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Francesco Petrella, MD



BACKGROUND

- Bronchopleural fistula is a pathological connection between the airway (bronchus) and the pleural space that may develop after lung resection
- Its mortality rate ranges from 12.5 to 71.2%
- The clinical effect of impaired bronchial stump healing after anatomic lung resection may culminate in a life-threatening septic and ventilatory catastrophe
- For many patients with empyema, the presence or absence of a fistula makes the difference between recovery, chronicity or death

BACKGROUND

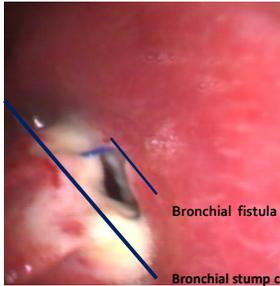


Normal bronchial division



Normal bronchial stump following right pneumonectomy

BACKGROUND



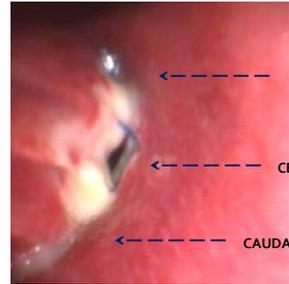
Bronchial fistula in a right main stem bronchus

Bronchial fistula caliber (30%)

Bronchial stump caliber



BACKGROUND



APICAL

CENTRAL

CAUDAL



EXPERIMENTAL STUDY DESIGN



18 GOATS (♂): EXPERIMENTAL GROUP (MSC + fibrin glue)

12 GOATS (♂): CONTROL GROUP (fibrin glue alone)

GENERAL ANAESTHESIA

DOUBLE LUMEN VENTILATION

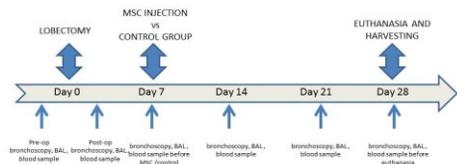
BRONCHIAL STUMP MANUAL SUTURE

VASCULAR LIGATION OR STAPLING

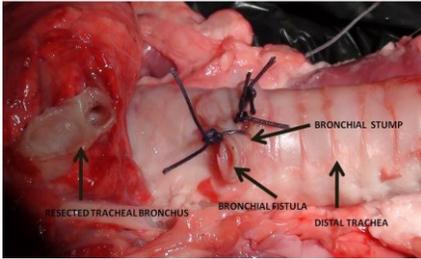


EXPERIMENTAL STUDY DESIGN

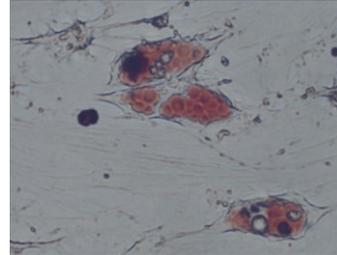
Step-by-step Transplant Procedures



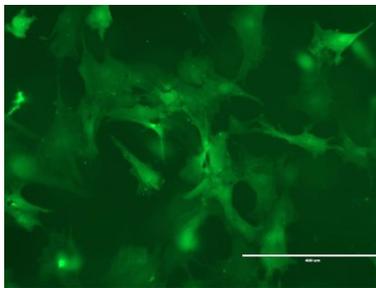
BPF EXPERIMENTAL MODEL



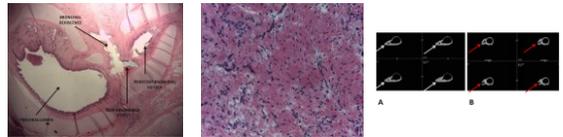
GOAT MSC ADIPOGENIC DIFFERENTIATION



GOAT MSC GROWTH ON MODIFIED GLUE



EXPERIMENTAL RESULTS



EXPERIMENTAL RESULTS

EDUCATIONAL TRENDS

Stem Cell Transplantation Effectively Occludes Bronchopleural Fistula in an Animal Model

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(Ann Thorac Surg 2014;97:1480-3)
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CLINICAL EXPERIENCE - BACKGROUND

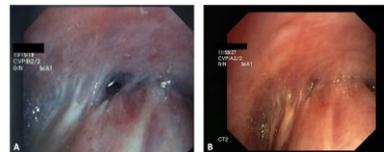
- 42-year-old male firefighter suffering from early stage malignant mesothelioma
- Post chemotherapy right extrapleural pneumonectomy
- On post-operative day 18, the patient developed BPF
- Permission from the Ethics Committee
- Notification to the Italian drug agency (AIFA)
- Written informed consent from the patient



