Regenerative engineering: designing grafts, processes and signals

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Cellular grafts for the regeneration of cartilage and bone have been engineered using a variety of cell sources, scaffolds and manufacturing systems. Clinical implementation of some of these approaches by the own group has led to promising outcome results (Fulco+, Lancet 2014; Mumme+, Lancet 2016; Saxer+, Stem Cells 2016), but is still associated with manufacturing and robustness challenges. In order to gain repeatability of processes, alternative strategies have been conceived, based on delivering signals capable to recapitulate developmental events, with proofs of principle in the context of bone and cartilage regeneration (Scotti+, PNAS 2013; Occhetta+, PNAS 2018). Along this line, it was identified that regeneration-inductive signals may not require living cells to be efficiently delivered, but could be encoded in cell-laid and subsequently devitalized extracellular matrices (ECM) (Bourgine+, PNAS 2014; Bourgine+, Adv Funct Mater 2017). The resulting off-the-shelf biomaterials contain a combination of multiple cytokines and morphogens, presented to the recipient site through physiological sets of ECM molecules, which synergistically potentiate their effects. Grafts in this new class represent an alternative to synthetic matrices and would not function primarily as tissue replacements, but rather as “germs” for de novo tissue development. They could be generated based on highly standardized processes, thanks to the use of cell lines and bioreactor-based systems, and at the same time customized to address specific disease stages and patient profiles, in a perspective of personalized medicine (Haumer+, Adv Drug Del Rev 2017).