# Stem Cells in Pulmonary Diseases

Dr Shailesh Agrawal

# Outline

- Introduction
- Mesenchymal stem cells
- Mechanism of action
- Routes, timing and adverse effects
- Role in individual pulmonary disorders
- Conclusion

# Stem Cells

- All adult tissues, including the lung, have some capacity to self repair or regenerate through the replication and differentiation of stem cells resident within these organs
- Knowledge regarding lung resident stem cells remains relatively incomplete
- Considerable interest in the therapeutic potential of exogenous cells, particularly mesenchymal stem/stromal cells (MSCs), for lung diseases

da Silva Meirelles L, Chagastelles PC. 2006. J Cell Sci 119:2204–2213
Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

# Stem Cells

- Normally resident in the bone marrow
- 2 well distinct subpopulations of cells
- Hematopoietic stem cells(HSCs)
  - Supporting blood cell formation
- Mesenchymal stem/stromal cells (MSCs)
  - Constitute a small fraction of cells (0.001%–0.01%)
  - Act in the marrow to facilitate maturation of HSCs
  - Also capable of differentiating into other cell types

Friedenstein AJ, Chailakhyan RK et al. Cloning in vitro and retransplantation in vivo. Transplantation 1974;17:331–40
Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

# Mesenchymal stromal cells

- No single defined characteristic
- Identified according to the following consensus criteria
  - Adherence to plastic under standard culture conditions
  - Expression of CD105, CD73, and CD90
  - Lack of CD45, CD34, CD14, cd11b, CD79, CD19, and HLA-DR
  - Ability to differentiate into adipocytes, chondrocytes, and osteocytes in vitro

Dominici M et al 2006. The International Society for Cellular Therapy position statement. Cytotherapy 8:315–317

# Mesenchymal stromal cells

- MSCs can be obtained from various sources
  - Bone marrow (BMMSC)
  - Umbilical cord tissue (wharton's jelly derived-WJMSC)
  - Adipose tissue (ATMSC)
  - Umbilical cord blood (UCMSCS)
  - Menstrual blood (MBMSC)
- BMMSCs of either human or animal origin have been studied mainly

A. C. Inamdar & A. A. Inamdar;Experimental Lung Research 2013, 39:8, 315-327

# Homing

- Chemokine stromal cell derived factor-1 (SDF-1, also known as CXCL12) -mesenchymal cell chemotaxis and organ-specific homing in injured tissue after IV administration
- Interacts with CXCR4 receptor on the surface of these cells
- Intravenously infused MSCs are trapped by the lung vasculature, adding convenience in treatment of lung disoders

Lee RH et al; Cell Stem Cell 2009 Jul 2;5(1):54-63
Leah A. Marquez-Curtis and Anna Janowska-Wieczorek; Biomed Res Int. 2013: 561098

# Effects of MSC

- MSCs homed to injured tissue exert their immunomodulatory activity
- Cell-cell contact
- Paracrine mechanisms, secretion of specific mediators
  - angiogenic (VEGF)
  - anti-apoptotic (Bcl-2)
  - anti-inflammatory (IL-10, VEGF, hepatocyte growth factor)

Shi M et al; Haematologica. 2007;92:897–904
Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

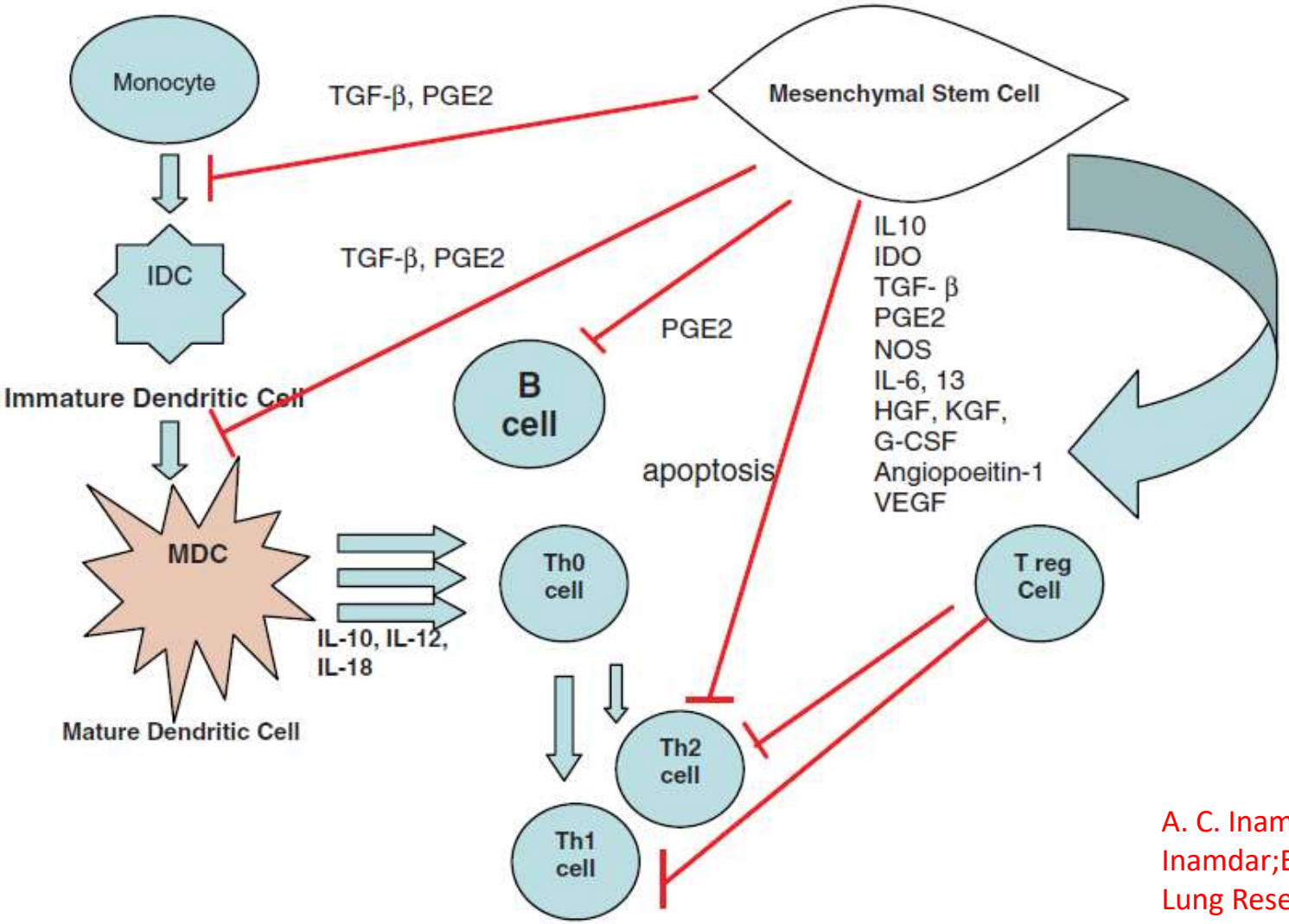
- Transfer of cellular materials including mitochondria to injured host cells via microvesicles

