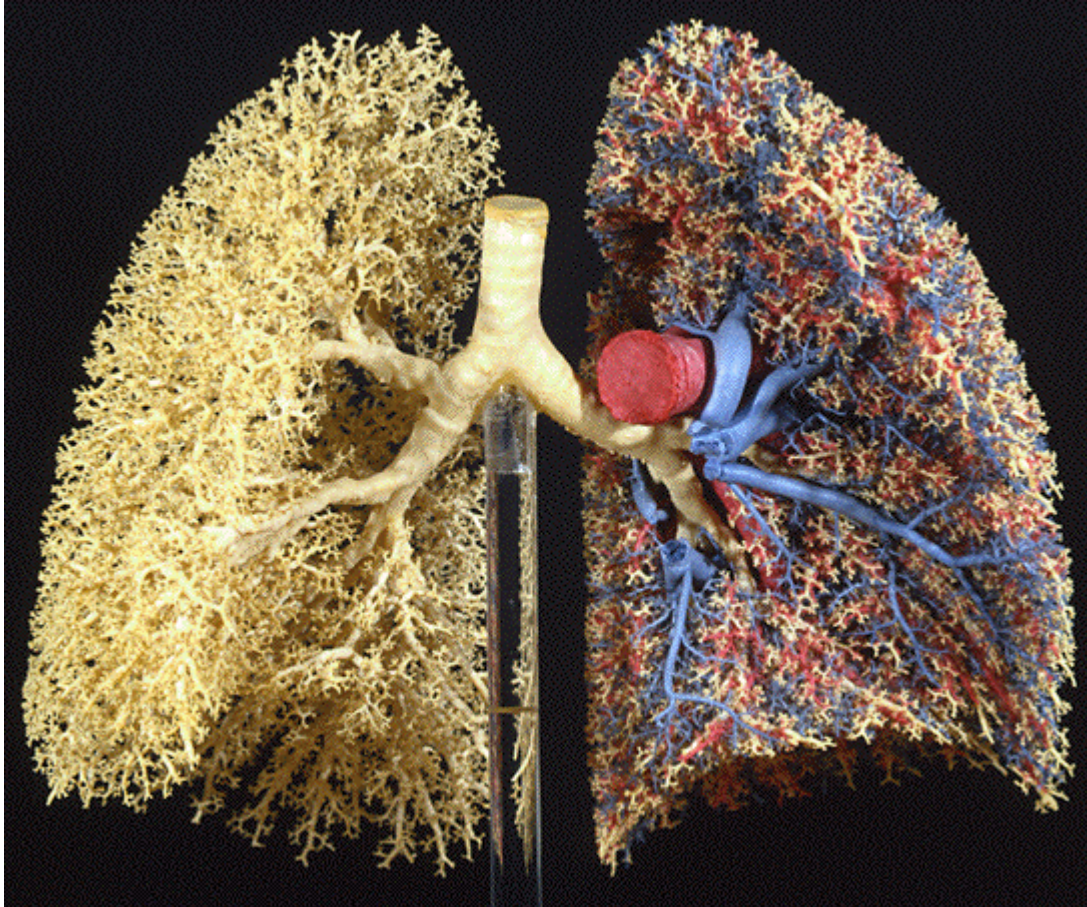


Present and future of regenerative medicine: Lung transplantation

Ramon Farré, Ph.D.
Facultat de Medicina
Universitat de Barcelona

Structural complexity of the lungs

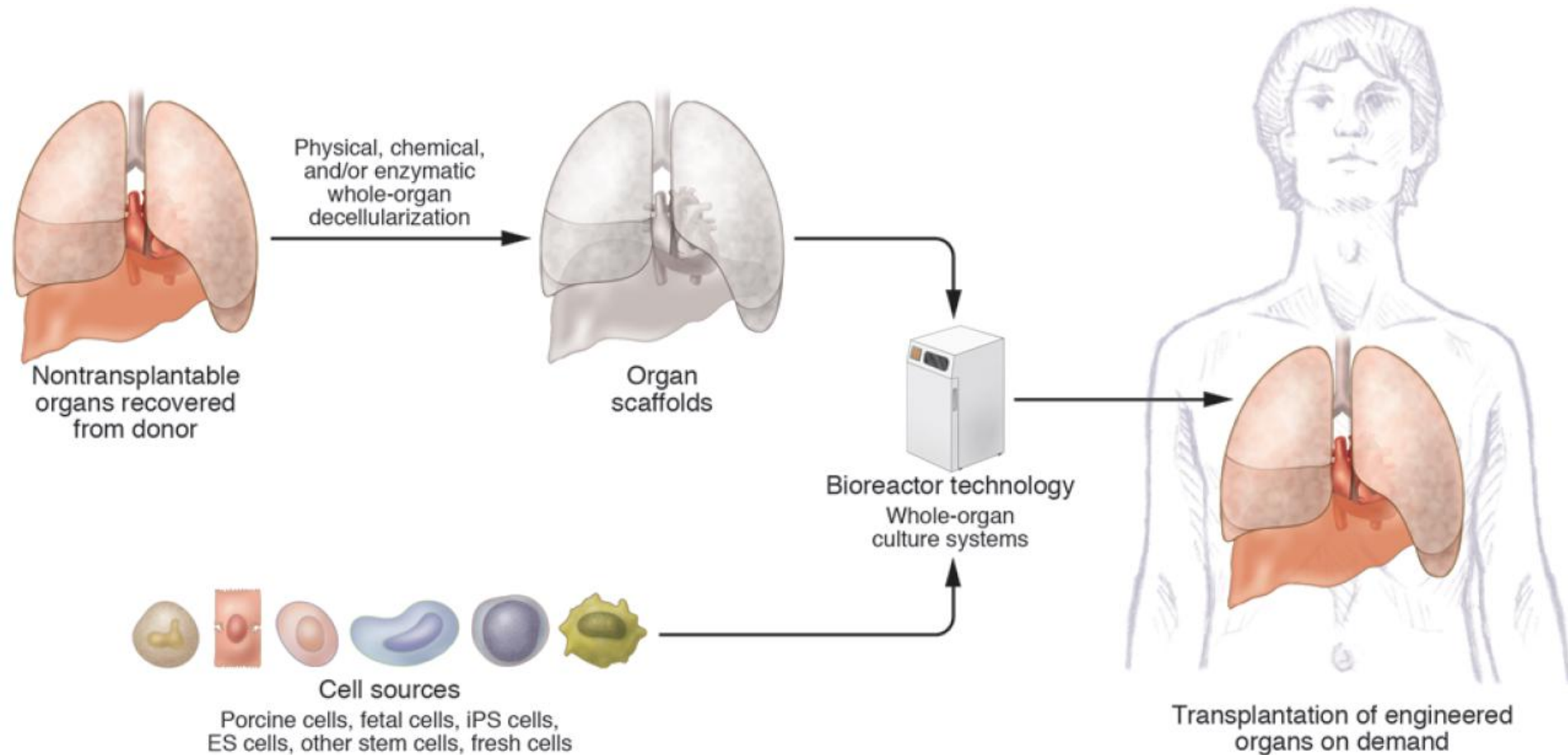


Alveoli: N = 300 millions
d = 0.3 mm

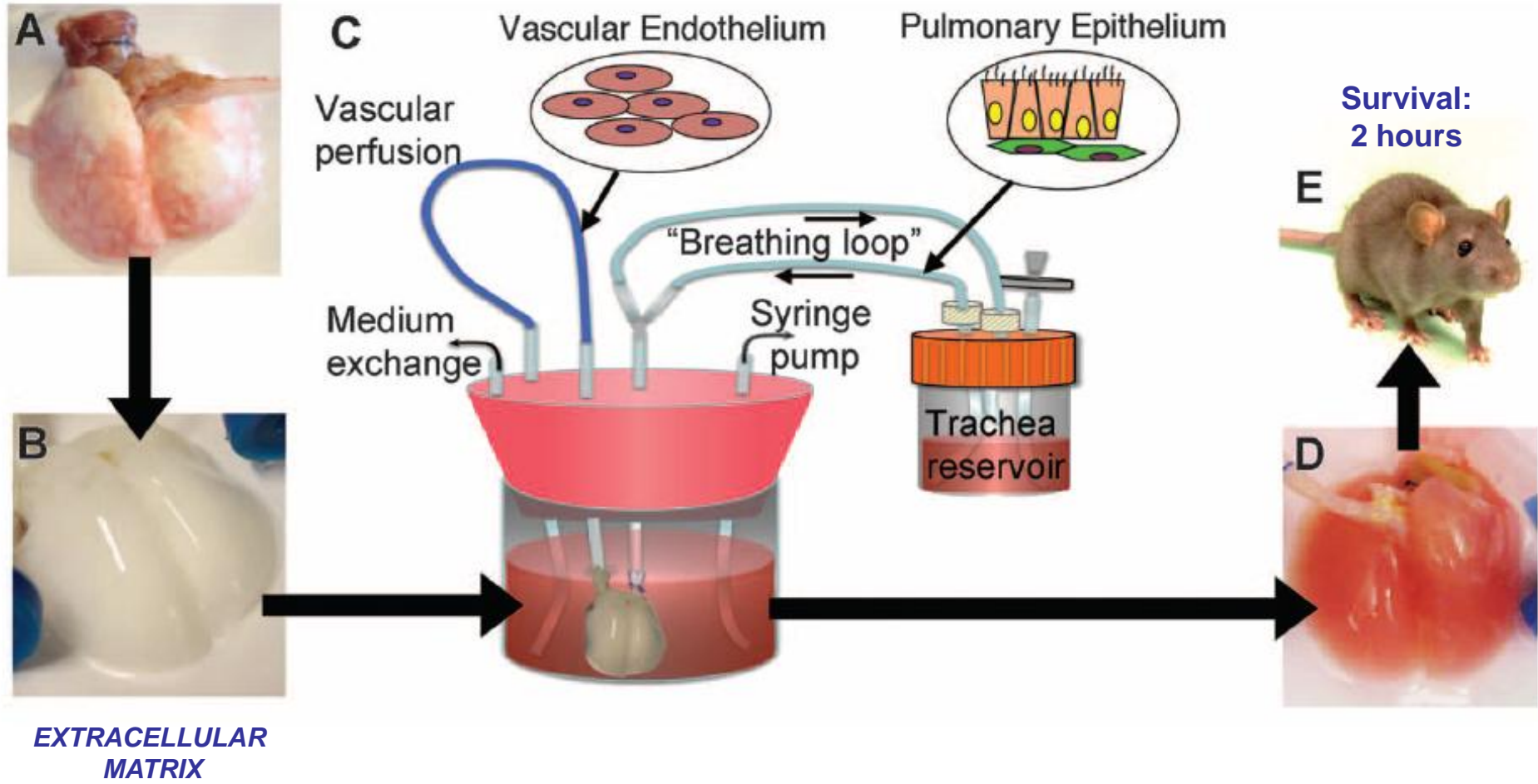
Membrane: S = 70 m²
w = 0.003 mm

Bioengineered lung based: Artificial substrate?
Natural substrate

Lung bioengineering approach



Lung biofabrication: Proof of concept



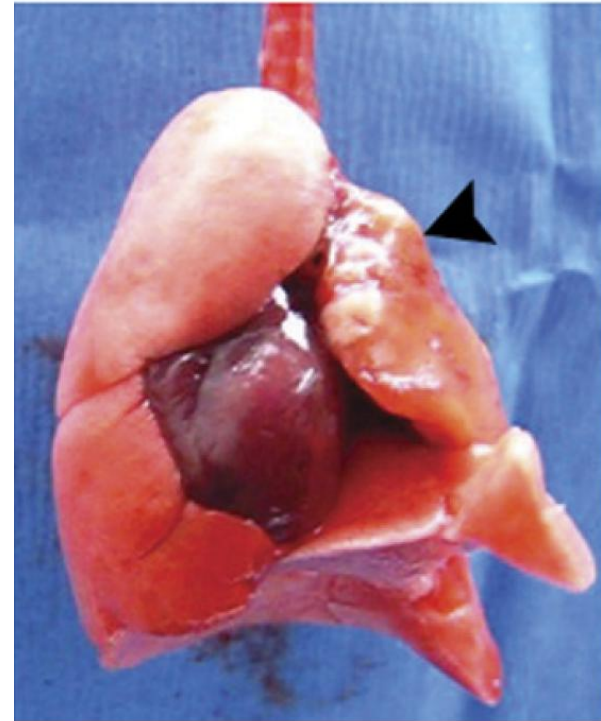
Lung biofabrication: Proof of concept

Survival: 14 days (~1 year in humans)

