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Therapeutic applications of mesenchymal stroma cells in pediatric diseases: Current aspects and future perspectives

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Summary

Mesenchymal stem cells or stroma cells (MSCs) were recently proven to play various therapeutic roles when used in clinical trials to control various inflammatory, neoplastic and immunologic diseases in children. Clinical trials show some promising results, particularly in diseases where conventional therapy is still ineffective**.** However, experimental studies sometimes show conflicting results.

This review aims to assess the current therapeutic role of MSCs in the control of several pediatric diseases and elaborate on their future applications by reviewing published studies.

A review of published studies on this subject based on Pubmed and Medical Subject Heading databases, with search for all relevant articles focusing on results of clinical trials to evaluate the clinical applications of MSCs.

The review includes documentation of positive as well as negative applications of MSCs focused on pediatric diseases.

MSCs have important immunosuppressive and antifibrotic effects that need to be employed to help patients with diseases for which no conventional management has proven to be effective. They may be also be used as an adjuvant to conventional therapeutic modalities to consolidate recovery.

This review sheds light on the significance of the use of MSCs for the treatment of various pediatric diseases and focuses on promising applications. Most of the reported studies agree about the favorable use of MSCs in various diseases; however, more clinical trials, involving larger numbers of patients, need to be conducted in order to refine the outcome of the therapeutic methods and establish standardized protocols.

key words: **bone marrow mesenchymal stem cells • tissue regeneration • hematolocical diseases**

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Background

Mesenchymal stem cells (MSCs) are a heterogeneous population of stem/progenitor cells with capacity to differentiate into mesodermal and non-mesodermal cell lineages, including osteocytes, adipocytes, chondrocytes, myocytes, cardiomyocytes, fibroblasts, myofibroblasts, epithelial cells, and neurons [1]. MSCs reside primarily in the bone marrow, but also exist in other sites such as adipose tissue, peripheral blood, cord blood, liver, and fetal tissues. When stimulated by specific signals, these cells can be released from their niche in the bone marrow into the circulation and recruited to the target tissues where they undergo *in situ* differentiation and contribute to tissue regeneration and homeostasis. Several characteristics of MSCs, such as the potential to differentiate into multiple lineages and the ability to be expanded *ex vivo* while retaining their original lineage differentiation commitment, make these cells very interesting targets for potential therapeutic use in regenerative medicine and tissue engineering. The feasibility for transplantation of primary or engineered MSCs as cell-based therapy has been demonstrated.

Bone marrow contains at least 2 kinds of stem cells – hematopoietic stem cells and stem cells for non-hematopoietic tissues [2], variously referred to as marrow stromal cells. MSCs are of interest because they are easily isolated from a small aspirate of bone marrow and readily generate single-cell-derived colonies [3], which can be expanded through as many as 50 population doublings in about 10 weeks [4]. They can differentiate into osteoblasts, adipocytes, chondrocytes [5], myocytes [6], astrocytes, oligodendrocytes, neurons [7] and hepatocytes [8]. For these reasons, the cells are currently being tested for their potential use in cell and gene therapy for a number of diseases [9].

Zhao et al. [10] have established that bone marrow (BM)-derived MSCs can engraft injured tissue, such as bone marrow, lung, liver, heart or brain, and recover its function. Their results indicate that MSCs are an attractive cell source for regenerative medicine. MSCs administration could repair injured lung, liver or heart by reducing inflammation, collagen deposition and remodeling [11]. This implies that MSCs may not only be able to repair acutely damaged tissues, but also have the ability to reduce chronic fibrogenesis.

The aim of this review is to summarize the latest information from basic science advances and the outcome of their use in clinical practice with a particular focus on pediatric patients. We discuss the role of MSCs in the treatment of graft-versus-host disease, in the acceleration of hematopoietic recovery, in tissue repair/tissue engineering, and in the treatment of selected inherited disorders.

Human MSCs (hMSCs)

The advantage of using human MSCs (hMSCs) is that they are immuno-modulatory and versatile due to their secreted bioactive molecules that are anti-inflammatory and regenerative. These cells have the potential to orchestrate reparative processes in diseased or injured tissues. Much of the diversity and uniqueness of hMSCs is defined by their response to the microenvironment of the host tissue. hMSCs can deliver bioactive agents in a site-specific manner quite different from the way pharmaceutical drugs work [12]. Currently, there is no single unique marker for hMSCs, although the absence of CD34 and CD45 and the presence of SH2, SH3, SH4, Stro-1, and others are used to identify hMSCs [13].

