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# Gene Therapy for Human Osteoarthritis

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## 1. Introduction

Articular cartilage has a reduced capacity for self-regeneration. Delivery of candidate genes to articular chondrocytes is an attractive strategy that has the potential to allow for a durable reestablishment of the structural integrity in osteoarthritic (OA) cartilage. Gene transfer approaches might be better suited to treat a slow and irreversible disorder such as OA over time instead of systems that are based on the application of recombinant factors with relatively short pharmacological half-lives. Current approaches that aim at re-equilibrating the metabolic balance in OA cartilage are based on the transfer of sequences coding for agents that either counteract the processes of matrix degradation or enhance the synthesis of matrix components. Importantly for the treatment of OA, the development of effective gene treatments will necessitate that the gene vehicle chosen allows for high and also sustained levels of expression of the sequence to be delivered due to the slow and irreversible progression of this disorder. The method elected to administer the therapeutic composition will be also important to achieve successful and long-term cartilage regeneration in OA patients.

## 2. Gene therapy

Gene therapy aims at treating human diseases via gene transfer techniques that introduce foreign genes or sequences in various cell types. The foreign material enters the cell where it is transferred towards the nucleus. Once there, it either integrates in the host genome or stays extrachromosomal under episomal forms that generally allows only for transient transgene expression. Gene transfer in sufficient number of cells is essential to allow for the production of therapeutically relevant concentrations of transgene products. The currently most employed vectors used in gene therapy trials include nonviral compounds (naked DNA, physical and chemical methods) and different viral gene carriers including adenoviral, herpes simplex virus-derived, retroviral, lentiviral, and recombinant adeno-associated viral vectors that utilize natural entry pathways in human cells (Cucchiarini et al., 2009a; Cucchiarini & Madry, 2005; Evans, 2004; Evans et al., 2004) (**Table 1**).

### 2.1 Nonviral vectors

Chemical methods of complexing DNA to various macromolecules include cationic lipids and liposomes, polymers, polyamines and polyethylenimines, and nanoparticles, besides the use of calcium phosphate coprecipitates. Nonviral methods avoid the risk of acquiring

replication competence inherent to viral vectors. They can be repeatedly administered, have the capacity to deliver large therapeutic genes, and are easy to produce on a large scale. Also, they do not elicit immune responses in the host organism. Still, their efficacy is often much lower than those of viral vectors. In addition, as the transgenes remain as episomes in their targets, only short-term transgene expression is achievable. To overcome these shortcomings, nonviral gene transfer strategies *in vivo* are generally based on the use of *ex vivo*-modified cells for readministration in sites of damage.

|                  |                                                              | Benefits                                                     | Shortcomings                                                                                | Integration |
|------------------|--------------------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------|
| Nonviral vectors | Liposomes, others (chemical, electrical, mechanical methods) | Noninfectious, low toxicity, easy to produce, large capacity | Relatively low efficiency, short-term transgene expression                                  | No          |
| Viral vectors    | Adenovirus                                                   | Very high efficiency                                         | Potential replication competence, toxicity, immunogenicity, short-term transgene expression | No          |
|                  | Retrovirus                                                   | High efficiency, long-term transgene expression              | Potential replication competence, risk of insertional mutagenesis                           | Yes         |
|                  | Herpes simplex virus                                         | High efficiency, large capacity                              | Relative cytotoxicity, short-term transgene expression                                      | No          |
|                  | Adeno-associated virus                                       | Very high efficiency, long-term transgene expression         | Relative difficulty to produce                                                              | No          |

Table 1. Gene Transfer Vectors.

2.2 Adenoviral vectors

Adenoviruses have been among the most employed systems so far. They allow for high transduction efficiencies and transgene expression in a variety of cells, allowing for direct approaches *in vivo*. Yet, there are serious concerns about their safe use in the clinics due to the development of strong host immune responses to the remaining adenoviral gene products. Another problem is the limited period of transgene expression (1-2 weeks) as the sequences delivered remain as episomes that are cleared shortly after being introduced in the cells.

