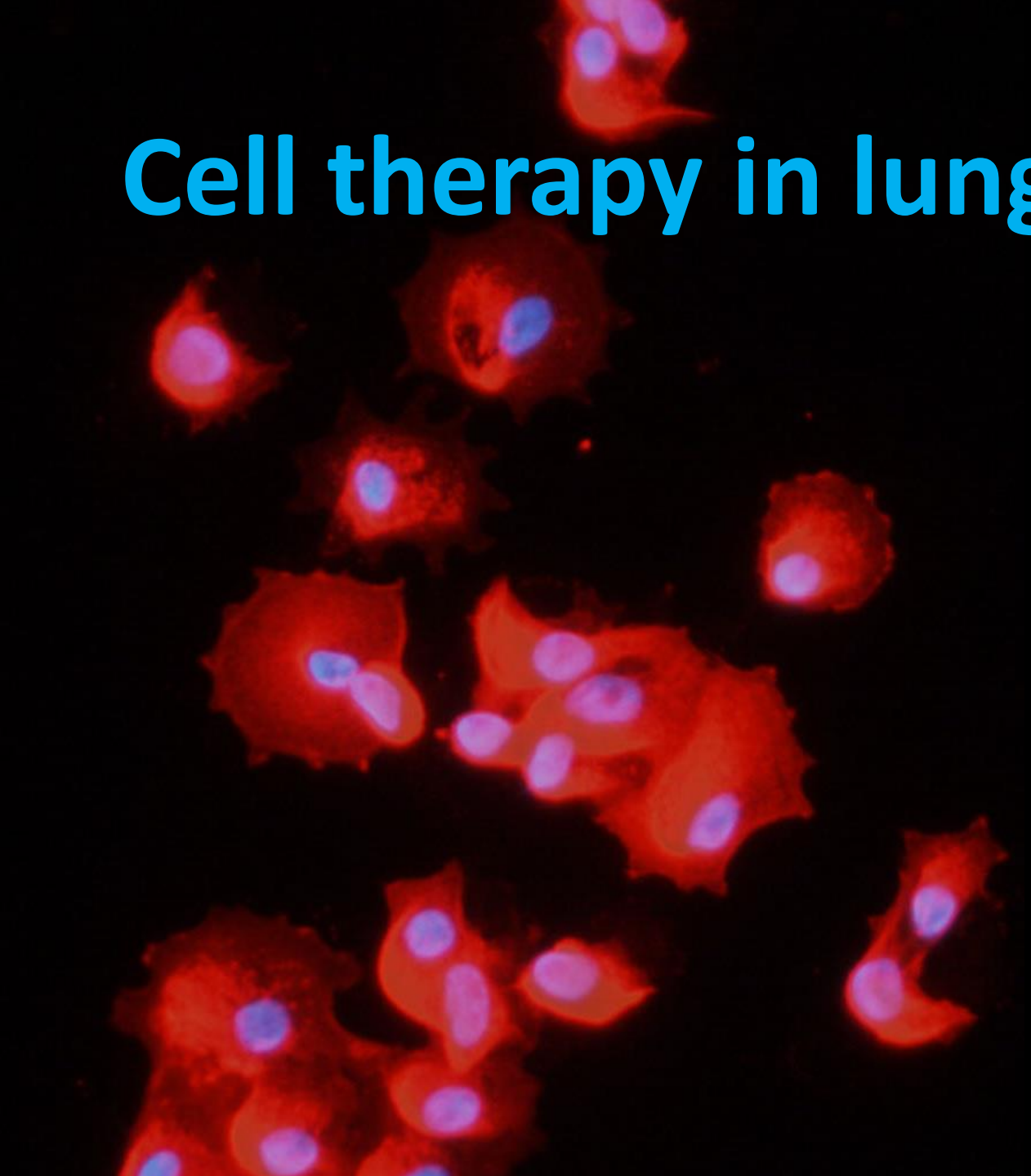
Faculty / Presenter Disclosure

- Faculty: Anna Serrano-Mollar
- Relationships with commercial interests:
  - Grants/Research Support:
  - Speakers Bureau/Honoraria:
  - Consulting Fees:
  - Other: Dr. Anna Serrano-Mollar has a patent for the Use of type II pneumocytes in the treatment of pulmonary diseases associated with pulmonary fibrosis. Granted European patent EP1961423, based on Spanish priority patent application ES200502939

Cell therapy in lung diseases



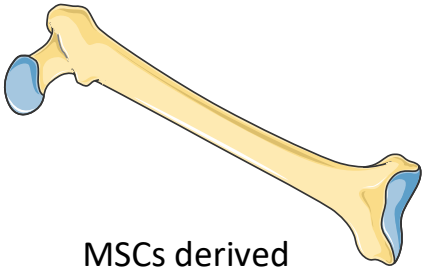
Anna Serrano Mollar
IIBB-CSIC

BANFF FOUNDATION FOR ALLOGRAFT PATHOLOGY
THE CATALAN TRANSPLANTATION SOCIETY
SOCIETAT CATALANA DE TRASPLANTAMENT
2017 BANFF-SCT
Joint Scientific Meeting
BARCELONA
27-31 March 2017

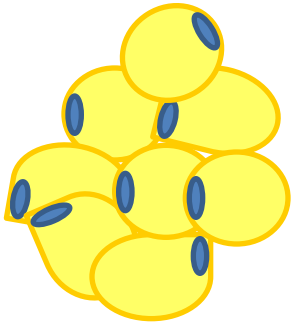
Cell therapies

A great variety of stem cells with the ability to proliferate and differentiate into different pulmonary cells have been proposed with the aim to restore damaged lungs

