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Review Article

Update on the Clinical Applications of Mesenchymal Stem Cells

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Abstract

Mesenchymal stem cells are heterogenous adult multipotent stromal cells that can be isolated from various sources including bone marrow, peripheral blood, umbilical cord blood, dental pulp, and adipose tissue. They have certain regenerative, anti-inflammatory, immunomodulatory, immunosuppressive, antimicrobial, and other properties that enable them to have several therapeutic and clinical applications including treatment of various autoimmune disorders; role in hematopoietic stem cell transplantation and regenerative medicine; treatment of skin, pulmonary and cardiovascular disorders; treatment of neurological and eye diseases; as well as treatment of various infections and their complications.

Different factors including donor age, biological source, route of administration, and signaling pathways have an impact on the functions and consequently the clinical applications of mesenchymal stromal cells. The products of mesenchymal stem cells such as extracellular vesicles and exosomes reproduce the biological effects and most of the therapeutic actions of the parent stem cells. Genetic engineering and the use of specific mesenchymal stromal cell products have improved their clinical efficacy and decreased their adverse effects. However, despite the recent progress in the use of mesenchymal stem cells, the clinical application of these cells in the treatment of several diseases still faces real challenges that need to be resolved. The current status of mesenchymal stem cells and the controversies related to their clinical utilization in various disease conditions will be thoroughly discussed in this review.

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Introduction

Mesenchymal Stem Cells (MSCs) are heterogeneous, non-hematopoietic, adult multipotent stromal progenitor cells that are capable of self-renewal and differentiation into multiple lineages and various cell types [1-9]. Adult MSCs were first isolated from Bone Marrow (BM) by Alexander Friedenstein and his colleagues in the year 1976 [2,10,11]. Subsequently, MSCs have been isolated from several adult as well as neonatal sources such as Adipose Tissue (AT), peripheral blood, Umbilical Cord (UC), placenta, amniotic fluid, breast milk, skin, and skeletal muscles (Table 1) [2,11-24]. MSCs have the following distinguishing features: (1) the ability to adhere to the plastic vessel under optimal culture conditions; (2) the capability to differentiate into osteoblasts, adipocytes, and chondrocytes; and (3) having a characteristic immunophenotypic profile on flowcytometry (Table 2) [2,21,25-32]. In the year 2006, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) issued a position statement that proposed the following minimal criteria for defining multipotent MSCs: (1) MSC must be plastic-adherent when maintained in standard culture conditions; (2) MSC must express CD105, CD73 and CD90, and lack the expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR surface molecules; and

Table 1: Sources of mesenchymal stem cells.
1. Bone marrow.
2. Peripheral blood.
3. Umbilical cord blood and Wharton's jelly of the umbilical cord.
4. Chorionic villi and chorionic membrane of the placenta.
5. Human amniotic fluid and decidua of the uterus.
6. Menstrual blood.
7. Fallopian tubes and cervical tissues.
8. Breast milk.
9. Adipose tissues: body fat.
10. Dental pulp, periodontal ligaments, exfoliated deciduous teeth.
11. Oral mucosa, palatal tonsils and salivary glands.
12. Skeletal muscle, muscle tendons and dermal tissues.
13. Lung tissues and alveolar epithelium.
14. Adult human liver tissues and fetal liver.
15. Synovial membrane and synovial fluid.
16. Parathyroid glands.

Table 2: Surface Markers of Mesenchymal Stem Cells on Flowcytometry.

	Positive	Negative
Characteristic surface markers	CD 105 CD 73 CD 90	CD 45 CD 34 CD 14 CD 11b CD 19 CD 79a HLA-DR
Other surface markers that may/may not be expressed	CD 117 CD 166 CD 29 CD 44 CD 106 CD 9 CD 10 CD 13 CD 28 CD 33 CD 49b CD 71 CD 164 CD 271 HLA-class I Stro-1 SSEA-4 ITGA-11	CD 3 CD 33 CD 133

MSCs: Mesenchymal Stem Cells; HLA: Human Leukocyte Antigen.

(3) MSC must differentiate to osteoblasts, adipocytes and chondroblasts *in vitro* [8,31,33]. However, certain types of MSCs can occasionally show positivity or negativity for specific surface markers as illustrated in Table 2 [1-3,5,6,8,31,34-38]. Several studies have shown that MSCs can differentiate into other cell types such as cardiomyocytes, myocytes, and neurons, and that MSCs derived from BM, AT, and other sources do express CD 34 surface markers under certain circumstances [5,9,39-42]. Additionally, MSCs can be seen in abundant numbers in the circulation under the following conditions: stem cell mobilization with growth factors, stroke, hypoxia, tissue injuries, as well as inflammatory conditions [9,43-48]. Unfortunately, little is known about the molecular basis underlying the stemness of MSCs and it is still unclear whether the recently discovered transcriptional factors and genes regulate stemness or only differentiation of MSCs [7]. In the year 2019, the International Society for Cell & Gene Therapy (ISCT®) Mesenchymal Stromal Cell (ISCT-MSC) committee issued a position statement to continue supporting the acronym MSCs but it recommended that the acronym MSCs must be: (1) supplemented by the tissue-source origin of the cells, which would highlight tissue-specific properties; (2) intended as MSCs unless rigorous evidence for stemness exists that can be supported by both *in vitro* and *in vivo* data; and (3) associated with robust matrix of functional assays to demonstrate MSC properties, which are not generically defined but informed by the intended therapeutic mode of actions [32].

Factors affecting the functions and clinical applications of mesenchymal stem cells

Human MSCs are multipotent stem cells capable of self-renewal and differentiation *in vitro* into cells of different lineages [33,49,50]. They interact with immune cells both in innate and adaptive immune systems so as to: (1) enable immunosuppression and tolerance induction, and (2) modulate the immune responses [51]. MSCs possess immunomodulatory functions that enable them to be investigated as potential treatments for various immune disorders [35,50].

