Published in final edited form as:
Curr Opin Pharmacol. 2009 June ; 9(3): 268–273. doi:10.1016/j.coph.2009.03.002.

Cell Therapy Approaches for Lung Diseases: Current Status

Viranuj Sueblinvong, MD[1] and **Daniel J. Weiss, M.D., PhD**[2]

[1]Division of Pulmonary, Critical Care and Allergy, Department of Medicine, Emory University, Atlanta, GA

[2]Division of Pulmonary, Critical Care and Allergy, Department of Medicine, University of Vermont, Burlington, VT

Summary and recent advances

Recent findings suggest that embryonic stem cells and stem cells derived from adult tissues, including bone marrow and umbilical cord blood, could be utilized in repair and regeneration of injured or diseased lungs. This is an exciting and rapidly moving field that holds promise as a therapeutic approach for variety of lung diseases. Although initial emphasis was on engraftment of stem cells in lung, more, recent studies demonstrate that mesenchymal stem cells (MSCs) can modulate local inflammatory and immune responses in mouse lung disease models including acute lung injury and pulmonary fibrosis. Further, based on initial reports of safety and efficacy following allogeneic administration of MSCs to patients with Crohn's disease or with graft-versus-host disease, a recent trial has been initiated to study the effect of MSCs in patients with chronic obstructive pulmonary disease. Notably, several recent clinical trials have demonstrated potential benefit of autologous stem cell administration in patient with pulmonary hypertension. In this review, we will describe recent advances in cell therapy with the focus on MSCs and their potential roles in lung development and repair.

Keywords

Mesenchymal Stem Cells; Lung; Cell Therapy; Tissue Bioengineering

Introduction

Over the past decade, a number of reports have suggested that both embryonic and adult tissue-derived stem cells can participate in the regeneration and repair of diseased adult organs including the lungs (1**). These findings present an exciting potential therapeutic

Daniel J. Weiss, MD, PhD (Corresponding author and reprints): University of Vermont College of Medicine, 149 Beaumont Ave, HSRF 226, Burlington, Vermont 05405, Phone: (802) 656-8925, Fax: (802) 656-8926, dweiss@uvm.edu.
Address: Viranuj Sueblinvong, MD Whitehead Biomedical Research Building, 615 Michael Street, NE, Suite 205, Atlanta, GA 30322, vsuebli@emory.edu

approach for a variety of lung diseases particularly as investigations of stem cells and cell therapies in lung biology and diseases have continued to expand.

However, the field has undergone some changes in emphasis. While both embryonic and adult stem cells can be induced *in vitro* to express phenotypic markers of airway and/or alveolar epithelial cells, engraftment of airway or alveolar epithelium by stem or progenitor cells following systemic administration is rare and of unclear physiologic or therapeutic significance (1–3). Structural repair or replacement of injured lung epithelial cells by administering exogenous stem cells is now felt to be less likely. In contrast, engraftment of pulmonary vascular endothelium by autologous bone marrow-derived endothelial progenitor cells and stimulation of neoangiogenesis has been the basis of recent clinical trials of EPCs for pulmonary hypertension (4–7*). These initial trials have suggested improvement in both clinical measures of pulmonary hypertension as well as in cardiopulmonary physiologic variables in both adult and pediatric patients. Although, only short term assessments have been made and the number of patients studied relatively small, these are encouraging studies that are being followed up with larger longer term studies. Importantly, no significant adverse effects have been reported.

More recently, focus has been on exploration of 3-dimensional culture systems and bioengineering approaches to generate functional lung tissue *ex vivo* and *in vivo* (8**, 9*). Further, MSCs have been demonstrated to have an immunomodulatory effect as demonstrated by suppression of inflammation in murine models of lung injury (10, 11). These studies have been the basis of a recently initiated trial of allogeneic MSC administration in patients with chronic obstructive pulmonary disease.