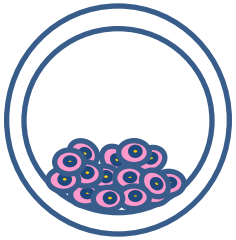
MSCs derived endothelial cells



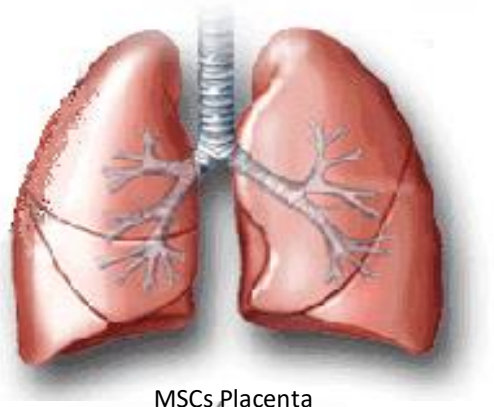
MSCs derived bone marrow



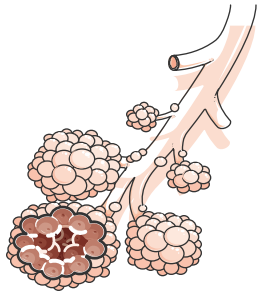
MSCs derived adipose tissue



MSCs derived embryonic cells



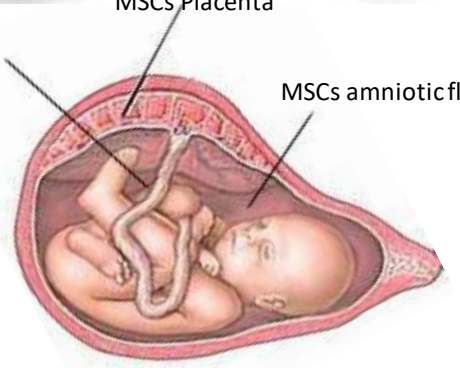
MSCs Placenta



Lung resident stem cells

MSCs Umbilical cord /cord blood

MSCs amniotic fluid



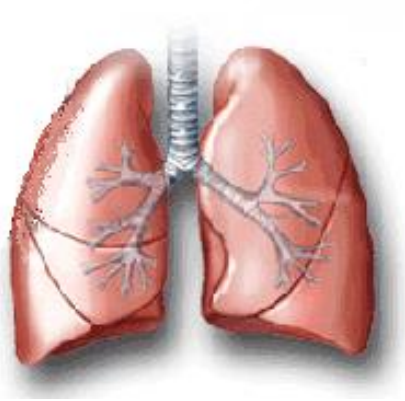
Adult Mesenchymal stem cells features

- Abundant
- Easy to isolate and characterize
- Home to sites of injury
- Ability to differentiate into different pulmonary cells
- Pleotropic properties:

  - ✓ Immunomodulation
  - ✓ Enhancement of angiogenesis
  - ✓ Inhibition of oxidative stress
  - ✓ Inhibition of apoptosis
  - ✓ Inhibition of fibrosis

- Autologous
- Allogenic (low immunogenic potential)

Pulmonary diseases



ACUTE LUNG INJURY (ALI) /
ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

OBSTRUCTIVE BRONCHIOLITIS (OB)/
BRONCHIOLITIS OBLITERANS SYNDROME (BOS)

IDIOPATHIC PULMONARY FIBROSIS (IPF)

- No effective treatment
- High mortality

Cell therapies have been developed with the aim that the administered cells proliferate and differentiate into alveolar or endothelial cells

Preclinical studies

Routes of administration

- Intravenous
- Intratracheal
- Intranasal
- Intraperitoneal

Dose

- $1x10^5$
- $5x10^5$
- $1x10^6$
- $2,5x10^6$
- $4x10^6$
- $5x10^6$

Time of cell administration

- Immediately after the induction of the disease
- 15 min after
- 4 h after
- 6 h after
- 12 h after
- 24 h after
- 3 days after
- 7 days after
- 15 days after…

Preclinical studies

Results

Early after the induction of disease

- ✓ Ameliorate inflammation
- ✓ Stop fibrosis progression
- ✓ Initiate tissue repair

Late after the induction of disease

- ✓ Increases in fibrosis

Clinical studies

Objectives

- Safety and tolerability

Routes of administration

- Intravenous
- Intratracheal

Dose

- $0.5x10^6$, $1x10^6$ cells/kg, $2x10^6$ cells/kg, $10x10^6$ cells/kg, $20x10^6$ cells/kg
- $12.5x10^6$ cells/ infusion
- $100x10^6$ cells/ infusion
- $200x10^6$ cells/ infusion
- Single, double or 4 doses

Results

- Safe and well tolerated
- Ameliorating tissue damage and/or improving lung function

Pulmonary diseases

Clinical trials with stem cells

	Open studies		Closed studies		Open/Closed
	Recruiting	Not yet recruiting	Completed	Active Not Recruiting	Unknown
Lung diseases	12	4	5	11	5

Data from www.ClinicalTrials.gov. March 2017

Clinical trials in lung diseases

	Studies	Type of cells	Administration	Dose	Results
COPD	1	Ex vivo cultured adult human mesenchymal stem cells	Intravenous	4 infusions /month (100×10^6 cells/infusion)	Safe (time frame: 2 years)
Emphysema	1				
IPF	2	Placental MSC	Intravenous	$1*10^6$ MSC / kg $2*10^6$ MSC / kg	Safe (time Frame 6 months)
IPF		Bone marrow MSC	Intravenous	$20*10^6$ MSC / kg $100*10^6$ MSC / kg $200*10^6$ MSC / kg	Safe (time frame: 60 weeks)
Broncopulmonary displasia in premature infants	1	Umbilical cord blood MSC	intratracheal	1×10^7 cells/kg 2×10^7 cells/kg	Safe and feasible