The past decade has seen an explosion of research directed toward a better understanding of the mechanisms of MSC function during the rescue and repair of injured tissue and organs. An improved understanding of MSC function holds great promise for the application of cell therapy and also for the development of powerful cell-derived therapeutics in regenerative medicine. However, the field has made particular progress in (1) delineating cell-cell signaling and molecular controls for MSC differentiation, and (2) defining several other mechanisms through which administered MSCs can promote tissue repair [52]. Properties and functions of MSCs that are essential in their clinical therapeutic effects include (1) self-renewal and high proliferation capacity, (2) multipotency, (3) secretory and trophic ability, (4) migration and homing properties with tropism towards inflamed and injured tissues, (5) immunosuppressive functions, (6) potent immunoregulatory and immunomodulatory properties, (7) tissue remodeling and regeneration, (8) regulation of cellular hemostasis, and (9) easy access and isolation [53-56]. The mechanisms by which MSCs promote tissue repair include (1) strong paracrine activity that involves secretion of proteins, cytokines, chemokines, and hormones; (2) transfer of mitochondria by way of tunneling nanotubes or microvesicles; and (3) transfer of exosomes or microvesicles containing RNA and other molecules [52,57]. The high immunomodulatory capacity of MSCs is reflected by: (1) their migration to the sites of injury and inflammation, (2) their differentiation into various functional cells at the sites of injury and inflammation, (3) their boosting of immunity, (4) their tumor suppression effects, and (5) their anti-angiogenic effects [56]. MSCs are characterized by: (1) an extraordinary capacity to modulate the phenotype and functional properties of various immune cells that play an essential role in the pathogenesis of inflammatory disorders, and (2) immunosuppressive properties that have enabled MSCs to emerge as promising tools for the treatment of inflammatory disorders such as acute Graft-Versus-Host Disease (GVHD), graft rejection in patients undergoing organ/cell transplantation, and Autoimmune Diseases (AIDs) [58].

Features of MSCs that favor their utilization in clinical practice include: (1) MSCs are immunologically tolerated in the recipient, (2) they do not show signs of cellular senescence, including compromised proliferation and differentiation capabilities, (3) compatibility with the biological sex of the recipient in regard to sex-specific immune processes, and (4) they are known to be effective in attenuating hyperactivated cytokine and immune cell activities in the recipient from transplantation clinical studies [59].

MSCs have been widely utilized for the treatment of diverse inflammatory diseases, due to their potent immunoregulatory functions. MSCs exert their therapeutic effects largely through their paracrine actions. Growth factors, cytokines, chemokines, extracellular matrix components, and metabolic products were all found to be functional molecules of MSCs in various therapeutic paradigms. These secretory factors contribute to immune modulation, tissue remodeling, and cellular homeostasis during regeneration. The paracrine actions of MSCs are powerful bioactive agents for treating various diseases, especially for refractory immune disorders and tissue damage [55]. Functions of MSCs are mediated by: (1) paracrine factors, (2) mitochondrial transfer, and (3) secretion of Extracellular Vesicles (ECVs) [56]. Ideally, autologous MSCs are the choice of safety as allogenic transplantation could lead to cell rejection, but cells obtained from patients suffering from AIDs may behave differently than those from healthy donors, including deficiency in the ability to proliferate and successfully differentiate. So, it is preferable to obtain MSCs from BMs of young healthy donors or from UCs directly after birth [59]. Recent studies suggest that factors including age, gender, and biological sources of MSCs can have a significant impact on therapy outcomes [54,56,59-61]. Hence, it is worthwhile to further establish MSC banks from multiple donors that span a range of biological ages, tissue sources, and genders for the selection of future transplantation therapies [59].

Impact of sources of mesenchymal stem cells on their clinical applications

Bone marrow-mesenchymal stem cells: As BM-derived MSCs were discovered first, they were initially considered the main source of MSCs for clinical application [62]. BM-MSCs are capable of differentiation into various mesodermal lineages but the availability of conventional BM-MSCs is limited [63,64]. BM-MSCs constitute an essential component of the hematopoietic niche, responsible for stimulating and enhancing the proliferation of HSCs by secreting regulatory molecules and cytokines to regulate hematopoiesis in the BM microenvironment [63,65-67]. Osteogenesis of BM-MSCs plays a central role in hematopoiesis, while adipogenesis of BM-MSCs has a negative effect on hematopoietic recovery [66]. Recently, by lineage tracing and single-cell sequencing, several new subgroups of BM-MSCs and their roles in normal physiological and pathological conditions have been clarified. The key regulators and mechanisms controlling the fate of BM-MSCs are being revealed and cross-talk among subgroups of BM-MSCs has been demonstrated [67]. Many factors, including aging, obesity, irradiation, and chemotherapy, can lead to the differentiation bias of BM-MSCs and related hematopoietic disorders. Rescuing the dysregulation of BM-MSC differentiation is crucial to bone hematopoietic recovery [66].

Human BM-MSCs differentially regulate the functional compartments of CD4(+) and CD8(+) T cells, which may differentially impact their therapeutic effect in immune disorders. The influence of MSCs on IL-9 expression can open new possibilities for MSC-based therapy in allergic diseases [68]. BM-MSCs displayed a striking inhibitory action over T cells from Rheumatoid Arthritis (RA) patients, reducing the expression of cytokines involved in RA physiopathology. Remarkably, BM-MSC-derived immunomodulation affected naive, effector, as well as memory T cells [69].

ECVs derived from BM-MSCs have similar therapeutic effects to BM-MSCs, including repairing damaged tissues, inhibiting macrophage polarization, and promoting angiogenesis. ECVs derived from BM-MSC, as efficient and feasible natural nanocarriers for drug delivery, have the advantages of low immunogenicity, no ethical controversy, good stability, and easy storage, thus providing a promising therapeutic strategy for many diseases. ECVs derived from BM-MSC have shown great potential in the treatment of bone metabolic diseases [70]. Exosomes derived from BM-MSCs showed superior regeneration ability, and exosomes derived from AT-MSCs played a significant role in immune regulation, whereas exosomes derived from UC-MSCs were more prominent in tissue damage repair [71].

Adipose tissue-mesenchymal stem cells: MSCs have been isolated from various other less invasive sources that comprise alternatives to BM including AT. AT-MSCs can be more easily isolated and considerably larger amounts of MSCs can be obtained from fat or AT compared with the BM. AT-MSCs and BM-MSCs share many biological characteristics but have some differences in their immunophenotype, differentiation potential, transcriptome, proteome, and immunomodulatory activity [62,64-72]. Human AT-MSCs support hematopoiesis *in vitro* and *in vivo* and thus provide the rationale for their use in supporting hematopoietic reconstitution in clinical settings [73]. AT represents a promising alternative to BM as a source of MSC to maintain hematopoiesis, but UC matrix-derived MSC demonstrated inferior hematopoietic supportive capacity compared to MSC from adult tissues [72]. AT-MSCs and BM-MSCs from the same donor have been found to display similar immunomodulatory capacities on both innate and acquired immunity cells. However, other variables such as the accessibility of samples or the frequency of MSCs in the tissue, should be considered to select the source of MSC for cell therapy [74].