- Promote a secure environment for host tissue recovery

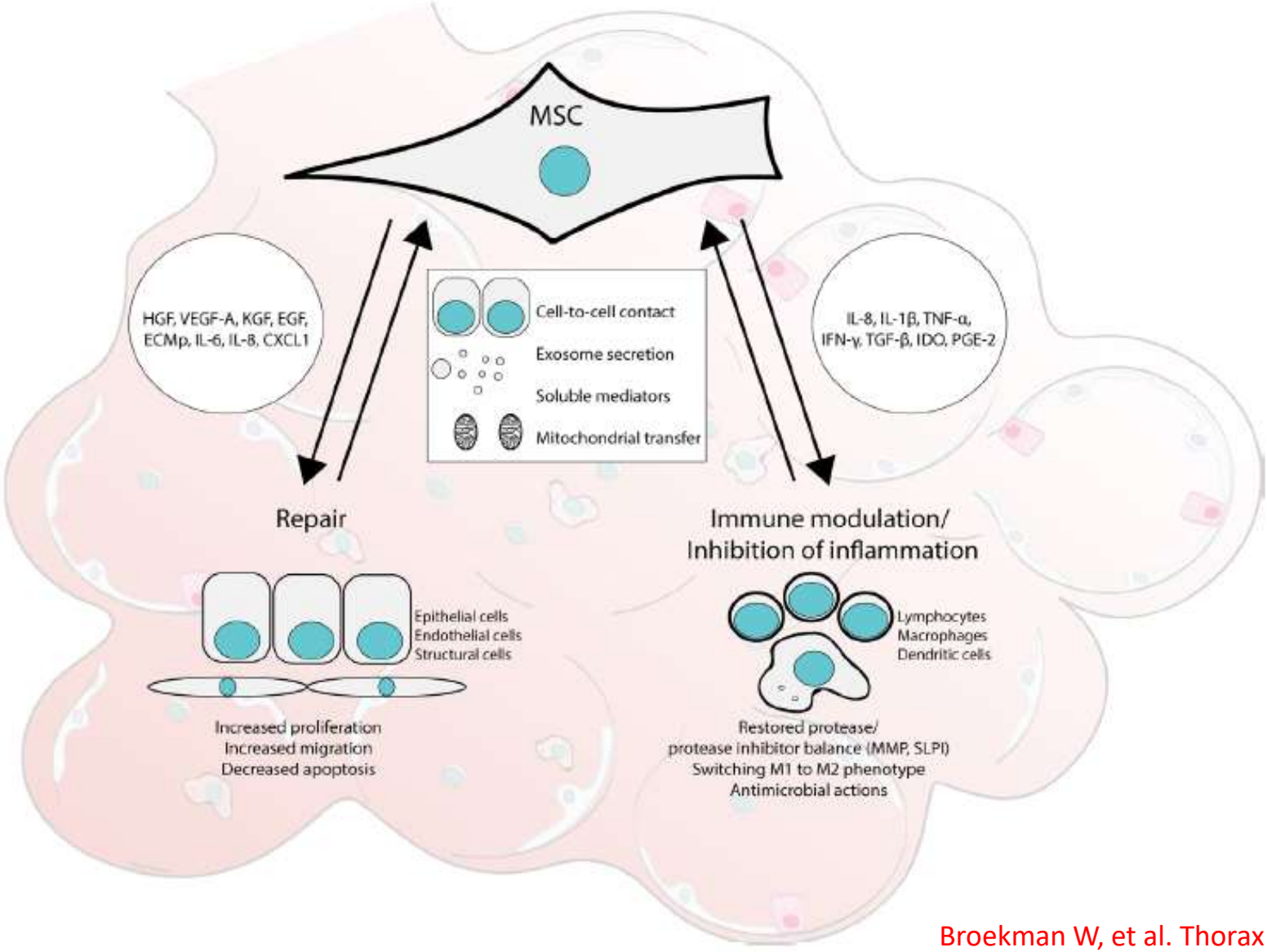
Shi M et al; Haematologica. 2007;92:897–904
Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

- In addition, antimicrobial effects are also described
- Includes direct inhibitory effects of MSCs and indirect effects via secretion of immune-mediators(like LL-37)
- In murine models of CF, MSCs and MSC-derived conditioned medium directly reduced the growth rate and survival of several respiratory pathogens

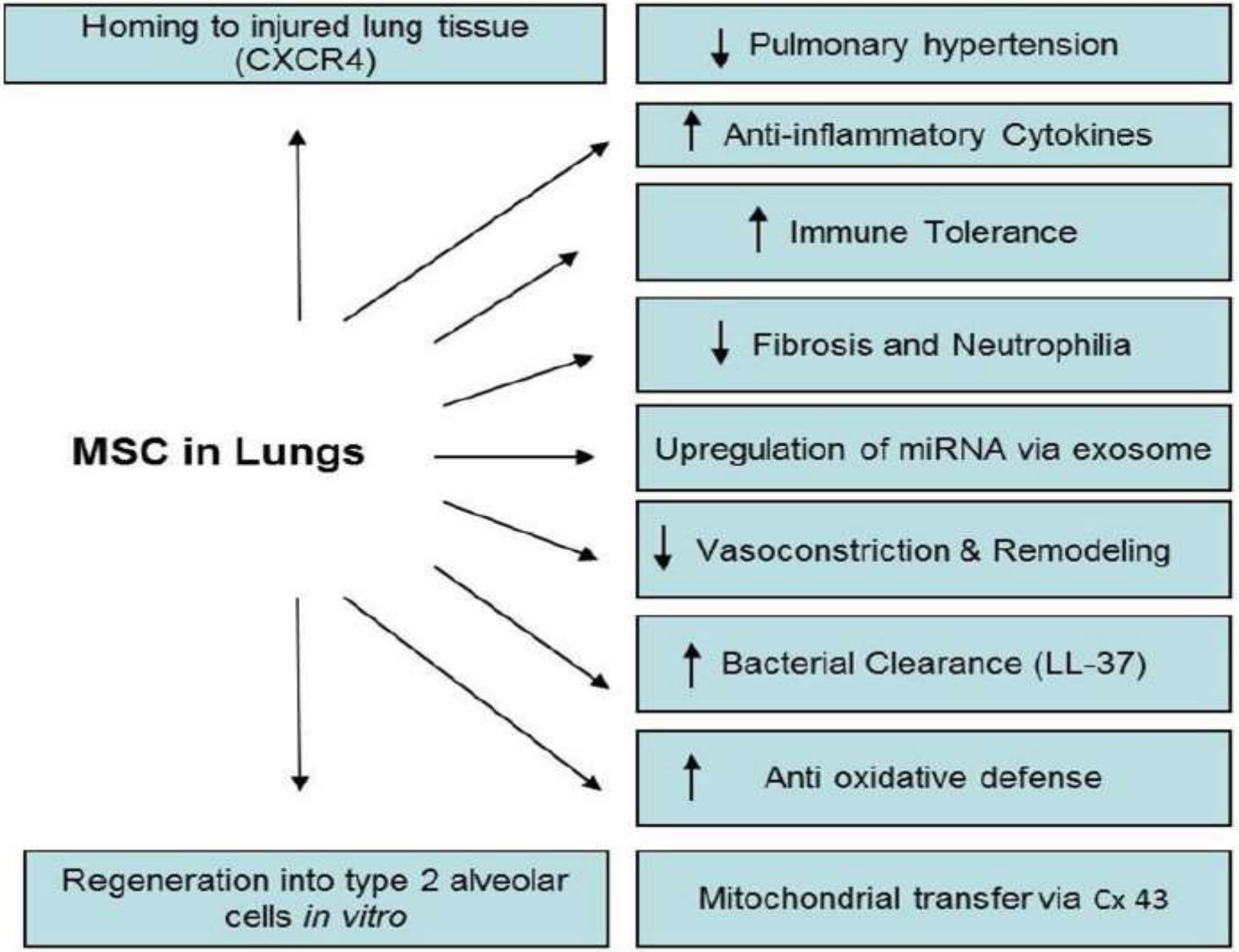
Sutton MT, Fletcher D, Ghosh SK, et al. Stem Cells Int 2016;2016:1–12
Krasnodembskaya A, Song Y, Fang X, et al. Stem Cells 2010;28:2229–38




