CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

1. COPD PROTOCOL

A. Clinical response: Patients may experience improvements in function and quality of life parameters. This could include improvements in lung capacity as measured by exercise capacity. Patients may also experience improvements in the St. George Respiratory Questionnaire.

B. Objective: To provide the patient with a treatment that stimulates his / her immune system, promote cellular regeneration and improve symptoms associated with COPD. The intravenous Ad-SVF Containing Adult Stem Cell Procedure should serve to compliment the patient's current treatment regimen or to promote healing when current treatment is not responding.

2. PRELIMINARIES

A. Background: COPD is a lung disease that blocks airflow, causing patients to experience a difficulty in breathing. COPD can also cause coughing, the production of mucus, shortness of breath, wheezing, and constriction of the chest [1]. COPD causes a restriction of airflow in and out of the body. COPD is a progressive disease that develops slowly, but consistently becomes worse over time. There are two main conditions characterized by patients with COPD: Chronic Bronchitis and Emphysema.

- ***Chronic Bronchitis***: results in a thickening of the airways inner lining due to mucus formation, which leads to a decrease in lung capacity
- ***Emphysema***: results in destruction of the air sacs walls and the walls between the air sacs, which leads to fewer air sacs and ultimately a reduction in gas exchange

B. Causes of COPD**:**

- ***Lung Irritants***: extended exposure to lung irritants that impair the lungs
  - Firsthand smoke (cigarette, pipe, cigar, etc)
  - Air pollution, chemical fumes, or dust from environment

- ***Alpha-1 Antitrypsin Deficiency***: A rare genetic condition where people have low levels of the protein made in the liver known as alpha-1 antitrypsin (AAT). This rare condition may make you more susceptible to lung irritants, causing COPD to progressive more aggressively.

- ***Asthma***: is a chronic lung disease that inflames and narrows the breathing airways

C. Treatment Options [2]:

- ***Avoid Lung Irritants***

- ***Make Lifestyle Changes***: These include: quitting smoking, maintain a healthy weight, meeting your nutritional needs, strengthening your muscles by increasing your physical activity, and any other initiative to improve your overall wellness.

- ***Medicines***
  - *Bronchodilators*: Administered with a device called an inhaler, bronchodilators help relax the muscles around your airways. There are two types of bronchodilators: Short acting, which is used on an as needed basis with effects that last 4-6 hour periods, or long acting bronchodilators, which is used daily basis with effects that last 12 hours.
  - *Combination Bronchodilators Plus Inhaled Glucocorticosteroids (Steroids)*: Steroids are used in conjunction with bronchodilators to help reduce airway inflammation.

- ***Vaccines***: COPD patients have higher risk for catching the flu and pneumonia. Vaccinations will help prevent serious health complications from occurring.
  - Flu Shots
  - Pneumococcal Vaccine

- ***Pulmonary Rehabilitation***: is a program that helps improve the well-being of people who have COPD. Programs usually include initiatives to make lifestyle changes to help manage the COPD including exercise program, disease management training, and nutritional and psychological counseling.

- ***Oxygen Therapy***: helps increase the level of oxygen in your blood by giving you oxygen through nasal prongs or a mask.

- ***Surgery***
  - *Bullectomy*: the removal of over enlarged bullae(s) from the lungs
  - *Lung Volume Reduction Surgery*: the removal of damaged tissue from the lungs
  - *Lung Transplant*: removal of your damaged lung and replacement with a healthy lung from a deceased donor

3. AD-SVF CONTAINING ADULT STEM CELLS TREATMENT OPTION

A. Ad-SVF Containing Adult Stem Cells Procedure

- ***Initial patient evaluation***: A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

- ***Pre-op Evaluation / post-op medical consultation***: A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

- ***Harvesting of adipose tissue***:
  - ***Application of anesthetic / injection of tumescent solution***
  - ***Waiting time***
  - ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. A tissue sample is then obtained using 60 cc syringe(s) to aspirate 50 to 100 cc of adipose tissue. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

- ***Autologous implant of Ad-SVF***: The stem cells obtained from the adipose tissue sample are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused in 5-10ml normal saline intravenously with a slow bolus push.

B. Risks: There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of perfect results, excellent results can be attained. The surgeon provides services in the most responsible, professional and diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Pain at site of injections
- Bleeding at injection site
- Malaise
- Low-grade fever
- Hot flashes
- Itching at injection site
- Vascular spasm or obstruction
- Bruising
- Nerve or muscle injury
- Allergic reaction
- Dizziness
- Nausea
- Vomiting

C. Benefit: Adipose derived stem cells exhibit immunomodulatory and anti-inflammatory properties that may help repair the airways and improve the elasticity of the patient's lungs.