BM-MSCs and AT-MSCs share a similar immunophenotype and capacity for *in vitro* multilineage differentiation. The immunomodulatory capacities of BM-MSCs and AT-MSCs are similar, but the differences in cytokine secretion cause AT-MSCs to have more potent immunomodulatory effects than BM-MSCs indicating that AT-MSCs can be considered a good alternative to BM-MSCs for immunomodulatory therapy [75]. Transplantation of BM-MSCs and UC-MSCs can alleviate the symptoms of neuropathic pain and result in subsequent motor

recovery after spinal cord injury. However, the survival rate and electrophysiological findings of UCMSCs are significantly better than BM-MSCs [76]. AT-MSCs are an attractive alternative to BM-MSCs for the treatment of severe Spinal Cord Injury (SCI) due to their enhanced stress resistance and secreted factor profile [77].

Wound healing is a complex process with a linear development that involves many actors in a multistep timeline commonly divided into four stages: hemostasis, inflammation, proliferation, and remodeling [78]. Studies on wound healing have shown that murine AT-MSCs and BM-MSCs have shown equivalent effects in enhancing diabetic wound healing. However, ECVs derived from BM-MSCs have been shown to promote proliferation, while ECVs derived from AT-MSCs exert major effects on angiogenesis [79,80]. Great interest is being focused on the paracrine activity of AT-MSCs for its potential therapeutic impact on chronic non-healing wounds [78]. The secretome from AT-MSCs and fibroblasts provides a safe and efficacious means for therapeutic development in contrast to the significant health problems that can result from using BM-MSCs and blood-derived MSCs and their secretome [81]. The secretome of AT-MSC represents a novel, promising alternative to cell-based therapy for wound repair as it has the following advantages over MSCs: (i) its feasible long-term storage, eliminating the need for toxic cryoprotectants, (ii) use of filter sterilization as the principal components as opposed to cells that cannot be terminally sterilized, (iii) convenience to alter the secretome profile for specific targeted applications, and (iv) cost-effective mass production overcoming the need for maintenance of huge clonal populations [82].

The main advantages of AT-MSCs over MSCs derived from other sources such as BM include: (1) the ease of methodology utilized in tissue collection, cell isolation using minimally invasive techniques with low morbidity compared to BM-MSCs; (2) obtaining abundant cells during isolation from a specific AT source; (3) ability to differentiate into various cell types of the tri-germ lineages, including osteocytes, adipocytes, neural cells, vascular endothelial cells, cardiomyocytes, pancreatic β-cells, and hepatocytes; (4) high self-renewal and proliferation capacity; (5) having anti-fibrotic, anti-apoptotic, anti-inflammation, and immunomodulatory properties; (6) having immunoregulatory and immunosuppressive properties with low immunogenicity; (7) ability to migrate to sites of inflamed and damaged tissues; (8) ability to act through autocrine and paracrine mechanisms including the secretion of broad spectrum of cytokines, growth factors, nucleic acids, and ECVs; and (9) ability of their secretome to: alter tissue biology, stimulate tissue resident stem cells, change immune cell activity, and mediate therapeutic outcome [83-86].

Umbilical cord-mesenchymal stem cells: Considered for a long time as a medical waste, UC appears these days as a promising source of MSCs. Several reports have shown that UC-derived MSCs are more primitive, proliferative, and immunosuppressive than their adult counterparts. Although UC-MSCs are until now not particularly used as an MSC source in clinical practice, accumulating evidence shows that they may have a therapeutic advantage in treating several diseases, especially autoimmune and neurodegenerative diseases [87]. MSCs derived from the Wharton's Jelly (WJ) of UC can easily differentiate into a plethora of cell types leading to a variety of applications. WJ-MSCs are slightly easier to harvest compared with other MSCs such as BM-derived MSCs. The fascinating stemness properties and therapeutic potential of WJ-MSCs provide great promise in many aspects of regenerative medicine and should be considered for further investigations as safe and effective donor cells for transplantation therapy in many debilitating disorders [88]. MSCs derived from WJ-UC have recently gained considerable attention in the field of regenerative medicine. The high proliferation rate, differentiation ability into various cell lineages, easy collection procedure, immuno-privileged status, and nontumorigenic properties along with minor ethical issues make WJ-MSCs an ideal approach for tissue repair. The number of WJ-MSCs in the UC samples is high as compared to other sources. WJ-MSCs have rapidly advanced into clinical trials for the treatment of a wide range of disorders [89]. Compared to other sources of MSCs including BM, placenta, and AT, MSCs derived from WJ-UC have the strongest immunomodulatory and immunosuppressive potential. So, WJ-MSCs are the most attractive cell population for use in immune cellular therapy when immunosuppressive action is required [90]. MSC from fetal sources can undergo more cell divisions before they reach senescence than MSC from adult tissue such as BM or AT [15].

The advantages of UC-MSCs include (1) a painless collection procedure, (2) fast and high self-renewal potential, (3) multilineage differentiation potential with ability to differentiate into the 3 germ layers, (4) having low immunogenicity, (5) secretion of effective molecules that regulate apoptosis, fibrosis, and neovascularization, (6) ability to modulate immune responses, (7) ability to accumulate in damaged tissues or inflamed sites, (8) ability to promote tissue repair, (9) ability to improve engraftment and suppress the immune system after HSCT, and (10) inhibition of tumor cell proliferation and migration to nest of cancer [91-93].

Products of mesenchymal stem cells

Extracellular vesicles of mesenchymal stem cells: MSC-ECVs are submicron circular lipid membrane vesicles that may be released from all human cells [94,95]. They were described as platelet dust in the year 1967 [96]. MSC-ECVs are involved in many cellular processes, both in physiological and pathological conditions [95,97]. They are mediators of cell-cell communication and they are active players in cell differentiation, tissue homeostasis, and organ remodeling [95,98,99]. ECVs carry or transfer biologically active molecules such as proteins, nucleic acids (mRNA/miRNA), and bioactive

lipids from stem cells to injured or diseased cells [97,98]. The efficiency of ECVs of MSCs can be further enhanced by: (1) selecting the appropriate ECV-producing cells and cell phenotypes, (2) optimizing the conditions in which the donor MSCs are cultured, and (3) engineering the ECVs produced to transport therapeutic and targeting molecules [96,100]. ECVs are fundamental paracrine effectors of MSCs that can overcome most of the limitations of MSC applications and they have allowed major advances in preclinical and clinical studies [96,99]. ECVs of MSCs maintain the stemness of the parent MSCs and retain their functions including modulation of the immune system, regulation of inflammation, inhibition of apoptosis, and induction of tissue regeneration [94,96,99].

