

## Editorial

# Cell-Based Therapy for Lung Diseases: Past, Present and Future

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Numerous lung diseases have high morbidity and mortality rates and there are no cures or treatments apart from lung transplantation. In United States, respiratory diseases kill more than 400,000 individuals each year and significantly reduce quality of life for millions more not only impacting the patient but all the members of the family. The National Institute of Health estimated that in 2009 the annual cost of providing healthcare related to all respiratory conditions, excluding lung cancer, was \$113 billion [1]. These choices are unacceptable for the society and the patients, so responding to the desperate need for new therapies, research has turned toward stem cells and the ways by which they can be used to treat pulmonary diseases. Cell-based therapies are currently an area of intense research, and preliminary data generated by many groups, including ours, foreseeing the translation of successful pre-clinical studies into therapies were we expect them to be not only effective for multiple lung diseases but also safe to the patients.

Our group has extensive experience on bone marrow derived mesenchymal stem cells. Bone marrow derived stem cells can be divided in two groups: hematopoietic stem cells (HSC) and mesenchymal stromal stem cells (MSC). HSC have been the most successful form of cell therapy, transplant of whole bone marrow or HSC have been used in clinic since the 50s and 60s for the repopulation of the different cell types present in the blood [2-6]. Bone marrow derived mesenchymal stromal cells (B-MSCs) were first described in the early 1970s by Friedenstein and collaborators [7-10], as clonal, plastic adherent cells capable of differentiating into cells of mesenchymal origin. *In vivo*, these cells are also required to support hematopoiesis providing extracellular matrix, cytokines, and growth factors to the HSC [11-13].

Characterization, isolation and study of the basic biology of B-MSCs has been a complicated issue since there are no specific cell surface marker that can be used to not only isolate the cells but also demonstrate, *in vivo*, their biological activity. All the therapeutic properties have been demonstrated for B-MSC are after *in vitro* isolation and expansion and subsequent infusion. Enrichment of B-MSCs from bone marrow suspensions can

be achieved by selecting a plastic-adherent population that expresses neither hematopoietic nor endothelial cell surface markers but is positive for the expression of stromal markers [14]. The criterion for establishing B-MSC phenotype is to use adherent cells that (i) express CD44, CD73, CD90 and CD105, (ii) lack the expression of hematopoietic markers like CD45, CD34 and CD31 and finally (iii) a multilineage differentiation assay to confirm their plasticity by the ability of the cells to differentiate into adipocytes, osteocytes, and chondrocytes [15-17].

Lung diseases can be divided into two groups: acute and chronic. Cell based therapy with B-MSCs have been demonstrated to be effective preventing the progression and inducing lung repair in both groups.

Acute lung injury or acute respiratory distress syndrome (ARDS) is a common complication in the intensive care unit. Even though extensive research has been done in the last years, the ARDS mortality rate still stands as high as 40% [18], and the only current treatments are supportive and include lung-protective ventilation together with a fluid conservative strategy. Since the publication of our original work in 2007 [19] we defined the beneficial effects of the systemic administration of B-MSC to control ARDS mainly by their anti-inflammatory properties. Multiple groups have obtained similar observations where the protective effect has been demonstrated in different animal models of ARDS and human *ex-vivo* lungs [20-25].

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease characterized by deposition of collagen resulting in scarring of the lung [26,27]. The current most accepted animal model of pulmonary fibrosis consists in the intratracheal instillation of bleomycin an anticancer agent commonly used in the treatment of Hodgkin's lymphoma and testicular cancer [28-30] which has a secondary effect of pulmonary fibrosis. Since the work published by Ortiz and subsequently by our group [31,32], we demonstrated that B-MSC infusion caused a decrease in the deposition of lung matrix metalloproteinase and lung collagen. Interestingly, B-MSCs effect was found to be insufficient when cells were infused late at 7 days after bleomycin challenge, highlighting the variety of factors that interact to play a role in B-MSC-based therapy.

For a better understanding of the protective abilities of B-MSCs and by which mechanisms they operate, our group administered bleomycin to myelosuppressed mice and to mice with normal, intact bone marrow. A subgroup of mice within each group received an additional infusion of (GFP)-positive MSCs 6 hours after bleomycin treatment. MSC infusion proved to confer a significant survival benefit in myelosuppressed bleomycin-treated mice from 80% mortality to 0%.

There is recent report on the safety of the use of B-MSC on chronic obstructive pulmonary disease or COPD, in which the authors were able to demonstrate the safety on the intravenous injection of B-MSC on this group of patients. Because the study was not designed to evaluate efficacy, we do not know if B-MSCs have a beneficial effect on COPD [33].

Finally, for patients with end-stage pulmonary disease where treating the disease is no longer viable, transplantation is the only feasible option. Transplants carry great risks and one of the major complications is the development of obliterative bronchiolitis (OB), accounting for almost 50% of the mortality of lung recipients within five years of transplantation [34]. Cellular therapy to treat OB has been promising in some animal studies. We recently demonstrated that in a murine model of heterotopic tracheal transplantation that systemic administration of B-MSCs inhibits inflammation and fibrosis, preventing the occlusion of the transplanted tracheas [35], demonstrating the viability of cell therapy options in attenuating the morbid complications of lung transplants.

The protective effects of B-MSCs are attributed to several mechanisms including secretion of anti-inflammatory cytokines IL-10 and TGF- $\alpha$ , KGF, mitochondrial transfer, elaboration of antibacterial peptides and more recently by transfer of micro RNAs inducing macrophage activation [36-39]. Additionally, it has been demonstrated that B-MSCs reduced mortality and organ injury when delivered systemically in a model of bacteremia and septic shock due to B-MSCs enhanced bacterial clearance consequent to increased phagocytosis of host immune cells [40]. As a result of these most recent studies, B-MSCs are increasingly recognized for having complex interactions with the host immune system and share properties with cells of the innate immune system. Given the pleiotropic mechanisms and their potential as therapy of multiple lung diseases, there is a considerable interest in initiating translational studies for the use of B-MSC in the pulmonary field.

Our group believes that in the next few years, to develop an effective cell-based therapy in the lung —with B-MSCs in particular- our research will need to focus on mechanism that can affect B-MSC function. In our experience, the two most important facts are on effect of aging on B-MSCs function and the novel posttranscriptional mechanisms driving regulation of the gene expression as microRNA, RNAlinks and DNA methylation. Little is known about the consequences that these different elements can have on the B-MSC function, questions like, are these elements synergistic or totally independent? Can they explain the age differences of the incidence of different lung diseases? All of these are questions that remain unanswered. Understanding their role on B-MSCs function can help enhance their activity by selecting the most appropriate type of cells to be use in an eventual cell

therapy.

In summary, it is our strong believe that the use of cell-based therapy, and specifically non-hematopoietic stem cells, is going to be real alternative to treat multiple lung diseases and since B-MSCs have such a high therapeutic potential that can be navigated in different ways, it is imperative to focus on each and every therapeutic aspect that B-MSCs can hold, including appropriate cell type and clinical trials to determine their safety in distinct types of patients.

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