CLINICAL EXPERIENCE - PROCEDURE

- Standard bone marrow aspiration
- Stem cells isolation, expansion and culture (GMP)
- MSC quality controls
- Bronchoscopic implantation
- Post operative care and monitoring
- 6 months clinical, lab and imaging follow up

CLINICAL EXPERIENCE - RESULTS

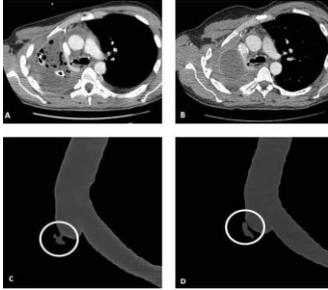


PRE - IMPLANT

POST - IMPLANT



CLINICAL EXPERIENCE - RESULTS



CLINICAL EXPERIENCE

The NEW ENGLAND JOURNAL OF MEDICINE

Airway Fistula Closure after Stem-Cell Infusion
N Engl J Med 2015; 372:26-37 | January 1, 2015 | DOI: 10.1056/NEJM1411174

Authors: Francesco Petrella, M.D., European Institute of Oncology, Milan, Italy; Francesco Petrella, M.D., University of Milan, Milan, Italy; Massimo Belloni, M.D., European Institute of Oncology, Milan, Italy; Massimo Belloni, M.D., University of Milan School of Medicine, Milan, Italy; Stefano Ricca, D.V.M., Ph.D., University of Milan, Milan, Italy; Stefano D'Amico, M.D., European Institute of Oncology, Milan, Italy; Giuseppe Giacinto, Ph.D., European Institute of Oncology, Milan, Italy; Francesco Di Lorenzo, M.D., Fondazione IRCCS Cà Grande Ospedale Maggiore Policlinico, Milan, Italy; Giuliana Quarta, M.D., European Institute of Oncology, Milan, Italy; Lorenzo Spaggiari, M.D., European Institute of Oncology, Milan, Italy; Tiziana Martorelli, Ph.D., Fondazione IRCCS Cà Grande Ospedale Maggiore Policlinico, Milan, Italy; Susanna Tardito, M.D., European Institute of Oncology, Milan, Italy; Stefano Ricca, M.D., European Institute of Oncology, Milan, Italy; Giulia Carli, Ph.D., European Institute of Oncology, Milan, Italy; Lorenzo Spaggiari, M.D., Ph.D., University of Milan School of Medicine, Milan, Italy.

Abstract: Large airway defects and bronchovascular dehiscence after lung resection present a problem for clinicians because there are few effective methods of treatment. Bronchopleural fistula is a pathological connection between the airway and the pleural space that may develop after lung resection. For many patients with emphysema, the presence or absence of a fistula makes the difference between recovery, chronic disease, and death.^{1,2}

Background: In our previous preclinical experiments, we found that bronchoscopic transplantation of mesenchymal stem cells derived from bone marrow could close a bronchopleural fistula with the embryonic proliferation of fibroblasts and the development of collagenous scars.³ Encouraged by this result and by keratinized human organ replacement elsewhere,^{4,5} we transplanted autologous bone marrow-derived mesenchymal stem cells bronchoscopically to treat a 62-year-old male. Recurrence in whom bronchopleural fistula had developed after right subsegmental pneumonectomy for early-stage non-small-cell lung cancer. The presence of the bronchopleural fistula was confirmed on flexible bronchoscopy (Figure 1A) and chest computed tomography (Figure 1B and Fig. S2 in the Supplementary Appendix, available with this full text at NEJM.org).

Results: The patient underwent bone marrow aspirate followed by mesenchymal stem-cell isolation and expansion. Bronchoscopy was performed, and 10 million autologous bone marrow-derived mesenchymal stem cells were injected into the pars membranacea of the right main bronchial stump as described in the text and video in the Appendix.

Conclusion: This study shows that bronchoscopic transplantation of autologous bone marrow-derived mesenchymal stem cells can close a bronchopleural fistula.



CLINICAL EXPERIENCE

Author	Date	Journal	Site	Cell	Country
Alvarez, PD	Apr, 2008	Thorax	Trachea	ADMSC	
Petrella, F	Jan, 2015	NEJM	Bronchus	BMMSC	
Diaz Agero, PI	Jan, 2016	Cytotherapy	Bronchus	ADMSC	
Dua KS,	Ap, 2016	Lancet	Esophagus	PRP	

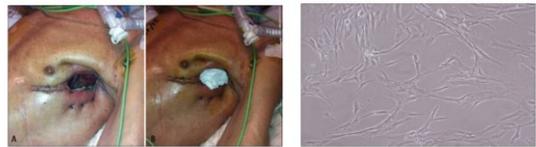


CLINICAL EXPERIENCE

Invited Editorial

Bronchopleural fistula treatment: From the archetype of surgery to the future of stem cell therapy