ECVs of MSCs have several advantages that include: (1) ability to reproduce the biological effects and most of the therapeutic actions obtained by using the patent MSCs; (2) stability for long periods of time; (3) easy isolation; (4) lower immunogenicity than MSCs; (5) higher safety profile and less adverse effects than MSCs; (6) their heterogeneity is dependent on the stromas of origin; (7) ability to alleviate cell aging; (8) regulation of immune responses and inflammation, that is, they play critical role in immunomodulation; (9) their therapeutic effects can be improved further by bioengineering to induce more precise targeting and transfer of drugs; (10) great contribution to homeostasis and intercellular communication through transportation of a wide variety of biomolecules including nucleic acids, signalling lipids, regulatory proteins, transcription factors, cytokines and growth factors to recipient cells; (11) alleviation of sepsis and protection against sepsis-induced organ dysfunction; and (12) having antitumor effects, thus they can be used as cell-free cancer therapy [101-110].

Despite the progress achieved in introducing ECVs of MSCs in clinical therapeutics, the use of ECVs has several disadvantages and challenges that limit their clinical applications and these include: (1) inconsistent manufacturing processes including scalability and isolation; (2) stability, biodistribution, and pharmacokinetics; (4) quantification and characterization; (5) transfer and specific tissue targeting; (6) safety concerns; (7) poor cell survival; (8) efficient and optimal cell dosing; (9) storage and handling of clinical grade ECVs; (10) immune rejection; (11) high costs; and (12) lack of quality control and validation assays and measurements [103,108,109,111-116].

Exosomes of mesenchymal stem cells: Exosomes are ECVs secreted by various cells and they are mainly composed of lipid bilayers without organelles [117]. Compared to MSCs themselves, MSC-derived exosomes have provided significant advantages by efficiently decreasing unfavorable adverse effects, such as infusion-related toxicities [118]. The exosomes secreted by MSCs have been broadly researched due to their elastic, immune, and tumor-homing properties [117].

MSCs are recognized to generate a wide range of exosomes in a clinically appropriate measure as compared to other cell origins. Exosomes of MSCs have been widely investigated because of their immune attributes, tumor-homing attributes, and flexible characteristics. The therapeutic efficiency of exosomes and their safety for transferring different cellular biological components to the recipient cell have attracted significant attention for their capability as miRNA carriers [119]. MSC-exosomes are becoming a promising cell-free therapeutic tool and an increasing number of clinical studies started to assess the therapeutic effect of exosomes of MSC in different diseases [118]. Targeted drug delivery in the body is a promising method for treating many refractory diseases such as tumors and Alzheimer's disease [117]. Accumulating literature shows that exosomes have great potential in the treatment of SCIs [120]. While exosomes of MSC have apparent advantages, some unresolved problems also exist [117].

Impact of signaling pathways on the functions of mesenchymal stem cells

Signaling pathways, transcription factors, and growth factors modulate the differentiation of MSCs into different cell lineages [121]. Successful MSC therapy, along with the homing, relies on the secretion of biologically active molecules including cytokines, growth factors, and chemokines known as the secretome of MSCs [122]. A critical problem for MSCs in tissue engineering is their low survival ability and functionality as most MSCs become apoptotic after transplantation. Increasing MSC survival ability and functionalities is the key to potential applications of MSCs. Hence, several approaches have been studied to increase MSC tissue forming capacity including application of growth factors, overexpression of stem cell regulatory genes, and improvement of biomaterials for scaffolds [123]. The effects of these approaches on MSCs have been associated with the activation of one of the intracellular signaling pathways; the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway; which plays central regulatory roles in MSC survival, proliferation, differentiation, migration, angiogenesis, cytokine production, and apoptosis [122,123].

MSCs express and secrete a broad spectrum of bioactive molecules, including Notch and Wnt molecules, that support all the phases of the hematopoiesis, including self-renewal, proliferation, and differentiation [124]. The peroxisome proliferator-activated receptor-γ (PPAR-γ) signaling pathway regulates the differentiation of MSCs into adipocytes, while the Wnt signaling pathway regulates the differentiation of MSCs into osteoblasts, that is, Wnt is the master moderator of osteogenesis [125]. However, the key signaling pathways that are involved in MSC differentiation and growth include: (1) activin-mediated transforming growth factor (TGF)-beta signaling, (2) Platelet-Derived Growth Factor (PDGF) signaling, and (3) Fibroblast Growth Factor (FGF) signaling [126].

Current and potential clinical applications of mesenchymal stem cells

The proliferative, immunomodulatory, anti-inflammatory, regenerative, and other properties of MSCs make them ideal candidates for use as therapeutic agents in several autoimmune, systemic inflammatory, and infectious diseases in addition to the fields of regenerative medicine and tissue engineering. Consequently, their potential clinical applications have expanded rapidly over the years as shown in Table 3 [2,6,15,21,24,49,60,127-140].

Table 3: Current and potential therapeutic indications of mesenchymal stem cells.

1.	**Hematopoietic stem cell transplantation:**
a.	Enhancement of engraftment.
b.	Prevention of graft versus host disease (GVHD).
c.	Treatment of acute and chronic GVHD.
2.	**Solid organ transplantation (SOT):** Improvement of outcome of SOT by:
a.	Immunomodulation.
b.	Induction of transplantation tolerance.
3.	**Treatment of autoimmune diseases:**
a.	Systemic lupus erythromatosus.
b.	Rheumatoid arthritis.
c.	Systemic sclerosis.
d.	Ankylosing spondylitis.
e.	Multiple sclerosis.
f.	Type 1 diabetes mellitus.
g.	Ulcerative colitis.
h.	Crohn's disease.
i.	Type II refractory celiac disease.
j.	Other autoimmune disorders: myasthenia gravis, uveitis, neuromyelitis optica and hearing loss.
4.	**Regenerative medicine and tissue repair:**
a.	Myocardial ischemia.
b.	Acute myocardial infarction .
c.	Cardiac dysfunction.
d.	Dilated cardiomyopathy.
e.	Chronic non-healing wounds.
f.	Critical limb ischemia
g.	Peripheral vascular disease.
h.	Ischemic stroke.
i.	Traumatic brain injury.
j.	Spinal cord injuries.
k.	Liver injury.
l.	Radiation-induced lung fibrosis.
m.	Tissue repair: bone, cartilage, muscle, skin, myocardium, trachea, etc.
5.	**Treatment of various infections and their complications:**
a.	Bacterial infections including sepsis and its associated adult respiratory distress syndrome.
b.	Viral infections such as human immunodeficiency virus, hepatitis B and C viruses, and COVID-19 infections.
c.	Parasitic infections such as Chagas disease, schistosomiasis, and malaria.
d.	Mycobacterial infections such as tuberculosis.
6.	**Other indications:**
a.	Macular degeneration, corneal regeneration or reconstruction and corneal transplantation.
b.	Liver fibrosis, liver cirrhosis, end-stage liver disease and hepatic failure.
c.	Bones and joints: osteogenesis imperfecta, osteoarthritis, osteoporosis, osteonecrosis, meniscus injury.
d.	Cancer gene therapy and anti-cancer cellular therapy such as breast and lung cancers.
e.	Aging frailty.
f.	Amyotrophic lateral sclerosis.
g.	Parkinson's Disease.
h.	Idiopathic pulmonary fibrosis.
i.	Chronic obstructive airway disease.
j.	Renal disorders.