MSCs are poor antigen-presenting cells, not expressing major histocompatibility class II (MHC II) or co-stimulatory molecules [12]. Clinical studies have exploited both the immune-modulatory properties of hMSCs as well as their hematopoietic supportive role. Thus, hMSCs are not antigen-presenting cells and are invisible to the host's immune system. It is important to note that in all of the clinical usages of human adult marrow-derived, culture-expanded MSCs, whether autologous or allogeneic, no adverse events have been recorded [14,15]. This establishes that the procedures for isolation and culture expansion are safe and that in certain clinical applications there has been a benefit from the intravenous delivery of hMSCs. hMSCs can be of great value by virtue of their ability to differentiate into distinctive and specialized cells and their secretion of site-specific proteins. Defining the mechanisms of MSCs therapeutic efficacy may require elaborate technology associated with delivery, imaging, and targeting, which has the potential to identify appropriate delivery mechanisms and the ability to localize hMSCs [16].

Hematological applications

Aplastic anemia

Maciejewski and Risitano [17] reported that aplastic anemia (AA), as a stem cell disease, is very instructive and provides insights into the function and quantity of normal hematopoietic stem cells and their ability to regenerate. Pathophysiologically, understanding of AA may reveal mechanisms of the evolution of other related bone marrow failure syndromes such as paroxysmal nocturnal hemoglobinuria (PNH) and myelodysplasia-clonal diseases of hematopoiesis associated with defective stem cells. PNH is likely due to pathogenic mechanisms similar to those involved in AA, and not to the intrinsic abnormality conferred to the clonal population by the PIG-A mutation.

In a pilot phase I-II clinical trial attempting to speed hematopoietic recovery after intensive chemoradiotherapy, 15 pediatric high-risk acute leukemia patients were enrolled [18]. Infusion of *ex-vivo* culture-expanded haploidentical MSCs into unrelated pediatric umbilical cord blood transplantation (UCBT) recipients was performed safely. Patients achieved neutrophil engraftment at a median of 19 days. Probability of platelet engraftment was 75% at a median of 53 days. Five patients remained alive and disease free, with a median follow-up of 6.8 years. This encouraging safety profile of haploidentical MSCs supports the investigation of unrelated 'off the shelf' allogeneic HLA-mismatched MSCs products.

Isaikina and Shaman [18] concluded that co-transplantation of autologous MSCs is a good way to improve hematopoietic stem cells engraftment and reduce the period of granulocytopenia after autologous HSCs transplantation in case of insufficient $CD34^+$ cell number in autologous transplants. The capacity of patients' MSCs to support HSCs proliferation and self-renewal was the same as for healthy donors' MSCs.

Muller et al. [19] studied the safety and feasibility of MSCs transfusion in pediatric patients who had undergone allogeneic stem cell transplantation from mismatched family donor (MMFD), matched unrelated donor (MUD), mismatched unrelated donor (MMUD) and matched sibling donor (MSD). They reported the first series of 11 transfusions of expanded MSCs in pediatric patients with immunological complications after allogeneic transplantation. They also reported the first case of a pediatric patient treated with MSCs for trilineage failure after haploidentical stem cell transplantation from her father. The transfusion of MSCs was safe and encouraging improvements in some patients were observed. They transfused *ex-vivo* expanded MSCs in 11 doses into 7 pediatric patients. No adverse effects were detected with a maximum follow-up of 29 months.

Graft-versus Host Disease (GvHD)

Preliminary studies using directed-donor *ex-vivo* expanded human mesenchymal stem cells have shown promise in the treatment of acute graft-versus-host disease (aGvHD). Fang et al. [20] reported the use of human adipose tissue-derived MSCs as salvage therapy for treatment of severe refractory acute graft-versus-host disease in 2 children. Their study included 2 pediatric patients who developed severe refractory acute GvHD following allogeneic stem cell transplantation (ASCT) and who were successfully treated with MSCs from HLA-mismatched unrelated donors. Severe steroid refractory GvHD was investigated by Ball et al. [21], who safely administered MSCs in a phase I/II multicenter study. The study included 25 children, of whom 80% responded to either 1or 2 infusions of MSCs derived mainly from third party donors.

