From engineering grafts to engineering developmental processes for regenerative medicine

I Martin[1]

[1] Department of Biomedicine & Department of Surgery, University Hospital Basel, Basel, CH.

SUMMARY: Following the exemplifying context of cartilage and bone regeneration, this lecture will describe and discuss alternative approaches currently pursued by the author's team to evolve classical tissue engineering paradigms towards possibly more effective grafts, with the potential for a broader clinical use.

The presentation will start from a short description of the clinical trials carried out at the University Hospital Basel for alar lobule reconstruction (1) or repair of articular cartilage defects based on the engineering of autologous cell-based cartilage grafts.

The lecture will then propose and discuss the concept of engineering regenerative strategies by recapitulating developmental processes, exploiting the own body as the in vivo bioreactor (2,3).

The implementation of such paradigm will be presented in two different scenarios. The first relies on the engineering of a living, autologous cell-based hypertrophic cartilage tissue, which is capable to undergo efficient remodelling into bone tissue upon in vivo implantation, according to the biological pathway of endochondral ossification (Figure 1). The second is based on the engineering of a cellular graft, which is however decellularized and stored off-the shelf (4). The resulting material would include in the extracellular matrix the diverse, cell-produced signals required to induce bone regeneration, and may be generated using standardized cell lines as opposed to autologous cells. These cell lines could be customized by genetic engineering techniques to overexpress specific factors aimed at enhancing the potency of the graft for defined indications (e.g., to increase the efficiency of remodelling or vascularization) (5).

The perspective will also address issues related to scalability, process control and regulatory compliance in manufacturing cell-based products and highlight the need not only to automate, but also to streamline and simplify typical production processes (6).

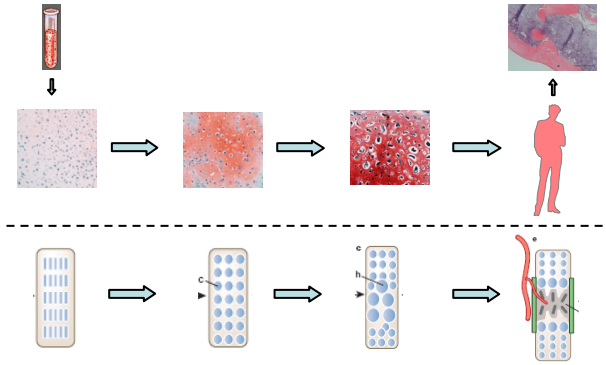

Figure 1: A "Developmental engineering" paradigm to induce tissue regeneration. Rather than engineering a tissue, the strategy targets the use of cells to engineer the different stages of a process (top part) which recapitulate events of development (e.g., endochondral ossification; bottom part). The product will be a tissue containing all necessary and sufficient cues to remodel into the target repair tissue upon grafting.

REFERENCES:

(1) I Fulco, S Miot et al. Engineered autologous cartilage for nasal reconstruction after tumour resection: an observational first-in-human trial. *The Lancet* (2014)

(2) C Scotti, B Tonnarelli et al. Recapitulation of endochondral bone formation using human adult mesenchymal stem cells as a paradigm for developmental engineering. *Proc. Natl Acad Sci USA* (2010)

(3) C Scotti, E Piccinini, H Takizawa et al. Engineering of a functional bone organ through endocondral ossification. *Proc. Natl Acad Sci USA* (2013)

(4) P Bourgine, B Pippenger at al. Tissue decellularization by activation of programmed cell death. *Biomaterials* (2013)

(5) I Martin. Engineered tissues as customized organ germs. *Tissue Eng-A* (2014)

(6) I Martin et al. Manufacturing challenges in regenerative medicine. *Sci Transl Med* (2014)

ACKNOWLEDGEMENTS: The presented work was funded by the SNF (Div III Grant No. 310030_133110/1 and Sinergia Grant No. CRSII3_136179 / 1)