Structural Engraftment and Functional Effects of Exogenous Stem or Progenitor Cells

Over the past decade, a number of publications have suggested that a variety of bone marrow-derived cells including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), multipotent adult progenitor cells (MAPC), and other populations could structurally engraft as mature differentiated airway and alveolar epithelial cells (2*, 3, 12). However, this is now felt to be a rare occurrence which raises the question whether functional epithelial engraftment does in fact occur (1**, 13). Nonetheless, recent studies have confirmed that engraftment of donor-derived airway and/or alveolar epithelium, although rare, can occur following perturbation of airway or alveolar epithelium in lung injury models. Engraftment by MSCs of bone marrow or cord blood origin (2*), side population cells (14*), plastic adherent marrow stromal cells (3, 15) or full marrow transplantation following a myeloablative regimen (16, 17) in lung tissues usually occurs following lung injury. Further, recent studies demonstrate that chronic or progressive lung injury may result in more substantial engraftment of type 2 alveolar epithelial cells and of interstitial and pulmonary vascular cells with donor-derived cells in mouse or rat models (16, 18).

One major focus is how engraftment of airway or alveolar epithelium with exogenous cells can be improved. There are many variables still left to be explored that may increase

epithelial, interstitial, or pulmonary vascular engraftment with circulating or donor-derived cells. These include (i) route of cell administration i.e. intratracheal (19) vs systemic administration (19). (ii) the type of cells used i.e. CD45+/CXCR4+/cytokeratin+ cells (20), (iii) other sources of stem or progenitor cells i.e. adipose tissues, placenta. Further, the mechanisms of airway epithelial cell engraftment by exogenously administered stem cells are not well elucidated. Both *in vitro* and *in vivo* studies suggest that fusion might play a role (21*, 22). However, other mechanisms might be involved. Further, the mechanisms by which stem or progenitor cells might be induced to acquire the phenotype of lung epithelial cells remain poorly understood. *In vitro* studies continue to demonstrate that soluble factors released from lung epithelial cells or from injured lung homogenates can induce expression of lung epithelial markers in several types of marrow-derived cells, possibly through activation of β-catenin signaling pathways (23). One novel mechanism of inducing phenotypic change might involve release of membrane-derived microvesicles, a recently appreciated means of inter-cellular communication that involves horizontal transfer of mRNA and proteins between cells (24*, 25).

Importantly, mechanisms by which circulating or systemically administered stem or progenitor cells might be recruited to lung remain poorly understood. Following systemic administration, many cells initially localize in lung and injury results in increased localization and/or retention of marrow-derived cells in lung (26–28). The timing of cell administration after lung injury can also influence recruitment and phenotypic conversion of donor-derived cells. Systemic administration of MSCs 4 hours after lung irradiation resulted in apparent engraftment of cells as epithelial and vascular endothelial cell (28) while administration of cells at the later time points resulted in MSC engraftment as interstitial cells and participation in development of fibrosis (28, 29). Recipient immune responses also play significant yet poorly characterized roles in retention of cells in lung (30). The range and identity of chemotactic soluble mediators released by injured lung cells and the role of up-regulation of adhesion molecules with which circulating cells might interact remains poorly understood (1**, 31). As with engraftment, a number of factors including age of donor or recipient, type of cell administered, route of administration, etc all might affect recruitment to lung.

Lung Tissue Bioengineering

One growing area of investigation is that utilizing three-dimensional matrices or other artificial scaffolding for growth of functional lung tissue from stem cells *ex vivo* and *in vivo*. These approaches have been increasingly successfully utilized in regeneration of other tissues including skin, vasculature, cartilage, and bone. Notably, MSCs isolated from amniotic fluid, umbilical cord blood, adipose tissues or bone marrow can be seeded on biodegradable polyglycolic acid or other biosynthetic scaffolds and generate tracheal cartilage for use in repair of congenital tracheal defects and also tendon tissue for use in congenital diaphragmatic defects (32, 33). Studies in animal models and a recent clinical investigation suggest safety and efficacy and clinical trials in neonates with congenital tracheal or diaphragmatic defects are planned (32–34). Most recently these approaches have resulted in successful clinical use of a bioengineered trachea (35).

