

# Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation



## Stem Cell Therapy for COPD: Where are we?

Ron Balkissoon, MD, MSc, DIH, FRCPC<sup>1</sup>

**Abbreviations:** chronic obstructive pulmonary disease, **COPD**; embryonic stem cells, **ESCs**; induced pluripotent stem cells, **iPSs**; mesenchymal stem cells, **MSCs**; human lung stem cells, **hLSCs**; adipocyte mesenchymal cells, **AD-MSCs**; bone marrow mesenchymal stem cells, **BM-MSCs**; Wharton's jelly mesenchymal stem cells, **WJ-MSCs**

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<sup>1</sup> Denver, Colorado

### Address correspondence to:

Ron Balkissoon, MD, MSc, DIH, FRCPC  
balkissoonr@njhealth.org

### Introduction

Over the last year I have had several patients ask me about stem cell therapy for chronic obstructive pulmonary disease (COPD). There are clinics currently offering this therapy, (typically at exorbitant out of pocket cost to the patient), even though there are no phase III randomized controlled trials or Food and Drug Administration approval. There have been several phase I clinical trials, mostly looking at safety, and a handful of small phase II clinical trials that essentially have been negative. Despite this, there remains keen interest in continuing to study so-called “regenerative therapy” for COPD. Indeed, current standard therapies including bronchodilators and inhaled corticosteroids and the phosphodiesterase-4 inhibitor, roflumilast, show modest efficacy at best in reducing exacerbations and improving lung function. There has been no definitive evidence that they impact mortality. Lung volume reduction surgery is reserved often for those with severe disease and has only modest benefits. Lung transplantation is limited by availability, age restrictions, complications and rejection issues. With these limitations of standard modalities of therapy, it is attractive to pursue novel regenerative therapies that may be capable of restoring pulmonary function and structures such as airways, terminal bronchioles and alveoli. It is also postulated that by replacing these damaged cells there can be a restoration of normal immune function and a reduction in the inflammatory response to variable exposures such

as cigarette smoke, air pollution and airway pathogens in susceptible individuals who develop COPD.

Stem cells can differentiate into several different lung cell types such as the alveolar epithelial cells that are destroyed by cigarette smoke leading to emphysematous changes and reduced tethering of small airways causing hyperinflation and gas exchange abnormalities. Pre-clinical trials in animal models have suggested regeneration of alveolar-like structures, repair of emphysematous lungs, and reduction of inflammatory responses. The greatest success has been in acute lung injury models, however. Currently, regenerative therapies are divided into extrinsic therapeutic strategies and intrinsic cell therapy methods. There has been some work looking at the potential to bioengineer fully intact 3-D lung units that could be transplanted but this is not a likely prospect for the near future. Extrinsic cell therapy refers to infusing (or endotracheal installation) of stem cells including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSs), mesenchymal stem cells (MSCs), and human lung stem cells (hLSCs). Intrinsic therapy refers to the delivery of small molecules (retinoid compounds have been the most studied) that can stimulate the endogenous lung stem/progenitor cells to regenerate and replace damaged structures (See Sun et al review paper below).

As mentioned above, human trials to date have largely failed in showing any benefit but there remain questions about appropriate candidates for such therapy, type of therapy, timing of therapy, dosing issues and a host of other variables that require further study. One of the salient questions is whether these therapies need to be started earlier in less severe stages of the disease process. Of course, if that is found to be the case then a

major issue will be whether early identification, smoking cessation, adherence to conventional treatments and addressing comorbid conditions may be as or more effective. The papers presented in this Journal Club include an excellent, comprehensive state of the art review of the studies to date and the important future lines of research. The other recent papers address some of the questions raised in the review article.

*Note: Abstracts are presented in their original, published format and have not been edited to match JCOPDF style.*

## **Abstract 1 Stem Cell Therapies for Chronic Obstructive Pulmonary Disease: Current Status of Pre-Clinical Studies and Clinical Trials**

Sun Z, Li F, Zhou X, Chung KF, Wang W, Wang J. J  
*Thorac Dis.* 2018;10(2):1084-1098.  
doi: <https://doi.org/10.21037/jtd.2018.01.46>.

