Gene Therapy for Osteoarthritis

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Key Points
- Interleukin-1 receptor antagonist appears to be a good transgene for expression in OA
- Appropriate vectors for gene therapy appears to still be a limitation

The term gene therapy is commonly understood to mean the use of molecular methods to replace defective or absent genes or to counteract those that are over-expressed. The key technologies needed for gene therapy are the methods by which genes are isolated (cloned), manipulated (engineered), and transferred (gene transfer) into host cells.

Two basic methodologies are utilized to transfer vectors into target tissues. In the first method, ex vivo gene transfer, cells are collected from the patient or host and grown in the laboratory. During a finite culture period the therapeutic genes are transferred into the cells often using a viral vector. Once tested for the correct behavior or, in many cases, protein production, the transduced cells are re-implanted in the patient. This methodology is currently quite prevalent in human gene therapy trials, partially because the administrator has the ability to control and test the cells prior to re-introduction into the patient, thus giving the utmost consideration to safety issues. The second method, in vivo, refers to the direct transfer of the vector to the target tissues in situ. Although this method does not allow for extensive safety testing, its utility and ease of application are very attractive, and for these reasons many planned gene therapy protocols are using this methodology in both human and veterinary applications. Having defined the methods available for transferring vectors to the target cells, further discussion on the specific types of available vectors is needed.

Vectors are generally either non-viral (synthetic) or viral. Non-viral vectors typically refer to synthetic molecules that facilitate the uptake of DNA into cells by condensing the DNA with lipids, peptides, proteins, inactivated virus particles, crystals of calcium phosphate, or coated microprojectiles. Viral vectors are viruses from which the viral genes have been removed to allow insertion of the therapeutic gene(s), and the viral vector has usually been rendered incapable of replicative spread. Viral vectors typically produce a greater efficiency of gene delivery than non-viral vectors. Many well-characterized viruses have been explored for use as vectors; however, to date retroviral, adenoviral and adeno-associated vectors have proven the most useful. The pro’s and con’s of each of these vectors will be discussed in the presentation.

Many different proteins have been considered for expression (transgenes) in the joint. The most commonly employed is interleukin receptor antagonist protein (IL-1ra). The administration of this protein via gene therapy has provided a nice proof of principle study in the horse. Further details of this study will be presented in the lecture. Other proteins of interest include insulin-like growth factor-I, transforming growth factor beta, and methods to block tumor necrosis factor receptor.
While gene therapy has great promise, currently vectors to deliver genes of interest are hampering the field. This includes transgene expression (therapeutic protein concentrations), the length of expression, the ability to control expression timing and the ability to re-dose when the transgene is no longer present. These limitations will be discussed in greater detail during the presentation.