### 2.3 Retroviral vectors

An advantage of these viruses is their ability to integrate in the host genome, allowing for the maintenance of the transgene over extended periods of time. Nevertheless, this might lead to insertional mutagenesis and a potential to activate tumorigenic sequences. Also, such vectors transduce only dividing cells with a restricted host range (and a low efficacy) and are only produce at relatively low concentrations. Therefore, *ex vivo* approaches with pre-selection of transduced cells are usually employed. Interestingly, lentiviral vectors, a subclass of retroviruses derived from the human immunodeficiency virus (HIV) that integrate in the genome of nondividing cells avoid the need for cell division and show higher levels of transduction *in vivo*. Nevertheless, there are still concerns associated with their application, including the potential for insertional mutagenesis and the psychological problem of introducing genetic material carrying HIV sequences.

### 2.4 Herpes simplex viral vectors (HSV)

HSV-derived vectors are large vehicles that can deliver large transgenes to almost all known cell types, including nondividing cells. Although first-generation vectors induced high levels of cytotoxicity, recent work has demonstrated that second-generation HSV were less deleterious, in particular for cartilage gene transfer. One problem remains the transient nature of transgene expression mediated by this family of vectors.

### 2.5 Recombinant adeno-associated viral vectors (rAAV)

Application of viral vectors raises additional safety concerns, as potentially infectious agents or sequences might be introduced *per se* in the body. This is particularly important for the treatment of OA as it is not a life-threatening disorder. In this regard, rAAV vectors based on the nonpathogenic, replication-defective human parvovirus AAV might be more adequate for gene therapy settings. rAAV are produced by complete removal of the viral gene coding sequences, making them less immunogenic than adenoviral vectors and less toxic than HSV. Also, rAAV can be transcribed in their targets at very high efficiencies for months to years due to the stabilization of the episomal transgene cassettes by concatemer formation, making them strong alternatives for direct gene transfer approaches *in vivo*. Cell division and integration are not required for expression of the foreign material delivered via rAAV, in marked contrast with retroviral vectors. Redosing of vectors is practicable with rAAV, based on the use of various serotypes of the virus. For these reasons, rAAV became a preferred gene transfer method for experimental settings *in vivo* and for clinical applications.

## 3. Osteoarthritis

### 3.1 Articular cartilage

Adult hyaline articular cartilage is an avascular and aneural tissue that does not possess a lymphatic drainage that allows for a smooth gliding of the articulating surfaces of a joint and protects the subchondral bone from mechanical stress. Hyaline articular cartilage has several laminar zones formed by chondrocytes surrounded by an intricate network of extracellular matrix rich in proteoglycans and collagen fibrils (mostly type-II collagen and also types type-VI, -IX, -XI, and -XIV collagens and additional macromolecules). Normal hyaline articular cartilage contains about 70-80% water bound to proteoglycans. The

chondrocytes regulate the structural and functional properties of the cartilage according to the applied loads by producing and degrading the extracellular matrix.

### 3.2 Osteoarthritis

Osteoarthritis (OA) is the most disabling condition and prevalent form of arthritis (80%). OA is a chronic disorder of diarthrodial joints, mainly characterized by a slow, progressive, and irreversible deterioration of the articular cartilage, with changes in the subchondral bone. OA also affects to a minor degree the synovial lining, ligaments, tendons, and muscles.

OA is a complex disorder characterized by the activation of inflammatory cascades and alterations of the chondrocyte phenotype, leading ultimately to cartilage breakdown (loss of the major components of the cartilage matrix). Under mechanical or biochemical stress (interleukin-1, i.e. IL-1; tumor necrosis factor alpha, i.e. TNF- $\alpha$ ; nitric oxide, i.e. NO, prostaglandins, matrix degradation products), the cells undergo pathological changes in gene expression patterns that impede the whole homeostasis: diminished production of matrix molecules, enhanced production of matrix-degrading enzymes (matrix metalloproteinases, i.e. MMPs; adamalysins), decreased responsiveness to reparative stimuli, degradation of the matrix, alteration of the cell viability, cell senescence with apoptosis (NO; Fas/FasL signaling).

Several nonsurgical options are available to manage the progression of OA, including pharmacological treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs), slow-acting drugs in OA (SADOAs) like glucosamine, chondroitin sulfate, and diacerin, being either symptomatic slow-acting drugs in OA (SYSADOAs) or disease-modifying OA drugs (DMOADs). However, there is no convincing evidence yet that such drugs indeed modify or inhibit the progression of OA. Surgical interventions such as débridement, marrow stimulation, and osteotomy are specifically indicated in early stages of OA. Yet, restoration of a native cartilage that is identical in its structure to the normal cartilage and capable of withstanding mechanical stresses over time in OA has not been achieved to date. Causative treatment for OA therefore remains a problem, particularly troublesome for patients that are too young to undergo endoprosthetic joint replacement.

