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 (1-4) but is still associated with manufacturing and standardization challenges. In order to gain repeatability and robustness, alternative strategies have been conceived, inspired by recapitulation of developmental processes, with proofs of principle in the context of bone and cartilage regeneration (5-6). Along this line, it was identified that signals inducing regeneration processes may not require living cells to be efficiently delivered but could be encoded in cell-laid and subsequently devitalized extracellular matrices (ECM) (7-8). 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. Such materials could be generated based on highly standardized processes, thanks to the use of cell lines and bioreactor-based systems, and at the same time enriched in defined factors to address specific disease stages and patient profiles, in a perspective of personalized medicine. They would not function primarily as tissue replacements, but rather as "germs" for *de novo* tissue development. Recent pre-clinical data substantiate that grafts in this new class exhibit unprecedented osteoinductive properties, unmatched by synthetic matrices or by living engineered tissues (8).

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