transplantation in Osteoarthritis of Hip Joint; NCT01499056	MSC, autologous, bone marrow derived	Hip OA	Phase I; open label
The Effects of Intra-articular Injection of Mesenchymal Stem Cells in Knee Joint Osteoarthritis; NCT01504464	MSC, autologous, bone marrow derived	Knee OA	Phase II; double-blind RCT
Allogeneic Mesenchymal Stem Cells in Osteoarthritis; NCT01453738	MSC, allogeneic, source unspecified	Knee OA	Phase II; double-blind RCT

(continued)

Table 2.6 (continued)

Study name; clinicaltrials.gov identifier	Cell type and source	Indication	Study phase; design
Allogeneic Mesenchymal Stem Cells for Osteoarthritis; NCT01448434	MSC, allogeneic, source unspecified	Knee OA	Phase II; double-blind RCT
Treatment of Knee Osteoarthritis With Allogenic Mesenchymal Stem Cells (MSV_allo); NCT01586312	MSC, allogeneic, bone marrow derived	Knee OA	Phase II; double-blind RCT, active comparator: hyaluronic acid
A Phase I/II Study of Chondrogen Delivered by Intra-Articular Injection Following Meniscectomy; NCT00225095	MSC, allogeneic, source unspecified	Meniscectomy	Phase I/II; double-blind; randomized
Follow-up Study of Chondrogen® Delivered by Intra-Articular Injection Following Meniscectomy; NCT00702741	MSC, allogeneic, source unspecified	Partial medial meniscectomy	Phase II; double-blind RCT
Safety and Efficacy Study of MSB-CAR001 in Subjects 6 Weeks Post an Anterior Cruciate Ligament Reconstruction; NCT01088191	MSC, allogeneic, source unspecified	ACL reconstruction	Phase I/II; double-blind RCT, active control: hyaluronan
Autologous Adipose Tissue Derived Mesenchymal Stem Cells Transplantation in Patients With Degenerative Arthritis; NCT01300598	MSC, autologous, adipose tissue derived	Knee OA	Phase I/II; open label
ADIPOA - Clinical Study; NCT01585857	MSC, autologous, adipose tissue derived	Knee OA, moderate or severe	Phase I; open label
Autologous Adipose-Derived Stromal Cells Delivered Intra-articularly in Patients With Osteoarthritis; NCT01739504	MSC, autologous, adipose tissue derived	OA	Phase I/II; open label
Outcomes Data of Bone Marrow Stem Cells to Treat Hip and Knee Osteoarthritis; NCT01601951	Bone marrow concentrate, autologous	Hip and knee OA	Phase unspecified; prospective, observational
Peripheral Blood-derived Stem Cell Trial on Damaged Knee Cartilage (PBSC); NCT01076673	Peripheral blood stem cells (identity unspecified)	Damaged articular cartilage	Phase unspecified; open label

(continued)

Table 2.6 (continued)

Study name; clinicaltrials.gov identifier	Cell type and source	Indication	Study phase; design
Allogeneic Mesenchymal Stem Cells in Osteoarthritis; NCT01453738	MSC, source unspecified, allogeneic	Knee OA, KLG II–III	Phase II; double blind
Autologous Adipose Tissue Derived Mesenchymal Progenitor Cells Therapy for Patients With Knee Osteoarthritis; NCT01809769	Mesenchymal progenitor cells, autologous, adipose tissue derived	Knee OA	Phase I/II; double blind
Autologous Bone Marrow Mesenchymal Stem Cells Transplantation for Articular Cartilage Defects Repair; NCT01895413	MSC, bone marrow, autologous	Knee OA	Phase I/II; open label
Transplantation of Bone Marrow Derived mesenchymal Stem Cells in Affected Knee Osteoarthritis by Rheumatoid Arthritis (*sic*); NCT01873625	MSC, bone marrow, not stated whether autologous or allogeneic	Knee OA	Phase II/III; randomized, open label
Safety and Efficacy Study of MSB-CAR001 in Subjects 6 Weeks Post an Anterior Cruciate Ligament Reconstruction; NCT01088191	MSC, source unspecified	Knee, ACL injury	Phase I/II; double-blind RCT
Autologous Adipose Stem Cells and Platelet Rich Plasma Therapy for Patients With Knee Osteoarthritis; NCT02142842	SVFs (from autologous adipose tissue)	Knee, OA	Phase I/II; randomized, open label
Clinical Study of Umbilical Cord Tissue Mesenchymal Stem Cells (UC-MSC) for Treatment of Osteoarthritis; NCT02237846	MSCs from umbilical cord (allogenic)	Knee, OA	Phase I/II