Prasad et al. [22] used a pre-manufactured, universal donor formulation of hMSCs (Prochymal™) in children with treatment-resistant Grade III and IV aGvHD who received therapy between July 2005 and June 2007 at 5 transplant centers. All patients had stage 3 or 4 gastro-intestinal (GI) symptoms and half had additional liver and/or skin involvement. Disease was refractory to steroids in all cases and additionally to a median of 3 other immunosuppressive therapies. The hMSCs were infused intravenously over 1 hour twice a week for 4 weeks. Partial and mixed responders received subsequent weekly therapy for 4 weeks. HLA or other matching was not needed.

The hMSCs were started at a median of 98 days (range 45–237) post-transplant. A total of 124 doses were administered with a median of 8 doses (range 2–21) per patient. Overall, 7 patients (58%) had complete response, 2 (17%) had partial response and 3 (25%) had mixed response. Complete resolution of GI symptoms occurred in 9 patients (75%). Two patients relapsed after initial response and showed partial response to re-treatment. The cumulative incidence of survival at 100-day from the initiation of Prochymal™ therapy was 58%. Five of 12 patients (42%) were still alive after a median follow-up of 730 days (range, 527–1211 days) in surviving patients. No infusional or other identifiable acute toxicity was seen in any patient. Multiple infusions of hMSCs were well tolerated and appear to be safe in children. Clinical responses, particularly in the GI system, were seen in the majority of children with severe refractory aGvHD. Given the favorable results observed in a patient population with an otherwise grave prognosis, it was concluded that hMSCs hold potential for the treatment of aGvHD and should be further studied in phase III trials in pediatric and adult patients.

Another study was reported by Lucchini et al. [23] and included 11 pediatric patients diagnosed with aGvHD or chronic GvHD (cGvHD). The patients were resistant to multiple lines of immune-suppression. They were treated for compassionate use with GMP-grade unrelated HLA-disparate donors' bone marrow-derived MSCs, expanded in platelet-lysate (PL)-containing medium. The patients (aged 4–15 years) received intravenous (IV) MSCs. No acute adverse effects were observed, and no late adverse effects were reported at a median follow-up of 8 months (range: 4–18 months). None of the patients presented GvHD progression upon MSCs administration, but 4 patients presented GvHD recurrence 2 to 5 months after infusion. Two patients developed chronic limited GvHD. This study underlines the safety of PL-expanded MSC use in children. MSCs efficacy seems to be greater in aGvHD than in cGvHD, even after failure of multiple lines of immunosuppression.

Recently, Wu et al. [24] infused, intravenously, third party, *in vivo* expanded umbilical cord-derived MSCs into 2 patients with severe, steroid resistant acute GvHD. They reported that umbilical cord-derived MSCs have higher proliferative potential and more immunosuppressive effect compared to bone marrow-derived MSCs. The aGvHD improved dramatically in both patients after 4 infusions. They thus documented the first report of human use of umbilical cord MSCs.

To conclude, it appears that MSCs have a low immunogenicity and immune regulation ability. MSCs can inhibit the activation and proliferation of T, B lymphocytes, NK cells and dendritic cells (DC). Additionally, MSCs are able to reconstruct the human hematopoietic microenvironment, improving the success rate of hematopoietic stem cell transplantation [25]. Graft-versus-host disease is the main factor causing hematopoietic stem cell transplantation-related mortality. Based on the above-mentioned properties, MSCs are used to treat autoimmune diseases and GvHD [25].

Patients with severe GvHD receive a number of immunosuppressive agents by the time the decision to administer MSCs is taken. Whether these drugs or antibodies may alter the response to MSCs remains largely unknown. On the other hand, the combined immunosuppression secondary to pharmacological agents and MSCs could in theory increase the risk of infections. In this regard, Ringden et al. [26] reported an increased incidence of opportunistic infections and virus-driven neoplasms in patients receiving MSCs and cyclosporin A simultaneously.

Mesenchymal stem cell infusions do not seem to be efficacious in prevention of GvHD. This was observed in a Phase I/II trial by Lazarus et al. [27]. This could be justified by the fact that MSCs require the presence of IFN-γ to exert their effects [28]. It would therefore appear that MSCs are only efficacious once the inflammatory reaction leading to GvHD has started.