Data from www.ClinicalTrials.gov. March 2017

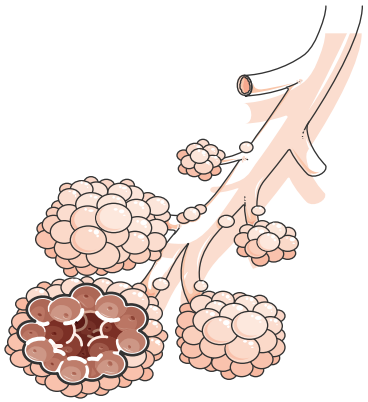
Summary

- Preclinical studies have demonstrated that stem cell therapies can attenuate lung injury in animal models of experimental pulmonary diseases
- Phase 1 clinical trials have proven safety of stem cell therapy for certain lung diseases

- Many questions remain in the air:
- Type of cells
- Dose
- Time and route of administration
- Control cell differentiation once administered

- The answers to these questions are a major challenge to have an efficient outcome in the future implementation of these therapies

Alveolar type II cells transplantation for the treatment of IPF



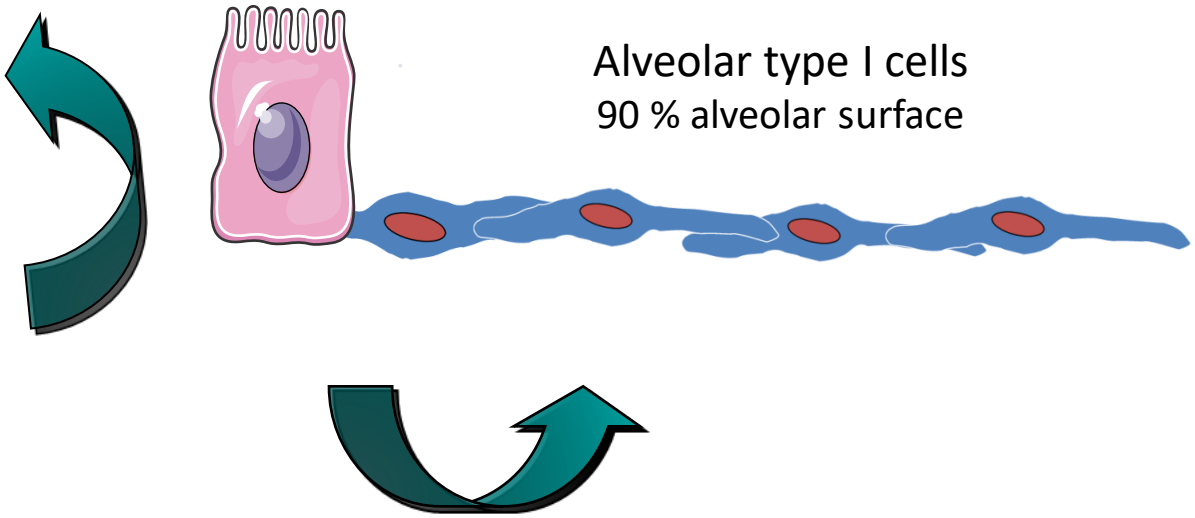
Alveolar type II cells

Idiopathic pulmonary fibrosis

Alveolar type II cells features

Alveolar type II cells 10 % alveolar surface

