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Research description

Our research group investigates different organs and tissues in the thorax and the potential to recover and/ or reconstitute their function. Therefore we evaluate and improve different methodologies in the field of tissue engineering and cell therapy. Cell types, such as adult progenitor/ stem cell, embryonic and induced pluripotent stem cells are currently under investigation for their potential use in the clinic. Culture and differentiation abilities of these cells are analyzed through in vitro and in vivo models. Strategies to mobilize and activate endogenous stem cells and increase their integration into the damaged tissues to stimulate tissue regeneration and in situ angiogenesis via specific growth and boosting factors **are investigated in preclinical and clinical settings.**

During the last year we focused on the development and improvements of both natural and synthetic scaffolds for different tissues and organs of the thorax, such as trachea, lung, esophagus, heart, chest wall and diaphragm. Within the last year we performed 3 transplantations of tissue engineered tracheae in patients and **analyzed obtained samples extensive.** In general, the early clinical transfer of this technology is the basic principle of our **clinical-orientated research group and the major aims of our efforts.**

a) Cell therapy: We investigated the different cell types (adult stem/progenitor cells, embryonic and induced pluripotent stem cells) for their potential use in various acute and chronic respiratory and cardiac disease models.

- Embryonic stem cells (ESCs)
- Induced pluripotent stem cells (iPSCs)
- Mesenchymal stem cells (MSCs)
- Mononuclear cells (MNCs)
- Neural crest cells (NCCs)
- Differentiated cells (epithelial and muscle cells, chondrocytes, adipocytes)

Our established animal model of pulmonary hypertension has also revealed improvements in the underlying disease after intratracheal treatment with mesenchymal stem cells. Burn injuries that affected the respiratory tract and esophagus also demonstrated a significant beneficial effect on the clinical outcome. Early data from patients with ECMO (extracorporeal membrance oxygenator) support with respiratory distress showed significant improvements, further downstream analysis are under progress.

b) Development of Scaffolds: Using tissue engineering with natural or synthetic scaffolds we are aiming to improve the recovery and/or reconstitution of different organs and tissues. We are investigating three-dimensional (3-D) scaffolds that can mimic the structural morphology of the target organ as well as providing the structural base (matrix) for attachment, proliferation and differentiation of cells. **Based on extensive experimental research during the last 12 months we designed 3 different synthetic tracheal scaffolds (using nanotechnology), each with improved characteristics compared to the former version.**
Electrospinning is one method that allows the fabrication of 3-D porous scaffolds with different architectures and morphologies. This technique includes the structural development from simple electrospun fibrous mats having random or aligned

orientation to fiber bundles, membranes and highly porous 3D complex scaffolds mimicking specific organs. The structural size of electrospun nanofibrous webs can be engineered to mimic the natural extracellular matrix (ECM) fibrous components. Besides, we established a small animal model for tracheal transplantation with in vivo cell tracking and imaging.

Development of mathematical modeling approaches: A key strategy in our research is the use of mathematical modeling techniques to assist the development of tissue engineering therapies. The extensive expertise from one of our colleagues in mathematical modeling helps to understand the interactions between cells and biomaterials 3, angiogenesis 4 and tissue growth into porous scaffolds 5. Based on our surgical operation in 2008 (Macchiarini et al . 2008), we developed a mathematical model to predict the regeneration in situ of a donor trachea seeded with mesenchymal stem cells (MSCs) and epithelial cells (EPCs). The model predicts the extent of inflammation and stenosis of the implanted trachea in terms of the seeding densities of EPCs and MSCs. This is a useful theoretical tool for exploring the mechanisms of tracheal regeneration and understanding why regeneration may fail. We started to extend such a model to make it more realistic, for example to include cell interactions with the electospun nanofibres in artificial tracheae, and the mechanisms contributing to neovascularisation. Incorporating these processes in the model will help us simulate novel cell-based therapies and to **explore in details the mechanisms** that can give rise to pathological conditions e.g. biomaterial-induced thrombosis.

Recently, we have also demonstrated successful clinical transplantations of tissue engineered trachea using synthetic scaffolds to show the feasibility of this promising methodology. These early clinical findings clearly demonstrate the enormous potential of RM: altering the current practice of treating patients affected by failing respiratory tissues and organs.