Chronic obstructive pulmonary disease (COPD) is a respiratory disease that has a major impact worldwide. The currently-available drugs mainly focus on relieving the symptoms of COPD patients. Novel regenerative therapeutic approaches have been investigated with the aim of repairing or replacing the injured functional structures of the respiratory system. We summarized the progress made by regenerative therapies for COPD by analyzing results from both pre-clinical studies and completed clinical trials. These approaches include the application of exogenous stem cells or small molecules to stimulate the regeneration by endogenous lung stem/progenitor cells. Exogenous mesenchymal stem cells (MSCs) have been reported to repair the structure and improve the function of the injured respiratory system in COPD models. However, the studies that used MSCs in patients with moderate-to-severe COPD patients did not lead to clear respiratory functional improvements. Exogenous human lung stem cells applied to cryo-injured (CI) lungs of mice have been shown to organize into human-like pulmonary structures, indicating a new property of stem cells that is potentially capable of curing COPD patients. Small molecules like retinoic acid has been shown

to lead to regeneration and repair of the damaged lung structures in COPD mouse models probably by activation of endogenous lung stem/progenitor cells. However, retinoic acid or agonists of retinoic acid receptor administered to moderate or severe COPD patients did not improve the density and function of the damaged lung. These novel regenerative approaches have failed in preliminary clinical trials, possibly due to the advanced severity of the disease. Further work should be done to develop the current regenerative approaches for curing patients at different stages of COPD. We suggest that some modifications of the approach in the clinical studies may lead to more successful outcomes of regenerative therapy for COPD.

## **Comments**

This is a superb review article. Not only do the authors provide significant background behind the scientific rationale and methodology for the various regenerative techniques but they also provide a comprehensive review of many preclinical and early clinical studies that have been conducted. There are excellent summary charts of the most important preclinical and clinical studies. The authors provide insightful critiques of these studies. One of the most pertinent concerns the authors raise is related to the advanced stage of patients studied in the clinical trials. The animal models that were used in preclinical studies only mimic the mild stage or, at most, moderate stage of COPD patients. The authors also suggest that further research is required on how to enhance the engraftment of exogenous MSCs in damaged lungs. Further, considering the anti-inflammatory and immunomodulatory effects of exogenous MSCs, it may be that they are most effective in acute lung disease rather than in chronic progressive disease with severe structural damage. Other methodological concerns include the practice of thawing the MSCs immediately before infusion. Newly thawed MSCs lose some of their immunomodulatory capabilities, and it may be more effective to use fresh MSCs or cultured MSCs approximately 24 hours after thawing. The authors also point out that bone marrow derived MSCs have decreased differentiation potential and may be suboptimal for this line of therapy. Autologous adipocyte mesenchymal cells (AD-MSCs) may be a better option than bone marrow derived autologous

cells. Other significant modifiable parameters that may play a role include the doses of cells, dosing approaches, frequency of dosing, selection of study endpoints, age and number of patient cases. The hLSCs differentiate into both epithelial cells and vascular cells in preclinical studies. They seem to have greater integrative and replacement potential compared to the MSCs. There has been limited work with these cells so far in COPD models. Intrinsic cell therapy studies based on the mobilization of endogenous stem cells or progenitor cells have largely emphasized retinoic acid compounds. This included two phase II clinical trials. These trials were for 52 weeks and unfortunately did not show any significant benefit. More preclinical research is required to show if retinoid compounds can activate endogenous human stem progenitor cells.