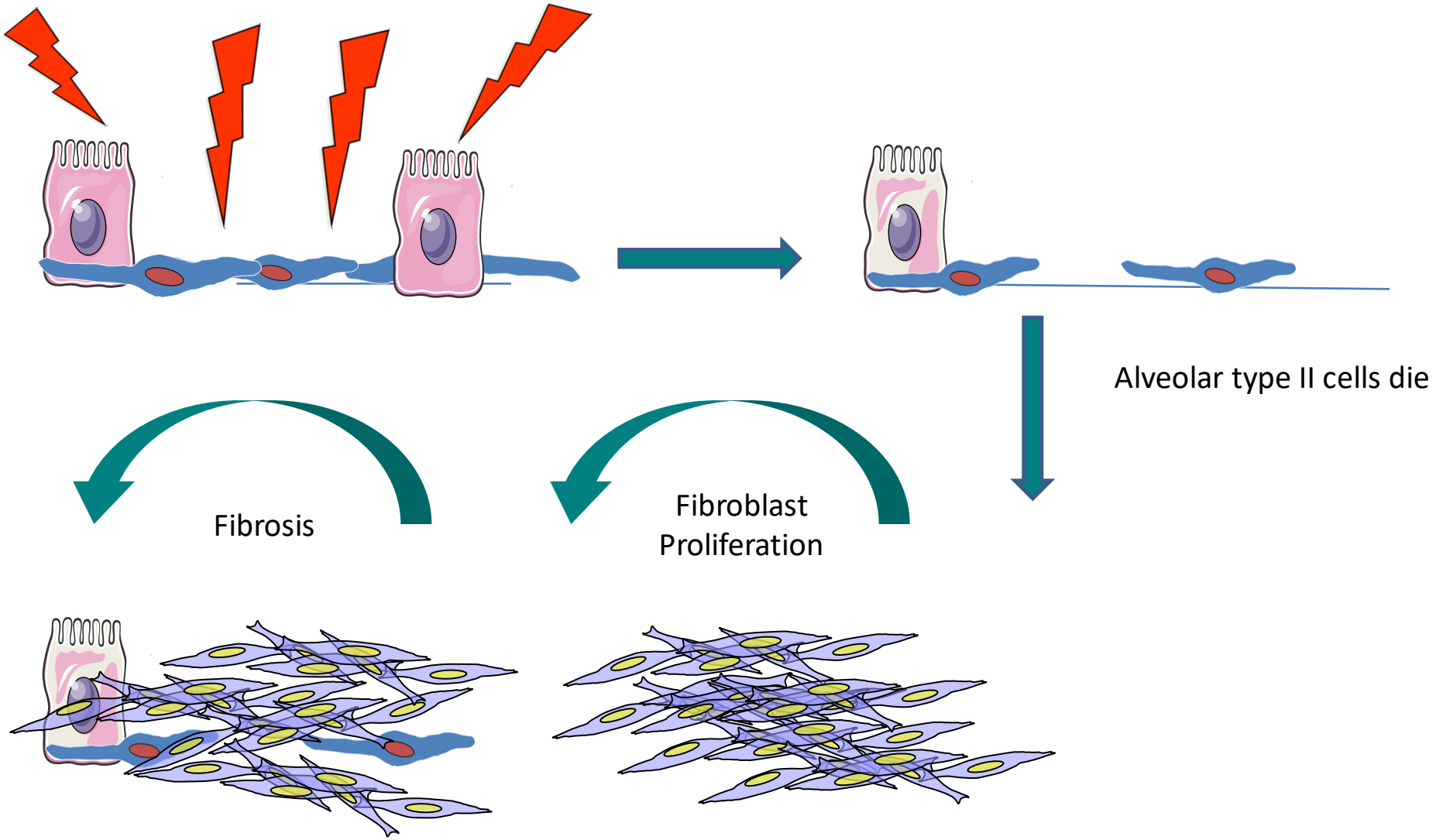
Pulmonary Surfactant



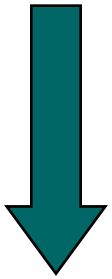
Alveolar type I cells
90 % alveolar surface

Progenitors

Idiopathic pulmonary fibrosis

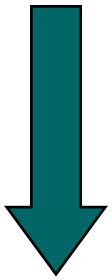


Alveolar type II cell transplantation



Proliferation
Differentiation

Alveolar type I cells



Re-epithelization of damaged alveolus

Bleomycin model

3 days: inflammatory

7 days: profibrotic

15 days: fibrotic

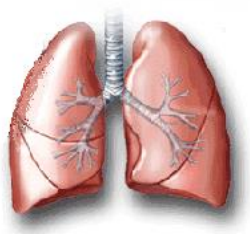
Experimental design

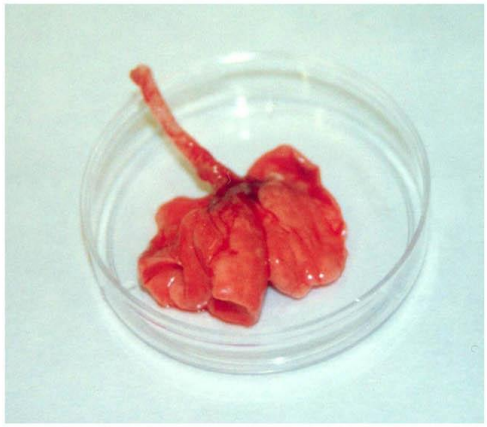
0 days — 3 days — 7 days — 15 days — 21 days

Saline

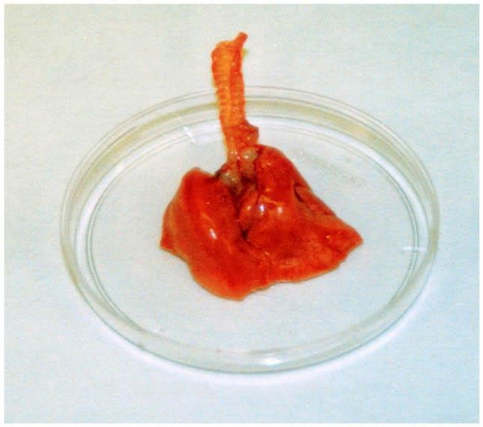
Bleomycin

Intratracheal transplantation
Alveolar type II cells
$2{,}5 \times 10^6$ cells

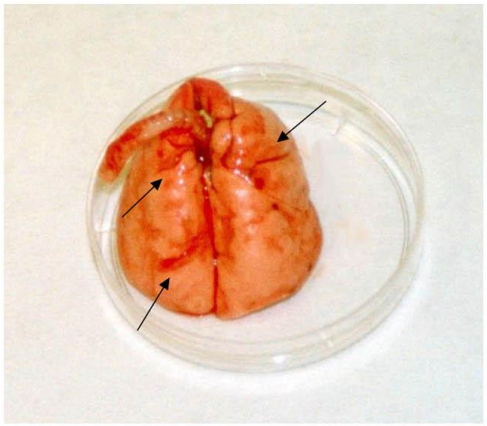




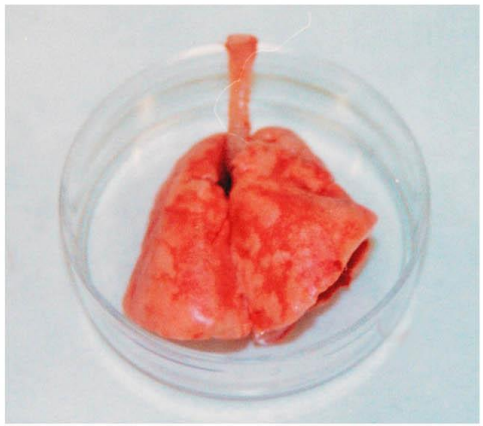
Control (saline)