Examples of the therapeutic applications of MSCs are discussed below.

Use of mesenchymal stem cells in autoimmune diseases: AIDs are associated with an abnormal immune system, chronic inflammation, and immune reaction against self-antigens leading to injury and failure of several tissues and organs [141]. Even with the advancements in developing novel therapies and biological agents, AIDs are still incurable [142].

MSCs can migrate to the sites of inflammation and exert potent immunosuppressive and anti-inflammatory effects through the interaction between lymphocytes associated with both the innate and adaptive immune systems [6]. Recently, MSCs have been used in clinical trials to treat various AIDs because of their beneficial properties such as safety and ease of isolation, high proliferation ability, multipotent differentiation capacity, as well as their anti-inflammatory, immunomodulatory, and regenerative properties [141]. After widespread in-vitro and *in-vivo* preclinical studies, autologous and allogeneic MSCs and their ECVs have been applied in the treatment of several AIDs including type 1 Diabetes Mellitus (DM); GVHD; Multiple Sclerosis (MS); Systemic Lupus Erythematosus (SLE); RA; systemic sclerosis; Sjogren's syndrome; and Inflammatory Bowel Diseases (IBDs) such as Crohn's disease [142-144]. Studies on the use of MSCs in AIDs have shown no remarkable association with the evolution of malignancies or infectious diseases [141]. Additionally, genetic modification of MSCs to express anti-tumor genes has provided a rationale for their utilization as anticancer therapy [6].

The results of 6 systematic reviews and meta-analyses on the use of MSCs in several AIDs showed the following findings: in patients with DM, 2 systematic reviews and meta-analyses that included 36 Randomized Clinical Trials (RCTs) comprising 900 patients showed that treatment with MSCs ± hematopoietic stem cells (HSCs) resulted in: transient insulin independence or decrease in daily insulin requirements, significant decrease in Hb A1C level, and improvement in C-peptide levels, and that administration of MSCs was shown to be generally safe with the exception of some hypoglycemic episodes [145,146]; (2) in patients with RA, 1 systematic review and metaanalysis showed that administration of MSCs resulted in clinical effectiveness in 54% of treated patients as the following results were reported: decrease in disease activity, improvement in symptoms, and improvement in laboratory indices [147]; (3) in patients with SLE, the results of 2 systematic reviews and meta-analyses showed that MSC administration resulted in: reduction in the rate of flare-ups, reduction in urinary protein levels, and increase in serum C3 complement levels, while some of the RCTs included reported adverse effects such as fever, headache, and diarrhea during MSC infusion [147,148]; (4) in patients with systemic sclerosis, 1 systematic review and meta-analysis that

included 9 studies comprising 133 patients showed that the use of MSC therapy resulted in improvement in: lung function, skin thickening, mouth opening, digital ulcerations, and pain in the absence of severe adverse effects [149]; (5) in patients with ankylosing spondylitis, MSC administration resulted in improvement in activity, reduction in pain, and reduction in disease indices such as erythrocyte sedimentation rate and tumor necrosis factor-α (147); (6) in patients with IBD, the use of MSCs resulted in improvement in clinical conditions of the treated patients [147]; and (7) in patients with MS, 2 systematic reviews and meta-analyses showed that the use of MSCs showed equivocal results [147,150].

Use of mesenchymal stem cells in hematopoietic stem cell transplantation: BM-derived MSCs play a crucial role in the regulation of hematopoiesis [151]. In addition to supporting hematopoiesis, MSCs are capable of modulating immune and inflammatory responses and participating in tissue repair [152,153]. Also, once ECVs of MSCs are given in combination with HSCs, they can modulate the immune system and inhibit the development of GVHD following HSCT [151,152].

The clinical applications of MSCs in HSCT include (1) prevention and treatment of GVHD, (2) enhancement of hematopoietic engraftment and prevention of engraftment failure, (3) acceleration of lymphocyte recovery, (4) repair of tissue damage, and (5) reduction in aplasia post-chemotherapy [152-156]. The safety and therapeutic potential of the clinical application of MSCs in HSCT have been well established by numerous clinical trials. Commercial MSC products for pediatric steroid-refractory GVHD have already been licensed in Japan, conditionally licensed in Canada and New Zealand, and may get approval by the Food and Drug Administration (FDA) in the United States of America (USA) soon [155].

Three systematic reviews and meta-analyses, that included 85 studies comprising 2334 patients, on the use of MSCs in prevention of GVHD, treatment of both acute including steroid-refractory and chronic GVHD showed the following results: (1) in patients with acute GVHD, 39% - 67% of patients achieved Complete Response (CR) and one-third of patients achieved partial response (PR); (2) in patients with chronic GVHD, 23% of patients achieved CR while 66% of patients achieved PR; (3) acute GVHD grade II responded to MSCs much better than grades III and IV acute GVHD; (4) acute GVHD of the skin responded to MSC therapy better than acute GVHD of the liver or gastrointestinal tract; (5) children with acute GVHD showed better responses than adults with acute GVHD; (6) response to MSC therapy correlated well with the dose of MSCs administered; and (7) once used prophylactically, MSC treatment was effective in reducing the incidence of chronic GVHD and the overall survival (OS) was increased by 17% [157-159]. However, prophylactic co-transplantation of MSCs in addition to HSCs in patients with severe aplastic anemia undergoing haploidentical HSCT failed to show efficacy [160]. Additionally, one major review that included 9 studies on the use of MSCs in the treatment of steroid-refractory acute GVHD showed: (1) CR of steroid-refractory acute GVHD was achieved in up to 50% - 83% of patients; (2) CR, but not PR, was associated with prolonged OS; and (3) no serious adverse effects of MSC therapy were reported [161].

Use of mesenchymal stem cell therapies in lung diseases: Systematically infused MSCs have been found to migrate directly to the lung where they can: ameliorate cytokine release, protect alveolar epithelial cells, aid in alveolar fluid clearance, promote epithelial and endothelial recovery, repair injured airways, reduce the risk of allograft rejection, resist pulmonary fibrosis, and improve lung function by secreting many factors and modulating multiple biological processes involved in the immune response. Hence, MSCs have shown great potential and benefit in treating severe incurable pulmonary disorders [162]. Clinical trials on the use of autologous or allogeneic MSCs to treat various respiratory conditions have shown adequate evidence of safety as well as evidence of significant improvement in the quality of life of patients [163,164].