Given the complex three-dimensional architecture of the lung, engineering functional lung parenchyma *ex vivo* is a daunting task. However, both *in vitro* and *in vivo* studies utilizing mixed fetal lung cells cultured in a three dimensional glycosaminoglycan (GAG) or other type of scaffolds resulted in formation of alveolar-like structures in the scaffold (9*, 36). Notably, stimulation of murine fetal lung cells in polymer scaffolds with different isoforms of fibroblast growth factor resulted in different patterns of development demonstrating the power of three-dimensional culture systems to evaluate lung development and repair (37). *In vivo*, a recent study demonstrated that fetal rat lung cells cultured in a biodegradable gelatin sponge, and subsequently injected into normal rat lungs, induced formation of branching, sacculated epithelial structures reminiscent of lung parenchymal architecture (36). Mixed fetal murine epithelial cells admixed with Matrigel and injected subcutaneously into the abdominal wall of adult mice demonstrated cells that expressed pro-surfactant protein C after 1 week (38). These studies demonstrate the potential of *in vivo* lung tissue generation utilizing mixed populations of fetal lung cells. However, this is not a practical approach and lung tissue engineering with stem or progenitor cells is a more feasible potential therapeutic option. Further, there are few studies as yet evaluating whether stem or progenitor cells isolated from adult bone marrow, cord blood, or other sources can also comparably form airway or alveolar-like structures when cultivated in a three-dimensional matrix or other scaffolding material and whether stem or progenitor cells cultured in such fashion can be utilized for functional lung regeneration *in vivo*. A population of cells described as adult lung somatic progenitor cells isolated from adult sheep lungs cultured in synthetic polymer constructs resulted in expression of airway and alveolar epithelial markers by the cells (39). Structures resembling lung airways and parenchyma developed when impregnated constructs were implanted subcutaneously in nude mice or inserted into the wound cavity following wedge lung resection in sheep. Adipose-derived MSCs, cultured *ex vivo* in sheets of polyglycolic acid and then applied to wound edges following lung volume reduction surgery in rats, accelerated alveolar and vascular regeneration (40). Further studies to understand the role of three-dimensional scaffold on stem cell differentiation and cell fate will be important.

Immunomodulatory Property of MSCs

The ability to structurally engraft in adult lung may not be the only potentially relevant property of exogenously administered stem or progenitor cells. For example, MSCs have been shown to differentiate into a wide range of cell types and to produce a number of growth factors and cytokines that are important for tissue repair and remodelling. Further, MSCs express intermediate to low levels of HLA class I, low levels of HLA class II , and low levels of co-stimulatory molecules allowing the MSCs to escape alloreactive recognition (41**). Moreover, MSCs suppress allogeneic T-cell proliferation and do not elicit an immune response after transplantation in immunocompetent recipients (42). These properties result in modulation of the immune response by MSCs and have been the basis for clinical trials of allogeneic MSC administration to patients with several inflammatory and immune-mediated diseases including Crohn’s and graft-versus-host disease (43–45). The mechanisms of MSCs actions on inflammatory and immune cells are not well

understood but likely involve both secretions of soluble mediators as well as cell-cell contact.

In mouse models of lung disease, systemic administration of MSCs immediately after intratracheal bleomycin administration decreased subsequent lung collagen accumulation, fibrosis, and levels of matrix metalloproteinases (1**). Only minimal putative engraftment of the MSCs as lung epithelial cells was observed and secretion of IL-1 receptor antagonist by the MSCs has been hypothesized to account for at least some of these effects (46*). Intratracheal administration of MSCs 4 hrs after intratracheal endotoxin administration decreased mortality, tissue inflammation, and concentration of pro-inflammatory mediators, such as TNFα and MIP-1β, in bronchoalveolar lavage fluid compared to endotoxin-only treated mice (19). Systemic MSCs administration also decreased lung inflammation following endotoxin administration in mice and co-culture of MSC with lung cells obtained from LPS-treated mice resulted in decreased pro-inflammatory cytokine release from the lung cells (19, 47). More recent data suggests that release of angiopoietin-1 by the MSCs and stabilization of alveolar-capillary permeability and endothelial fluid leak in the setting of endotoxin effects on the alveolar capillary barrier may be a relevant mechanism (48, 49). These results suggest potent actions of MSCs in lung but there is still much to be learned.