Long-term Biological Safety of MSCs Remains Unknown

To date, the long-term safety of administering MSCs remains unknown, mainly because of the limited follow-up of existing

experiences. Areas of potential risk have been pointed out. Since most groups use the adherent properties to select MSCs, enzymes such as trypsin are required to detach cells from culture layers. Although exposure to trypsin is purposely reduced to a minimum to avoid the toxicity of this enzyme on MSCs, several passages are required to achieve a clinically effective cell dose. This multiplies the exposure to trypsin, which can have mutagenic effects. Whether there is a real risk for developing sarcomas in MSC recipients remains to be determined. Thus far, the clinical experience does not appear to support this possibility [29]. The introduction of 'cell factories' where MSCs are maintained in suspension by a continuous flow of culture media overcomes this problem. On the other hand, the potential of MSCs to undergo differentiation into bone or cartilage in abnormal sites is another concern that to date has not been reported in patients treated for GvHD. In addition, whether the infusion of MSCs may have an effect on the development of chronic GvHD, a somewhat mesenchymal disease, remains a matter of concern. Again, clinical experiences do not support this possibility. Still, even if any of these possibilities would become a real concern, the fact that patients had low or no possibilities of surviving to GvHD could counterbalance the drawbacks for using MSCs in this setting [30].

Pediatric Surgery

Despite the advancements that have been made in treating infants with congenital malformations, these still represent a major cause of disease and death during the first years of life and childhood. Regeneration of natural tissue from living cells to restore damaged tissues and organs is the main purpose of regenerative medicine [31]. This relatively new field has emerged by the combination of tissue engineering and stem cell transplantation as a possible strategy for the replacement of damaged organs or tissues [31]. Using autologous adipose tissue-derived MSCs to enhance wound healing is currently under experimental and clinical trials (personal communication, unpublished data).

Cardiovascular Disorders

Zeinaloo et al. [32] reported that intracoronary injection of autologous bone marrow-derived mesenchymal stem cells in a boy with progressive dilated cardiomyopathy is feasible and safe. Furthermore, it may positively influence functional class, quality of life, and echocardiographic indices of cardiac function. However, they did not comment on the long-term follow-up of the patients.

It is important to note that stem cells are not an alternative to heart transplantation; selected patients should be in an early stage of heart failure, as the goal of this regenerative approach is to avoid or delay organ transplantation. Since the cell niche provides crucial support needed for stem cell maintenance, the most interesting and realistic perspectives include the association of intra-myocardial cell transplantation with tissue-engineered scaffolds and multisite cardiac pacing in order to transform a passive regenerative approach into a 'dynamic cellular support', a promising method for the creation of 'bioartificial myocardium'.

In an experimental study performed in 2008 by Abdel Aziz et al. [33], MSCs were reported to improve myocardial contractility in diabetic rats.

Musculoskeletal Disorders

Current strategies for reconstructing bony defects are fraught with inadequacies [34] – cell-based therapies for skeletal regeneration may provide alternative solutions. Substantial work has identified a host of cellular sources that possess the potential for osteogenic differentiation. Significant efforts have been devoted toward characterizing the role of postnatal cellular sources that are relatively abundant and easily accessible. Among these, the potential of using adipose-derived stromal cells for skeletal regeneration has garnered much interest. Integral to these efforts directed at characterizing cellular sources are studies that seek to understand the factors that initiate and regulate osteogenic differentiation of progenitor cells. Specifically, focus has been directed at elucidating the role of bone morphogenetic protein and fibroblast growth factor signaling in regulating osteogenic differentiation of osteo-progenitor cells. Concurrent studies in the field of scaffold design have also helped to advance the potential for cell-based therapies [34].

Salvade et al. [35] reported that MSCs, seeded onto a scaffold and associated with platelet-gel, may represent an innovative treatment to improve bone repair. The purpose of their study was to validate a GMP-grade protocol of tissue engineering for bone regeneration, seeding platelet lysate (PL)-cultured MSCs onto hydroxyapatite clinical-grade scaffolds that were precoated with Retronectin before MSCs seeding. In this work, MSC expansions were performed comparing fetal bovine serum 10% and PL 5%. The study demonstrated that PL lots contain high levels of growth factors possibly responsible for the accelerated growth rate, since the number of colony-forming unit-fibroblast and population doublings were always significantly higher in PL cultures. Gene expression analysis revealed higher expression of typical osteogenic genes of PL-cultured MSCs when compared to fetal bovine serum MSCs. Cell transformation was excluded by analysis of karyotype, absence of growth without anchorage, and p53/c-myc gene expression. Their report offers a model of an MSC-based bioengineered device, using a hydroxyapatite clinical-grade scaffold, and supports its potential use in tissue engineering to repair bone defects.