MSCs and their secretome have been used in the treatment of various respiratory diseases including viral and community-acquired pneumonia; emphysema, bronchial asthma, chronic obstructive airway disease; bronchiolitis obliterans; chronic idiopathic pulmonary fibrosis; acute lung injury and Acute Respiratory Distress Syndrome (ARDS); pulmonary fibrosis due to bleomycin or radiation; cystic fibrosis; and pulmonary hypertension [162-168]. Due to their potent and broad-spectrum properties and activities including immunomodulation, inhibition of bacterial growth and enhancement of bacterial clearance, anti-inflammatory; tissue-regenerative, pro-angiogenic, and anti-fibrotic properties which rely on cell-to-cell contact and paracrine mechanisms, MSCs offer novel and promising therapeutic options for several acute and chronic lung disorders [162,163,166,167,169]. However, the use of MSCs in the treatment of radiation-induced lung injury has shown beneficial as well as adverse effects such as enhancement of the progression of lung injuries [168].

Use of mesenchymal stem cells in the treatment of cardiovascular disorders: The therapeutic effects of MSCs in the treatment of cardiovascular diseases are based on the following: (1) their antifibrotic and anti-inflammatory actions in reducing cardiac fibrosis and inflammation; (2) their migration into the sites of infarcted cardiac tissues; (3) neovascularization or their promotion of new blood vessel formation; (4) their differentiation into cardiomyocyte-like cells; (5) their contribution to the repair of infarcted myocardium; and (6) their other distinguished properties such as the wide range of sources, the easy isolation and amplification, the low immunogenicity, their immunomodulatory effects, and the ability of MSCs to exert

effects through their paracrine activities [170-173]. The following cardiac conditions can benefit from MSC therapy: ischemic heart disease and Acute Myocardial Infection (AMI); heart failure; and cardiac fibrosis [170-177].

The results of 4 systematic reviews and meta-analyses, which included 53 RCTs comprising 3043 patients, on the use of MSCs in the treatment of various cardiac disorders have shown: (1) safety and efficacy of MSCs in the treatment of AMI and heart failure with no significant increase in mortality; (2) significant improvement in overall left ventricular ejection fraction by 3.2% to 5.7%; (3) improvement in prognosis and exercise capacity; and (4) significant reduction (47%) in the incidence of hospitalization. However, the factors that favored better responses included: allogeneic sources of MSCs; intracoronary injections; and MSC doses of 1 x 10^8 - 10 x 10^8 cells [174-177].

Use of mesenchymal stem cells in the treatment of neurological and eye diseases: MSCs have proliferative, immunomodulatory, neuroprotective, and regenerative properties that make them promising cell-therapy candidates for various neurological disorders [178]. MSCs have been widely studied as cellular therapies for several neurological disorders in animal studies and early clinical trials and their use has shown safety, tolerability, and functional improvement, in addition to delay in disease progression after transplantation [178,179]. Genetic engineering and modification of MSCs as well as the use of ECVs of MSCs have emerged as new tools to enhance the therapeutic efficacy of MSCs in treating various neurological diseases [178]. Several studies have shown that MSCs and their exosomes can differentiate into dopaminergic neurons thus they can replace the neuronal loss in neurodegenerative diseases such as Parkinson's disease (PD) [180-183]. In a PD model, exosomes of human UC-MSCs have been shown to traverse the blood-brain barrier indicating their potential to treat patients with PD [184].

The immunoregulatory, anti-inflammatory, anti-apoptotic, and regenerative properties of MSCs in addition to their safety profile make them ideal cell therapy candidates to treat various eye diseases such as diabetic retinopathy, glaucoma, retinal degeneration, and retinitis pigmentosa [185-187]. The use of ECVs of MSCs and genetic manipulation of MSCs can further improve their ability to treat various eye disorders [186-188].

Use of mesenchymal stem cells in the treatment of various infectious diseases: MSCs are applied in the treatment of various infectious diseases due to: (1) having immunomodulatory effects, that is, modulation of host innate and adaptive immune cells; (2) having anti-inflammatory properties; (3) having antimicrobial effects against the major classes of human pathogens [bacteria, viruses, fungi, and parasites]; and (4) their ability to promote the restoration of the epithelium and to stimulate tissue regeneration [189,190]. MSCs are being investigated in more than 80 clinical trials for difficult-to-treat infectious diseases including sepsis, intra-abdominal and cutaneous infections, as well as viral infections. The completed clinical trials have reported not only safety but also promising efficacy against some infectious diseases [190]. Cell-free treatments such as ECVs of MSCs have demonstrated high therapeutic efficacy in preclinical studies. Hence, they can become a promising tool for the treatment of various infectious diseases particularly in combination with antimicrobial drugs [189]. MSCs have shown promising potential to inhibit bacterial infections. Therefore, MSCs can be considered a novel strategy to enhance antibiotic activity against Multidrug-Resistant (MDR) organisms [191].

Sepsis and septic shock are serious and life-threatening disorders that are associated with high rates of morbidity and mortality [192,193]. Due to the failure of conventional therapies in recent years, research is focusing on innovative treatments such as cellular therapies [192]. The immunomodulatory, anti-inflammatory, anti-apoptotic, regenerative, and antimicrobial properties of MSCs can protect against organ failure caused by sepsis and septic shock. Hence, MSCs have been extensively utilized in both preclinical and clinical trials in various infectious diseases [192,193]. However, the way in which MSCs exert their beneficial effects to control inflammation and prolong survival in septic conditions remains unclear [194]. ECVs of MSCs exert therapeutic effects that are similar to MSCs and they can protect against sepsis-induced organ dysfunction [193]. In animal studies, the use of ECVs derived from BM-MSCs was associated with less organ damage in comparison to ECVs derived from MSCs obtained from other sources [195]. Additionally, ECVs derived from MSCs have shown superior safety profiles and the ability to be stored safely without loss of function compared to the parent cells. Therefore, MSC-ECVs may be used as a novel alternative to MSC-based therapy in sepsis [193].

Several studies have shown that MSCs are recruited at the periphery of tuberculous granulomas that harbor Mycobacterial Tuberculosis (MTB) bacilli and that MTB uses MSCs as a niche to evade host protective immunity surveillance mechanisms and to establish dormancy [196-199]. MSCs help MTB organisms to tolerate and even resist treatment with antiTB drugs [197,200]. MSCs have emerged as a fifth element capable of regulating immune responses during TB infection [201]. MSCs play a role in the dormancy and reactivation of MTB and in the capacity of MTB to evade host immune responses [202,203]. Transplantation of MSCs and their exosomes have been used in the treatment of MDR-TB. MSCs have been used in 3 clinical trials that included 135 patients to treat MDR-TB and extensively DR (XDR)-TB [201,204]. The results of these studies were as follows: (1) MSCs induced clinical and radiological improvements in 70% - 80% of patients; (2) MSC transplantation induced

persistent remission and even cure in 53% - 56% of patients; and (3) the addition of autologous MSC transplantation to conventional anti-TB therapy significantly enhanced the response rates in patients with MDR-TB and XDR-TB [205-207].

