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Gene therapy applications in orthopaedics.

Dear Editor,

With great interest and enthusiasm, we read the article „Orthopaedic applications of gene therapy“ [1]. The authors should be congratulated for their concise yet very thorough and excellent coverage of the gene application in orthopaedics. However, it is our opinion that articular cartilage deserved more attention in the mentioned review. First of all we think that even subchapter title “Cartilage repair” should be expanded to “Cartilage repair and regeneration” especially because authors did mention “stimulation of cartilage regeneration” which would imply the possibility to induce intrinsic healing of the damaged cartilage by hyaline cartilage formation. When treating localized cartilage defects we should ask ourselves: what kind of new tissue formation inside the defect do we want to induce? Idealistically we aim for articular cartilage regeneration, not repair, which would mean a hyaline cartilage, not fibrocartilage formation. Treatment options published in the literature could be roughly divided into two concepts – reparative and restorative. The end result of the first concept is fibrocartilage, and microfracture technique is the most popular representative. However, restorative concept aims for hyaline cartilage implantation/formation and includes implantation of osteochondral plugs with perfectly organized cartilage and matrix and/or cell therapy, namely autologous chondrocyte transplantation. Anabolic factors including members of the TGF-beta superfamily, such as BMPs have proven their potential to stimulate chondrogenesis and synthesis of cartilage-specific matrix components in animal models [2,3]. However,

those proteins have short half-lives and it is difficult to maintain adequate *in situ* concentrations necessary for their proper functioning. Furthermore, many proteins act intracellularly and because cells cannot normally import these proteins, they cannot be used in soluble forms. These problems are the reason why gene therapy has acquired so much attention lately. The transfer of the respective genes into the joint, possibly in combination with the supply of chondroprogenitor cells, might be an elegant method to achieve a sustained delivery of such therapeutic factors at the required location *in vivo* [4]. Pascher et al.[5] developed a novel *ex vivo* method by using coagulated bone marrow aspirate as a mean of gene delivery to cartilage. Vector-seeded and cell-seeded bone marrow clots (“gene plugs”) were found to maintain their structural integrity following extensive culture and maintained transgenic expression for several weeks.

Therefore, we conclude that there is a huge potential for new tissue formation by gene therapy transduction of cells of different origin. Cells originating subchondrally, in combination with gene therapy, may form tissue of higher quality when compared to classical microfracture technique. On the other hand, hyaline cartilage formation by gene therapy induction in combination with cell implantation (possibly on biodegradable scaffolds) might be the answer to the current limitations of cartilage treatment modalities, and may provide permanent solution for the patients. Many animal studies are currently investigating the gene therapy induced cartilage regeneration of chondral and osteochondral defects, some of which are expected to develop into clinical trials and give answers to these open issues.

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