Haleem et al. 2010 [36], used MSCs to repair traumatic ulcers in the articular cartilage of the knee joint. Autologous bone marrow-derived MSCs were seeded on a scaffold of platelet-rich fibrin glue and were placed in the defect after sealing it with a periosteal patch. The patients demonstrated a remarkable clinical and radiological improvement.

Autoimmune Diseases

Tragiai et al. [37] indicated that multipotent MSCs modulated T and B cell proliferation and differentiation, dendritic cell maturation, and natural killer activity. They studied the influence of bone marrow mesenchymal stem cells on highly purified B cell subsets isolated from healthy donors and total B cells from pediatric systemic lupus erythematosus patients. BM- MSCs promoted proliferation and differentiation into immunoglobulin-secreting cells of transitional and naive B cells stimulated with an agonist of Toll-like receptor 9, in the absence of B cell receptor triggering. They strongly enhanced proliferation and differentiation into plasma cells of memory B cell populations. A similar effect was observed

in response to polyclonal stimulation of B cells isolated from pediatric patients with systemic lupus erythematosus. This study poses important questions about BM-MSCs as a therapeutic tool in autoimmune diseases in which B-cell activation is crucially implicated in the pathogenesis of the disease [32].

Lung Diseases

Bonfield and Caplan 2010 [12] stated that Application of hMSCs in lung disease is a complex process with tissue communication, secretion of paracrine factors, and disease-specific outcomes. In conditions with a large amount of fibrotic disease, the hMSC activity would involve reversal of extracellular matrix deposition and collagen synthesis.

The genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) impact the entire body, causing progressive decrease in quality of life, and premature death. Although CF is an endocrine disorder, the main causes of morbidity and mortality are pulmonary insufficiency, deficient mucociliary clearance, and chronic infection with Pseudomonas aeruginosa [12].

Published studies [38,39] implicated the potential of using bone marrow transplantation as a method of attenuating the overt inflammatory response in the CF lung. Bonfield and Caplan [12] reported that bone marrow transplantation into CFTR-null animals significantly improved the response of mice chronically infected with Pseudomonas aeruginosa, ultimately improving clinical scores and lung pathology. Further, in preliminary unpublished observations, administration of adult hMSCs improved outcome measures and decreased inflammation in the same chronic model of infection and inflammation. These studies implicate the potential of cell-based therapy in CF.

Urinary Bladder Reconstruction

Atala [40] reported on the bioengineering of tissues for urogenital repair in children with hypospadias or bladder extrophy in which the bladder develops on the outer surface of the abdomen. Children with these conditions require immediate and multiple reconstructive surgeries. Currently, reconstruction is performed with native non-urologic tissues (skin, gastrointestinal segments, or mucosa), homologous tissues from a donor (cadaver or living donor kidney), heterologous tissues or substances (bovine collagen), or artificial materials (silicone, polyurethane, Teflon). However, these materials often lead to complications after reconstruction, either because the implanted tissue is rejected, or because inherently different functional parameters cause a mismatch in the system. The replacement of lost or deficient urologic tissues with functionally equivalent ones would improve the outcome of reconstructive surgery in the genitourinary system. This goal may soon be attainable with the use of tissue engineering techniques.

Zhu et al. [41] assessed the feasibility of seeding adipose-derived stem cells (ADSCs) onto bladder acellular matrix grafts (BAMGs) for bladder reconstruction in a rabbit model. They concluded that seeding ADSCs onto BAMGs promote regeneration of smooth muscle and nervous tissue regeneration. This compound graft was more suitable for bladder reconstruction than BAMG alone.