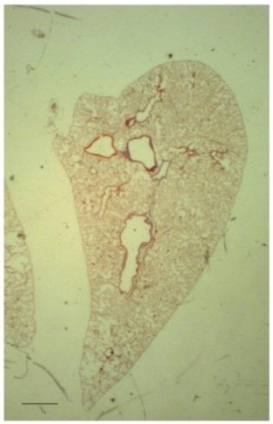
Control (transplanted)



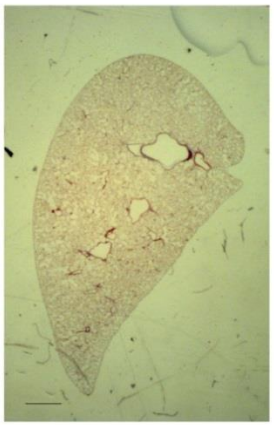
BLM



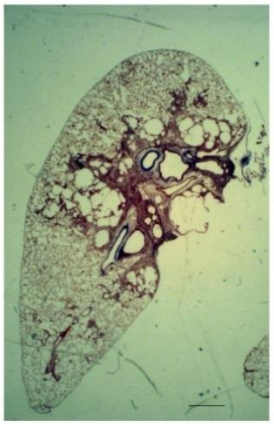
BLM + Trp 15 days



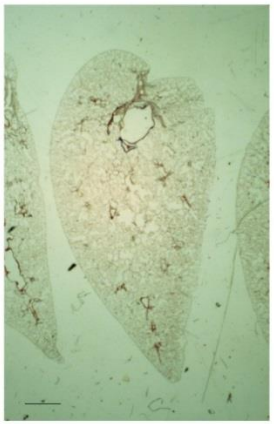
Control (Saline)



Control (trasplanted)