## **Abstract 2 Mesenchymal Stem Cell Administration in Patients with Chronic Obstructive Pulmonary Disease: State of the Science**

Cheng SL, Lin CH, Yao CL. *Stem Cells Int.* 2017; Epub 2017 Feb 20.

doi: <https://doi.org/10.1155/2017/8916570>

Patients with chronic obstructive pulmonary disease (COPD) have chronic, irreversible airway inflammation; currently, there is no effective or curative treatment and the main goals of COPD management are to mitigate symptoms and improve patients' quality of life. Stem cell-based therapy offers a promising therapeutic approach that has shown potential in diverse degenerative lung diseases. Preclinical studies have demonstrated encouraging outcomes of mesenchymal stem/stromal cells (MSCs) therapy for lung disorders including emphysema, bronchopulmonary dysplasia, fibrosis, and acute respiratory distress syndrome. This review summarizes available data on 15 studies currently registered by the ClinicalTrials.gov repository, which used different stem cell therapy protocols for COPD; these included bone marrow mononuclear cells (BMMCs), bone marrow-derived MSCs, adipose-derived stem/stromal cells (ADSCs), and adipose-derived MSCs. Published results of three trials indicate that administering BMMCs or MSCs in the setting of

degenerative lung disease is safe and may improve patients' condition and quality of life; however, larger-scale studies are needed to evaluate efficacy. Results of another completed trial (NCT01872624) are not yet published, and eleven other studies are ongoing; these include MSCs therapy in emphysema, several studies of ADSCs in COPD, another in idiopathic pulmonary fibrosis, and plerixafor mobilization of CD117 stem cells to peripheral blood.

## **Comments**

This is another review article from early 2017 that provides a comprehensive list of the registered studies, but it is more of a catalogue of the studies completed and in progress, (both preclinical and clinical) rather than providing significant critique of the study designs or findings. Nonetheless, it is a good resource for anyone wishing to do further review of the state of current research on this topic.

## **Abstract 3 Exhaustion of Airway Basal Progenitor Cells in Early and Established Chronic Obstructive Pulmonary Disease**

Ghosh M, Miller YE, Nakachi I, et al. *Am J Respir Crit Care Med.* 2018;197(7):885-896.

doi: <https://doi.org/10.1164/rccm.201704-0667OC>

### **RATIONALE:**

Up to 40% of smokers develop chronic obstructive pulmonary disease (COPD) over a period that spans decades. Despite the importance of COPD, much remains to be learned about susceptibility and pathogenesis, especially during early, pre-diagnostic stages of disease. Airway basal progenitor cells are crucial for lung health and resilience because of their ability to repair injured airways. In COPD, the normal airway epithelium is replaced with increased basal and secretory (mucous) cells and decreased ciliated cells, suggesting that progenitors are impaired.

### **OBJECTIVES:**

To examine airway basal progenitor cells and lung function in smokers with and without COPD.

**METHODS:**

Bronchial biopsies taken from smokers at risk for COPD and lung cancer were used to acquire airway basal progenitor cells. They were evaluated for count, self-renewal, and multipotentiality (ability to differentiate to basal, mucous, and ciliated cells), and progenitor count was examined for its relationship with lung function.

**MEASUREMENTS AND MAIN RESULTS:**

Basal progenitor count, self-renewal, and multipotentiality were all reduced in COPD versus non-COPD. COPD progenitors produced an epithelium with increased basal and mucous cells and decreased ciliated cells, replicating the COPD phenotype. Progenitor depletion correlated with lung function and identified a subset of subjects without COPD with lung function that was midway between non-COPD with high progenitor counts and those with COPD.

**CONCLUSIONS:**

Basal progenitor dysfunction relates to the histologic and physiologic manifestations of COPD and identifies a subset that may represent an early, prediagnostic stage of COPD, indicating that progenitor exhaustion is involved in COPD pathogenesis.