Preclinical and Clinical Uses of MSCs

Currently, there are a total of 67 clinical trials on the use of both autologous and allogeneic MSCs for variety of diseases including Crohn's disease, multiple sclerosis, end-stage liver diseases, as a prevention for graft-versus-host-disease following transplantation, for patients with ventricular dysfunction, refractory systemic lupus erythematosus, diabetes mellitus, and most recently for chronic obstructive pulmonary disease (COPD) (50**). A phase I trial of a commercial MSC preparation, Prochymal™ (Osiris Therapeutics Inc, Columbia MD), has been completed in steroid resistant GVHD in 46 patients. There were no drug related serious adverse events (SAEs) and over the two year study there was a reduction in observed mortality from 45 to 22% (51). Based on this data, a phase II trial was initiated in 32 patients with acute GVHD, which has shown a 90% response rate (partial and complete responses) (44). A phase 3 clinical trial is currently underway (52). A comparable phase II open label trial utilizing Prochymal™ has recently been completed for patients with moderate to severe Crohn's disease who had previously failed treatment with steroids, infliximab and other immunosuppressive agents. Every patient evaluated reported an improvement of symptoms as indicated by a reduction of Crohn's Disease Activity Index (CDAI) by day 28 after the infusion with an average improvement of CDAI of 62 points by day 7 (52). One-third of the patients achieved clinical remission of the disease based on reported Inflammatory Bowel Disease Questionnaire (IBDQ) scores of at least 170 points (52). Further, no significant SAE's were observed (52). Currently, Prochymal™ is approved by FDA to advance into a phase III double-blind placebo-controlled trial for the treatment of Crohn's Disease (43). Future studies are being designed to determine optimal dose, dosing frequency, and durability of response, suitability of biomarkers as surrogate outcome measures, and effects on mucosal healing, as well as long-term safety.

Most recently, a multicenter double-blinded placebo control Phase II trial of allogeneic MSC infusions utilizing PROCHYMAL™ for patients with moderate-severe chronic obstructive pulmonary disease (COPD) (FEV1/FVC <0.70, 30% ≤ FEV1 ≤ 70%) was initiated in May 2008 (45). This trial parallels comparable trials utilizing allogeneic MSC infusion for graft-versus-host disease and for Crohn's disease. It is based on the hypothesis that anti-inflammatory actions of MSCs will decrease pulmonary and perhaps systemic inflammation associated with COPD and improve lung function, dyspnea, and quality of life. Engraftment and/or regeneration of destroyed lung tissue is not hypothesized to be a significant potential mechanism of MSC action in this trial. Primary efficacy endpoint assessments include pulmonary function testing, and health related quality of life assessments. Safety assessments further include monitoring of blood counts, electrolytes, liver function tests, urinalyses, physician global assessments, time to hospitalization and hospitalization rates, time to COPD exacerbation and COPD exacerbation rates, use of rescue inhalers, and assessment of pulmonary hypertension by echocardiography. Safety endpoints also include monitoring of adverse events, toxicity, and overall survival and survival time.

Conclusion

A continuing accumulation of data in both animal models and in clinical trials suggests that cell based therapies may be potential therapeutic strategies for lung repair and remodeling after injury. In parallel, further understanding of the role of endogenous lung progenitor cells will provide further insight into mechanisms of lung development and repair after injury and may also provide novel therapeutic strategies. It is hoped that new research programs will provide further understanding of mechanisms of repair of lung injury and further provide a sound scientific basis for therapeutic use of stem and cell therapies in lung diseases.

References

* Of special interest

** Of outstanding interest

1**. Weiss DJ, Kolls JK, Ortiz LA, Panoskaltsis-Mortari A, Prockop DJ. Stem cells and cell therapies in lung biology and lung diseases. Proc Am Thorac Soc. 2008; 5:637–667. This article by Weiss et al is a comprehensive summary of a conference entitled "Stem Cells and Cell Therapies in Lung Biology and Lung Diseases" with extensive review of recent literature related to cell therapy for lung diseases. This includes the current status of structure engraftment by exogenous stem cells, new development related to lung tissue engineering and the immunomodulation role of mesenchymal stem cells in lung injury. We would recommend this article as an overview review of current status of cell therapy for lung diseases field. [PubMed: 18625757]

2*. Sueblinvong V, Loi R, Eisenhauer PL, Bernstein IM, Suratt BT, Spees JL, Weiss DJ. Derivation of lung epithelium from human cord blood-derived mesenchymal stem cells. Am J Respir Crit Care Med. 2008; 177:701–711. This article by Sueblinvong et al reported the use of cord blood as a source of mesenchymal stem cells. The authors reported approximately 39% of human cord blood sample yield mesenchymal stem cells (MSC). After characterization, they subsequently injected stem cells into NOD/SCID mice following low dose irradiation. They reported small number of human derived-airway epithelial cells up to 3 months following the injection. This study demonstrated that MSCs obtained from human umbilical cord blood can engraft NOD/SCID mice airway following low dose irradiation. However, the yield of engraftment is not significantly better than that achieved with bone marrow-derived MSCs. Although this study did

not showed benefit of MSCs derived from cord blood over bone marrow cells, this is a well designed study. [PubMed: 18063840]