Atala [42], in a review of available current bladder reconstruction techniques, stated that tissue engineering techniques may be useful in the development of alternatives to current methods of bladder reconstruction. A number of animal studies and several clinical experiences show that it is possible to reconstruct the bladder using tissues and neo-organs produced in the laboratory. Current research suggests that the use of biomaterial-based, bladder-shaped scaffolds seeded with autologous urothelial and smooth muscle cells is currently the best option for bladder tissue engineering. Further research to develop novel biomaterials and cell sources would be beneficial, as well as information gained from developmental biology, signal transduction studies and studies of the wound healing response.

Treatment of Type 1 Diabetes

Type 1 diabetes is a major disease in children and adolescents. The World Health Organization (WHO) estimates that 220 million people suffer from diabetes worldwide, while approximately 3.4 million individuals died as a result of hyperglycemic complications in 2004 [43].

Administration of exogenous insulin is the fundamental means of treating hyperglycemia in type 1diabetes, but it does not restore the physiological regulation of blood glucose. Additionally, patients with poorly controlled type 2 diabetes are increasingly being prescribed insulin therapy, with studies suggesting that intensive insulin therapy, even in newly diagnosed type 2 diabetes, can improve beta-cell survival and function compared with oral hypoglycemic agents [44]. However, tight glycemic control, with its inherent risk of hypoglycemia, is required to prevent many of the long-term complications of diabetes, including cardiovascular disorders, nephropathies, and diabetic retinopathy. WHO figures show that 50% of people with diabetes die of cardiovascular disease, while kidney failure accounts for 10–20% of deaths. Given these shortcomings, recent research has been directed towards establishing cellular-based therapies that avoid the need for exogenous insulin delivery by conventional injection or more modern pump technology [45].

Although this review deals with MSCs, we cannot overlook the trials to treat this disease using stem cell therapy. All the available studies used hematopoietic rather than MSCs for treatment of type 1 diabetes.

In 2007, Voltarelli et al. [46] reported on the effects of the autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) in 15 patients with type 1 diabetes mellitus (DM). Most patients became insulin-free with normal levels of glycated hemoglobin A1c (HbA1c) during a mean 18.8-month follow-up. To investigate if this effect was due to preservation of beta-cell mass, in 2009, Couri et al. [47] continued the monitoring of C-peptide levels after stem cell transplantation in the 15 original and 8 additional patients. The patients were followed for a period of 7–58 months. Twenty patients without previous ketoacidosis and not receiving corticosteroids during the preparative regimen became insulin-free. Twelve patients maintained this status for a mean of 31 months (range, 14–52 months) and 8 patients relapsed and resumed insulin use at low dose (0.1–0.3 I U/kg). In the continuous insulin-independent group, HbA1c levels were less than 7.0% and

mean (SE) area under the curve (AUC) of C-peptide levels increased significantly. In the transient insulin-independent group, mean (SE) AUC of C-peptide levels also increased, which was sustained at 48 months. In this group, 2 patients regained insulin independence after treatment with sitagliptin, which was associated with increase in C-peptide levels. Two patients developed bilateral nosocomial pneumonia, 3 patients developed late endocrine dysfunction, and 9 patients developed oligospermia. There was no mortality. They concluded that after a mean follow-up of 29.8 months following autologous nonmyeloablative HSCT in patients with newly diagnosed type 1 DM, C-peptide levels increased significantly and the majority of patients achieved insulin independence with good glycemic control.

Translation of Mesenchymal Stem Cell Therapy to Clinical Applications

The issues related to translating MSCs from animal models into the clinical setting include standardization of methods to define MSC classification, isolation, efficacy, and potency, which are required for consistency in clinical trials [13,48]. Different preparations and, indeed, different donors have different biological impacts based upon the *in vivo* model and the potency of the preparations. A standardization of protocols and classifications needs to be accomplished prior to understanding both the potency and efficacy of MSC preparations. The heterogeneity in hMSC effectiveness is also clouded by the potential variation in the tissue sources for MSCs, which can also impact efficacy and potency *in vivo*. Currently there are no *in vivo* efficacy models to measure MSC "bioactivity. Since mechanistically it is unknown whether the hMSCs act directly or through the orchestration of the immune response, attention must be focused on the endpoints and markers of evaluation. This will also impact the success of the studies, since different models have, at their respective centers, different pathological processes. Finally, developments in imaging technology capable of tracking hMSCs post-administration will help in delineating function and site of action in the context of the lung disease.

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