Five systematic reviews and meta-analyses; that included 62 RCTs comprising 2316 patients; on the use of MSCs in the treatment of COVID-19 infection and its complications have shown the following results: (1) MSCs can reduce the mortality rates in patients with COVID-19 infection; (2) MSCs can induce remission of symptoms related to COVID-19 infection; (3) MSCs can reduce the severity of COVID-19 pneumonia; (4) MSCs can improve lung function and radiological appearances in patients with COVID-19 pneumonia; (5) MSCs can reduce the levels of C-reactive protein and interferon-gamma in patients with severe COVID-19 infection; and (6) MSCs can reduce the duration of hospitalization and the requirement for invasive mechanical ventilation; [208-212]. Additionally, the included RCTs showed safety of MSC therapy in COVID-19 infection without an increase in the incidence of adverse effects [208-211].

Use of mesenchymal stem cells in the treatment of skin disorders: Stem cells are present in different locations in the skin; interfollicular epidermis, hair follicles, dermis, and adipose tissue; in order to maintain normal skin homeostasis and they are involved in tissue repair and skin regeneration during injury [213]. Several studies have demonstrated the involvement of MSCs in the pathogenesis of certain skin disorders such as psoriasis [214]. Due to their immunomodulatory, anti-inflammatory, antimicrobial, and regenerative capabilities, MSCs can be used in the treatment of various congenital, acquired, inflammatory, and autoimmune skin diseases [214]. Two systematic reviews and several other studies have shown that MSCs obtained from various sources including AT and their secretome; ECVs and exosomes; have been used in the treatment of several skin disorders including psoriasis; vitiligo; epidermolysis bullosae; atopic dermatitis; scarring, androgenic, and areata alopecia; skin fibrosis due to aging, burns and scelomyxedema; Merkel cell carcinoma; and cutaneous photoprotection, wound healing, and promotion of hair growth [213-218].

Mesenchymal stem cells in regenerative medicine and musculoskeletal disorders: Advances in isolation, culture, differentiation, and expansion techniques for MSCs have enabled their large-scale therapeutic utilization [60,219]. The following properties make MSCs optimal for tissue regeneration: (1) immunomodulatory capacity to alleviate abnormal immune responses; (2) paracrine or autocrine functions that generate growth factors; (3) the ability to differentiate into target cells; (4) anti-inflammatory and immunosuppressive properties; (5) migration to the areas having tissue injury; and (6) anti-aging, reconstructive, and wound healing potentials [60,219,220]. As a result of 5 decades of research and investigations, MSCs have emerged as a versatile and frequently utilized cell source in the fields of tissue engineering and regenerative medicine [221]. Studies in regenerative medicine have shown: (1) administration of MSCs in the treatment of bone and heart diseases appears to be effective, useful, and broadly established; (2) several clinical trials have reported the value of both autologous and allogeneic MSCs in tissue formation; (3) no significant association was established between the use of MSCs and cancer or infections; (4) intravenous (IV) route has been established as the optimal route of administration of MSCs and doses between 1 x 10^6 and 2 x 10^8 cell/kg body weight; and (5) repeated administration of MSCs is more beneficial than single injection [60].

Studies suggest that expanded MSCs have multiple therapeutic effects on musculoskeletal disorders that can be applied in bone regeneration, restoration of cartilage defects, and treatment of OA, spinal fusion, disc regeneration, and tendon repair [222]. MSC-related osteobiologic products are available either in the market or in development [222]. Several approaches using MSCs for regenerating damaged periodontium are under study with variable degrees of clinical applications [223].

Autologous MSCs represent the primary source considered safe for transplantation and minimization of immunological risk despite the lack of documented complaints regarding allogeneic MSC-based therapies [220]. However, MSCs have been shown to be able to survive and engraft in allogeneic recipients [222]. Scaffold; materials that have been engineered to cause desirable cellular interactions to contribute to the formation of new functional tissues; have the following advantages: (1) they provide the environment and stimulation of MSCs to proliferate and differentiate, and (2) they enhance the therapeutic effects of MSCs as they are loaded with the required induction factors [220]. Despite the current challenges, MSC-based tissue engineering represents a promising clinical strategy in the field of regenerative medicine. However, improving the cultural environment of MSCs and selecting appropriate scaffolds and induction factors are essential components of MSC therapy [220,221].

With high expectations, many ongoing clinical trials are investigating the safety and efficacy of MSCs in the treatment of arthritic diseases [224]. Over the last few decades, MSCs have been extensively explored as an emerging technique for the treatment of OA. However, therapeutic efficacy depends on a number of factors including the source of MSCs and the technique used in the treatment of OA [225]. However, studies on OA have shown positive clinical outcomes and improvement of joint function, pain level, and quality of life without serious adverse events [224]. MSCs may limit cartilage degeneration in OA by interfering with cellular immunity and secreting a number of active chemicals [225].

Mesenchymal stem cells derived from induced pluripotent stem cells

Studies have shown that conventional tissue-derived MSCs are heterogeneous in nature as they have donor-specific and tissue-specific differences such as age, sex, and tissue source which limit their proliferative capacity and lead to inconsistent long-term therapeutic outcomes [226-228]. Due to the clinical potential of MSCs, there has been considerable interest in the generation of functional MSC preparations from induced pluripotent stem cells (iPSCs) [229,230]. iPSCs can differentiate through several techniques including: growth factor induction, three-dimensional cell culture, biomaterials, and epigenetics into induced MSCs (iMSCs) [227,228]. Currently, iPSCs represent a new reliable source to generate MSCs from iPSCs (iMSCs) from heterogeneous and well-characterized cell lines and are now regarded as a potential source of unlimited standardized high-quality cells for therapeutic applications in regenerative medicine [229,230]. Studies have shown that: (1) irrespective of donor age and cell source, iMSCs acquire a rejuvenation gene signature thus overcoming the age-associated drawbacks of native MSCs, and (2) iMSCs have specific features such as their single-cell clone origins as well as defined and controllable cultural conditions for their derivation and proliferation [231-233]. Autologous iMSCs represent a unique source of standardized cellular therapy that can be used to fulfill unmet clinical needs and to overcome most of the obstacles still facing the broad clinical application of MSCs as advanced medicinal products [226,233-237]. Recent studies have shown that, compared to adult MSCs and UC-MSCs, iMSCs have demonstrated superior immunosuppressive capacity and clinical superiority when applied in tissue regeneration such as wound healing [226,228,234,235,237]. Compared to adult MSCs, exosomes derived from iMSCs have shown superior therapeutic quality with enhanced growth proliferation and migration in tissue regeneration [228,236].