3. Loi R, Beckett T, Goncz KK, Suratt BT, Weiss DJ. Limited restoration of cystic fibrosis lung epithelium in vivo with adult bone marrow-derived cells. Am J Respir Crit Care Med. 2006; 173:171–179. [PubMed: 16179642]

4*. Marsboom G, Janssens S. Endothelial progenitor cells: New perspectives and applications in cardiovascular therapies. Expert Rev Cardiovasc Ther. 2008; 6:687–701. This article by Marsboom et al reviewed literature over the past 10 years on endothelial progenitor cells (EPC) and their role in cardiovascular diseases. The field of EPCs has advanced rapidly and now, although limited, there are clinical trials underway including pilot trial in patients with pulmonary hypertension. This is an excellent review on EPCs and related translational research. [PubMed: 18510485]

5. Fadini GP, Schiavon M, Rea F, Avogaro A, Agostini C. Depletion of endothelial progenitor cells may link pulmonary fibrosis and pulmonary hypertension. Am J Respir Crit Care Med. 2007; 176:724–725. author reply 725. [PubMed: 17881591]

6. Wang XX, Zhang FR, Shang YP, Zhu JH, Xie XD, Tao QM, Chen JZ. Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension: A pilot randomized controlled trial. J Am Coll Cardiol. 2007; 49:1566–1571. [PubMed: 17418297]

7*. Zhu JH, Wang XX, Zhang FR, Shang YP, Tao QM, Chen JZ. Safety and efficacy of autologous endothelial progenitor cells transplantation in children with idiopathic pulmonary arterial hypertension: Open-label pilot study. Pediatr Transplant. 2008; 12:650–655. This article by Zhu JH et al is done to look at the safety and efficacy of autologous endothelial progenitor cells (EPC) transplantation in children with idiopathic pulmonary arterial hypertension (IPAH). This group from China previously reported potential benefit of autologous EPC transplantation in adult with IPAH (see reference 6). This study was performed with 13 children with IPAH receiving intravenous infusion of autologous EPC and found an improvement in functional class based on NYHA classification, 6-minute walk distance, mean pulmonary artery pressure and cardiac output at 12 weeks. This is an interesting study however, longer follow up time to assess for potential side effects would be required. Further, a larger multi-center trial to establish the efficacy would be important. [PubMed: 18466198]

8**. Nichols JE, Cortiella J. Engineering of a complex organ: Progress toward development of a tissue-engineered lung. Proc Am Thorac Soc. 2008; 5:723–730. This is an excellent review article by Nichols et al on the rapid advancing field of lung tissue engineering. This article reviewed the overall tissue engineering with in depth discussion on issues pertain to complexity of the lung. It is a well structured and concise review of current status of this field. [PubMed: 18684725]

9*. Tomei AA, Boschetti F, Gervaso F, Swartz MA. 3d collagen cultures under well defined dynamic strain: A novel strain device with a porous elastomeric support. Biotechnol Bioeng. 2008 Tomei AA et al presented a unique composite matrix and strain device for culturing cells in physiological, mechanically dynamic 3-dimension environment using engineered polyurethane sponge computerized strain device. Over the past few decades, it is well accepted that dynamic stresses and strains have an impact on cells and tissues organization. This study reported a potential device to be use in combination of stem cells for potential tissue engineering of the lung.

10. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nat Rev Immunol. 2008

11. Iyer SS, Rojas M. Anti-inflammatory effects of mesenchymal stem cells: Novel concept for future therapies. Expert Opin Biol Ther. 2008; 8:569–581. [PubMed: 18407762]

12. Aliotta JM, Passero M, Meharg J, Klinger J, Dooner MS, Pimentel J, Quesenberry PJ. Stem cells and pulmonary metamorphosis: New concepts in repair and regeneration. J Cell Physiol. 2005; 204:725–741. [PubMed: 15744751]

13. Kotton DN, Fabian AJ, Mulligan RC. Failure of bone marrow to reconstitute lung epithelium. Am J Respir Cell Mol Biol. 2005; 33:328–334. [PubMed: 15961722]

14*. Macpherson H, Keir P, Webb S, Samuel K, Boyle S, Bickmore W, Forrester L, Dorin J. Bone marrow-derived SP cells can contribute to the respiratory tract of mice in vivo. J Cell Sci. 2005; 118:2441–2450. It has been shown that bone marrow-derived cells could contribute to cell of other organs including lung. This study by Macpherson et al further defined the specific bone marrow cell populations called side population (SP). They demonstrated increased survival among lethally irradiated mice receiving systemic injection of these cells. They found only 0.8% of tracheal epithelial cells are donor in origin. Although, they did not find an increase in donor-derived cells engrafted in recipient airways as compared to other studies using bone marrow-derived mesenchymal stem cells (MSC) or stromal cells, this study showed that SP might also have the same immunomodulatory effect as MSC as demonstrated by improvement in mortality in lethally irradiated mice received cells. [PubMed: 15923657]

15. Rojas M, Xu J, Woods CR, Mora AL, Spears W, Roman J, Brigham KL. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. Am J Respir Cell Mol Biol. 2005; 33:145–152. [PubMed: 15891110]

16. Spees JL, Pociask DA, Sullivan DE, Whitney MJ, Lasky JA, Prockop DJ, Brody AR. Engraftment of bone marrow progenitor cells in a rat model of asbestos-induced pulmonary fibrosis. Am J Respir Crit Care Med. 2007; 176:385–394. [PubMed: 17496228]

17. Spees JL, Whitney MJ, Sullivan DE, Lasky JA, Laboy M, Ylostalo J, Prockop DJ. Bone marrow progenitor cells contribute to repair and remodeling of the lung and heart in a rat model of progressive pulmonary hypertension. FASEB J. 2008; 22:1226–1236. [PubMed: 18032636]

18. Yan C, Lian X, Dai Y, Wang X, Qu P, White A, Qin Y, Du H. Gene delivery by the hsp-b promoter to lung alveolar type ii epithelial cells in lal-knockout mice through bone marrow mesenchymal stem cells. Gene Ther. 2007; 14:1461–1470. [PubMed: 17700706]

19. Gupta N, Su X, Popov B, Lee JW, Serikov V, Matthay MA. Intrapulmonary delivery of bone marrow–derived mesenchymal stem cells improves survival and attenuates endotoxin-induced acute lung injury in mice. J Immunol. 2007; 179:1855–1863. [PubMed: 17641052]

20. Hackett TL, Shaheen F, Johnson A, Wadsworth S, Pechkovsky DV, Jacoby DB, Kicic A, Stick SM, Knight DA. Characterization of side population cells from human airway epithelium. Stem Cells. 2008; 26:2576–2585. [PubMed: 18653771]

21*. Herzog EL, Krause DS. Engraftment of marrow-derived epithelial cells: The role of fusion. Proc Am Thorac Soc. 2006; 3:691–695. This is one of the studies which identify fusion as a potential mechanism in which stem cells engrafted and differentiate into airway epithelial cells. [PubMed: 17065375]

22. Spees JL, Olson SD, Ylostalo J, Lynch PJ, Smith J, Perry A, Peister A, Wang MY, Prockop DJ. Differentiation, cell fusion, and nuclear fusion during ex vivo repair of epithelium by human adult stem cells from bone marrow stroma. Proc Natl Acad Sci U S A. 2003; 100:2397–2402. [PubMed: 12606728]

23. Zhang Y, Goss AM, Cohen ED, Kadzik R, Lepore JJ, Muthukumaraswamy K, Yang J, DeMayo FJ, Whitsett JA, Parmacek MS, et al. A gata6-wnt pathway required for epithelial stem cell development and airway regeneration. Nat Genet. 2008; 40:862–870. [PubMed: 18536717]