defects by regeneration of hyaline-like articular cartilage (Jo et al. 2014). Intra-articular autologous activated peripheral blood stem cells also improved quality of life and regenerated articular cartilage in early osteoarthritic knee disease (Saw et al. 2011, 2013; Turajane et al. 2013).

2.3.2.2 Cardiovascular Diseases

Today, more than 40 clinical trials are listed with a majority of bone marrow, Wharton's jelly, and adipose stem cells (Chen et al. 2004; Gee et al. 2010; Hare et al. 2009; Trachtenberg et al. 2011). Both autologous and allogeneic MSCs have been used to treat MI. In 2012, Hare et al. (2012) compared allogeneic vs. autologous BM-MSCs delivered by transendocardial injection in patients with ischemic cardiomyopathy. The authors showed that there was no difference between allogeneic and autologous BM-MSC injection, and MSC injection favorably affected patient functional capacity, quality of life, and ventricular remodeling (Hare et al. 2012). Efficiency of MSCs or mononuclear cells (MNCs) derived from bone marrow was also compared in a recent study (Heldman et al. 2014). Although both MSCs and MNCs from bone marrow were safe by transendocardial injection in ischemic cardiomyopathy patients, improvements such as the 6-min walk distance score, infarct size as a percentage of LV mass, and regional myocardial function as peak Eulerian circumferential strain at the site of injection were only improved in MSC-injected patients (Heldman et al. 2014). Gao et al. (2015) intracoronary infused Wharton's jelly-derived MSCs (WJMSCs) to treat acute MI. After 18 months of follow-up, the absolute decreases in LV end-systolic volumes and end-diastolic volumes at 18 months in the WJMSC group were significantly greater than those in the placebo group (Gao et al. 2015). In another randomized placebo-controlled clinical trial, Musialek et al. (2015) showed that allogeneic transplantation of WJMSCs is safe and effective in MI patients (Musialek et al. 2015). However, the efficiency of treatment based on MSCs differs based on the age of patients. By transendocardial injection of expanded MSCs, Golpanian et al. (2015) showed that MSC injection improved the 6-min walk distance and quality of life using the Minnesota Living with Heart Failure Questionnaire score and reduces MI size in younger patients (younger than 60 years old); in older patients, these scores were not improved (Golpanian et al. 2015).

Other diseases related to cardiovascular diseases, especially hind limb ischemia, were studied for treatment with MSC injection. ADSCs were collected and expanded ex vivo to treat non-revascularizable critical limb ischemia (Bura et al. 2014). ADSCs were intramuscularly injected into the ischemic leg of patients; no complications were observed, transcutaneous oxygen pressure tended to increase in most patients, and ulcer evolution and wound healing were improved (Bura et al. 2014). Allogeneic MSCs also can improve critical limb ischemia (Gupta et al. 2013). However, different than MSCs, BM-MNCs injection was insufficient to treat critical lower limb ischemia (Moazzami et al. 2014).

2.3.2.3 MSCs for Chronic Inflammatory and Autoimmune Diseases

MSCs have a strong capacity of immune modulation that affects all kinds of immune cells. Several clinical studies have examined MSCs in refractory and severe systemic lupus erythematosus treatment. Some results showed that MSC transplantation