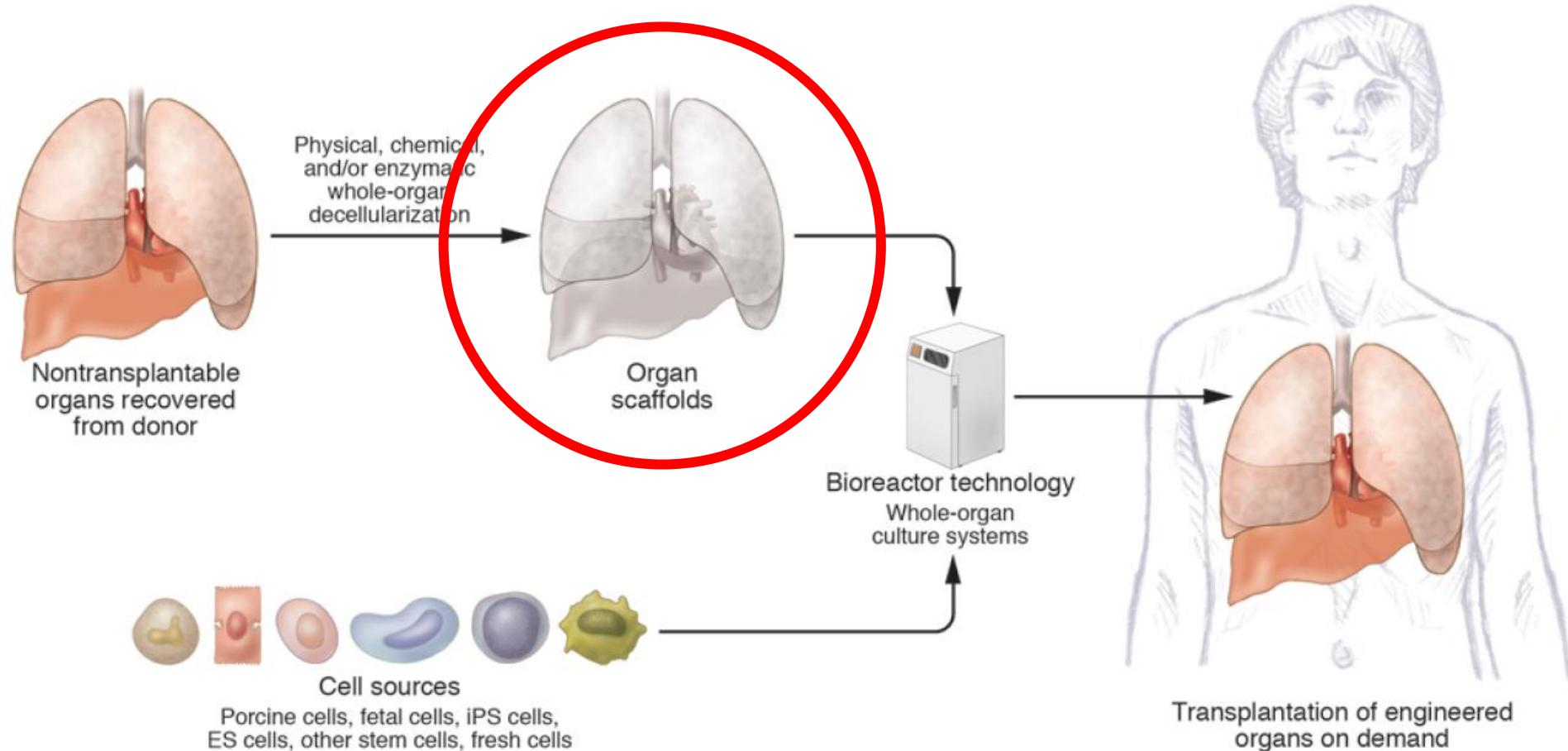
1 day



14 days

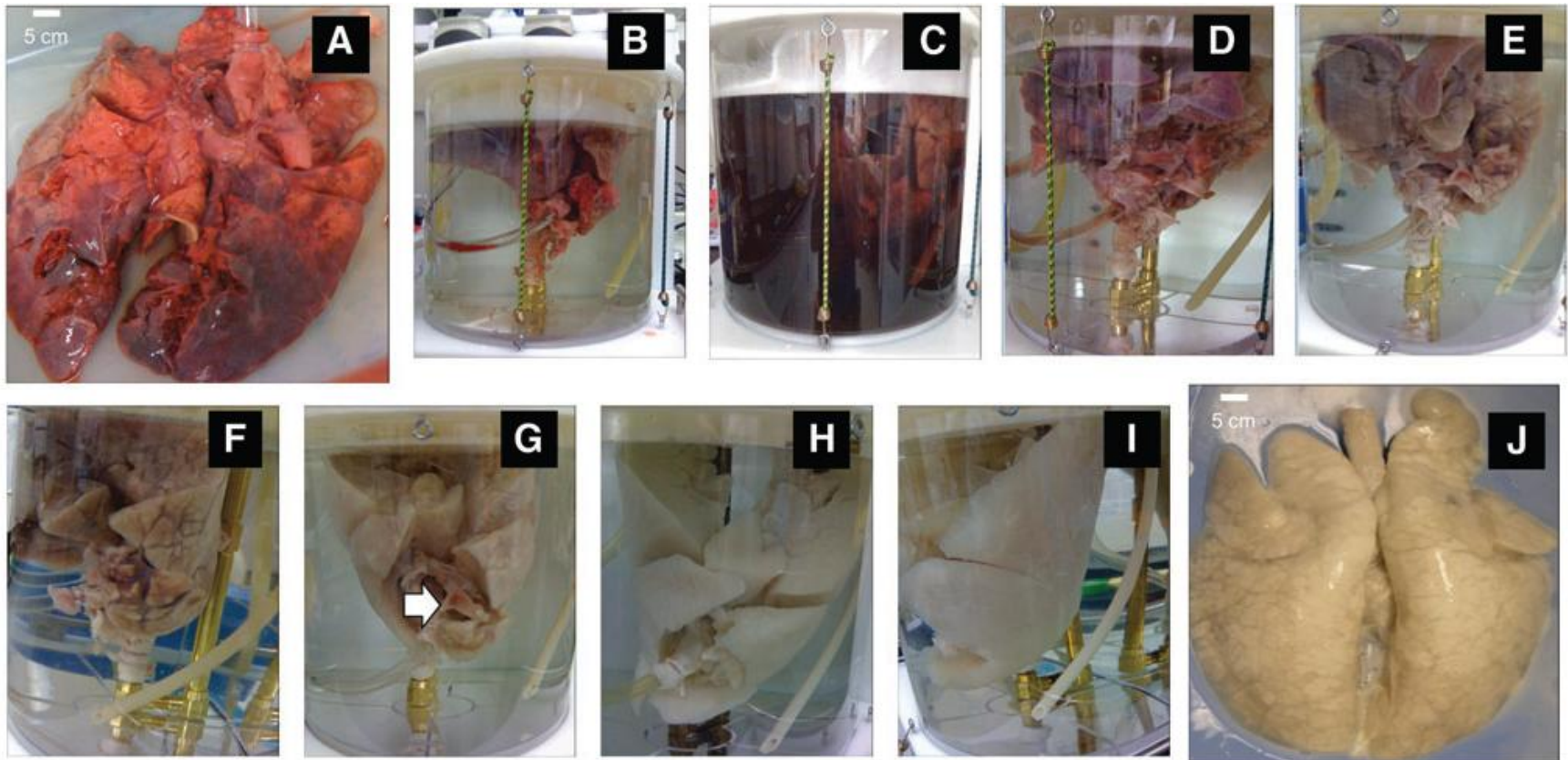


Lung bioengineering approach

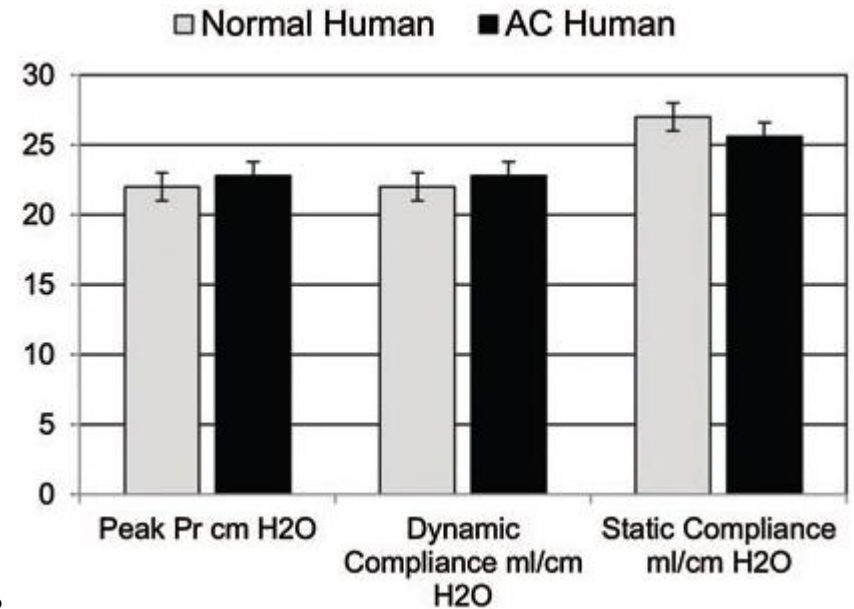
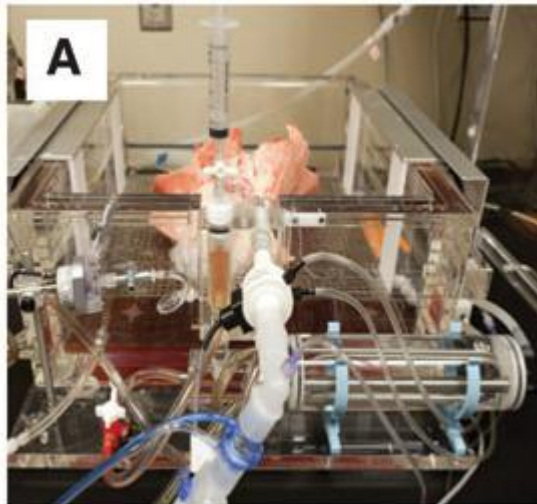
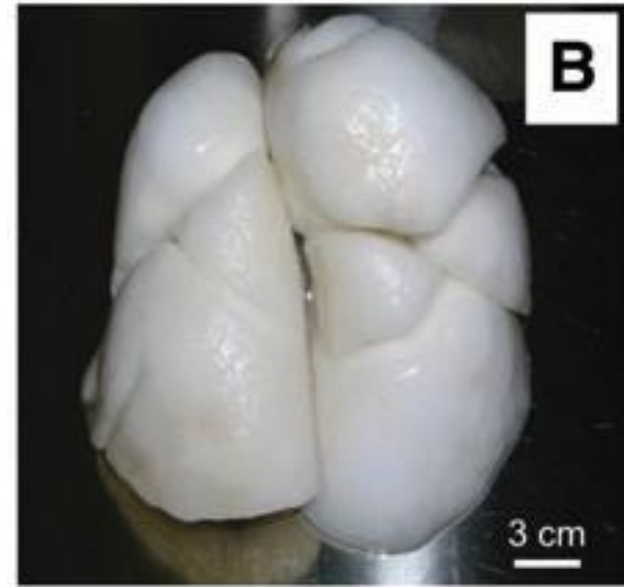
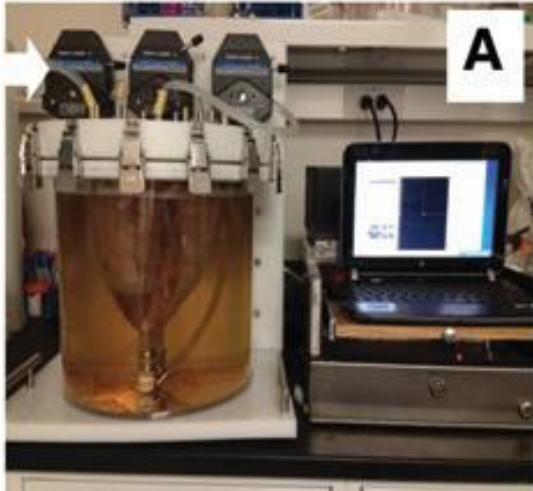


Lung Decellularization:

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

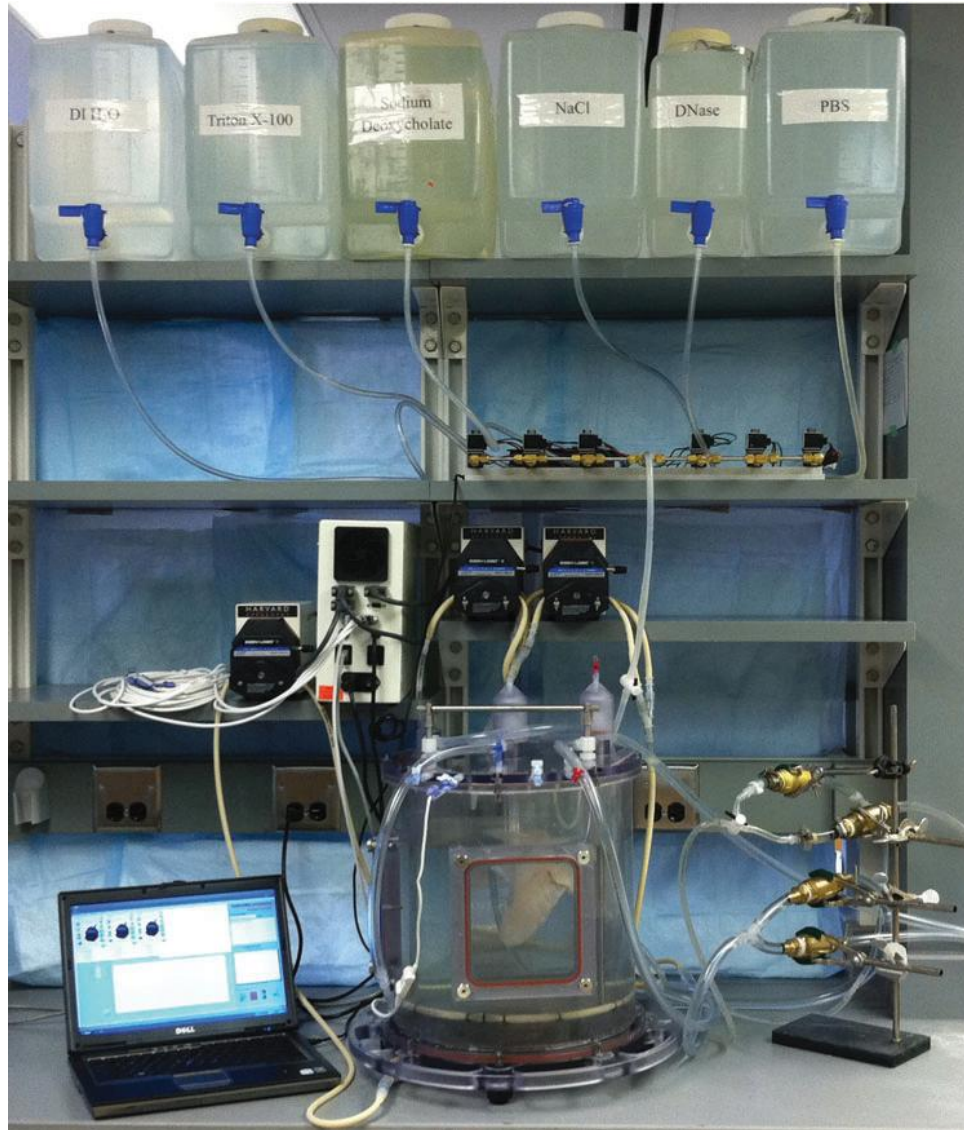


Preparation and assessment of human lung scaffolds



Towards scalation:

**Full automatization
of human-size lung
decellularization**

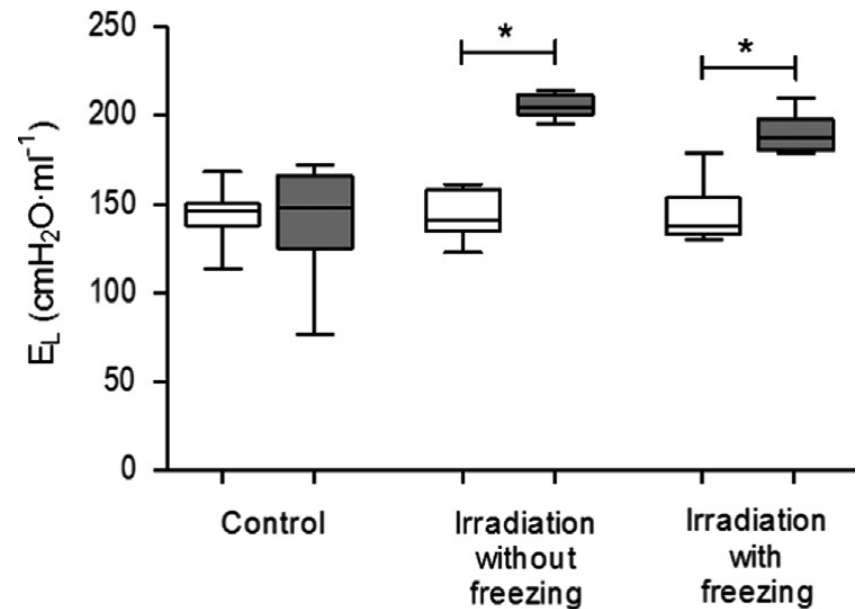
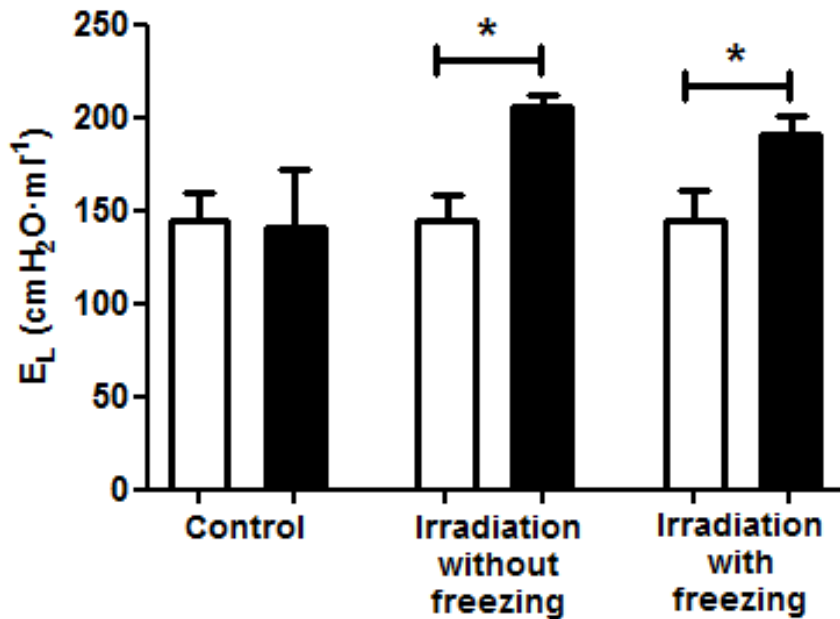


Towards scalation:

