

### Molecular approaches to cartilage repair

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Gene transfer offers the possibility of delivering chondrogenic factors to sites of cartilage damage in a sustained, cost-effective and efficacious manner. Depending upon the sophistication of the construct, more than one transgene may be delivered and levels of transgene expression may be independently regulated. The strategies employed will differ depending on the size of the lesion and whether it is an isolated injury in an otherwise healthy joint or part of the degenerative process associated with osteoarthritis.

Gene transfer to synovium is technically quite straightforward and has already been achieved in human clinical trials of arthritis. In the context of cartilage repair, it is a convenient intra-articular depot from which to synthesize secreted growth factors that can influence the metabolism of articular cartilage by diffusion. This has been demonstrated for IGF-1 and BMP-2 in rabbits' knees. However, delivery of TGF- $\beta_1$  in this fashion has serious adverse effects.

Disadvantages of gene delivery to synovium include its failure to increase the cellularity of the cartilaginous lesion and its limitation to secreted, diffusible gene products. *Ex vivo* protocols permit the implantation of genetically modified chondrocytes or chondroprogenitor cells that can, if required, be engineered to express increased levels of intracellular proteins, such as transcription factors. Although successful in animal models, this strategy involves cell culture and scaffolding issues that render it tedious and uneconomical in clinical practice. Two

approaches are being developed to obviate these limitations. Madry and colleagues have pioneered the direct application of recombinant adeno-associated virus vectors to cartilaginous lesions at the time of repair by subchondral drilling. By this means, genes are transferred to chondroprogenitor cells as they enter the defect *via* the subchondral bone. Using a rabbit model, they have reported success with various transgenes, including IGF-1 and FGF-2. In a related approach, we have removed bone marrow from rabbits, allowed it to clot in the presence of viral vectors carrying chondrogenic genes, and inserted the resulting autologous "gene plug" into full-thickness lesions in articular cartilage. Encouraging preliminary data have been obtained.

For lesions in osteoarthritic joints, where repair is attempted in the presence of a disease process, it may be advantageous to combine the synovial delivery of a cDNA encoding IL-1Ra with intra-lesional delivery of a chondrogenic cDNA.