24*. Aliotta JM, Sanchez-Guijo FM, Dooner GJ, Johnson KW, Dooner MS, Greer KA, Greer D, Pimentel J, Kolankiewicz LM, Puente N, et al. Alteration of marrow cell gene expression, protein production, and engraftment into lung by lung-derived microvesicles: A novel mechanism for phenotype modulation. Stem Cells. 2007; 25:2245–2256. It has been observed that mesenchymal stem cell (MSC) can differentiate into lung epithelial cells in co-culture system and when cultured in lung-conditioned medium (LCM). Aliotta JM et al found that LCM contained pulmonary epithelial cell-specific RNA-filled microvesicles which influenced MSC differentiation suggesting a possible mechanism in which stem cells lung phenotypic differentiation. Although other mechanisms by which stem cells could differentiate into cell of other organ tissues including fusion (see reference no. 21 and 22), this study reported a novel concept of microvesicles for RNA transfer between mature cells and stem cells. [PubMed: 17556595]

25. Quesenberry PJ, Aliotta JM. The paradoxical dynamism of marrow stem cells: Considerations of stem cells, niches, and microvesicles. Stem Cell Rev. 2008; 4:137–147. [PubMed: 18665337]

26. Kahler CM, Wechselberger J, Hilbe W, Gschwendtner A, Colleselli D, Niederegger H, Boneberg EM, Spizzo G, Wendel A, Gunsilius E, et al. Peripheral infusion of rat bone marrow derived endothelial progenitor cells leads to homing in acute lung injury. Respir Res. 2007; 8:50. [PubMed: 17620112]

27. Suzuki H, Hogg JC, van Eeden SF. Sequestration and homing of bone marrow-derived lineage negative progenitor cells in the lung during pneumococcal pneumonia. Respir Res. 2008; 9:25. [PubMed: 18315863]

28. Yan X, Liu Y, Han Q, Jia M, Liao L, Qi M, Zhao RC. Injured microenvironment directly guides the differentiation of engrafted flk−1(+) mesenchymal stem cell in lung. Exp Hematol. 2007; 35:1466–1475. [PubMed: 17637496]

29. Epperly MW, Franicola D, Zhang X, Nie S, Wang H, Bahnson AB, Shields DS, Goff JP, Shen H, Greenberger JS. Reduced irradiation pulmonary fibrosis and stromal cell migration in smad3-/- marrow chimeric mice. In Vivo. 2006; 20:573–582. [PubMed: 17091762]

30. Rossignol J, Boyer C, Thinard R, Remy S, Dugast AS, Dubayle D, Dey ND, Boeffard F, Delecrin J, Heymann D, et al. Mesenchymal stem cells induce a weak immune response in the rat striatum after allo or xenotransplantation. J Cell Mol Med. 2009

31. Viswanathan A, Painter RG, Lanson NA Jr, Wang G. Functional expression of n-formyl peptide receptors in human bone marrow-derived mesenchymal stem cells. Stem Cells. 2007; 25:1263–1269. [PubMed: 17234990]

32. Omori K, Tada Y, Suzuki T, Nomoto Y, Matsuzuka T, Kobayashi K, Nakamura T, Kanemaru S, Yamashita M, Asato R. Clinical application of in situ tissue engineering using a scaffolding technique for reconstruction of the larynx and trachea. Ann Otol Rhinol Laryngol. 2008; 117:673–678. [PubMed: 18834070]

33. Urita Y, Komuro H, Chen G, Shinya M, Saihara R, Kaneko M. Evaluation of diaphragmatic hernia repair using plga mesh-collagen sponge hybrid scaffold: An experimental study in a rat model. Pediatr Surg Int. 2008; 24:1041–1045. [PubMed: 18668247]

34. Omori K, Nakamura T, Kanemaru S, Magrufov A, Yamashita M, Shimizu Y. In situ tissue engineering of the cricoid and trachea in a canine model. Ann Otol Rhinol Laryngol. 2008; 117:609–613. [PubMed: 18771079]

35. A pipe dream becomes reality. Nat Med. 2009; 15:4.

36. Andrade CF, Wong AP, Waddell TK, Keshavjee S, Liu M. Cell-based tissue engineering for lung regeneration. Am J Physiol Lung Cell Mol Physiol. 2007; 292:L510–518. [PubMed: 17028264]

37. Mondrinos MJ, Koutzaki S, Lelkes PI, Finck CM. A tissue-engineered model of fetal distal lung tissue. Am J Physiol Lung Cell Mol Physiol. 2007; 293:L639–650. [PubMed: 17526596]