D. Follow-up plan: Clinical response showing improvements in quality of life or quantitative parameters. International standards for follow-up:

- ***Pre- Ad-SVF implant:*** St. George Questionnaire, 6 minute walk test, pulmonary function test

- ***3 months after Ad-SVF implant:*** St. George Questionnaire, 6 minute walk test, pulmonary function test

- ***6 months after Ad-SVF implant:*** St. George Questionnaire, 6 minute walk test, pulmonary function test

COPD – Adult Stem Cells Schedule of Events

1. **Initial Patient Evaluation:** A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

   A. Pre-Examination:
   - You will have a physical exam, which will include measuring your blood pressure, temperature and heart rate (vital signs).
   - Your doctor will discuss your medical history and any medications that you are taking.
   - Your doctor will assess how well you can perform your daily activities
   - If needed, you will have a urine or blood pregnancy test.
   - Blood will be taken.

   B. Additional Tests: should be done during or soon after this visit

   - Pulmonary Function Tests
   - Determine exercise capacity with the six minute walk distance test
   - St. George Questionnaire

   C. Review Results: After your doctor has reviewed the results of these tests, he or she will assess whether you are a good candidate for stem cell therapy. If you decide to obtain this therapy you will sign a consent form. A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

2. **Pre-Operation / Stem Cell Procedure:**

   A. Two Weeks Before Procedure:

   - No Aspirin or medicines that contain aspirin or Ibuprofen since it interferes with normal blood clotting.
   - Discuss with your primary physician to discontinue anticoagulant drugs at least 1 week before the procedure.
   - Please discontinue all herbal medications as many have side effects that could complicate a surgical procedure by inhibiting blood clotting, affecting blood pressure, or interfering with anesthetics.
   - Please discontinue all diet pills whether prescription, over-the-counter or herbal.
   - NO SMOKING because nicotine reduces blood flow to the skin and can cause significant complications during healing.
   - You may take Tylenol or generic forms of this drug.
   - Purchase a compressive garment to wear after the lipoaspiration procedure.

B. Morning of the Procedure:

- Have a light breakfast.
- Take your regular prescribed medications
- Wear comfortable, loose-fitting clothes that do not have to be put on over your head.

3. Stem Cell Procedure:

A. Preparation & Harvesting of Adipose Tissue:

- ***Application of anesthetic / injection of tumescent solution***
- ***Waiting time (~15 – 20 minutes)***
- ***Acquisition of blood sample***
- ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

B. ***Autologous implant of Ad-SVF***: The stem cells obtained from the adipose tissue sample are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused in 5-10ml normal saline intravenously with a slow bolus push.

4. Recommended Post-Operation / Stem Cell Therapy Schedule:

- Post-Op Medical Instruction - **(Please follow these instructions closely!)**
  - ***Post-op medication*** will be given to you the day of your surgery. They will consist of an antibiotic and a painkiller:
    - *Antibiotic*: Cephalexin/Cipro, please take as directed beginning the day after surgery
    - *Painkiller:* Please take as directed and only as needed for pain

      * If you are unable to take any of these medications, please contact your patient coordinator so we can arrange for other medications.
  - ***Resume previous medication*** as directed by the physician
  - ***Report any symptoms of feeling unwell***: fever, pain etc. Patients should be seen promptly by an ophthalmologist for full evaluation should any of the above symptoms be encountered.
  - It is recommended that the ***patient have a companion stay with him or her*** for at least 24 hours after discharge.
  - You should ***expect some of blood-tinged anesthetic solution to drain from the incision sites*** during the first 24 to 48 hours. This will vary from patient to

patient. Maxi-pads are recommended for bandages over your incision sites. You may take a shower 24 hours after the procedure.

- ***Compressive garments should be worn*** 24 hours a day for the first week and 12 hours a day for the second week.
- ***Do not shower for the first 24 hours***. ***Do not submerge yourself in any water*** (i.e. taking a bath or swimming) for the 1st week.
- ***If you experience nausea or vomiting it is probably due to the medication***. Please try to take it with food. If it persists, please contact our office.
- ***Diet-meals are not restricted.***
- ***Drink plenty of clear fluids***. We recommend 8 glasses of water or fruit juice every day.
- ***Do not drink any alcohol*** for 48 hours and limit alcohol intake for the first week.