## 4. Osteoarthritis gene therapy

### 4.1 Target cells in OA – Gene transfer *in vitro*

Target cells in the OA joint include:

1. chondrocytes,
2. osteocytes,
3. cells of the synovial lining,
4. progenitor cells, or
5. cells of surrounding tissues (muscle, tendons, ligaments, meniscus).

Application of nonviral (Gerich et al., 1997b; Grossin et al., 2006; Kaul et al., 2006; Madry et al., 2004b; Madry et al., 2005; Madry et al., 2001; Nita et al., 1996; Tsuchiya et al., 2003; Zhang, H. N. et al., 2009), adenoviral (Baragi et al., 1995; Brower-Toland et al., 2001; Gelse et al., 2001; Gerich et al., 1997a; Gerich et al., 1996; Gerich et al., 1997b; Goto et al., 1999; Haupt et al., 2005; Ikeda et al., 2004; Li et al., 2004; Lou et al., 1997; Mehrara et al., 1999; Musgrave et al., 2002; Nita et al., 1996; Nixon et al., 2000; Nixon et al., 2005; Saxer et al.,

2001; Shuler et al., 2000; Smith et al., 2000; Steinert et al., 2007; Steinert et al., 2009; Steinert et al., 2008), or retroviral vectors (Baltzer et al., 1999; Gerich et al., 1997a; Gerich et al., 1996; Gerich et al., 1997b; Goto et al., 2000; Gouze, J. N. et al., 2003; Hildebrand et al., 1999; Li et al., 2004; Mason et al., 2000; Nita et al., 1996; Piera-Velazquez et al., 2002; Roessler et al., 1995; Tew et al., 2005) has been achieved in such cells with more or less success. rAAV are potent alternatives as they efficiently and durably transduce synoviocytes (Adriaansen et al., 2007; Apparailly et al., 2002; Goater et al., 2000; Goodrich et al., 2009; Hiraide et al., 2005; Traister et al., 2006; Zhang, H. G. et al., 2000), chondrocytes (Arai et al., 2000; Cucchiarini et al., 2005; Cucchiarini et al., 2009c; Cucchiarini et al., 2007; Dai & Rabie, 2007; Goodrich et al., 2009; Madry et al., 2003; Ulrich-Vinther et al., 2002; Ulrich-Vinther et al., 2005; Yokoo et al., 2005), mesenchymal stem cells (MSCs) (Chamberlain et al., 2008; Chamberlain et al., 2004; Chen, M. et al., 2011; Cucchiarini et al., 2011; Cucchiarini et al., 2005; Dai & Rabie, 2007; Ito et al., 2004; Kim, S. J. et al., 2007; Pagnotto et al., 2007; Shi & Wang, 2010; Stender et al., 2007), and other cell types relevant of the pathogenesis of OA (Arsic et al., 2004; Basile et al., 2008; Cucchiarini et al., 2009b; Gerich et al., 1997a; Gerich et al., 1997b; Ito et al., 2005; Kessler et al., 1996; Luk et al., 2003; Madry et al., 2004a; Tang et al., 2008; Wang et al., 2007; Wang et al., 2005). Regeneration of a native (structural and functional) cartilage architecture might be achieved by:

1. inhibiting inflammatory and catabolic pathways,
2. stimulating anabolic pathways to rebuild the matrix,
3. impeding cell senescence,
4. avoiding the pathological formation of osteophytes,
5. prevention of apoptosis, and/or
6. influencing several of these processes.