A. C. Inamdar & A. A. Inamdar;Experimental Lung Research 2013, 39:8, 315-327




Broekman W, et al. Thorax 2018;73:565–574




A. C. Inamdar & A. A. Inamdar;Experimental Lung Research 2013, 39:8, 315-327

# Preconditioning

- Preconditioning of MSCs with pro-inflammatory cytokines or hypoxic culture conditions polarises MSCs towards an anti-inflammatory profile

- Inflammatory mediators present in areas of tissue damage can alter the secretome of MSCs in such a way that it promotes wound repair

Silva LHA, Antunes MA, Dos Santos CC, et al. Stem Cell Res Ther 2018;9:45

- Initial clinical trials in the late 90s assessed safety of MSCs in non-haematopoietic diseases
- 1st evidence on effficacy of MSCs came in 2004 in case report of a paediatric patient with refractory graft-versus-host disease
- This boosted the interest in MSC-based cell therapy in diseases of dysregulated immune responses

Le Blanc K, Rasmusson I, Sundberg B, et al. Treatment of severe acute graft versus-host disease with third party haploidentical mesenchymal stem cells. Lancet 2004;363:1439–41

# Why so much interest

- Intravenous administration
- No need of conditioning/myeloablation
- No issues with allogeneicity- lack various MHC and costimulatory cell surface antigens
- Possible role as guardians against excessive inflammatory response

Hare JM , Traverse JH et al . *J Am Coll Cardiol . 2009 ; 54 ( 24 ):* 2277 – 2286
Darwin J Prockop and Joo Youn Oh*Molecular Therapy vol. 20 no. 1 jan. 2012*

- Preclinical studies reported promising results using MSCs for lung disorders, including asthma, emphysema, pulmonary fibrosis and acute respiratory distress syndrome

A. C. Inamdar & A. A. Inamdar;Experimental Lung Research 2013, 39:8, 315-327

TABLE 1. Selected Animal Studies on Asthma, ARDS, COPD, and ILD

| Lung disease | MSCs source | Type of model | Outcome/mechanism |
|---|---|---|---|
| Asthma | BM-human | Ovalbumin to BALB/c mouse | ↓Allergic mediators (eosinophils, macrophages, and neurotrophils)<br>↓Pathophysiological features of asthma<br>↓IFN-$\alpha$, IL-5,13, macrophage inflammatory protein, iNOS |
| Asthma | BM- C57BL/6J or BALB/c mouse | Ovalbumin | ↓Allergic mediators (eosinophils)<br>↓Airway hypersensitivity and inflammation<br>↓ IL-4,5,13 plus<br>Role of T regulatory cells and T helper 1 type of CD4 T lymphocytes<br>↑IDO and PGE2 |
| Asthma | BM-C57BL/6J or BALB/c mouse | Ragweed | ↓Pathophysiological features of asthma<br>↓IgG1, IgE, IL-5,13<br>TGF-$\beta$ production via STAT6 pathway |
| Asthma | BM-Sprague Dawley rat | Toluene diisocyanate | ↓Allergic mediators (eosinophils, neurotrophils)<br>↓Collagen deposition, $\alpha$-SMA, PCNA |
| Lung Injury (ARDS) | human-UC | *E. coli* derived LPS | ↓Lung inflammation, edema, bacterial load, myeloperoxidase activity and pro-inflammatory cytokines |
| Lung injury | BM-C57BL/6J mouse | *E. coli* derived LPS | ↓Neutropenia, interalveolar thickness and edema, and injury, pro-inflammatory cytokines<br>↑Anti-inflammatory cytokines (IL-1ra,10,13) |
| Lung injury | BM-human | Human *ex vivo* | ↓In extravascular lung water,<br>↑Permeability of lung endothelial barrier<br>↑Capability of alveolar fluid clearance<br>Role of angiopoietin-1 and suppression of NF-kappa$\beta$ |
| Lung injury | BM-human | *E. coli* to C57BL/6J | ↓Bacterial growth, neurophila macrophage inflammatory protein-2<br>↑Bacterial clearance<br>Expression of human cathelicidin antimicrobial peptide, hCAP-18/LL-37 |
| COPD | BM-C57BL/6J | elastase induced | ↓ IL-1$\beta$, ↑ HGF, EGF, SLPI |
| COPD | BMC-Lewis rat | cigarette smoke | ↑Cell proliferation, pulmonary vascularity, repair of emphysema<br>↓Apoptosis |
| COPD | Human BM-and in vitro studies | cigarette smoke | ↓TNF-$\alpha$, IL-1$\beta$, MCP-1, and IL-6<br>↓MMP9 and MMP12<br>↑VEGF and TGF-$\beta$ |
| COPD | rat | Papain induced | ↑Bcl-2 and Bax<br>Differentiation into type II alveolar epithelial cells<br>↑VEGF-A and ↓ apoptosis |
| Lung fibrosis | Human-UC | Bleomycin | ↓Inflammation and collagen deposition<br>↓TGF-$\beta$, MIP, IFN-$\alpha$ |
| Lung fibrosis | BM-BALB/c | Bleomycin | ↓Inflammation and collagen deposition<br>↓TNF- and IL 1 via IL1 receptor |
| Lung fibrosis | BM-Sprague Dawley rat | Bleomycin | ↓Collagen deposition<br>↓TGF- $\beta$ 1, PDGF-A, PDGF-B, and IGF-I, NOS |

A. C. Inamdar & A. A. Inamdar;Experimental Lung Research 2013, 39:8, 315-327

# Routes

- The migration of MSCs to the injured tissues is central to the efficacy of cell therapy
- Lung offers the intratracheal/endobronchial route as a direct pathway for cell delivery, this route of administration may potentiate MSC efficacy

Antunes et al. Respiratory Research 2014, 15:118
http://respiratory-research.com/content/15/1/118