- <u>Post-Op Medical Consultation Schedule: 3 months & 6 months</u>
  - Review of medical history
  - Review of medication history
  - Review of any adverse events since the previous visit
  - Pulmonary Function Tests
  - Determine exercise capacity with the six minute walk distance test
  - St. George Questionnaire

Your doctor will contact you by phone within the first week to follow up then future follow up visits will be arranged through your patient coordinator. If you need assistance before do not hesitate to contact us.

COPD – 6 Minute Walk Test (6MWT)

Details of performing Six Minute Walk Test (6MWT)

These details have been taken from the following:
American Thoracic Society (ATS) statement: Guidelines for the Six-Minute Walk Test
(Am J Respir Crit Care Med 2002; 166:111-117).

The six-minute walk test (6MW) should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom used. The walking course must be:

- 15 m - 30 m /50 ft -100 ft in length.
- The length of the corridor should be marked every 3 m / 10 ft.
- The turnaround points should be marked with a cone (such as a traffic cone).
- A starting line, which marks the beginning and end of each 30 m - 60 m lap, should be marked on the floor using brightly colored tape.

The same course used for baseline evaluation should be used throughout the study.

The use of a treadmill for 6-minute walk testing is not recommended.

What you will need:
- A stopwatch or countdown timer;
- A mechanical lap counter;
- Two small cones to match the turnaround points;
- A chair that can be easily moved along the walking course;
- Worksheets;
- A source of oxygen;
- A sphygmomanometer;
- A telephone; and
- An automated electronic defibrillator

The patient should be told to wear comfortable clothing and appropriate shoes for the test. The patient should also be informed to use their usual walking aids during the test. The patient should continue to use their usual medicine regime and should not have had a heavy meal before the test. The patient should not have exercised vigorously within 2 hours of the test.

Instructions:

1. Repeat testing should be performed about the same time of day to minimize intra-day variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artefact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.
5. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
6. Instruct the patient as follows:

7. ***"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.***

8. ***You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."***

9. ***Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.***

10. ***"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line.***

11. ***Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.***

12. ***Start now or whenever you are ready."***

13. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

14. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

15. Do not use other words of encouragement (or body language to speed up). Only the standardized phrases for encouragement (as specified previously here) must be used during the test, as follows:
16. *After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."*
17. *When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."*
18. *When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."*
19. *When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."*
20. *When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."*
21. If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.
22. When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."
23. When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.
24. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
25. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
26. Record the number of laps from the counter (or tick marks on the worksheet).
27. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
28. Congratulate the patient on good effort and offer a drink of water.

COPD – Pulmonary Function Tests

Pulmonary Function Tests: a.k.a lung function tests

- Measure the effectiveness and efficiency of your lungs based on various metrics
- Potentially help determine the causes of your breathing problems

Types of Pulmonary Function Tests:

Breathing Tests:

- ***Body Plethysmography***: measures your lung capacity – how much air can you retain in your lungs when you take a full breath, as well as how much air is left over in your lungs once you release your breath
- ***Lung Diffusion Capacity***: How efficient are your lungs are at delivering oxygen to your bloodstream
- ***Spirometry***: measures how effective are your lungs – how much air can you expel from your lungs and how quickly you are able to do it

Blood Oxygen Level Tests:

- ***Pulse Oximetry***: utilizes a specialized light to measure your blood oxygen level
- ***Arterial Blood Gas Test***: utilizes a sample of your blood to measure your oxygen level

What Are Lung Function Tests?. *National Heart Lung and Blood Institute*. 2012. Web. 12/11/13.

COPD – Supporting Studies

Chest. 2013 Jun;143(6):1590-8. doi: 10.1378/chest.12-2094.

A placebo-controlled, randomized trial of mesenchymal stem cells in COPD.

Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. Source. Vermont Lung Center, University of Vermont College of Medicine, Burlington, VT 05405, USA. dweiss@uvm.edu

Abstract

BACKGROUND:

COPD is a devastating disease affecting millions worldwide. As disease pathogenesis includes both chronic pulmonary and systemic inflammation, antiinflammatory effects of systemically administered mesenchymal stem cells (MSCs) may decrease inflammation, resulting in improved lung function and quality of life. The goal of this study was to assess safety and to perform an initial evaluation of the potential efficacy of systemic MSC administration to patients with moderate to severe COPD.