38. Mondrinos MJ, Koutzaki SH, Poblete HM, Crisanti MC, Lelkes PI, Finck CM. In vivo pulmonary tissue engineering: Contribution of donor-derived endothelial cells to construct vascularization. Tissue Eng Part A. 2008; 14:361–368. [PubMed: 18333788]

39. Cortiella J, Nichols JE, Kojima K, Bonassar LJ, Dargon P, Roy AK, Vacant MP, Niles JA, Vacanti CA. Tissue-engineered lung: An in vivo and in vitro comparison of polyglycolic acid and pluronic f-127 hydrogel/somatic lung progenitor cell constructs to support tissue growth. Tissue Eng. 2006; 12:1213–1225. [PubMed: 16771635]

40. Shigemura N, Okumura M, Mizuno S, Imanishi Y, Matsuyama A, Shiono H, Nakamura T, Sawa Y. Lung tissue engineering technique with adipose stromal cells improves surgical outcome for pulmonary emphysema. Am J Respir Crit Care Med. 2006; 174:1199–1205. [PubMed: 17008641]

41**. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop D, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cytotherapy. 2006; 8:315–317. This article is the latest guidelines for defining mesenchymal stem cell. [PubMed: 16923606]

42. Ventura C, Cantoni S, Bianchi F, Lionetti V, Cavallini C, Scarlata I, Foroni L, Maioli M, Bonsi L, Alviano F, et al. Hyaluronan mixed esters of butyric and retinoic acid drive cardiac and endothelial fate in term placenta human mesenchymal stem cells and enhance cardiac repair in infarcted rat hearts. J Biol Chem. 2007; 282:14243–14252. [PubMed: 17363374]

43. Lanzoni G, Roda G, Belluzzi A, Roda E, Bagnara GP. Inflammatory bowel disease: Moving toward a stem cell-based therapy. World J Gastroenterol. 2008; 14:4616–4626. [PubMed: 18698675]

44. Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, Lanino E, Sundberg B, Bernardo ME, Remberger M, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: A phase ii study. Lancet. 2008; 371:1579–1586. [PubMed: 18468541]

45. Prochymal clinical trial information for the treatment of acute gvhd. 2008. Available from: http://www.osiris.com/clinical_trials_prochymal_phaseII.php

46*. Ortiz LA, Dutreil M, Fattman C, Pandey AC, Torres G, Go K, Phinney DG. Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. Proc Natl Acad Sci U S A. 2007; 104:11002–11007. Ortiz et al reported a potential mechanism in which mesenchymal stem cells (MSC) attenuate inflammation and fibrosis in bleomycin-induced lung injury model. It is one of the first studies to identify a potential molecule producing by MSC. It is a well designed study. Although, more than one mechanism might be responsible for anti-inflammatory effect by MSC, this article is one of the important article to review in this field. [PubMed: 17569781]

47. Xu J, Woods CR, Mora AL, Joodi R, Brigham KL, Iyer S, Rojas M. Prevention of endotoxin-induced systemic response by bone marrow-derived mesenchymal stem cells in mice. Am J Physiol Lung Cell Mol Physiol. 2007; 293:L131–141. [PubMed: 17416739]

48. Xu J, Qu J, Cao L, Sai Y, Chen C, He L, Yu L. Mesenchymal stem cell-based angiopoietin-1 gene therapy for acute lung injury induced by lipopolysaccharide in mice. J Pathol. 2008; 214:472–481. [PubMed: 18213733]

49. Mei SH, McCarter SD, Deng Y, Parker CH, Liles WC, Stewart DJ. Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1. PLoS Med. 2007; 4:e269. [PubMed: 17803352]

50**. U.S. National institutes of health. 2008. http://clinicaltrials.govAn excellent resource of ongoing clinical trials related to stem cells in variety of diseases including COPD, pulmonary hypertension, etc.

51. Ozawa K, Sato K, Oh I, Ozaki K, Uchibori R, Obara Y, Kikuchi Y, Ito T, Okada T, Urabe M, et al. Cell and gene therapy using mesenchymal stem cells (MSCs). J Autoimmun. 2008; 30:121–127. [PubMed: 18249090]

52. Taupin P. Oti-010 osiris therapeutics/jcr pharmaceuticals. Curr Opin Drugs. 2006; 7:473–481.