RESPIRATORY RESEARCH

RESEARCH Open Access

# Effects of different mesenchymal stromal cell sources and delivery routes in experimental emphysema

Mariana A Antunes[1], Soraia C Abreu[1], Fernanda F Cruz[1], Ana Clara Teixeira[1], Miquéias Lopes-Pacheco[2], Elga Bandeira[1,2], Priscilla C Olsen[1], Bruno L Diaz[3], Christina M Takyia[4], Isalira PRG Freitas[5], Nazareth N Rocha[6], Vera L Capelozzi[7], Débora G Xisto[1,2], Daniel J Weiss[8], Marcelo M Morales[2] and Patricia RM Rocco[1*]

- Emphysema was induced in mice by intratracheal (IT) administration of porcine pancreatic elastase weekly for 1 month
- After the last elastase instillation, saline or MSCs ($1\times10^5$), isolated from either mouse bone marrow (BM), adipose tissue(AD) or lung tissue (L), were administered intravenously (IV) or IT

- In contrast with IV, IT MSC administration further reduced alveolar hyperinflation (BM-MSC) and collagen fiber content (BM-MSC and L-MSC)
- IV administration of BM- and AD-MSCs reduced the number of M1 macrophages and pulmonary HTN on echo, while increasing VEGF

- Only BM-MSCs (IV > IT) increased the number of M2 macrophages
- IV administration of lung-derived MSCs led to immediate death of all mice
- Possibly due to larger size of the L-MSCs or with cellular clumping resulting in pulmonary embolism

- Thus, different MSC sources and administration routes variably reduced elastase-induced lung damage
- IV administration of BM-MSCs resulted in better cardiovascular function and change of the macrophage phenotype from M1 to M2

# Effective dose for cell therapy

- Effective dose in most animal studies is commonly $1 \times 10^6$ cells per 30 g mouse
- Equivalent dose for humans would be $2.3 \times 10^9$ cells per average human
- Such high doses have not been utilised in human studies

Hare JM, Traverse JH, Henry TD, et al. J Am Coll Cardiol. 2009;54:2277–2286

# Effective dose for cell therapy

- No efficacy data on dosing in human studies of pulmonary disorders
- In a study by *Hare et al* safety and efficacy of BM hMSC administered in patients experiencing a first acute MI, IV dose of BM MSC ranged from 0.5, 1.6 and 5 million cells/kg
- There was no evidence of increased toxicity or infusion reaction with the administration of hMSCs at any dose

Hare JM, Traverse JH, Henry TD, et al. J Am Coll Cardiol. 2009;54:2277–2286

- Among parameters analyzed for efficacy, VPCs count exhibited clear dose-responsiveness
- Did not differ between the placebo and low-dose cell groups
- Evident in the mid- and high-dose groups

Hare JM, Traverse JH, Henry TD, et al. J Am Coll Cardiol. 2009;54:2277–2286

# Timing of cell therapy

- Most animal studies in IPF models have demonstrated that early administration of cells within 24 h of lung injury had promising results in healing fibrotic lesions
- While administration at 30 and 60 days post injury increased fibrosis on scarred lung areas

Maliheh Ghadiri et al (2016), Expert Opinion on Biological Therapy, 16:3, 375-387

# Adverse effects

- Possible risks of infusion related reactions
- Stem cells may increase risk of teratogenicity or malignancies
- Unknown organ specific adverse effects

Runzhen Zhao et al. Oncotarget, 2017, Vol. 8, (No. 18)

# Adverse effects of cell therapy

**Serious adverse events of cell therapy for respiratory diseases: a systematic review and meta-analysis**

**Runzhen Zhao[1,*], Zhenlei Su[2,*], Jing Wu[2] and Hong-Long Ji[1]**

- Systematic review and meta-analyses of 23 clinical studies of cell therapy
- Either infusion or instillation of MSCs were well tolerated without serious adverse events causally related to cell treatment

Runzhen Zhao et al. Oncotarget, 2017, Vol. 8, (No. 18)

# Menschymal stem cells in COPD

# COPD

- Enhanced chronic inflammatory response in the airways and lung to noxious particles or gases
- Increased numbers of CD8+ (cytotoxic) Tc1 lymphocytes
- Release inflammatory mediators and enzymes
- Damage of structural cells in the airways, lung parenchyma and pulmonary vasculature
- Inflammatory mediators in blood- muscle wasting and cachexia

Global Strategy for the
Diagnosis, Management and Prevention of COPD, Updated 2016

# COPD

- Current therapies- mainly symptomatic
- No available therapy has been able to reconstitute the alveolar architecture or halt the fibrogenic process
- Potential space for research in MSC therapy for COPD

Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

# Preclinical studies in COPD

| | | |
|---|---|---|
| BM-C57BL/6J | elastase induced | ↓ IL-1$\beta$, ↑ HGF, EGF, SLPI |
| BMC-Lewis rat | cigarette smoke | ↑Cell proliferation, pulmonary vascularity, repair of emphysema<br>↓Apoptosis |
| Human BM-and in vitro studies | cigarette smoke | ↓TNF-$\alpha$, IL-1$\beta$, MCP-1, and IL-6<br>↓MMP9 and MMP12<br>↑VEGF and TGF-$\beta$ |
| rat | Papain induced | ↑Bcl-2 and Bax<br>Differentiation into type II alveolar epithelial cells<br>↑VEGF-A and ↓ apoptosis |

A. C. Inamdar & A. A. Inamdar;Experimental Lung Research 2013, 39:8, 315-327

PLOS ONE

RESEARCH ARTICLE

# Preclinical Studies of Mesenchymal Stem Cell (MSC) Administration in Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review and Meta-Analysis

**Xiangde Liu[1], Qiuhong Fang[2], Huijung Kim[3]***

**1** Pulmonary, Critical Care, Sleep and Allergy Medicine, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, United States of America, **2** Department of Pulmonary and Critical Care, Beijing Chaoyang Hospital, The Capital Medical University, Beijing, China, **3** Pulmonary and Critical Care Division, WonKwang University, Sanbon Medical Center, Seoul, Korea

- Systemic review of 20 studies
- MSC administration was significantly in favor of attenuating acute lung injury, stimulating lung tissue repair and improving lung function

Liu X, Fang Q, Kim H (2016) PLoS ONE 11(6)

- Pre-clinical studies demonstrate that MSC hold promise in the treatment of COPD
- Although the COPD models may not truly mimic COPD patients

Liu X, Fang Q, Kim H (2016) PLoS ONE 11(6)