BLM

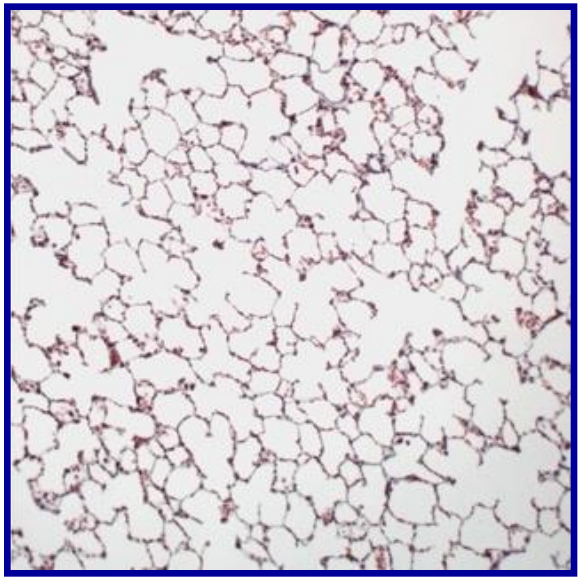


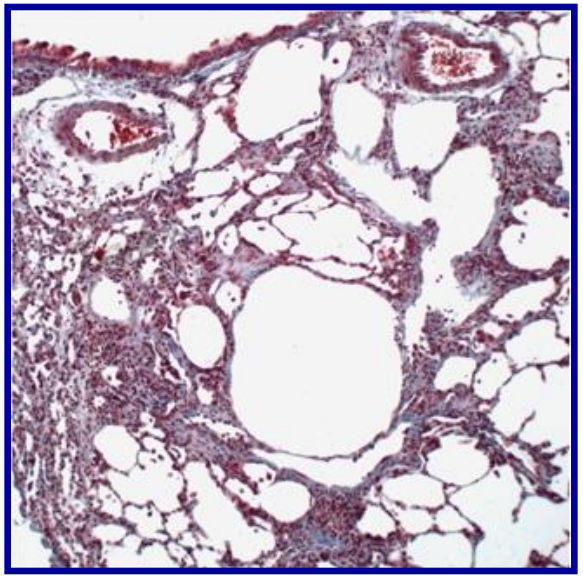
BLM + Trp 15 days

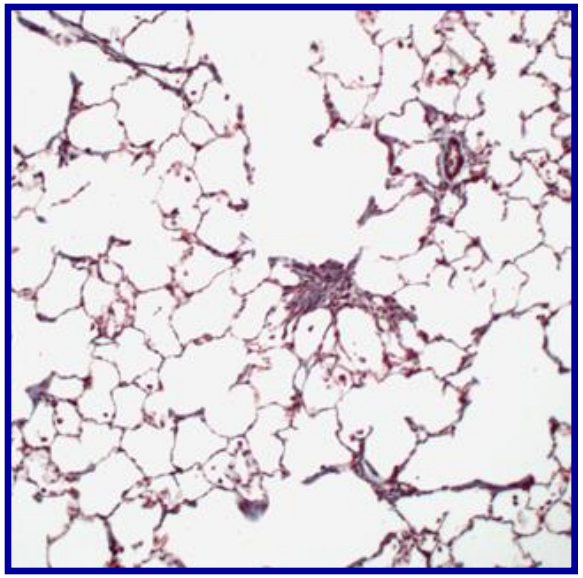
Control

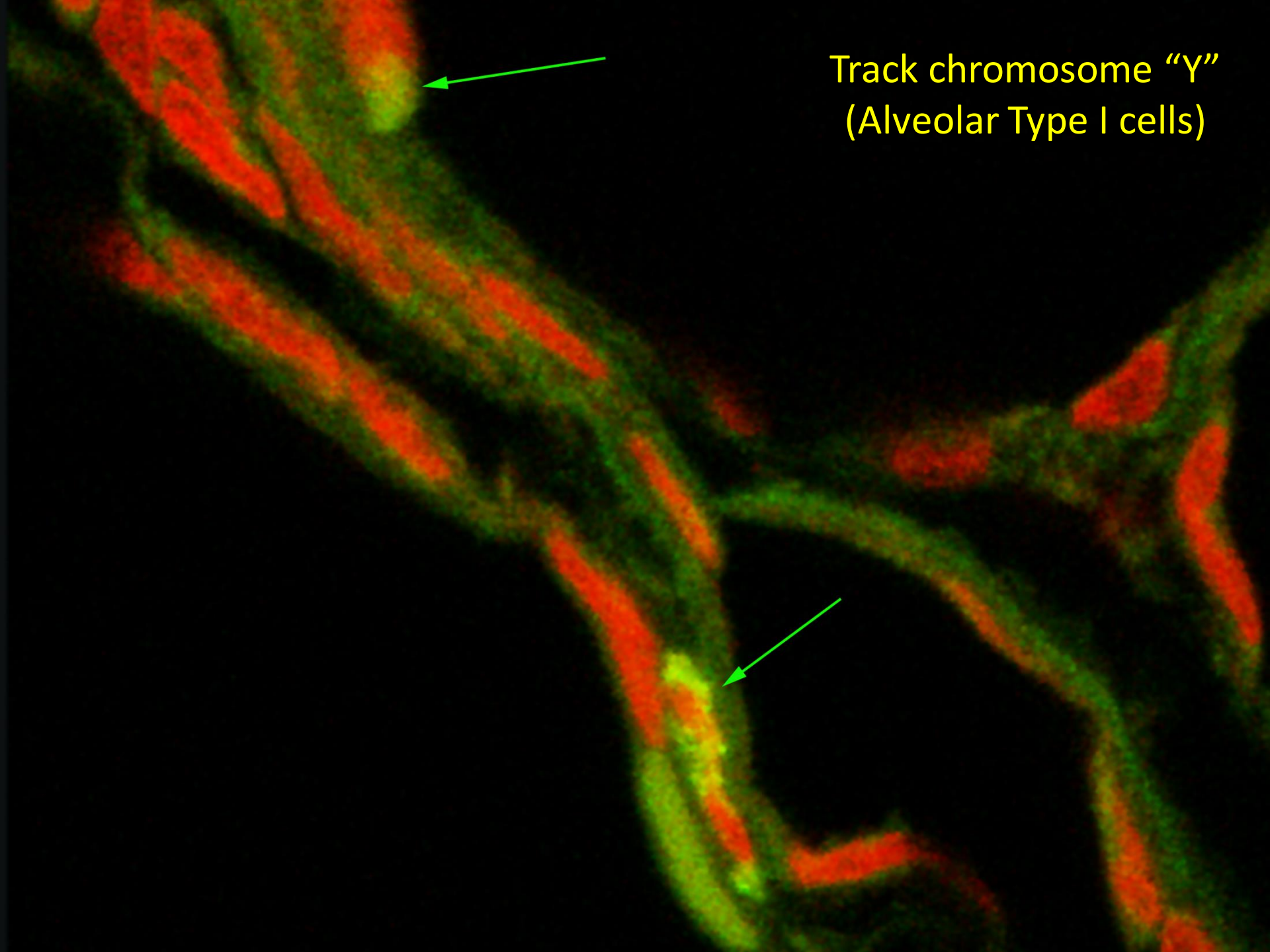
Lung fibrosis
BLM

Lung fibrosis
Trp 15 days








Track chromosome “Y”
(Alveolar Type I cells)

Alveolar type II cell transplantation

Donor selection criteria

Age ≤ 80 years

Medical history

- No evidence of aspiration
- No evidence of sepsis,
- Absence of microorganisms on bronchial aspirates samples,
- No history of primary pulmonary disease or active pulmonary infection,
- Smoking history did not prevent the use of donor lungs for cell isolation
- Traumatic lungs

Pulmonary function tests:

PaO_2 > 300 mmHg, FiO_2 = 1 y PEEP = 5 cm o fH_2O during 5 min.

Morphologic studies:

- Clear chest X-ray
- Fibrobronchoscopy without evidence of purulent secretions

Data extraction:

Colour, easy of inflation, atelectasia or adhesions

Patient inclusion criteria

- Age ≤ 70 years

- Moderated disease

FVC > 50 %
DLCO > 35 %

- Progressive disease

✓ Increased dyspnea
✓ Increase disease extent observed in the CT scan
✓ Decrease ≥ 10 % FVC
✓ Decrease ≥15 % DLco

- Absence of pulmonary complications FPI

- Absence of other diseases with poor prognosis

Protocol

- Patients: n=16
- Pre-transplantation vaccination program
- Cell instillation: 4
- Interval between cell instillations: 15 days
- Number of cells per instillation: 300 x 10^6 (saline)
- Fibrobronchoscopy (conscious sedation)
- Right middle and lower lobe / lingula and left lower lobe
- Stay in the hospital: 1 day
- Immunosuppressive treatment and antibiotic prophylaxis:

Tacrolimus (0,15 mg/kg /12 h)adjusted between 5 and 8 ng/ml

Mycophenolate Mofetil (500 mg/12 h)

Prednisone (20 mg /24 h)

Trimethoprim-sulfamethoxazole (160/800 mg) and folinic acid (15 mg) three days a week for 48 weeks