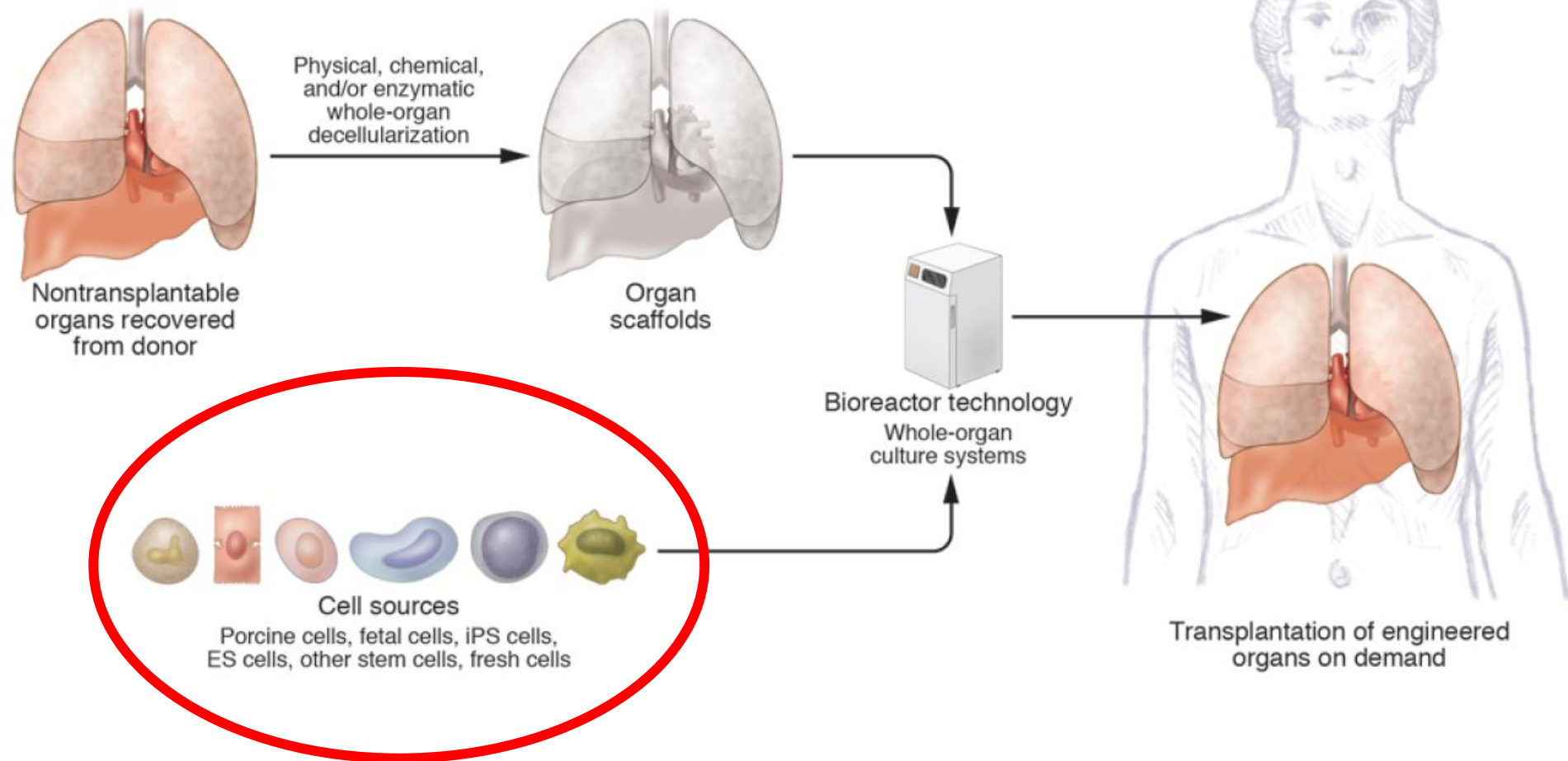
Freezing-thawing

Sterilization by irradiation

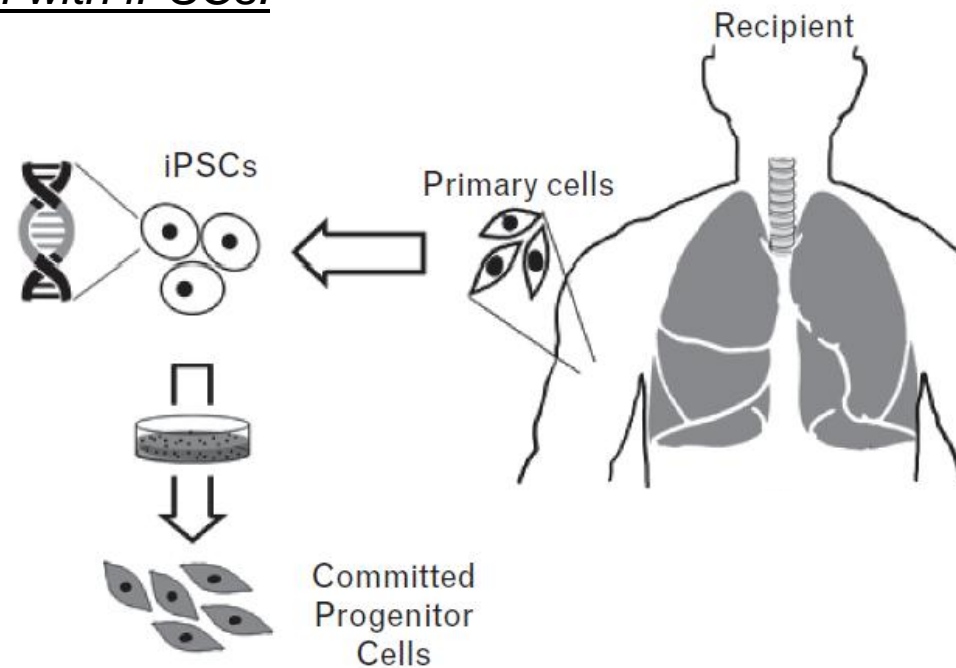
Lung scaffold elastance



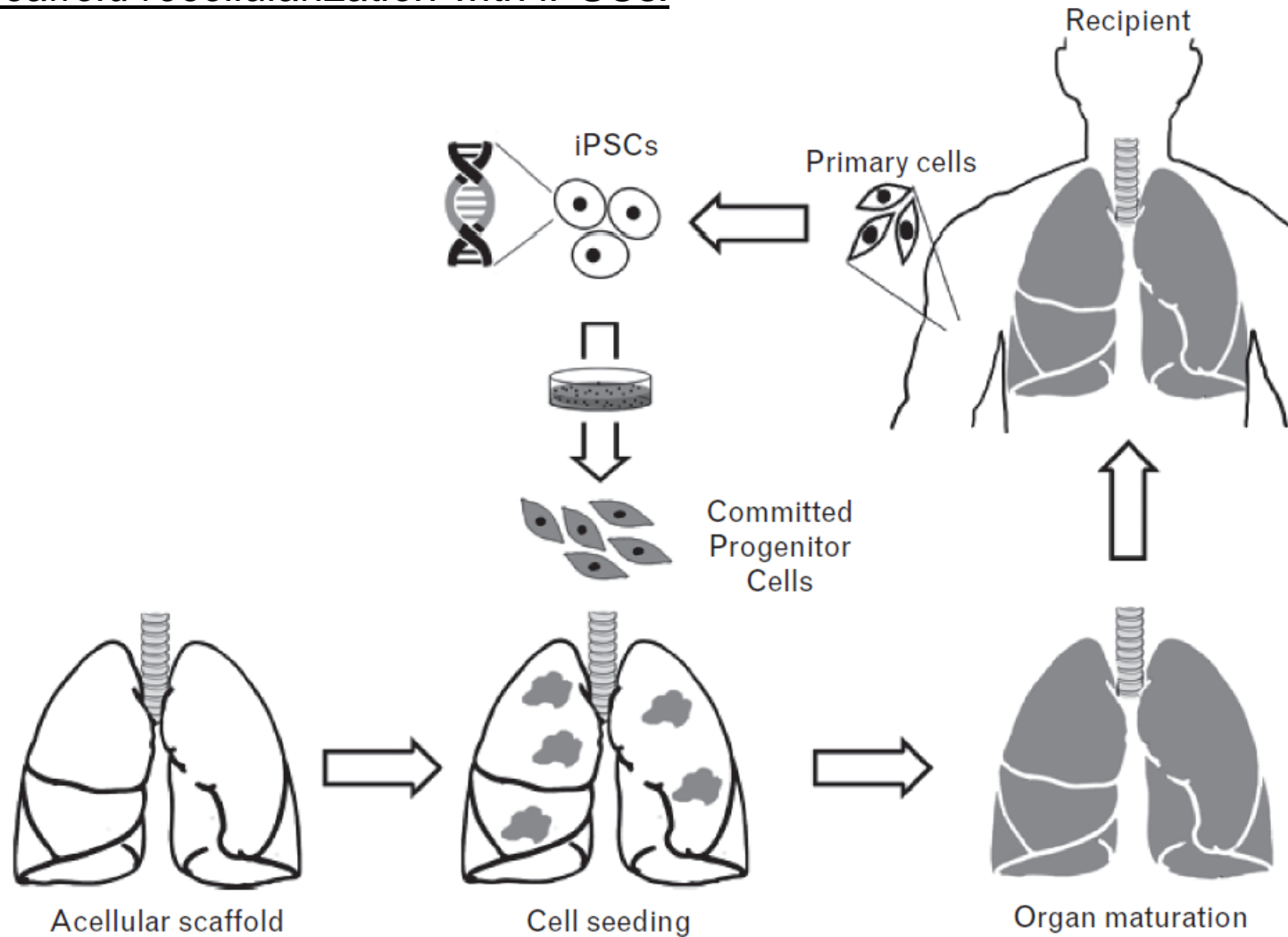