Inhibition of catabolic pathways has been observed when expressing inhibitors of matrix-degrading enzymes (tissue inhibitor of MMPs, i.e. TIMP) (Kafienah et al., 2003), inhibitors of proinflammatory cytokines (IL-1Ra; the soluble receptors sIL-1R or sTNFR) (Attur et al., 2002; Baragi et al., 1995; Gouze, J. N. et al., 2003; Haupt et al., 2005; Roessler et al., 1995; Zhang, H. G. et al., 2000; Zhang, X. et al., 2006), and chondroprotective cytokines (IL-4; IL-10) (Kim, S. H. et al., 2001; Zhang, X. et al., 2006). Activation of anabolic processes has been noted by single or combined administration of components of the cartilage matrix or of the enzymes that synthesize them (Dharmavaram et al., 1999; Venkatesan et al., 2004), of growth factors and receptors (insulin-like growth factor I, i.e. IGF-I; fibroblast growth factor 2, i.e. FGF-2; bone morphogenetic proteins, i.e. BMPs; transforming growth factor beta, i.e. TGF- $\beta$ ) (Brower-Toland et al., 2001; Chen, B. et al., 2010; Cucchiarini et al., 2011; Cucchiarini et al., 2005; Cucchiarini et al., 2009c; Haupt et al., 2005; Lee et al., 2005; Madry et al., 2004b; Madry et al., 2001; Nixon et al., 2000; Nixon et al., 2005; Saxer et al., 2001; Schmal et al., 2005; Shuler et al., 2000; Smith et al., 2000; Ulrich-Vinther et al., 2005), and of transcription factors (SOX family of DNA-binding proteins, i.e. SOX5, SOX6, SOX9) (Cucchiarini et al., 2007; Ikeda et al., 2004; Li et al., 2004; Tew et al., 2005; Tsuchiya et al., 2003). Restoration of cell vitality and activation of proliferation have been achieved by application of IGF-I or FGF-2 (Cucchiarini et al., 2011; Cucchiarini et al., 2005; Cucchiarini et al., 2009c; Kaul et al., 2006; Madry et al., 2004b; Madry et al., 2001; Schmal et al., 2005), telomerase (hTERT) (Piera-Velazquez et al., 2002), of inhibitors of apoptosis (bcl-2) (Surendran et al., 2006), or of the heat shock protein 70 (HSP70) (Grossin et al., 2006). Remarkably, approaches that influence several of these

processes have been also successfully attempted, like combining the transfer of inhibitors of catabolism pathways and of activators of anabolic events (IGF-I/IL-1Ra) (Haupt et al., 2005; Nixon et al., 2005), as well as that of activators of anabolic and proliferative processes (FGF-2/SOX9 or FGF-2/IGF-I) (Cucchiaroni et al., 2009c; Orth et al., 2011).

## 4.2 Gene transfer *in vivo*

### 4.2.1 Direct gene transfer

The key issue in establishing an efficient therapy against OA is to access the targets of the treatment when the cells reside in the joint cavity. The following approaches have been therefore developed:

1. systemic delivery and
2. intraarticular administration:
  - 2.1 by injection or
  - 2.2 using arthrotomy

Systemic approaches are better suited to target diseases that are systemic in nature like rheumatoid arthritis (RA) (Evans et al., 2006b, 2009; Jorgensen & Apparailly, 2010).

Local administration of components might be preferable for OA that affects only a limited number of joints without major systemic manifestations. Intraarticular injection of most vector types preferentially transduce the synovium (Ghivizzani et al., 1997; Gouze, E. et al., 2002; Nita et al., 1996; Roessler et al., 1993), being rather suited for strategies aiming at inhibiting inflammatory and catabolic pathways (and a common approach employed against experimental RA). Direct application of gene vectors has been attempted in experimental OA using sequences coding for IL-1Ra (Fernandes et al., 1999; Frisbie et al., 2002; Frisbie & McIlwraith, 2000; Zhang, X. et al., 2006), IL-10 (Zhang, X. et al., 2006), HSP70 (Grossin et al., 2006), gene silencers (Chen, L. X. et al., 2008), or kallistatin and thrombospondin-1 (Hsieh et al., 2009; Hsieh et al., 2010). Yet, even if cartilage breakdown is contained, this may not be sufficient to fully compensate for the loss of matrix elements and cells noted during the disease progression. In this regard, synthesis of cartilage matrix components might be stimulated by providing vectors carrying genes for anabolic factors (FGF-2, IGF-I) (Chen, B. et al., 2010).

### 4.2.2 Indirect gene transfer

*Ex vivo* gene therapy is more complex but safer as no free vector particles are introduced in the body. Also, modified cells can be controlled, tested, and selected in culture. Administration of cells is also a means to increase the cellularity like needed for cases of severe OA.