resulted in the induction of clinical remission and improvements in serological markers of organ dysfunction (Liang et al. 2010; Sun et al. 2009; Wang et al. 2013a). MSCs have also been used in treatment of Crohn's disease, which is a chronic inflammatory disorder of the gastrointestinal tract. Crohn's disease is currently treated by steroids, immunosuppressive agents, or anti-TNF therapy; however, the efficiency of these therapies is low. MSCs from various sources, such as the bone marrow, adipose tissue, and umbilical cord of both autologous and allogeneic forms, were tested to treat Crohn's disease. Autologous BM-MSCs were safe and beneficial in refractory fistulizing Crohn's disease (Ciccocioppo et al. 2011; Duijvestein et al. 2010). Molendijk et al. (2015) showed that local administration of allogeneic BM-MSCs was not associated with severe adverse events in patients with perianal fistulizing Crohn's disease and promoted healing of perianal fistulas (Molendijk et al. 2015). These results were consistent with the study by Forbes et al., in which administration of allogeneic MSCs reduced CDAI and CDEIS scores in patients (Forbes et al. 2014).

2.3.2.4 MSCs for Liver, Lung, and Kidney Disease

The numbers of MSC-based treatments for liver, lung, and kidney diseases have increased over the past several years. The lungs are susceptible to edema and endothelial permeability caused by traumatic injury and represent good targets for MSC-based cell therapy. Three kinds of pulmonary diseases are clinically treated by MSCs, including idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and severe acute respiratory distress syndrome (ARDS). Recent clinical trials have clearly assessed the safety and feasibility of MSCs for the treatment of IPF patients. Both MSCs from the placenta (Chambers et al. 2014) and adipose tissue (Tzouvelekis et al. 2013) were used to treat IPF. The first clinical study of MSC transplantation for COPD was performed in 2013 (Weiss et al. 2013). In this report, Weiss et al. (2013) used in vitro expanded allogeneic MSCs from bone marrow with good results, showing a significant decrease in levels of circulating C-reactive protein in patients treated with MSCs (Weiss et al. 2013). Both BM-MSCs and AD-MSCs were transplanted into ARDS patients. While the clinical results showed that this is a safe method, the disease did not significantly improve after treatment (Simonson et al. 2015; Zheng et al. 2014).

MSC transplantation also shows great promise for the treatment of impaired livers, especially advanced fibrosis. Several clinical studies have examined liver fibrosis treatment by MSC transplantation. Almost all these clinical studies (over ten studies) used BM-MSCs, while four studies used allogeneic MSCs, with three studies using UC-MSCs and one study using BM-MSCs (Shi et al. 2012; Wang et al. 2014b, 2013b; Zhang et al. 2012). Interestingly, allogeneic MSC infusion is clinically safe, without side effects, and improved liver function. Zhang et al. examined the safety and efficacy of UC-MSCs in patients affected by liver cirrhosis. The results showed significantly improved liver function in transplanted patients without side effects or complications (Zhang et al. 2012). UC-MSCs were also used to treat acute chronic liver failure patients. The results showed that UC-MSC transfusions

significantly increased the survival rates in acute chronic liver failure patients (Shi et al. 2012). In summary, these data demonstrated that MSC transfusions are safe and may serve as a novel therapeutic approach for liver diseases.

MSC transplantation is also considered as a promising therapy for kidney failure based on several results in animal models. To date, three phase I/II clinical trials have examined the use of MSCs for kidney failure treatment (Gaspari et al. 2010; Gooch et al. 2008; Togel and Westenfelder 2010). Some initial results showed that MSC infusion could prevent and treat acute renal failure patients (Togel and Westenfelder 2010). Preliminary data indicate that MSC infusion is safe and feasible and that it reduced the length of hospital stay and readmission rates by 40 % (Gooch et al. 2008; Togel and Westenfelder 2010). Gooch et al. indicated that the infusion of allogeneic MSCs seemed to prevent all complications in patients with post-cardiopulmonary bypass-induced acute kidney injury and promote kidney recovery (Gooch et al. 2008).

2.3.2.5 Diabetes Mellitus (DM)

Several clinical trials have examined the application of MSCs in T1DM patients. The first clinical trial was performed by Haller et al. (2008) to assess the safety and efficacy of using MSC-containing autologous cord blood infusion for DM in children (Haller et al. 2008). This study suggested that cord blood infusion was feasible and safe; there was an increase of peripheral regulatory T-cell level and reduced insulin requirement 6 months after cord blood infusion (Haller et al. 2008). Nevertheless, after 2 years, the therapeutic effect disappeared (Haller et al. 2011).