CHEST Original Research

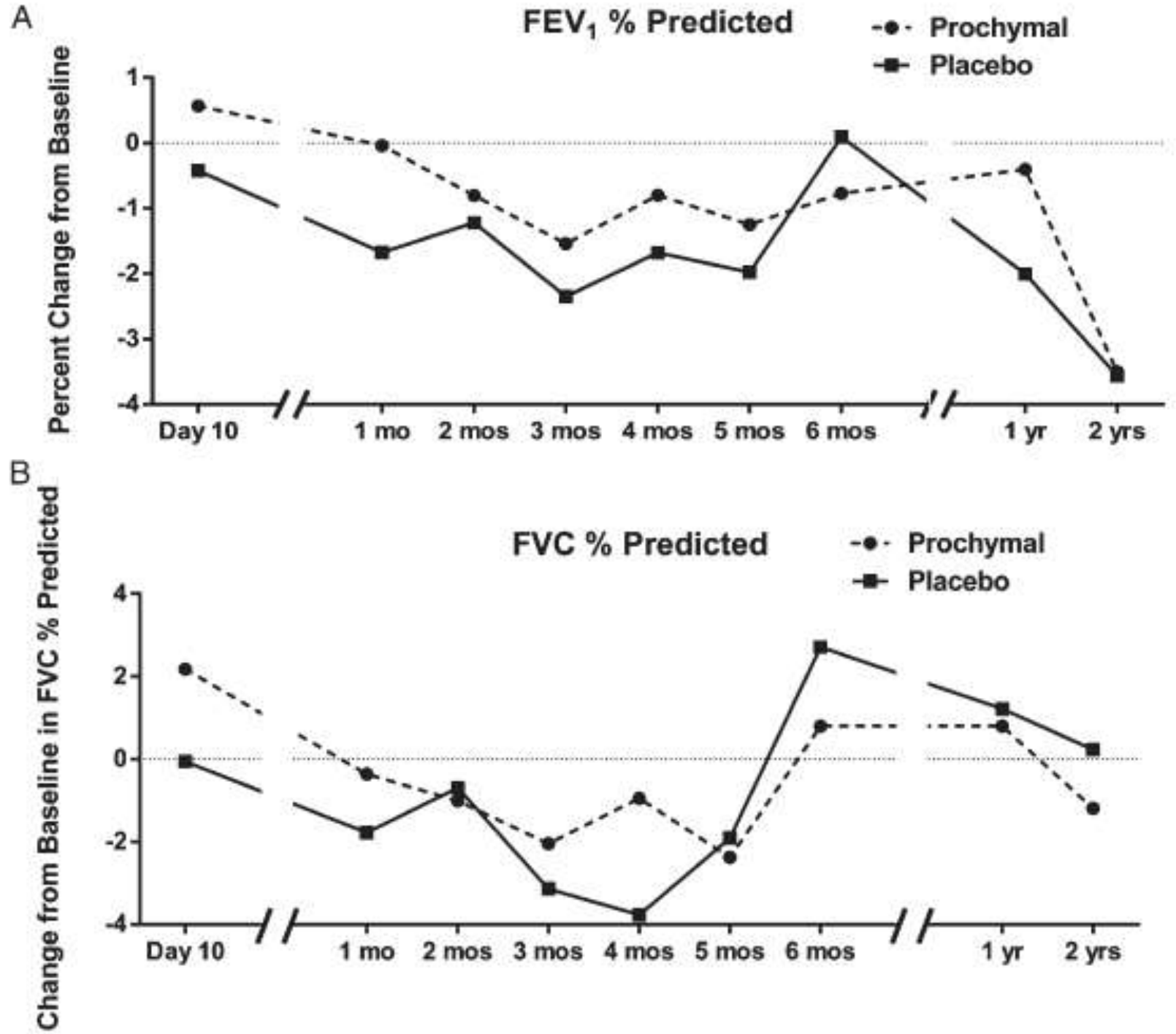
COPD

# A Placebo-Controlled, Randomized Trial of Mesenchymal Stem Cells in COPD

*Daniel J. Weiss, MD, PhD; Richard Casaburi, PhD, MD, FCCP; Robin Flannery; Michelle LeRoux-Williams, PhD; and Donald P. Tashkin, MD, FCCP*

- 62 patients, Double-blinded multicentric RCT
- IV infusions of either allogeneic MSCs or vehicle control
- Monthly infusions for 4 months ($100x10^6$cells/infusion)
- Followed for 2 years after the first infusion

- **End points**- safety, PFT, and quality-of-life indicators including questionnaires, 6MWT, and assessments of systemic inflammation
- **Results**- No infusional toxicities/deaths or serious adverse events deemed related to MSC administration


A
FEV1 % Predicted
Prochymal
Placebo
Percent Change from Baseline
1
0
-1
-2
-3
-4
Day 10
1 mo
2 mos
3 mos
4 mos
5 mos
6 mos
1 yr
2 yrs
B
FVC % Predicted
Prochymal
Placebo
Change from Baseline in FVC % Predicted
4
2
0
-2
-4
Day 10
1 mo
2 mos
3 mos
4 mos
5 mos
6 mos
1 yr
2 yrs

| Study Days | CRP, ng/mL | | TGF-β, ng/mL | |
|---|---|---|---|---|
| | Prochymal | Placebo | Prochymal | Placebo |
| Day 0 | 7.55 | 6.38 | 38,555 | 36,853 |
| Day 10 | 6.87 | 6.17 | 39,269 | 39,534 |
| 1 mo | 4.97 | 6.58 | 40,513 | 40.985 |
| 2 mo | 5.57 | 4.68 | 41,799 | 42,147 |
| 3 mo | 4.94 | 3.88 | 41,689 | 36,625 |
| 4 mo | 6.68 | 5.22 | 41,637 | 34,331 |
| 5 mo | 4.24 | 7.03 | 43,065 | 34,165 |
| 6 mo | 9.76 | 6.56 | 37,425 | 31,998 |
| 1 yr | 5.63 | 3.42 | 34,623 | 30,709 |
| 2 yr | 5.68 | 4.26 | 44,936 | 35,914 |

- No significant differences in the overall number of adverse events, frequency of COPD exacerbations, or worsening of disease in patients treated with MSCs
- However, no significant differences in PFTs or quality-of-life indicators
- An early, significant decrease in CRP levels in patients with baseline elevated CRP levels

# Explaination for lack of efficacy

- Clinical COPD being a chronic inflammation while animal studies used acute models
- Dosing and treatment schedules used were empirically based on data from MSC trials in other diseases
- Advanced stage disease

- MSCs could be more effective in subgroups of patients with COPD with higher levels of inflammatory markers or during active inflammation (eg, during exacerbations)
- Need to investigate the effect of preconditioning of MSCs

# Mesenchymal Stem cells in ILD

- CTD-ILD: systemic dysregulated immune response, which also involves lungs
  - Abnormal activation and development of auto-reactive immune cells
  - Role of HSCT