Synoviocytes have been mostly employed to deliver inhibitors of inflammatory and catabolic processes (Pelletier et al., 1997; Zhang, X. et al., 2004). Such pathways were regulated by injecting cells overexpressing an IL-1Ra alone (Pelletier et al., 1997; Zhang, X. et al., 2004) or with IL-10 (Zhang, X. et al., 2004). Again, although OA was reduced in association with decreased cartilage breakdown, complete resurfacing was not reported. Nevertheless, the use of differentiated cells is impaired by the invasive methods of preparation from unaffected sites with a limited supply and by common changes in cell phenotype observed upon passaging in culture. Also, implantation of committed cells generally leads to the formation of a poorly differentiated (fibrous) cartilage. Progenitor cells might be better suited to generate a cartilage of enhanced quality in transplantation settings.

They can be easily isolated from multiple tissues (bone marrow, periosteum, perichondrium, muscle, fat, subdermis, cartilage, bone, synovial membrane, ligaments), even in OA patients, maintaining a multilineage potential with a reliability for differentiation and a capacity for expansion (Barry & Murphy, 2004; Yoo et al., 2000). Remarkably, injection of muscle-derived stem cells modified by combined gene transfer of BMP-4 with sFlt1 (an antagonist of the vascular endothelial growth factor, i.e. VEGF) allowed for cartilage repair in a rat model of OA (Matsumoto et al., 2009).

## 5. Clinical trials

Preclinical data, as those described above, have encouraged the initiation of human clinical trials mostly for RA. The first studies were based on retroviral gene transfer of human IL-1Ra in synoviocytes from RA patients and reinjection in the metacarpophalangeal joint (Evans et al., 2000a; Evans et al., 1996; Wehling et al., 2009). Transgene expression was noted locally without adverse events, leading to clinical improvements in some patients, encouraging the implementation of phase II studies (Evans, 2005; Evans et al., 2005a; Evans et al., 2000b; Evans et al., 2006a, 2008; Evans et al., 2004; Evans et al., 2005b; Robbins et al., 2003). Direct intraarticular injection of rAAV carrying an sTNFR-immunoglobulin in RA patients revealed that the treatment was safe and well tolerated (Evans, 2005; Evans et al., 2005a; Evans et al., 2006a, 2008; Mease et al., 2009), and a phase I/II trial was subsequently started. Regarding OA, a phase I protocol is ongoing, based on an *ex vivo* approach using the retroviral transfer of TGF- $\beta$  (Evans et al., 2008).

## 6. Conclusions

Gene therapy holds great promise, but issues that need to be addressed include the duration of transgene expression, extended analyses in clinically relevant animal models, the benefit of *ex vivo* genetically modified cells versus direct approaches, and the identification of optimal therapeutic factors. Future studies will also have to shed light on the safety of these approaches regarding the nonlethal nature of OA. Successful application of gene therapy for OA requires a combined effort of surgeons and basic scientists in order to improve the currently available gene transfer systems.

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The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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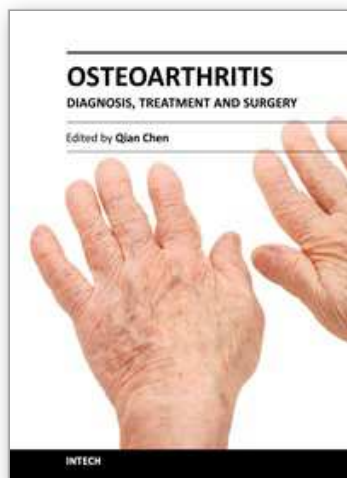
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Osteoarthritis is one of the most debilitating diseases affecting millions of people worldwide. However, there is no FDA approved disease modifying drug specifically for OA. Surgery remains an effective last resort to restore the function of the joints. As the aging populations increase worldwide, the number of OA patients increases dramatically in recent years and is expected to increase in many years to come. This is a book that summarizes recent advance in OA diagnosis, treatment, and surgery. It includes wide ranging topics from the cutting edge gene therapy to alternative medicine. Such multifaceted approaches are necessary to develop novel and effective therapy to cure OA in the future. In this book, different surgical methods are described to restore the function of the joints. In addition, various treatment options are presented, mainly to reduce the pain and enhance the life quality of the OA patients.

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