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Structural complexity of the lungs



Alveoli:	N = 300 millions
	d = 0.3 mm

Membrane: $S = 70 \text{ m}^2$ w = 0.003 mm

Bioengineered lung based:

Artificial substrate? Natural substrate



Lung bioengineering approach



Soto-Gutierrez et al. J Clin Invest. 2012;122(11):3817-3823



Lung biofabrication: Proof of concept



EXTRACELLULAR MATRIX



Lung biofabrication: Proof of concept

Survival: 14 days (~1 year in humans)









Song et al. Ann Thorac Surg, 2011



Lung bioengineering approach



Soto-Gutierrez et al. J Clin Invest. 2012;122(11):3817–3823

Lung Decellularization:

- Complete clearing of donor cell material
- Preservation of the lung extracellular matrix proteins



Nichols et al. Tissue Eng Part A. 2013; 19(17-18): 2045–2062





<u>Preparation and assessment</u> <u>of human lung scaffolds</u>





Nichols et al. Tissue Eng Part A. 2013 Sep; 19(17-18): 2045–2062



Normal Human

AC Human





Towards scalation:

Full automatization of human-size lung decellularization



Price et al. Tissue Eng Part C Methods. 2015 Jan 1; 21(1): 94–103.



Towards scalation:

Freezing-thawing

Sterilization by irradiation





Uriarte et al. J Mech Behav Biomed Mater. 2014; 40:168-77

Nonaka et al. J Biomed Mater Res A. 2014;102(2):413-9.





Soto-Gutierrez et al. J Clin Invest. 2012;122(11):3817-3823



Lung scaffold recellularization with iPSCs:



Moser and Ott. Curr Opin Organ Transplant 2014, 19:603–609







Lung scaffold modullates stem cell differentiation:

MSCs differentiation towards alveolar phenoype is enhanced by seeding on lung scaffold



Mendez et al. Tissue Eng Part A. 2014 Jun;20(11-12):1735-46

- CONGRESS

Lung scaffold modullates stem cell differentiation:

Stem cells seeded on the lung scaffold differentiate depending on the homing site



Cortiella et al. 2010

The mechanical microenvironment sensed by stem cells (stiffness, stretch) drives the differentiation onto the different lung cell phenotypes.



Lung scaffold modullates stem cell differentiation:

Differentiation of both embryonic and adults stem cells depends on substrate stiffness



- CONGRESO

Lung scaffold modullates stem cell differentiation:

There is a considerable inhomogeneity in stiffness within the lung scaffold



Collagen Elastin

Melo et al. Tissue Engineering, 2014





Soto-Gutierrez et al. J Clin Invest. 2012;122(11):3817-3823

Importance of the bioreactor in modullating stem cell differentiation:



Badylak et al. Lancet 2012; 379: 943-52

Importance of the bioreactor in modullating stem cell differentiation:

5% O₂ enhances differentiation towards lung cell types



Garreta et al., Physiol Rep, 2014, 2 (7): e12075.

Current perspective in lung bioengineering

SOCIETAT CATALANA DE TRASPLANTAMEN

ONGRESC



Tsuchiya et al. Organogenesis 10:2, 196–207, 2014

CONCLUSIONS

✓The current approach for lung bioengineering is based on using decellularized lungs as natural 3-D scaffolds for seeding cells.

✓ Several experimental proofs of concept of the approach have been carried out.

✓ Lung decellularization procedures are reasonably optimized and almost ready for pre-industrial production.

✓ Cells pre-differentiated onto lung precursor phenotypes seem to be suitable candidates for lung scaffold recellularization.

 \checkmark Future improvement in bioreactor settings (ventilation, perfusion, O₂) should improve the maturation process in recellularized lungs.

✓ Lung biofabrication is a recent approach with exciting laboratory results and with expected successful preclinical results in the very next years.