**Comments**

Airway progenitor cells are critical for lung health and resilience. These investigators postulate that alterations in the airway epithelium may be related to airway basal progenitor cell dysfunction. Progenitor count was chosen as the primary outcome largely because it required the least manipulation and was completed within 7 days after bronchoscopy and likely best mirrored the *in vivo* phenotype. This was a small study with 31 patients in the non-COPD group and 19 patients in the COPD group. In the COPD cohort, 4 patients had Global Initiative for Chronic Obstructive Lung Disease<sup>1</sup> Stage 1 COPD by spirometric criteria, 12 had stage 2, 2 had stage 3 and 1 patient had stage 4 COPD. The finding, that a subset of individuals without COPD but with lower lung function than the rest of the non-COPD control group appeared to have a proportional reduction in the basal progenitor count, raises the question that this methodology could enable identification of individuals who have increased COPD

susceptibility early on. Another interesting finding was that co-immunostaining for Muc 5B and Muc 5Ac, (2 major mucins of the airways), showed that both have comparable expression in individuals without COPD. However, for those with COPD, the Muc 5B expression was higher for former smokers and both Muc 5 and Muc 5Ac were upregulated in current smokers. These findings all support the notion that COPD airway basal progenitors have been programmed to create a COPD-like epithelium. Further understanding of this mechanism may allow discovery of methods to reverse the phenotype and restore normal airway epithelium. Ideally, it may be possible to discover biologic surrogates of progenitor dysfunction allowing earlier identification of those at risk. Ultimately, this line of research may lead to improving the ability to detect, prevent and treat COPD earlier when maximum benefit can be achieved.

**Abstract 4****Can Youthful Mesenchymal Stem Cells from Wharton's Jelly Bring a Breath of Fresh Air for COPD?**

Janczewski AM, Wojtkiewicz J, Malinowska E, Doboszyńska A. *Int J Mol Sci.* 2017;18(11): E2449. doi: <https://doi.org/10.3390/ijms18112449>

Chronic obstructive pulmonary disease (COPD) is a major global cause of morbidity and mortality, projected to become the 3rd cause of disease mortality worldwide by 2020. COPD is characterized by persistent and not fully reversible airflow limitation that is usually progressive and is associated with an abnormal chronic inflammatory response of the lung to noxious agents including cigarette smoke. Currently available therapeutic strategies aim to ease COPD symptoms but cannot prevent its progress or regenerate physiological lung structure or function. The urgently needed new approaches for the treatment of COPD include stem cell therapies among which transplantation of mesenchymal stem cells derived from Wharton's jelly (WJ-MSCs) emerges as a promising therapeutic strategy because of the unique properties of these cells. The present review discusses the main biological properties of WJ-MSCs pertinent



to their potential application for the treatment of COPD in the context of COPD pathomechanisms with emphasis on chronic immune inflammatory processes that play key roles in the development and progression of COPD.

## Comments

The authors point out that there are concerns that the therapeutic efficacy of autologous bone marrow mesenchymal stem cells (BM-MSCs) and AD-MSCs in older patients may be compromised by several age-related factors including oxidative stress, telomere length, DNA damage, chronic disease and long-term use of various medications. It is believed that the neonatal tissue derived MSC's such as found in Wharton's jelly (WJ-MSCs) may adapt better to the host tissue environment and possess superior anti-inflammatory and immunomodulatory actions. Wharton's jelly is a gelatinous substance found within the umbilical cord and is largely made up of mucopolysaccharides and is derived from extra embryonic mesoderm.

Mesenchymal cells that are derived from Wharton's jelly represent a primitive stromal cell population. WJ-MSCs have been studied in diabetes and systemic lupus erythematosus but not in COPD to date. As the authors point out, WJ-MSCs have unique properties that make them a favorable source for mesenchymal cells including factors such as their more primitive characteristics, abundant availability, noninvasive and painless collection, technically simple isolation, lack of teratogenicity and immunogenicity and the lack of ethical concerns. The authors offer that they are considered to be comparable to bone marrow derived MSCs and adipose tissue derived MSCs in terms of surface markers and cellular characteristics but have a higher proliferation capacity and a longer lifespan. The authors provide the background and rationale for why there is increased interest in the use of these WJ-MSCs in stem cell therapy in COPD patients and discuss some of the pre-clinical studies performed to date. This is a well written paper with helpful summary tables of previous studies and a comprehensive and current reference list.

## References

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