In another study, Hu et al. evaluated the long-term effects of injecting WJMSCs for new-onset T1DM patients (Hu et al. 2013). Treated T1DM patients had better glycemic control and increased C-peptide levels after 2 years of follow-up (Hu et al. 2013). Ten other clinical trials using MSCs for DM were registered in clinicaltrials.gov. In addition to autologous MSCs, some clinical trials used allogeneic and expanded MSCs for treatment. Prochymal was also evaluated for DM treatment. Some improvements were recorded in treated patients such as glycemic control in newly diagnosed T1DM patients (NCT00690066). Four kinds of MSCs have been used in the clinic, including MSCs from the umbilical cord blood, umbilical cord, adipose tissue, and bone marrow.

MSCs have also been used to treat T2DM. Although, the mechanism of MSCs in T2DM treatment is not yet clear, some clinical trials showed that MSC transplantation is promising. Kong et al. (2014) showed that UC-MSC transfusion was safe and well tolerated, effectively alleviated blood glucose, and increased the generation of C-peptide levels and Tregs in a subgroup of T2DM patients (Kong et al. 2014). This result was similar to another study (Liu et al. 2014b). Placenta-derived MSCs also showed huge potential for T2DM treatment. Transplanted T2DM patients had no fever, chills, liver damage, or other side effects. More importantly, renal function and cardiac function were improved after infusion (Jiang et al. 2011).

2.3.2.6 MSCs in Acute Brain Injury: Stroke

In recent years, clinical trials using MSC in stroke have increased dramatically. Since 2009, there were 22 clinical trials in phase I/II (Bang et al. 2005; De Keyser 2005; Smith and Gavins 2012). Bang et al. performed the first phase I study to assess safety of intravenous administration of 10^8 autologous MSCs in patients with severe neurological deficits due to subacute ischemic stroke. The results showed that intravenous cell infusion appeared safe and feasible. In 2010, Lee et al. transplanted MSCs in 16 patients with stroke. Some neurological recovery scores were improved in the MSC group compared with the placebo group (Lee et al. 2010). Both autologous and allogeneic MSCs have been used to treat stroke. All clinical studies showed that MSC transplantation for stroke is safe, with improvement of functional recovery such as neurological scores and size of infarct. These results suggest the potential therapeutic use for MSC in stroke management.

2.4 Safety of MSCs in Clinical Applications

Although the number of clinical applications of MSCs has increased over recent years, the safety of MSCs is still a focus for scientists and medical doctors. The highest risk for MSC transplantation is tumorigenesis in vivo after transplantation. Some hypothesis demonstrated tumorigenesis related to MSC characteristics and some modifications in MSCs during the in vitro expansion. Some studies showed that MSCs without in vitro expansion were safe in both preclinical and clinical applications. For this reason, in 2014, the FDA clarified minimal manipulation of cell/tissue products to be used in the clinic.

In regard to in vitro expanded MSC transplantation, some concerns about the genetic alterations of expanded MSCs were addressed with recent in vitro studies as well as several clinical trials using expanded MSCs. In vitro assays showed that three commonly used MSC types, including BM-MSCs, ADSCs, and UC-MSCs, maintained phenotype and genotype after extended culture. For example, Bernardo et al. showed that BM-MSCs can be cultured long-term in vitro without losing their morphologic, phenotypical, and functional characteristics. These cells can maintain normal karyotype after 44 weeks of culture (Bernardo et al. 2007). ADSCs also did not bypass senescence after 2 months of culture, with no evidence of transformation in vitro (Meza-Zepeda et al. 2008). Chen et al. reported that human UC-MSCs maintained their biological characteristics and function after long-term in vitro culturing and were not susceptible to malignant transformation (Chen et al. 2014). In this study, MSCs could be expanded up to the 25th passage without chromosomal changes by G-band (Chen et al. 2014).