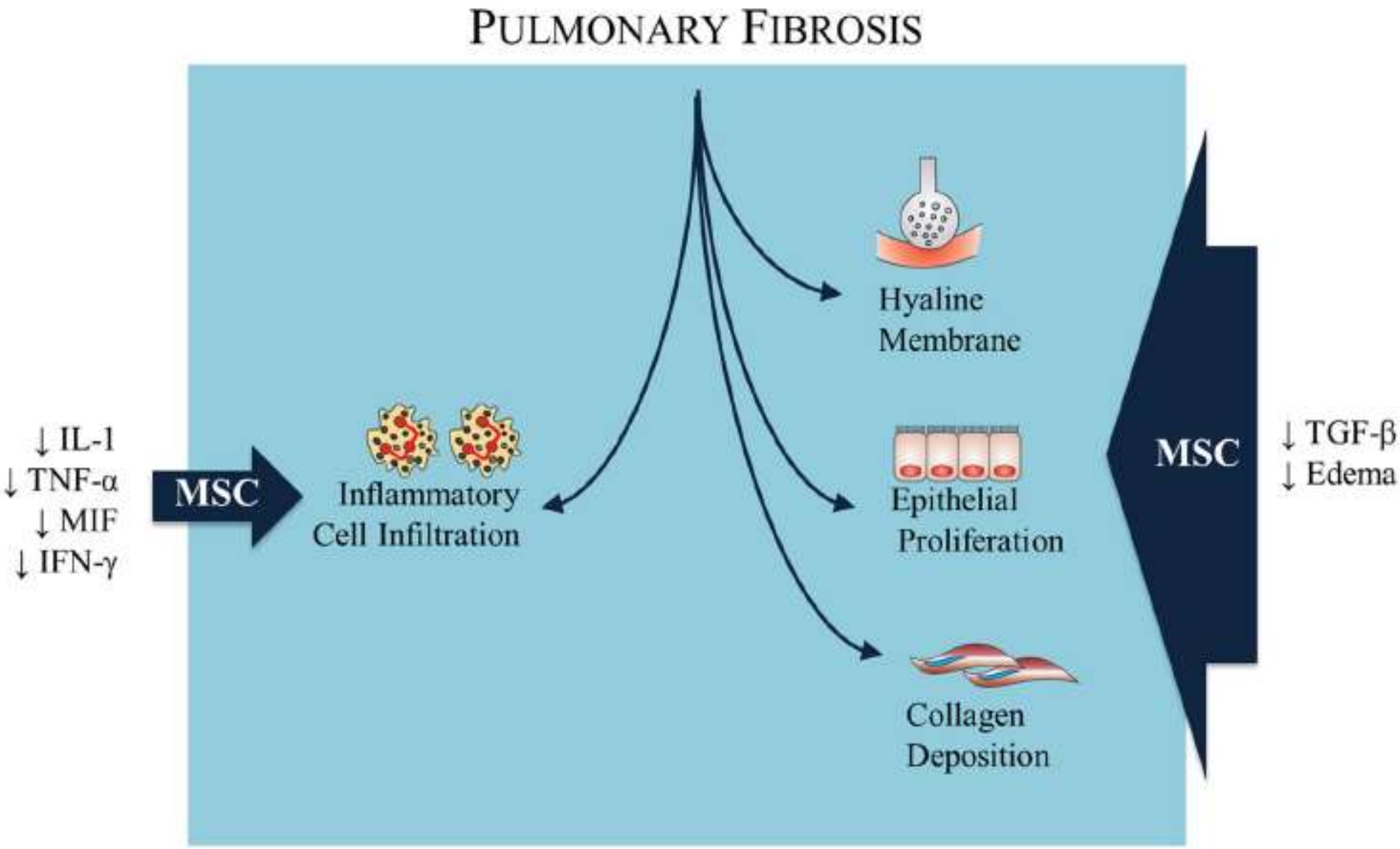
- Other ILDs: localised inflammation/fibrosis confined to lungs
  - Possible role of MSC therapy

CIPRIANI P, RUSCITTI P, GIACOMELLI R: *Br J Haematol 2015; 168: 328-37*

# Preclinical studies in ILD

- Bleomycin-induced IPF models
  - stem cells decreased inflammation, with reductions in neutrophil infiltration, fibrosis, and collagen deposition and an increase in epithelial repair

Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)




Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

- Telomerase mutations have been associated with IPF
- Allogenic MSCs could be the logical option in treating IPF associated with aging, replacing old stem cells with the younger stem cells

# Idiopathic Pulmonary Fibrosis

**Table 1.** Preclinical studies of cell-based therapy for idiopathic pulmonary fibrosis.

| Study | Model | Cell type | Dose | Cell delivery | Time of cell transplantation after injury | Efficacy results |
|---|---|---|---|---|---|---|
| Ortiz *et al.* [39] | Mouse-BLM induced | Bone marrow-MSCs | $5 \times 10^5$ | Intravenous | Immediately after BLM instillation | Reduced inflammation and collagen deposition |
| Banerjee *et al.* [25] | Mouse-BLM induced | Emberyonic-MSCs | $1 \times 10^5$ | Intratracheal | 7 days | Significant reduction inexpression of ECM (extra cellular molecules) (i.e. collagen and fibronectin) and profibrotic (i.e. TGF-β, FGF and VEGF) genes in the lungs |
| Rojas *et al.* [40] | Mouse-naphthalene or sulfur dioxide induced | Bone marrow-MSCs | $5 \times 10^5$ | Intravenous | 6 h | Return of expression of IFN-γ, IL-2, IL-1β and IL-4, cytokines toward normal after cell transplantation. Transplanted mesenchymal stem cells through localization or paracrine effect contributed in the rapier |
| Gupta *et al.* [41] | Mouse–*Escherichia coli* endotoxin induced | Bone marrow-MSCs | 750,000 cells in 30 µl of PBS | Intratracheal | 4 h | MSC improve survival over 72 h and indices of lung injury at 24 and 48 h, decrease in excess lung water, mediated a downregulation of proinflammatory responses to endotoxin (reducing TNF-α in the bronchoalveolar lavage and plasma) while increasing the anti-inflammatory cytokine IL-10 |
| Zhao *et al.* [42] | Rat- BLM induced | Bone marrow-MSCs | $5 \times 10^6$ | Intravenous | 12 h | MSCs differentiated into alveolar epithelial cells, decrease in TGF-β1, PDGF-A, PDGF-B and IGF-I |
| Cargnoni *et al.* [43] | Mouse-BLM induced | Placenta-MSCs | $4 \times 10^6$ or $1 \times 10^6$ | Intraperitoneal or Intratracheal | 15 min | Reduction in neutrophil infiltration |
| Moodley *et al.* [44] | Mouse-BLM induced | Human umbilical cord cells derived from Wharton's jelly | $1 \times 10^6$ | Intravenous | 24 h | uMSCs reduced inflammation and inhibited the expression of transforming growth factor-β, interferon-γ and the pro-inflammatory cytokines macrophage migratory inhibitory factor and tumor necrosis factor-α. Collagen concentration in the lung was significantly reduced |

Maliheh Ghadiri et al (2016), Expert Opinion on Biological Therapy, 16:3, 375-387

- Even though preclinical and in vitro data look promising, stem cell approaches in IPF are still at the early experimental stage
- Few human studies on role of MSC in IPF are going on with no published data yet

**Table 2.** Summary of ongoing clinical trials on IPF.

| Agent /treatment | Delivery route | Study design | Current status | Objectives | Identifier |
|---|---|---|---|---|---|
| Allogeneic human MSCs | Intravenous delivery | A Phase I, Randomized, Blinded and Placebo-controlled Trial | This study is ongoing, but not recruiting participants | Evaluate the safety, tolerability and potential efficacy of allogeneic human MSCs in treatment of IPF | NCT02013700 |
| Autologous adipose derived MSCs | Intravenous delivery | A Prospective, Multicentre, Phase I/II, Open Label, Randomized, Interventional Study | This study is currently recruiting participants | Evaluate safety and efficacy of autologous adipose derived MSCs in treatment of IPF | NCT02135380 |
| Autologous MSCs | Endobronchial infusion | Phase I, open, multicentre, non-randomized, escalating doses | This study is currently recruiting participants | Evaluate the safety and feasibility of treatment of IPF with MSCs | NCT01919827 |
| MSCs | Intravenous delivery | Phase I Study | Completed | Evaluate the potential role of MSCs in treatment of IPF | NCT01385644 |
| Clinical grade umbilical cord MSCs | Injected directly into the lesion | Phase I, open, single-centre, non-randomized | This study is currently recruiting participants | Evaluate the safety and effectiveness of the treatment and evaluate the possible immunomodulatory effects of the umbilical cord MSCs. | NCT02277145 |