Mesenchymal stem cells as advanced therapeutic medicinal products and their approvals for clinical use

Stem cell research has resulted in the emergence of cell-based therapies for disorders that are resistant to conventional drugs and therapies, and these cell therapies are considered under the category of an Advanced Therapeutic Medicinal Product (ATMP) [238]. ATMPs are innovative medicinal products, developed mainly as individualized and patient-specific treatments, and represent new opportunities for diseases characterized by unmet medical needs, including rare, genetic and neurodegenerative disorders, hematological malignancies, cancer, AIDs, and inflammatory conditions [239]. Since ATMPs often target serious diseases, the industry and authorities are interested in providing treatment to patients in a timely manner through optimized and expedited regulatory pathways [240]. The FDA in the USA and the European Medicines Agency (EMA) devised a new strategy in 2017 with the aim of unifying the standards for the development of ATMPs such that it is easy to exchange information at the international level [238]. Various diseases have been treated by MSCs in animal models and hundreds of human clinical trials related to the potential benefits of MSCs are in progress [241]. Autologous MSCs can be affected by the disease status of patients and this compromises their clinical utilization. Consequently, allogeneic therapy seems to be the most cost-effective method [241,242]. Standardized procedures based on instrumented single-use bioreactors have been shown to provide billions of MSCs with consistent product quality and to be superior to traditional expansions in planar cultivation systems [242,243]. Currently, more than 27 human MSC-derived therapeutics are currently commercially available [243]. However, the immunomodulatory and anti-inflammatory properties of UC-MSCs, associated with fewer ethical, availability, and safety issues, position UCMSCs as promising active substances to develop medicinal products to treat immune and inflammatory diseases. Since 2007, UC-MSC-based products have been classified as ATMP according to the European Regulation 1394/2007/EC [244].

Currently, there is no FDA-approved MSC therapy on the market in the USA [133]. However, regulatory authorities have already approved MSC therapies for several clinical conditions including GVHD in Japan, Canada, and New Zeeland, perianal fistula due to Crohn's disease in Europe, and critical limb ischemia in India [137,245-247]. In the year 2018, the EMA authorized the first marketing of allogeneic AT-derived MSCs for the treatment of complex perianal fistulas in Crohn's disease and this represented a breakthrough in the field of MSC therapy [248]. Due to the complexity of the production process of MSCs, the prices of MSC medicinal products have been reported to range between 25,000 and 40,000 US dollars per dose of MSCs [249]. Nevertheless, the development of enhanced MSC products of clinical relevance in a cost-effective manner holds the potential to offer therapeutic solutions with fewer adverse effects compared to the drugs that are currently available for the treatment of inflammatory and autoimmune disorders [250].

Safety and efficacy of mesenchymal stem cell therapies

Eleven systematic reviews and meta-analyses that included 266 studies; 105 of them were RCTs; on the clinical utilization of MSCs in more than 34 different disease conditions revealed the safety of MSC therapies in general, with few and tolerable adverse effects, regardless of the source or the route of administration of MSCs [147,174,177,208, 251-258].

24 systematic reviews and meta-analyses that included 445 studies; 69 of them were RCTs; on the clinical utilization of MSCs in 47 different disease conditions; including autoimmune, infectious, liver, cardiac, and neurological disorders; revealed the efficacy of MSC therapies in general with improvement in clinical status and improvement in

laboratory indices reflecting disease activity regardless the source, the dose, or the route of administration of MSCs [147-150,176,177,208,223,254, 256-269].

Challenges facing the clinical utilization of mesenchymal stem cells

There are several challenges that face the clinical application of MSCs and these include: (1) safety issues related to the immediate and late adverse events such as: aggravation of arthritis, promotion of tumor growth and metasteses, and transmission of infectious diseases; (2) clinical grade production of MSCs requires large numbers of cells so *in vitro* expansion of MSCs is required and that MSCs which are used in clinical trials must be manufactured under the conditions required by the good manufacturing practice; (3) quality control measures covering all aspects including: cell production and harvest, viability and phenotype testing, oncogenicity tests, endotoxin assays, timing of administration, cell dose and schedule of administration, engraftment of MSCs, sources of MSCs (peripheral blood versus BM versus AT versus UC), autologous versus allogeneic transplantation, use of certain products such as ECVs of MSCs, donor related issues such as age and comorbidities, and use of fresh versus frozen and thawed MSCs; (4) in the period of clinical transition, plenty of work is still needed to: (a) increase knowledge on mechanisms involved in development, homeostasis, and tissue repair, (b) provide new tools to implement the efficacy of trials on MSC therapy, and (c) implement stringent regulations, standards, and protocols to cover all stages of MSCbased therapies including: isolation, ex vivo expansion, culture, storage, shipment, and administration; (5) performance of more RCTs and prospective studies to determine the optimal conditions of MSC therapy; (6) development of more robust pharmacodynamic, pharmacokinetic models that need to be applied in different clinical situations and to study failure of therapy and resistance to treatment; (7) stemness stability, and immunocompatibility; (8) the high economic costs of MSC therapies; (9) heterogeneity and limited expansion of MSCs; (10) requirement of inflammatory environment to induce immunosuppression; (11) loss of extracellular matrix upon delivery; (12) deprivation of nutrients and oxygen at the recipient site; and (13) linking research teams, cell therapy laboratories, and clinical teams in an integrated network [6,21,129,130,133,270-278].

Conclusions and future directions

Recently, the clinical applications of MSCs have rapidly expanded to include: AIDs; HSCT; several viral, bacterial, fungal, and parasitic infections and their complications; skin, pulmonary, and cardiovascular disorders; neurodegenerative, musculoskeletal and eye diseases; as well as regenerative medicine. The safety and efficacy of MSCs have been well illustrated in several clinical trials, systematic reviews, and meta-analyses.

Genetic engineering as well as the use of iMSCs and specific products of MSCs such as ECVs and exosomes have further improved their clinical efficacy and decreased their adverse effects including predisposition to cancer and infections.

The use of specific sources of MSCs, the administration of MSCs through certain routes, and the use of certain stem cell doses are expected to produce more fruitful short-term as well as long-term outcomes. Unification of preparation and administration protocols and implementation of strict regulations, standards, and quality control measures will result in the elimination of most of the remaining challenges that face the widespread utilization of MSCs in the clinical arena. The performance of more RCTs and multicenter prospective studies will ultimately determine the optimal conditions of MSC therapies in various acute and chronic diseases.

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