Valganciclovir (450 mg/day) for 14 weeks

Mouthwashes of liquid-oral nystatin (100000 UI/ml) three times a day

Main objectives

- Security and tolerability
- Changes in the pulmonary tests
  - FVC %
  - DL_{co} %
  - 6 min walking tests
- Changes in the quality of life (cough and dyspnea)
- Changes in the extension of the disease measured by the CT scan

Evaluation of disease progression/stabilization

2 months

6 months

12 months

- FVC %
- DL_{co} %
- Distance in the 6 min walking tests
- Changes in the quality of life (cough and dyspnoea)
- Changes in the extension of the disease measured by the CT scan

IPF is stable :

< 15% for DLco

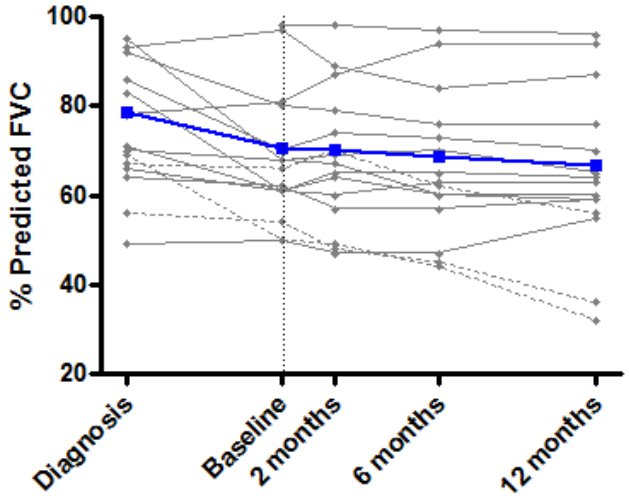
< 5% for FVC

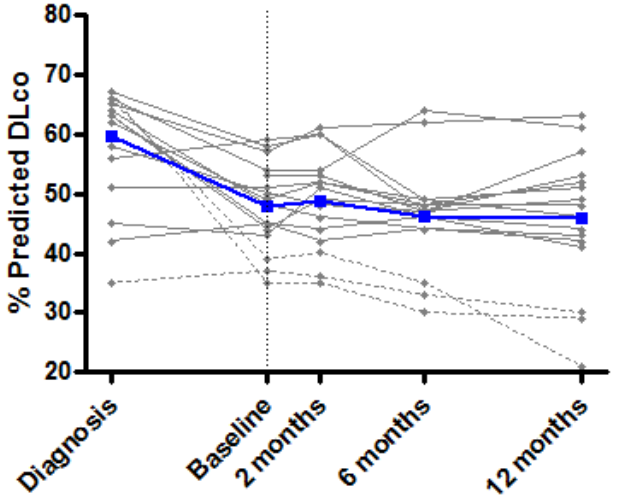
Stabilization in the 6 min walking test

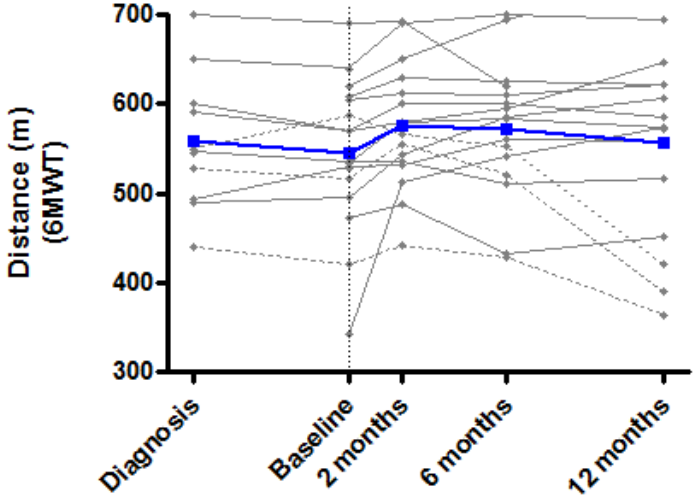
Stabilization and/or improvement in the CT scan images

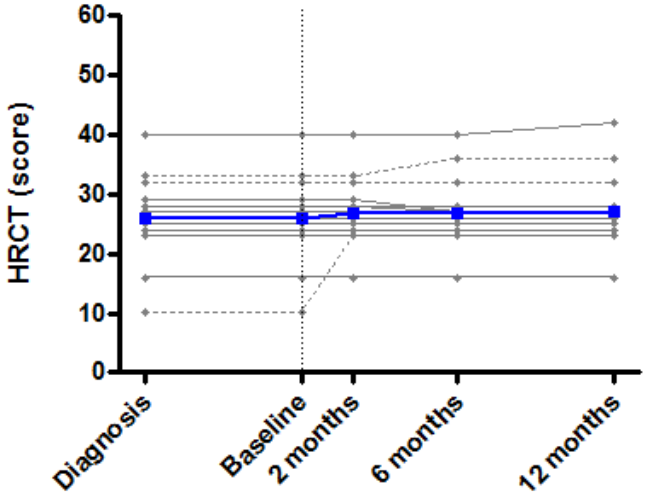
Stabilization in the degree of cough and dyspnea

Am J Respir Crit Care Med 2006;174:803-809
Am J Respir Crit Care Med 2011;184:1382-1389