Maliheh Ghadiri et al (2016), Expert Opinion on Biological Therapy, 16:3, 375-387

# Silicosis

- Inhaled silica particles engulfed by alveolar macrophages
- Phagocytosis of the silica particles leads to local inflammation and nitric oxide release, contributing to inflammation and remodeling

Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

# Preclinical studies in silicosis

- In experimental model of silicosis BMMCs reduced inflammation, with attenuation in neutrophil infiltration and inflammatory cytokine levels, and reduce fibrosis, with a decrease in collagen deposition

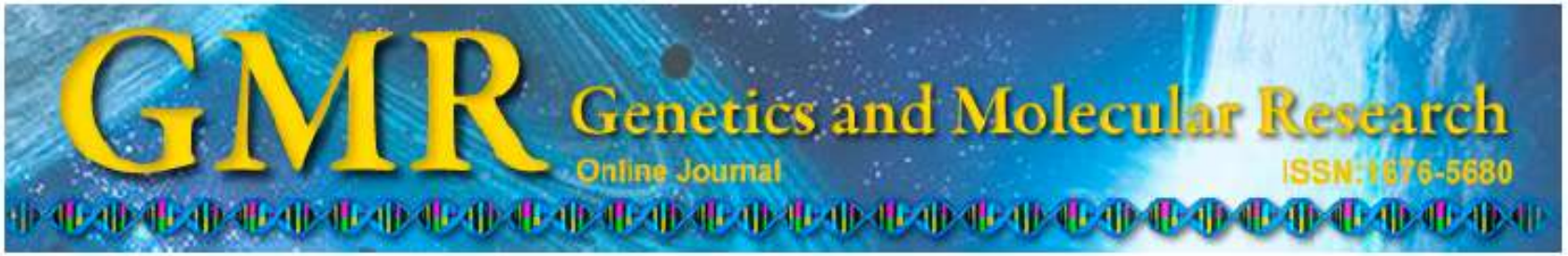
Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

# Clinical studies

- A non-randomized, phase I trial in 3 patients with chronic and accelerated silicosis, demonstrated that intrabronchial instillation of autologous BMMCs($2x10^7$ cells) is safe
- Scintigraphy showed an increase in lung perfusion in the basal region up to day 180 after the infusion

Loivos LP et al. Am J Respir Crit Care Med 181:A1595

# Silicosis




## Treatment of silicosis with hepatocyte growth factor-modified autologous bone marrow stromal cells: a non-randomized study with follow-up

W.W. Liu[1], H.X. Wang[2], W. Yu[1], X.Y. Bi[3], J.Y. Chen[1], L.Z. Chen[1], L. Ding[2], D.M. Han[2], Z.K. Guo[1] and Y.X. Lei[4]

WW Liu et al; Genetics and Molecular Research 14 (3): 10672-10681 (2015)

**Table 1.** Patient characteristicsof Silicosis.

| Cases | Gender | Age | Dust-contact time (year) | Silicosis stages* | Disease course | Types of job |
|---|---|---|---|---|---|---|
| 1 | M | 37 | 8 | II | 1 y | Sand blasting |
| 2 | F | 41 | 5 | I | 3 m | Sand blasting |
| 3 | F | 37 | 5 | II | 1 m | Sand blasting |
| 4 | M | 51 | 18 | I | 1 m | Mine blasting |

- Non-randomized study
- 4 patients with pulmonary silicosis who had developed lung fibrosis and received autologous bone marrow MSCs previously transfected by a vector containing human HGF cDNA (MSCs/HGF)

- MSCs/HGF were intravenously administered weekly for three consecutive weeks at a dose of $2 \times 10^6$ cells/kg
- Pulmonary function, high kilo-voltage chest X-ray radiography, computed tomography (CT) scan were evaluated
- The treatment was found to be generally safe

**Table 2.** Pulmonary function testing before and 6 months after cell therapy in the cases of silicosis.

| Cases | Treatment | FVC% | | FEV1% | | SpO2 | |
|---|---|---|---|---|---|---|---|
| | | Baseline | Post | Baseline | Post | Baseline | Post |
| 1 | MSCs/HGF | 89.5 | 91.8 | 85.2 | 87.9 | 87.7 | 92.2 |
| 2 | MSCs/HGF | 94.1 | 96.8 | 97.4 | 94.1 | 81.2 | 99.0 |
| 3 | MSCs/HGF | 67.0 | 64.6 | 70.3 | 82.0 | 87.4 | 99.0 |
| 6 | MSCs/HGF | 75.6 | 85.2 | 71.8 | 88.5 | 90.2 | 99.0 |
| Mean | | 81.6 | 84.6 | 81.2 | 88.1 | 86.6 | 97.3 |
| P value | | >0.05 | | >0.05 | | <0.05 | |

- Arterial blood oxyhemoglobin saturation was significantly enhanced, accompanied by partial relief of symptoms such as cough and dyspnea
- CT scans and chest X-rays demonstrated the disappearance of some silica nodules in two patients
- However, no definite conclusion could be drawn to fully elucidate the beneficial effects of MSCs/HGF