METHODS:

Sixty-two patients at six sites were randomized to double-blinded IV infusions of either allogeneic MSCs (Prochymal; Osiris Therapeutics Inc) or vehicle control. Patients received four monthly infusions (100×10^6 cells/infusion) and were subsequently followed for 2 years after the first infusion. End points included comprehensive safety evaluation, pulmonary function testing (PFT), and quality-of-life indicators including questionnaires, 6MWT, and assessments of systemic inflammation.

RESULTS:

All study patients completed the full infusion protocol, and 74% completed the 2-year follow-up. There were no infusional toxicities and no deaths or serious adverse events deemed related to MSC administration. There were no significant differences in the overall number of adverse events, frequency of COPD exacerbations, or worsening of disease in patients treated with MSCs. There were no significant differences in PFTs or quality-of-life indicators; however, an early, significant decrease in levels of circulating C-reactive protein (CRP) was observed in patients treated with MSCs who had elevated CRP levels at study entry.

CONCLUSIONS:

Systemic MSC administration appears to be safe in patients with moderate to severe COPD and provides a basis for subsequent cell therapy investigations.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00683722; URL: www.clinicaltrials.gov.

COPD – Supporting Studies

Rev Port Pneumol. 2013 Nov 25. pii: S0873-2159(13)00107-4. doi: 10.1016/j.rppneu.2013.06.008.

A protocol proposition of cell therapy for the treatment of Chronic Obstructive Pulmonary Disease.

Ribeiro-Paes JT, Stessuk T, Yonashiro Marcelino M, Arruda de Faria C, Quiqueto Marinelli T, de Oliveira Ribeiro-Paes MJ. Source Departamento de Ciências Biológicas, Universidade Estadual Paulista - Unesp - Assis, SP, Brasil. Electronic address: jtrpaes@yahoo.com.br.

Abstract

The main feature of pulmonary emphysema is airflow obstruction resulting from the destruction of the alveolar walls distal to the terminal bronchioles. Existing clinical approaches have improved and extended the quality of life of emphysema patients. However, no treatment currently exists that can change the disease course and cure the patient. The different therapeutic approaches that are available aim to increase survival and/or enhance the quality of life of emphysema patients. In this context, cell therapy is a promising therapeutic approach with great potential for degenerative pulmonary diseases. In this protocol proposition, all patients will be submitted to laboratory tests, such as evaluation of heart and lung function and routine examinations. Stem cells will be harvested by means of 10 punctures on each anterior iliac crest, collecting a total volume of 200mL bone marrow. After preparation, separation, counting and labeling (optional) of the mononuclear cells, the patients will receive an intravenous infusion from the pool of Bone Marrow Mononuclear Cells (BMMC). This article proposes a rational and safe clinical cellular therapy protocol which has the potential for developing new projects and can serve as a methodological reference for formulating clinical application protocols related to the use of cellular therapy in COPD. This study protocol was submitted and approved by the Brazilian National Committee of Ethics in Research (CONEP - Brazil) registration number 14764. It is also registered in ClinicalTrials.gov (NCT01110252).

COPD – Supporting Studies

Rev Bras Hematol Hemoter. 2013;35(5):352-357.

Phase I clinical trial of cell therapy in patients with advanced chronic obstructive pulmonary disease: follow-up of up to 3 years.

Stessuk T, Ruiz MA, Greco OT, Bilaqui A, Ribeiro-Paes MJ, Ribeiro-Paes JT. Source Universidade de São Paulo - USP, São Paulo, SP, Brazil.

Abstract

BACKGROUND:

Chronic obstructive pulmonary disease is a major inflammatory disease of the airways and an enormous therapeutic challenge. Within the spectrum of chronic obstructive pulmonary disease, pulmonary emphysema is characterized by the destruction of the alveolar walls with an increase in the air spaces distal to the terminal bronchioles but without significant pulmonary fibrosis. Therapeutic options are limited and palliative since they are unable to promote morphological and functional regeneration of the alveolar tissue. In this context, new therapeutic approaches, such as cell therapy with adult stem cells, are being evaluated.

OBJECTIVE:

This article aims to describe the follow-up of up to 3 years after the beginning of a phase I clinical trial and discuss the spirometry parameters achieved by patients with advanced pulmonary emphysema treated with bone marrow mononuclear cells.

METHODS:

Four patients with advanced pulmonary emphysema were submitted to autologous infusion of bone marrow mononuclear cells. Follow-ups were performed by spirometry up to 3 years after the procedure.