The key obstacle of stem cell therapy is related to whether stem cells may undergo malignant transformation. Some previous studies have described spontaneous transformation of MSCs in vitro (Pan et al. 2014; Ren et al. 2011). However, almost all of these studies have been retracted owing to cross-contamination with cancer cells

(de la Fuente et al. 2010; Garcia et al. 2010; Rubio et al. 2005; Torsvik et al. 2010). Roemeling-van Rhijn et al. (2013) showed that ADSCs can form aneuploid cells during in vitro culture. However, they also confirmed that aneuploidy was not a predecessor of transformation or tumor formation (Roemeling-van Rhijn et al. 2013). In preclinical trials, all studies on NOD mice, NOD/SCID mice, guinea pigs, rabbits, and monkey models showed that upon the use of UC-MSCs from the master MSC bank (passage 2, P2) and culturing for an additional five passages (P7) or 11 passages (P13) with a dose of 1×10^7/mouse or 2.10^6 or 1.10^7 cells/kg body weight for monkeys, no tumor formation was observed after 2 months (Wang et al. 2012a, b).

Based on these results, in vitro or ex vivo expanded MSCs were accepted for use in clinical trials in various diseases (Table 2.7). Almost all trials were in phase II, and some were in phase II. All trials showed that expanded MSC transplantation was safe and exhibited good effects for disease improvement. Using both methods of delivery of MSCs, including intravenous infusion and local injection, MSC transplantation was shown to be safe. Performed a meta-analysis of clinical trials examining the safety of MSC transplantation, and the results confirmed the safety of MSC transplantation. A total of 2347 citations and 36 studies were reviewed, which included a total of 1012 participants with diseases such as ischemic stroke, Crohn's disease, cardiomyopathy, MI, GVHD, and healthy volunteers. The authors showed that there was no association between acute infusional toxicity, organ system complications, infection, death, and malignancy. These authors also showed that there was no difference in safety between autologous MSC and allogeneic MSCs, between matched allogeneic MSCs and unmatched allogeneic MSCs, between non-expanded MSCs and in vitro expanded MSCs, and between fresh MSCs and cryopreserved MSCs. However, there was a significant association between MSC transplantation and transient fever.

2.5 Conclusions

MSCs have become the most frequently applied stem cell type in the clinic. To date, multiple degenerative diseases and several immune-related diseases have been clinically treated by MSC transplantation. Several sources of MSCs include MSCs from the bone marrow, adipose tissue, umbilical cord blood, umbilical cord, and placenta, both with and without in vitro expansion. With useful characteristics about immune modulation, MSCs not only autologously injected into patients but allogeneic graft also was used. After over 10 years of MSC-based treatments, all reports have shown that MSC transplantation is safe. Many reports demonstrate some improvements in disease treatment using MSCs, and several MSC-based products have been approved as stem cell drugs for diseases such as GVHD and osteoarthritis. Together this demonstrates that MSC transplantation is a safe and promising therapy for disease treatment.