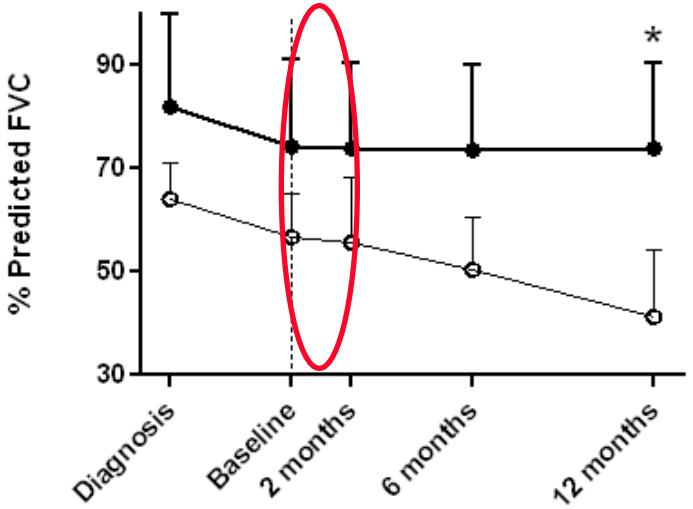


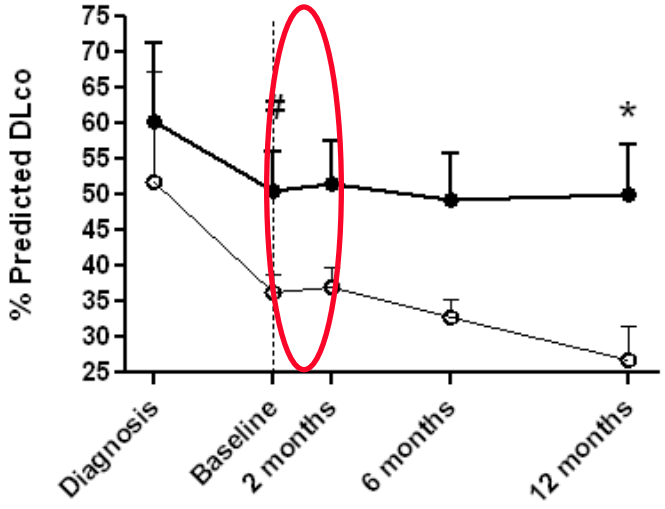


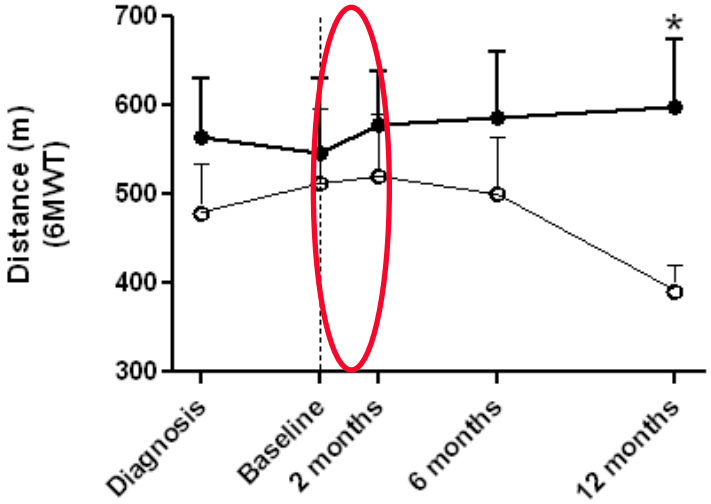
Total patients = 16

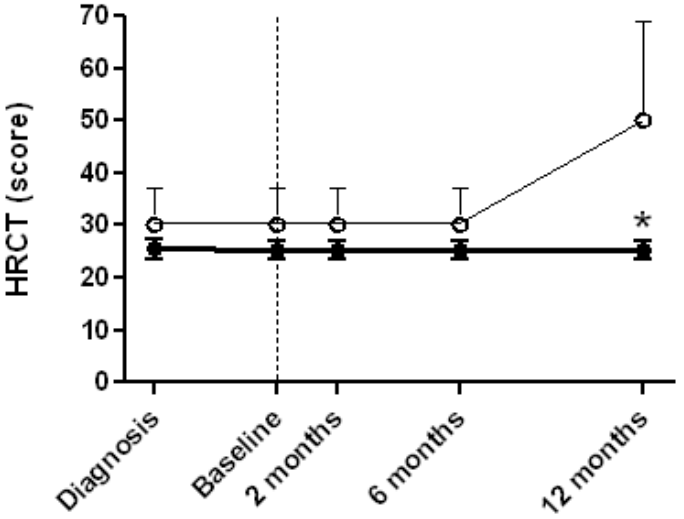
Stable= 13

Progression n= 3









Total patients = 16

Stable= 13

Progression n= 3

Complications

- Alveolar Type II cells
  - *HLA II alloantibodies (n = 1)*
  - *Transient alveolar infiltrate (n = 1)*
- Immunosuppressive Treatment
  - *Bronchial infection (n = 1)*
- Tacrolimus, mycophenolate mofetil
  - *Cramps lower extremities (n = 7)*
- Prednisone
  - *Diabetes (n = 1)*
- Trimethoprim sulfamethoxazole
  - *Skin rash (n = 1)*

Main results

- No side effects associated to the alveolar type II cells
- No alterations in vital signs (temperature, oxygen saturation, respiratory and heart rate) and on the electrocardiogram
- Immunosensitivity similar to that seen in a blood transfusion
- Stability in pulmonary function tests (FVC and DLCO)
- Increased distance (6 min)
- Stability of the extent of disease (CT scan)
- Improved quality of life (cough, dyspnoea)

Effective in patients with DLco > 40%

- Alveolar type II cell transplantation is a promising candidate for IPF therapy in future

Serrano-Mollar A. *et al*. Chest. 2016