RESULTS:

The results showed that autologous cell therapy in patients having chronic obstructive pulmonary disease is a safe procedure and free of adverse effects. There was an improvement in laboratory parameters (spirometry) and a slowing down in the process of pathological degeneration. Also, patients reported improvements in the clinical condition and quality of life.

CONCLUSIONS:

Despite being in the initial stage and in spite of the small sample, the results of the clinical protocol of cell therapy in advanced pulmonary emphysema as proposed in this study, open new therapeutic perspectives in chronic obstructive pulmonary disease. It is worth emphasizing that this study corresponds to the first study in the literature that reports a change in the natural history of pulmonary emphysema after the use of cell therapy with a pool of bone marrow mononuclear cells.

COPD – Supporting Studies

Exp Lung Res. 2013 Oct;39(8):315-27. doi: 10.3109/01902148.2013.816803. Epub 2013 Aug 30.

Mesenchymal stem cell therapy in lung disorders: pathogenesis of lung diseases and mechanism of action of mesenchymal stem cell.

Inamdar AC, Inamdar AA. Source 1Saiseva Biotech Pvt. Ltd., Satara, India.

Abstract

Lung disorders such as asthma, acute respiratory distress syndrome (ARDS), chronic obstructive lung disease (COPD), and interstitial lung disease (ILD) show a few common threads of pathogenic mechanisms: inflammation, aberrant immune activity, infection, and fibrosis. Currently no modes of effective treatment are available for ILD or emphysema. Being anti-inflammatory, immunomodulatory, and regenerative in nature, the administration of mesenchymal stem cells (MSCs) has shown the capacity to control immune dysfunction and inflammation in the lung. The intravenous infusion of MSCs, the common mode of delivery, is followed by their entrapment in lung vasculature before MSCs reach to other organ systems thus indicating the feasible and promising approach of MSCs therapy for lung diseases. In this review, we discuss the mechanistic basis for MSCs therapy for asthma, ARDS, COPD, and ILD.

COPD – Supporting Studies

Stem Cells. 2013 Aug 20. doi: 10.1002/stem.1506. [Epub ahead of print]

Current status of stem cells and regenerative medicine in lung biology and diseases.

Weiss DJ. Source. Department of Medicine, University of Vermont College of Medicine, Burlington, VT, 05405.

Abstract

Lung diseases remain a significant and devastating cause of morbidity and mortality worldwide. In contrast to many other major diseases, lung diseases notably chronic obstructive pulmonary diseases (COPD), including both asthma and emphysema, are increasing in prevalence and COPD is expected to become the 3rd leading cause of disease mortality worldwide by 2020. New therapeutic options are desperately needed. A rapidly growing number of investigations of stem cells and cell therapies in lung biology and diseases as well as in ex vivo lung bioengineering have offered exciting new avenues for advancing knowledge of lung biology as well as providing novel potential therapeutic approaches for lung diseases. These initial observations have led to a growing exploration of endothelial progenitor cells and mesenchymal stem (stromal) cells in clinical trials of pulmonary hypertension and chronic obstructive pulmonary disease (COPD) with other clinical investigations planned. Ex vivo bioengineering of the trachea, larynx, diaphragm, and the lung itself with both biosynthetic constructs as well as decellularized tissues have been utilized to explore engineering both airway and vascular systems of the lung. Lung is thus a ripe organ for a variety of cell therapy and regenerative medicine approaches. Current state-of-the-art progress for each of the above areas will be presented as will discussion of current considerations for cell therapy based clinical trials in lung diseases. Stem Cells 2013.

COPD – Supporting Studies

Respirology. 2013 May 7. doi: 10.1111/resp.12112. [Epub ahead of print]

Adult stem cells for chronic lung diseases.

Mora AL, Rojas M. Source Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA.; Vascular Medicine Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA.

Abstract

Idiopathic pulmonary fibrosis (IPF) and Chronic Obstructive Pulmonary Disease (COPD) are chronic, progressive and lethal lung diseases. The incidence of IPF and COPD increases with age, independent of exposure to common environmental risk factors. At present, there is limited understanding of the relationship between aging and the development of chronic lung diseases. One hypothesis is that chronic injury drives to exhaustion the local and systemic repair responses in the lung. These changes are accentuated during aging where there is a progressive accumulation of senescent cells. Recently, stem cells have emerged as a critical reparative mechanism for lung injury. In this review, we discuss the repair response of bone marrow derived mesenchymal stem cells (B-MSCs) after lung injury and how their function is affected by aging. Our own work has demonstrated a protective role of B-MSCs in several animal models of acute and chronic lung injury. We recently demonstrated the association, using animal models, between age and an increase in the susceptibility to develop severe injury and fibrosis. At the same time, we have identified functional differences between B-MSCs isolated from young and old animals. Further studies are required to understand the functional impairment of aging B-MSCs, ultimately leading to a rapid stem cell depletion or fatigue, interfering with their ability to play a protective role in lung injury. The elucidation of these events will help in the development of rational and new therapeutic strategies for COPD and IPF.