Lung India • Vol 32 • Issue 2 • Mar-Apr 2015



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CLINICAL EXPERIENCE

Review Article

Current Perspectives in Mesenchymal Stromal Cell Therapies for Airway Tissue Defects

Francesco Petrella,¹ Stefania Rizzo,² Alessandro Borri,¹ Monica Casiraghi,¹ and Lorenzo Spaggiari^{1,3}

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Stem Cells International
Article ID 746392



CLINICAL EXPERIENCE

Mini-review

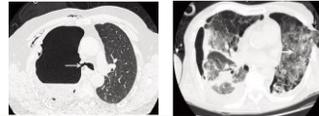
Treatments of post-surgical fistulas with particular emphases to stem cells therapy

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Shortness of Breath 2015; 4 (2): 42-46



ON GOING EXPERIMENTS

There is a need to specifically track MSC following transplantation in order to evaluate different methods of implantation, to follow their migration within the body, and to quantify their accumulation at the target.

Cellular magnetic resonance imaging (MRI) using fluorine-based nanoemulsions is a great means to detect these transplanted cells in vivo because of the high specificity for fluorine detection and the capability for precise quantification.



ON GOING EXPERIMENTS

Open Access Full Text Article

ORIGINAL RESEARCH

In vivo MR detection of fluorine-labeled human MSC using the bSSFP sequence

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International Journal of Nanomedicine

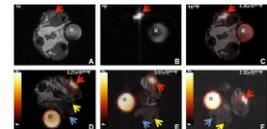


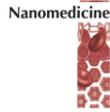
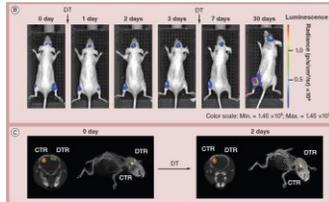
Figure 4: In vivo MR detection of fluorine-labeled human MSC using the bSSFP sequence. (A) T1-weighted MR image of the thorax. (B) T2-weighted MR image of the thorax. (C) T2-weighted MR image of the thorax. (D) T2-weighted MR image of the thorax. (E) T2-weighted MR image of the thorax. (F) T2-weighted MR image of the thorax.



ON GOING EXPERIMENTS

Cellular magnetic resonance with iron oxide nanoparticles: long-term persistence of SPIO signal in the CNS after transplanted cell death

Chiara Cianciaruso^{1,2}, Antonella Paganì¹, Cristina Martelli^{1,4}, Marco Bacigaluppi⁵, Mario Leonardo Squadrito^{6,7}, Alessia Lo Dico^{1,4}, Michele De Palma^{6,7}, Roberto Furlan⁵, Giovanni Lucignani^{6,8}, Andrea Falini^{1,2}, Alessandra Biffi⁹, Luisa Ottobri^{3,4} & Letterio Salvatore Politi^{1,3}



ON GOING EXPERIMENTS

Cellular magnetic resonance with iron oxide nanoparticles: long-term persistence of SPIO signal in the CNS after transplanted cell death

Aim: To study the specificity of cellular MRI based on superparamagnetic iron oxide particles (SPIOs), especially within the CNS.

Conclusion: Due to the *long-term persistence of signal after transplanted cell death*, caution is advised when SPIOs are employed for cell tracking.

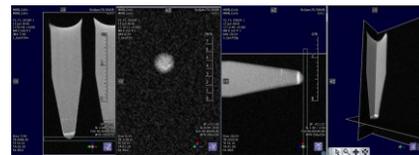


ON GOING EXPERIMENTS

In vitro MRI detection of fluorine-labeled VS. iron-labeled mesenchymal stromal cells: a comparative tracking study

The purpose of our study was to demonstrate that MSC can be labeled both with *iron oxide nanoparticles* as well as with *perfluorocarbon nanoemulsion formulations* without altering cell viability or differentiation and to compare imaging data coming from iron- and fluorine- labelled MSC.

ON GOING EXPERIMENTS



Personal data



ON GOING EXPERIMENTS

Ideal scaffold development for MSC engraftment and then delivery to human damaged tissues



PARTNERSHIPS



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- Fabio Acoella, Stefano Brizzola *Veterinary Medicine, University of Milan*
- Lorenza Lazzari, Rosaria Giordano, Tiziana Montemurro *Cell Factory, Policlinico di Milano*
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- Massimo Bellomi, Stefania Rizzo, *Division of Radiology, European Institute of Oncology*
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