Lung bioengineering approach



Lung scaffold recellularization with iPSCs:

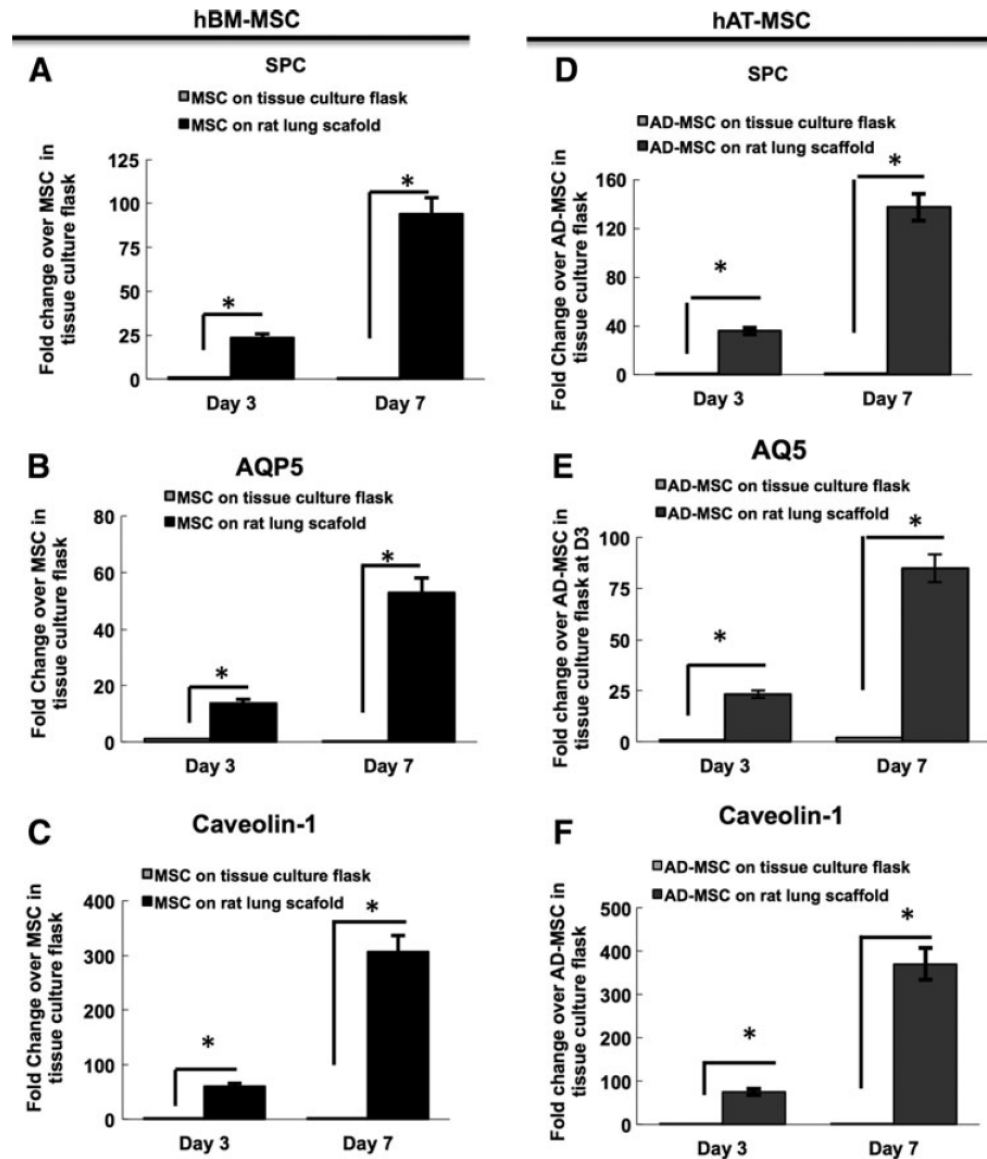


Lung scaffold recellularization with iPSCs:



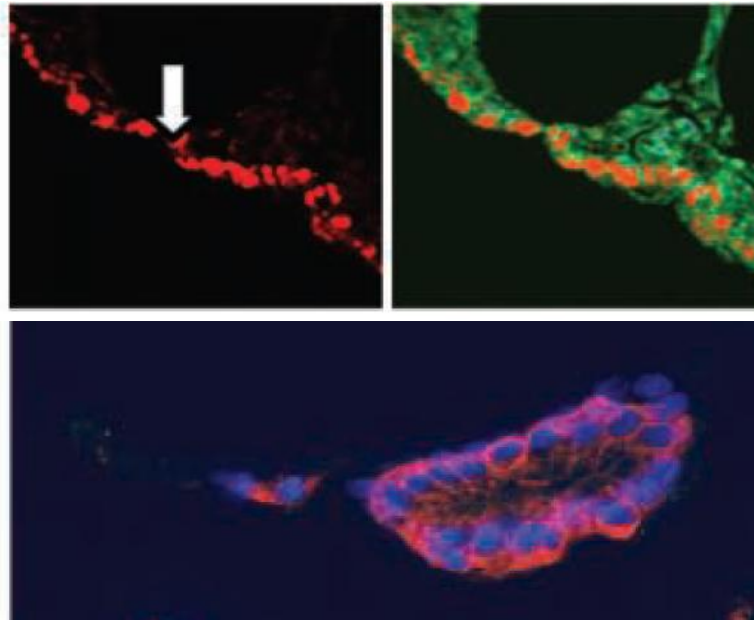
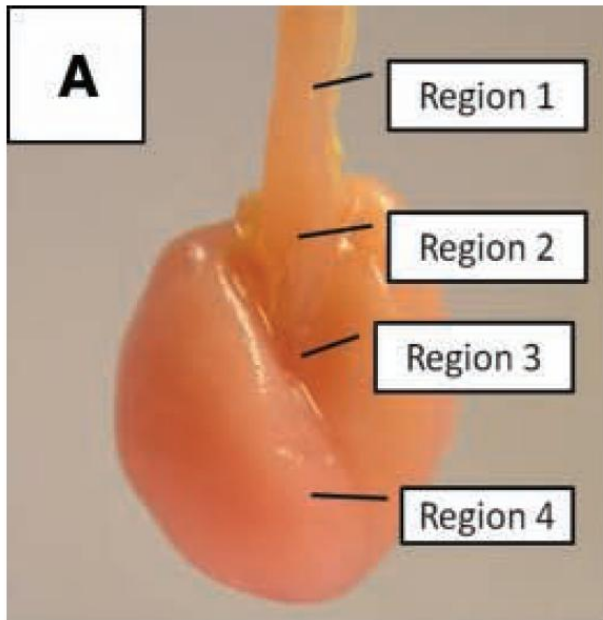
Lung scaffold modulates stem cell differentiation:

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



Lung scaffold modulates stem cell differentiation:

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

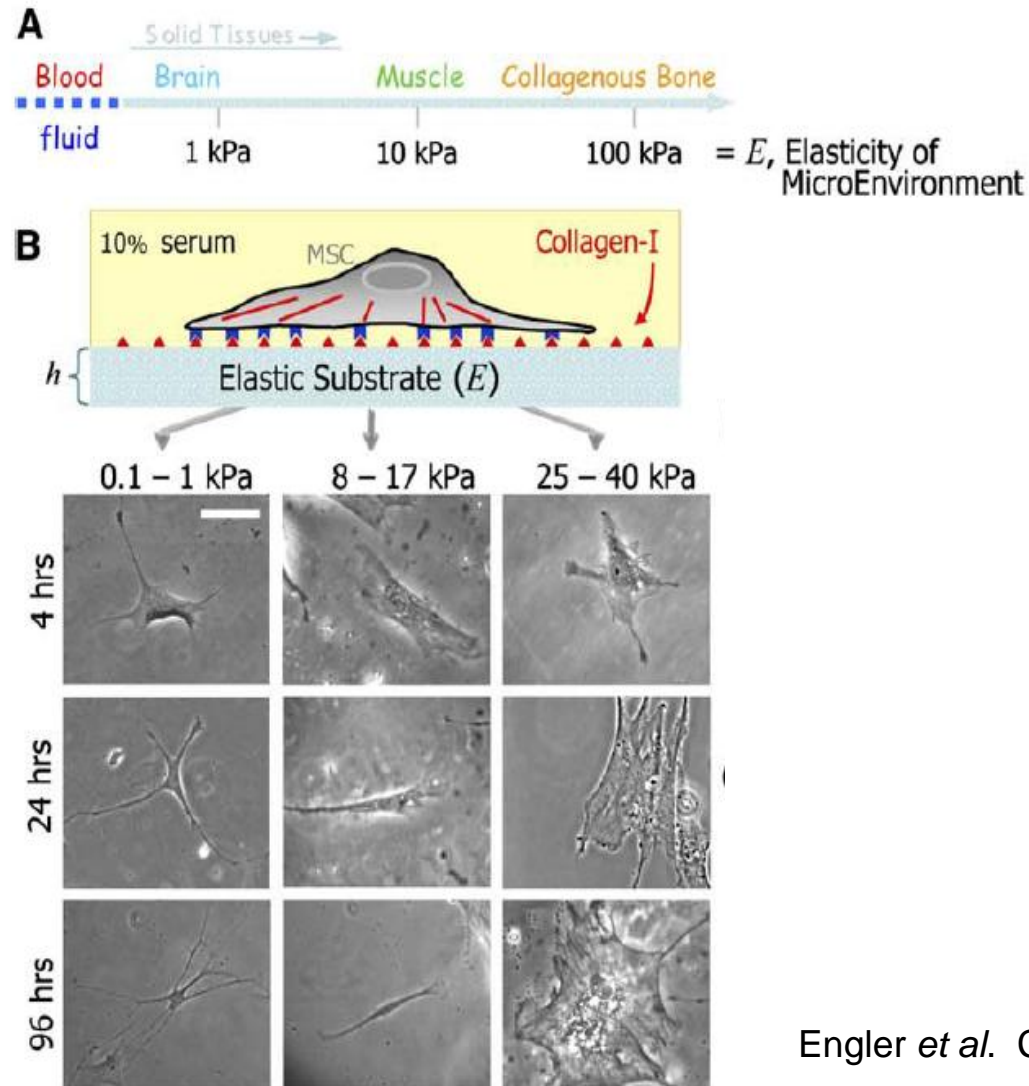


Cortiella *et al.* 2010

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

Lung scaffold modulates stem cell differentiation:

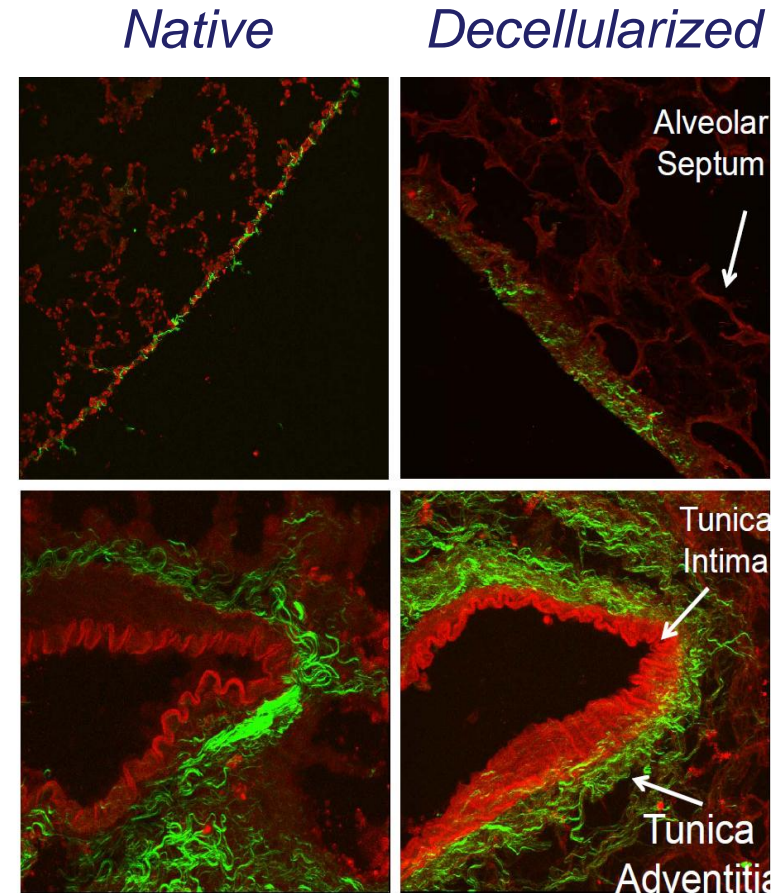
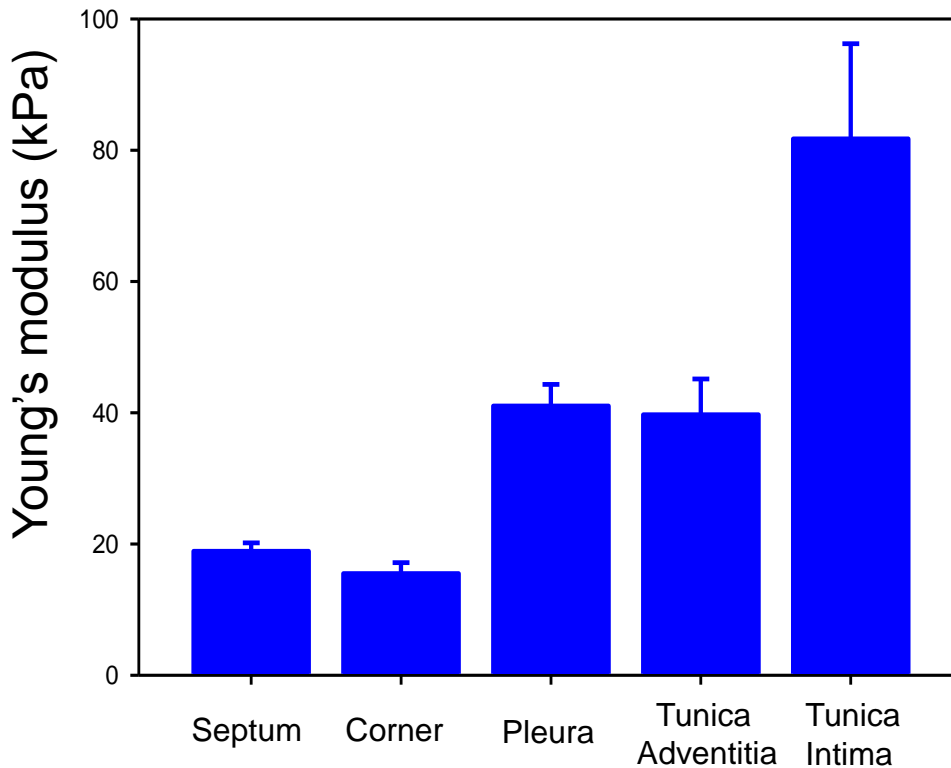
Differentiation of both embryonic and adults stem cells depends on substrate stiffness



Engler *et al.* Cell, 2006

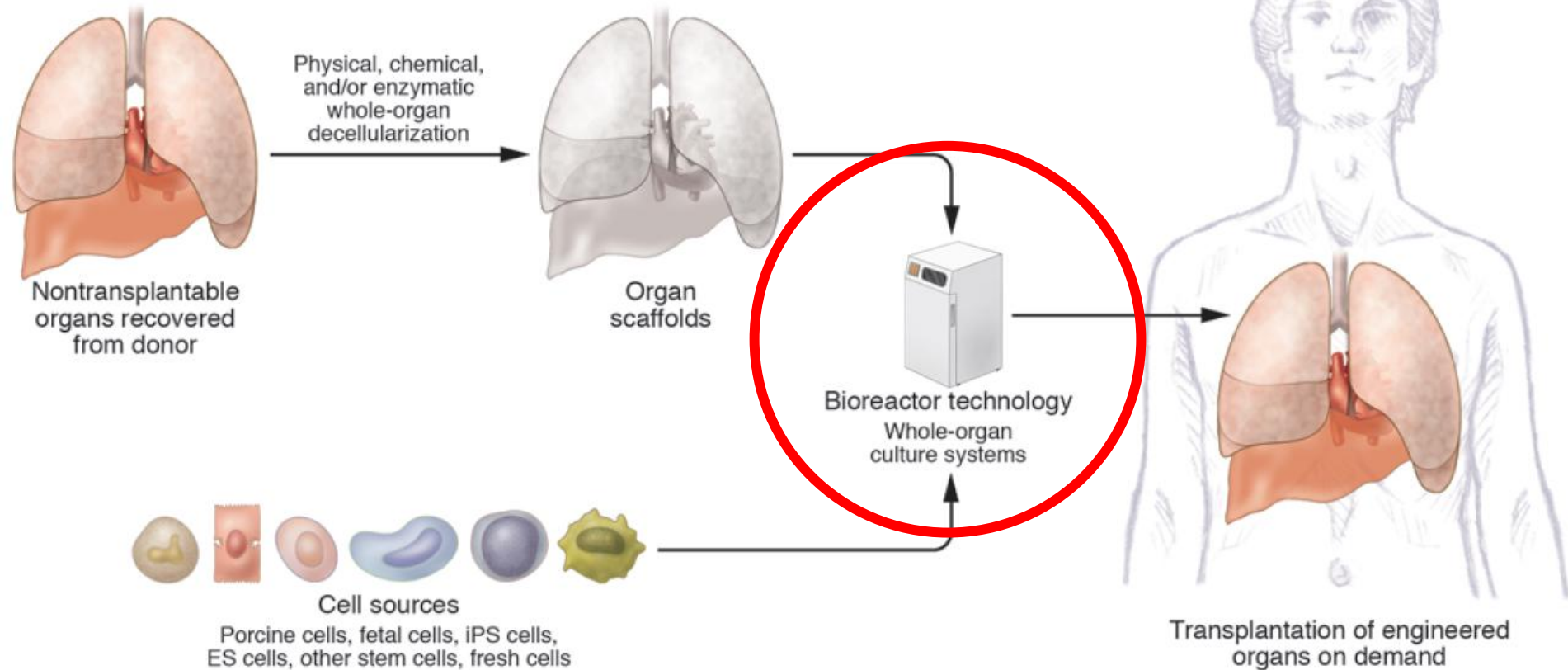
Lung scaffold modulates stem cell differentiation:

There is a considerable inhomogeneity in stiffness within the lung scaffold

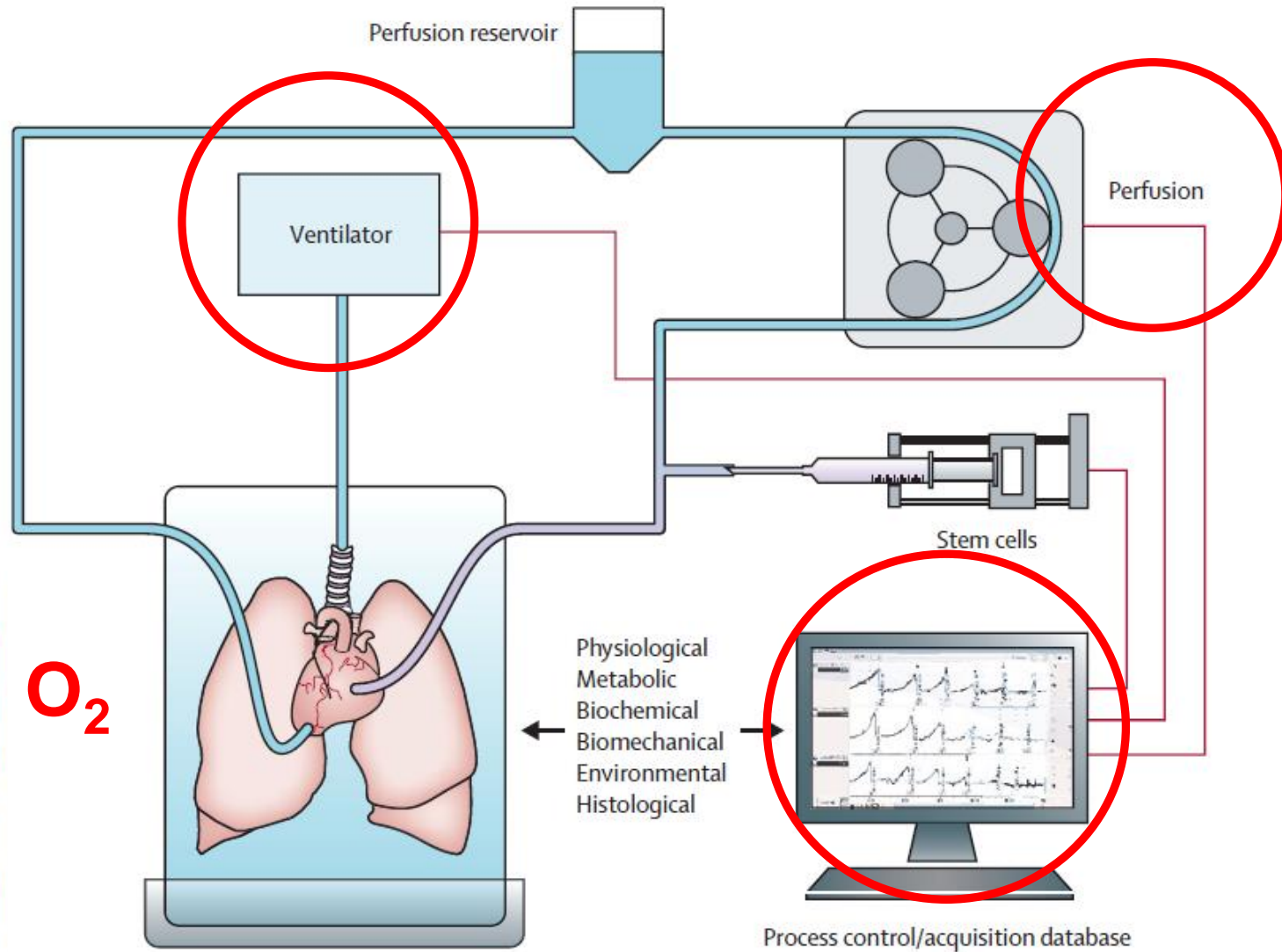


Collagen
Elastin

Lung bioengineering approach

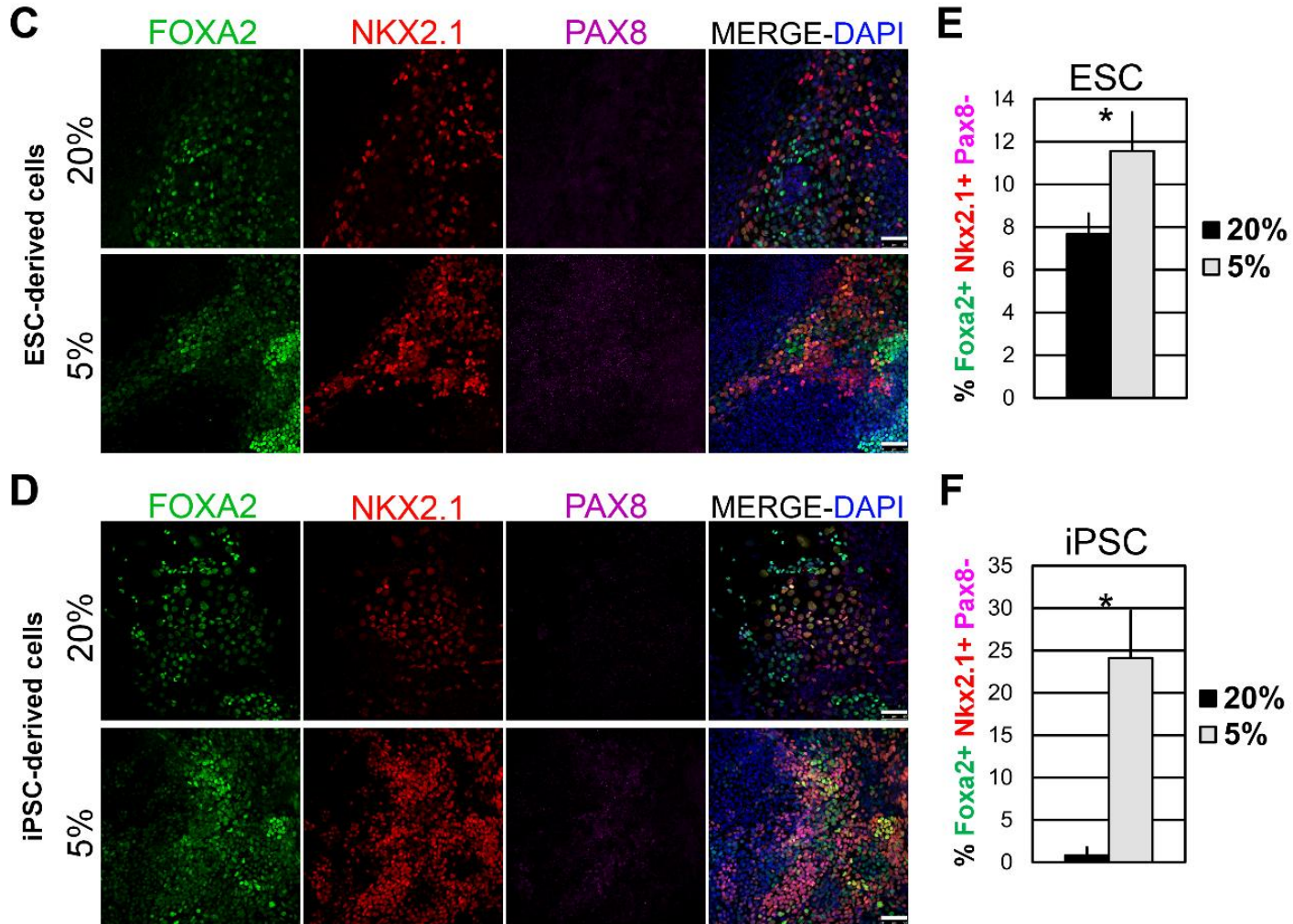


Importance of the bioreactor in modulating stem cell differentiation:

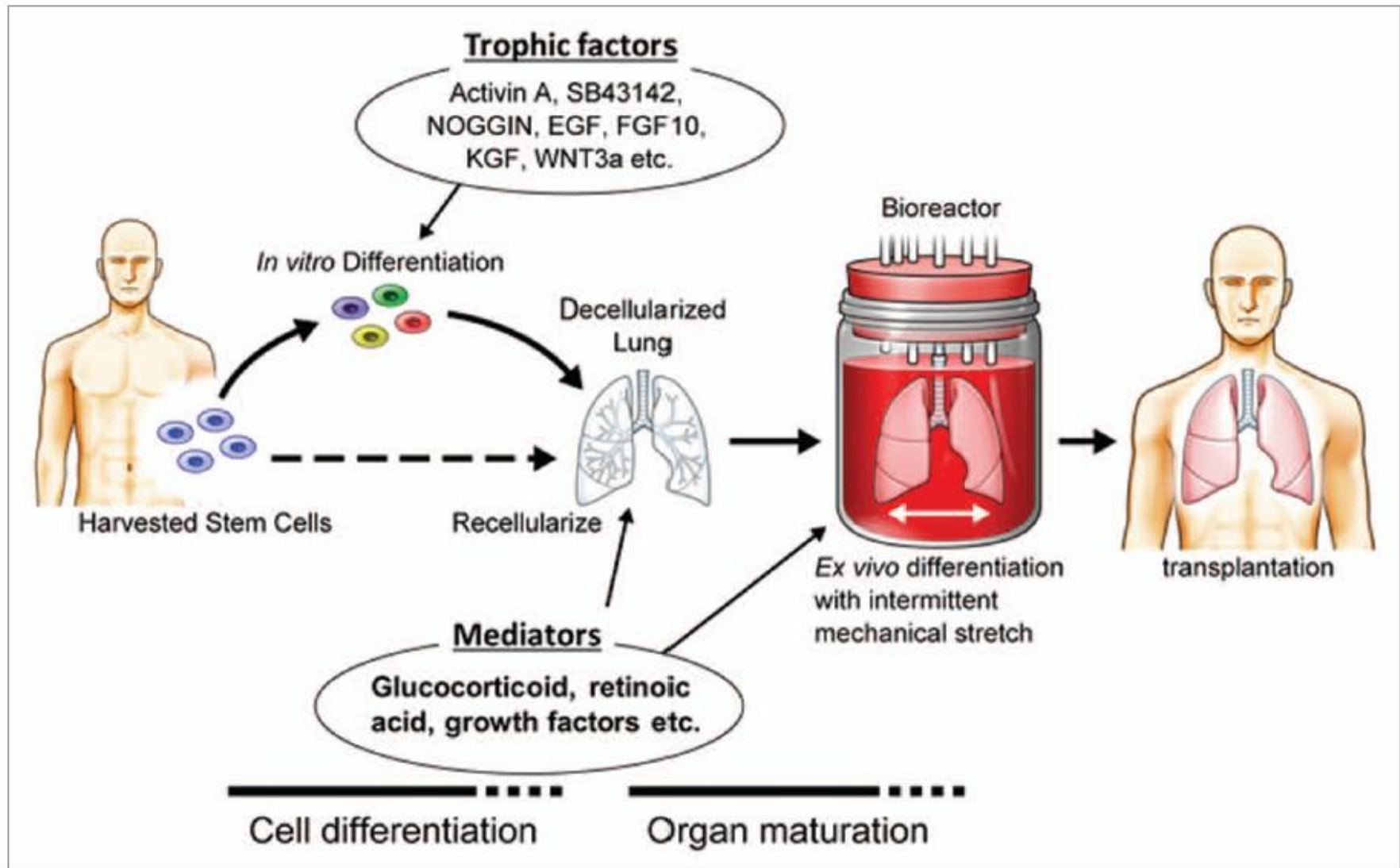


Importance of the bioreactor in modulating stem cell differentiation:

5% O₂ enhances differentiation towards lung cell types



Current perspective in lung bioengineering



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.**
- ✓ **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.**