COPD – Supporting Studies

Cells. 2012 Dec;1(4):874.

The Potential for Resident Lung Mesenchymal Stem Cells to Promote Functional Tissue Regeneration: Understanding Microenvironmental Cues.

Foronjy RF, Majka SM. Source. Department of Medicine, St. Luke's Roosevelt Health Sciences center, Antenucci Building, 432 West 58th Street, Room 311, New York, NY 10019, USA; rforonjy@chpnet.org ; Tel.: +1-212-523-7265.

Abstract

Tissue resident mesenchymal stem cells (MSCs) are important regulators of tissue repair or regeneration, fibrosis, inflammation, angiogenesis and tumor formation. Bone marrow derived mesenchymal stem cells (BM-MSCs) and endothelial progenitor cells (EPC) are currently being considered and tested in clinical trials as a potential therapy in patients with such inflammatory lung diseases including, but not limited to, chronic lung disease, pulmonary arterial hypertension (PAH), pulmonary fibrosis (PF), chronic obstructive pulmonary disease (COPD)/emphysema and asthma. However, our current understanding of tissue resident lung MSCs remains limited. This review addresses how environmental cues impact on the phenotype and function of this endogenous stem cell pool. In addition, it examines how these local factors influence the efficacy of cell-based treatments for lung diseases.

COPD – Supporting Studies

Cells. 2012 Dec;1(4):874. Pulm Med. 2013;2013:874161. doi: 10.1155/2013/874161. Epub 2013 Jan 14.

Using Cell-Based Strategies to Break the Link between Bronchopulmonary Dysplasia and the Development of Chronic Lung Disease in Later Life.

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Abstract

Bronchopulmonary dysplasia (BPD) is the chronic lung disease of prematurity that affects very preterm infants. Although advances in perinatal care have changed the course of lung injury and enabled the survival of infants born as early as 23-24 weeks of gestation, BPD still remains a common complication of extreme prematurity, and there is no specific treatment for it. Furthermore, children, adolescents, and adults who were born very preterm and developed BPD have an increased risk of persistent lung dysfunction, including early-onset emphysema. Therefore, it is possible that early-life pulmonary insults, such as extreme prematurity and BPD, may increase the risk of COPD later in life, especially if exposed to secondary challenges such as respiratory infections and/or smoking. Recent advances in our understanding of stem/progenitor cells and their potential to repair damaged organs offer the possibility of cell-based treatments for neonatal and adult lung injuries. This paper summarizes the long-term pulmonary outcomes of preterm birth and BPD and discusses the recent advances of cell-based therapies for lung diseases, with a particular focus on BPD and COPD.

COPD – Supporting Studies

Stem Cell Rev. 2012 Dec;8(4):1236-44. doi: 10.1007/s12015-012-9410-7.

Experimental basis and new insights for cell therapy in Chronic Obstructive Pulmonary Disease.

de Faria CA, de las Heras Kozma R, Stessuk T, Ribeiro-Paes JT.

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Abstract
Chronic Obstructive Pulmonary Disease (COPD) can be briefly described as air flow limitation and chronic dyspnea associated to an inflammatory response of the respiratory tract to noxious particles and gases. Its main feature is the obstruction of airflow and consequent chronic dyspnea. Despite recent advances, and the development of new therapeutic, medical and clinical approaches, a curative therapy is yet to be achieved. Therapies involving the use of tissue-specific or donor derived cells present a promising alternative in the treatment of degenerative diseases and injuries. Recent studies demonstrate that mesenchymal stem cells have the capacity to modulate immune responses in acute lung injury and pulmonary fibrosis in animal models, as well as in human patients. Due to these aspects, different groups raised the possibility that the stem cells from different sources, such as those found in bone marrow or adipose tissue, could act preventing the emphysematous lesion progression. In this paper, it is proposed a review of the current state of the art and future perspectives on the use of cell therapy in obstructive lung diseases.

PMID: 23054962 [PubMed - indexed for MEDLINE]

COPD – References

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