Table 2.7 List of completed clinical trials using ex vivo expanded MSCs

Clinical trial no.	Source of MSCS	Serum supplement	Disease treated	Dose No. of treatment	Route of administration	Phase	Design	References
NCT00395200	Au-BM	FBS	Multiple sclerosis	$1–2\times10^6$ cells/kg BW Single	Intravenous	I and II	Non-randomized, safety/efficacy study, single group assignment, Open label	Connick et al. (2012) and Connick et al. (2011)
NCT00504803	Allo-BM	Irradiated FBS	Graft-versus-host disease	– Single	Intravenous	II	Non-randomized, safety/efficacy study, single group assignment, open label	Baron et al. (2010)
NCT01087996	Au-BM	–	Ischemic cardiomyopathy	$20/100/200\times10^6$ cells	Transendocardial	I and II	Randomized, safety/efficacy study, parallel assignment, open label	Hare et al. (2012)
	Allo-BM			Single				
NCT00114452	Allo-BM	–	Myocardial infarction	$0.5/1.6/5\times10^6$ cells/kg BW Single	Intravenous	I	Randomized, safety study, parallel assignment, double blind (subject, caregiver, investigator, outcomes assessor)	Hare et al. (2009)
NCT00658073	Au-BM	–	Renal transplant rejection	$1–2\times10^6$ cells/kg BW Twice	Intravenous	–	Randomized, efficacy study, parallel assignment, open label	Tan et al. (2012)
NCT00734396	Au-BM	FBS	Renal transplant rejection	1×10^6 cells/kg BW Twice	Intravenous	I and II	Non-randomized, safety/efficacy study, single group assignment, open label	Reinders et al. (2013)
NCT00883870	Allo-BM	–	Critical limb ischemia	2×10^6 cells/kg BW Single	Intramuscular (gastrocnemius muscle)	I and II	Randomized, safety/efficacy study, parallel assignment, double blind (subject, caregiver, investigator)	Gupta et al. (2013)
NCT00823316	Allo-UCB	FBS	Graft rejection and graft-versus-host disease	$1–5\times10^6$ cells/kg BW Single	Intravenous	I and II	Randomized, safety/efficacy study, parallel assignment, open label	Lee et al. (2013)
NCT00911365	Au-BM	FBS	Multiple system atrophy	40×10^6 cells Multiple	Intra-arterial (one time) Intravenous (three times)	II	Randomized, parallel assignment, single blind (subject)	Lee et al. (2012)
NCT01274975	Au-AD	FBS	Spinal cord injury	400×10^6 cells Single	Intravenous	I	Randomized, safety study, single group assignment, open label	Ra et al. (2011)

NCT00683722	Allo-BM	–	Coronary obstructive pulmonary disorder	100×10^6 cells Multiple	Intravenous	II	Randomized, safety/efficacy study, parallel assignment, double blind (subject, caregiver, investigator, outcome assessor)	Weiss et al. (2013)
NCT00956891	Au-BM	FBS	Liver failure	$\approx100\times10^6$ cells Single	Hepatic artery	–	Case control, retrospective	Peng et al. (2011)
NCT00187018	Allo-BM	FBS	Osteogenesis imperfecta	$0.68–2.75\times10^3$ cells/kg BW Single	Intravenous	–	Non-randomized, safety/efficacy study, single group assignment, open label	Otsuru et al. (2012)
NCT00816803	Au-BM	Serum-free	Spinal cord injury	2×10^6 cells/kg BW Multiple	Lumbar puncture	I and II	safety/efficacy study, parallel assignment, single blind (outcomes assessor)	El-Kheir et al. (2014)
	Allo-UC		Severe systolic heart failure		Injected into left coronary artery	I and II	Improve cardiac remodeling and cardiac function and reduce the mortality rate	Zhao et al. (2015b)
	Allo-WJ	FBS	Acute myocardial infarction	30×10^6 WJMSCs	IRA using a cell-delivery perfusion catheter	I	Safety	Musialek et al. (2015)
NCT01218464	Allo-UC	FBS	Acute-on-chronic liver failure	0.5×10^6 UC-MSCs, three times at 4 weeks intervals	Intravenous	I and II	Serum total bilirubin and alanine aminotransferase levels were significantly decreased UC-MSC transfusions are safe	Shi et al. (2012)
NCT01662973	Allo-UC		Primary biliary cirrhosis	0.5×10^6 cells/kg body weight	Intravenous	I and II	UC-MSC transfusion is feasible and well tolerated in patients with PBC who respond only partially to UDCA treatment	Wang et al. (2013b)
	Allo-AD-MSC		Lateral epicondylosis	$10^6–10^7$/patient	Local injection	I and II	Allo-ASC therapy was thus safe and effective in improving elbow pain, performance, and structural defects for 52 weeks	Lee et al. (2015)
NCT00260338	Auto-BM-MSC		Myocardial ischemia		Intramyocardial injections	I and II	Not only improve symptoms but also slow down disease progression	Mathiasen et al. (2013)
NCT01392105	Auto-BM-MSC	FBS	Acute myocardial infarction	$7.2\pm0.90\times10^7$ cells	Intracoronary injection	II/III	Tolerable and safe with modest improvement in LVEF at 6-month follow-up by SPECT	Lee et al. (2014)

(continued)

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