# Radiation induced Lung Injury

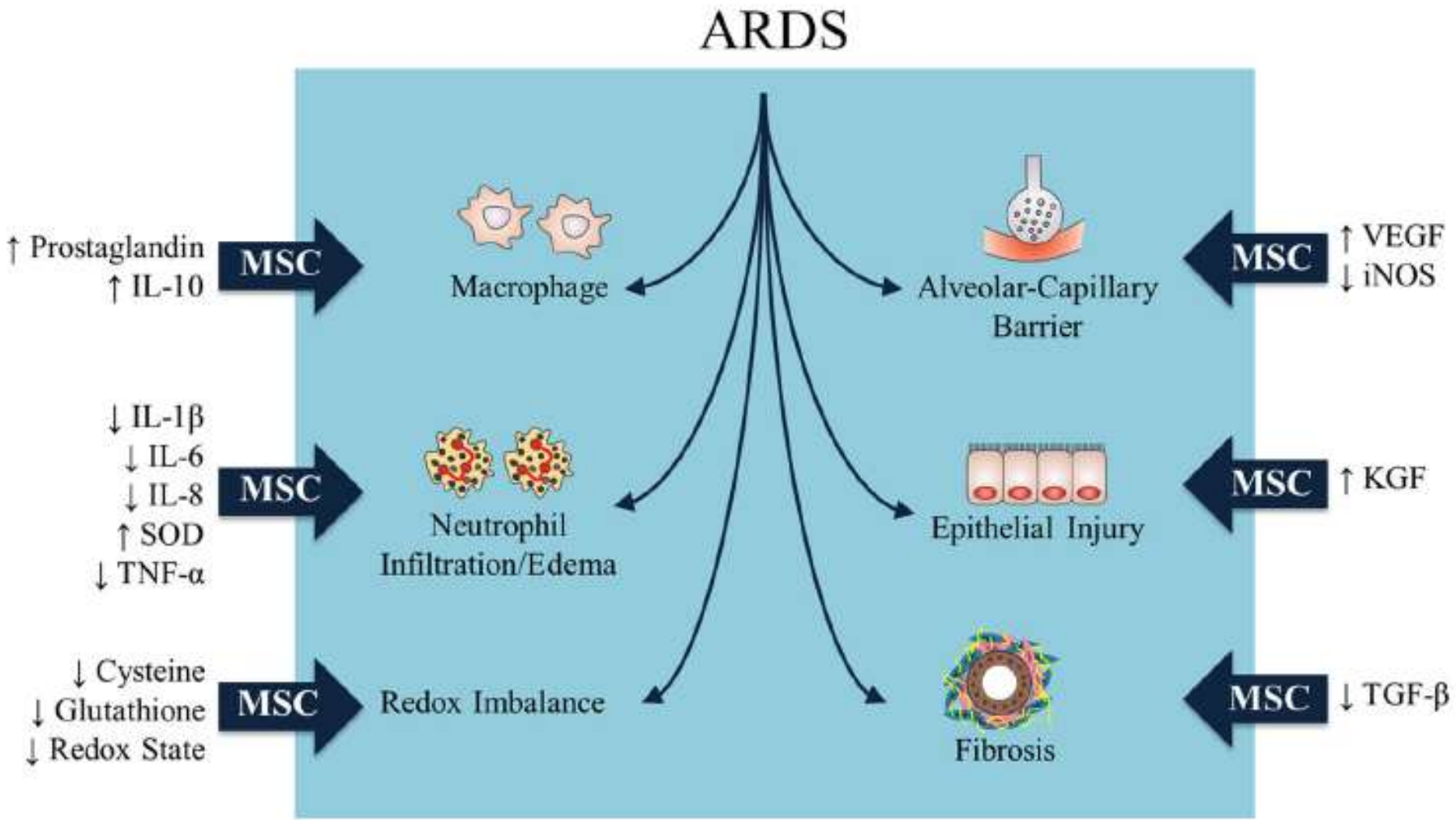
- Single transplantation of MSCs in 11 patients with RILI developed after combined chemotherapy and radiation therapy for lymphogranulomatosis or breast cancer was performed in a safety study
- Cell therapy with autologous mesenchymal stem cells did not induce progression of the underlying oncological disease

Kursova LV et al; Bull Exp Biol Med. 2009 Apr;147(4):542-6

# Other Pulmonary disorders

# ARDS

- Damage to alveolar epithelium and capillary endothelium
- Increased permeability and extravasation of protein-rich fluid into the alveolar space
- Damage worsened by alveolar neutrophil influx




Mariana A. Antunes, John G. Laffey et al; Journal of Cellular Biochemistry 115:1023–1032 (2014)

# Preclinical studies in ARDS

- *Hayes et al* reported that bone marrow hMSCs enhanced repair following ventilation induced lung injury, enhancing resolution of inflammation and restoration of lung structure
- *McAuley et al* demonstrated that bone marrow-hMSCs restore alveolar fluid clearance in explanted human lungs

Hayes M, Masterson C, Devaney J, et al. Anesthesiology 2015; 122:363–373
McAuley DF, Curley GF, Hamid UI, et al. Am J Physiol Lung Cell Mol Physiol 2014;306:L809–L815

# Preclinical studies in ARDS

| | | |
|---|---|---|
| human-UC | *E. coli* derived LPS | ↓Lung inflammation, edema, bacterial load, myeloperoxidase activity and pro-inflammatory cytokines |
| BM-C57BL/6J mouse | *E. coli* derived LPS | ↓Neutropenia, interalveolar thickness and edema, and injury, pro-inflammatory cytokines<br>↑Anti-inflammatory cytokines (IL-1ra,10,13) |
| BM-human | Human *ex vivo* | ↓In extravascular lung water,<br>↑Permeability of lung endothelial barrier<br>↑Capability of alveolar fluid clearance<br>Role of angiopoietin-1 and suppression of NF-kappa$\beta$ |
| BM-human | *E. coli* to C57BL/6J | ↓Bacterial growth, neurophila macrophage inflammatory protein-2<br>↑Bacterial clearance<br>Expression of human cathelicidin antimicrobial peptide, hCAP-18/LL-37 |

A. C. Inamdar & A. A. Inamdar;Experimental Lung Research 2013, 39:8, 315-327

# Clinical studies in ARDS

## Mesenchymal Stem (Stromal) Cells for Treatment of ARDS: A Phase 1 Clinical Trial

Jennifer G. Wilson[1], Kathleen D. Liu[2], Hanjing Zhuo[3], Lizette Caballero[4], Melanie McMillan[4], Xiaohui Fang[3], Katherine Cosgrove[5], Rosemary Vojnik[6], Carolyn S. Calfee[7], Jae-Woo Lee[8], Angela J. Rogers[6], Joseph Levitt[6], Jeanine Wiener-Kronish[9], Ednan K. Bajwa[5], Andrew Leavitt[10], David McKenna[11], B. Taylor Thompson[5], and Michael A. Matthay[12]

Wilson JG, LiuKD, Zhuo H, et al. Lancet Respir Med 2015; 3:24–32

- Multi-center, open-label, dose-escalation phase 1 clinical trial of a single dose of IV MSCs in patients with moderate-to-severe ARDS as per berlin definition
- The first three patients were treated with low dose MSCs (1million cells/kg)
- Next three patients received intermediate dose MSCs (5 million cells/kg)

- Final three patients received high dose MSCs (10 million cells/kg)

- Primary outcomes included the incidence of pre-specified infusion associated events and serious adverse events

- Serious adverse events were observed in three patients
- 2 patients expired >seven days after the MSC infusion
- 1 patient was discovered to have multiple embolic infarcts
- None of these SAEs were thought to be MSC-related

# Clinical studies in ARDS

- Study demonstrated that bone marrow hMSCs were safe in doses of up to 10 million cells/kg, in a phase 1b dose-escalation study
- Phase 2 study by same group going on
- Similarly *Zheng et al* demonstrated that adipose-derived hMSCs were well tolerated in their phase 1b study

Wilson JG, LiuKD, Zhuo H, et al. Lancet Respir Med 2015; 3:24–32.
Zheng G, Huang L, Tong H, et al. Respiratory Research 2014; 15:39

# Conclusion

- Mesenchymal stem cell therapy is safe
- Promising results in animal studies
- Evidence of efficacy in human studies of non-pulmonary diseases
- Not yet reciprocated in human studies of pulmonary disorders
- Effective route, dose and timing of administration needs to evaluated further
- Phase 2 studies in various diseases going on