

On the Horizon From the ORS

Emerging Concepts in Gene Therapy for Osteoarthritis

Muhammad Farooq Rai, PhD

Linda J. Sandell, PhD

From the Department of Orthopaedic Surgery, Musculoskeletal Research Center, Washington University School of Medicine at Barnes-Jewish Hospital, St. Louis, MO.

Dr. Rai or an immediate family member serves as a board member, owner, officer, or committee member of the Orthopaedic Research Society. Dr. Sandell or an immediate family member has received royalties from Merck; has stock or stock options held in ISTO Technologies; has received research or institutional support from Fidia Farmaceutici s.p.a (Italy); and serves as a board member, owner, officer, or committee member of the Osteoarthritis Research Society International.

J Am Acad Orthop Surg 2015;23:e56-e57

<http://dx.doi.org/10.5435/JAAOS-D-15-00339>

Copyright 2015 by the American Academy of Orthopaedic Surgeons.

Osteoarthritis (OA) is a disease of the total joint, affecting cartilage, bone, meniscus, synovium, and ligaments. It is estimated that 27 million Americans were affected with OA in 2008,¹ that 35 million are currently affected, and that 67 million will be affected by 2030.² Despite the high incidence, there is no treatment that significantly alters the course of disease. Unlike many other diseases, OA is well suited for local, intra-articular treatment because the disease affects a limited number of joints and lacks obvious extra-articular manifestations. Among several efforts made to treat OA, gene therapy has merit. Gene therapy is the intentional modulation and transfer of a therapeutic gene into the cells of injured tissue to achieve sustained and well-regulated synthesis of therapeutic protein at the site of injury. Gene transfer can be achieved through *ex vivo* or *in vivo* approaches. The goal is to augment the expression of a therapeutic gene or inhibit the expression of a disease-associated gene in cells.

Application of *ex vivo* gene therapy merges well with the tissue-engineering approach. *Ex vivo* gene therapy requires removal of cells from the body and genetic manipulation of the cells *in vitro* before reimplantation. In contrast, *in vivo* gene therapy provides delivery of the therapeutic genes directly into the cells of the synovial joint. In both approaches, the transfer of DNA into the cells can be made either by viral or nonviral vectors.³

In the nonviral approach, gene transfer is achieved through several nonionic, physical (electromagnetic

and biochemical modes. Although they have no obvious risks for immunogenicity/mutagenesis, nonviral vectors are less efficient than viral vectors. This barrier can be overcome with the use of responsive (self-limiting) promoters that are stimulated only when joint homeostasis is perturbed and express the therapeutic gene only when needed.^{4,5} In addition, vectors with two promoters (ie, dual expression vectors) are able to harbor two genes and provide an opportunity for augmented therapeutic potential and eliminate the limitation of single-gene selection.^{6,7} For example, an anti-catabolic and a proanabolic gene can be selected to ameliorate inflammation, improve matrix synthesis, inhibit apoptosis, enhance joint lubrication, and improve healing of microfractures and chondral defects.

Viral vectors, which have had the viral genes removed, provide a renewable source of gene expression. Although these vectors have been used in gene therapy trials,⁸ they have potential limitations such as immunogenicity, insertional mutagenesis, persistence, and sustainability of transgene expression and tissue/cell specificity. Recently, adeno-associated vectors have gained popularity as a gene therapy vector secondary to the commercialization of alipogene tiparvovec, an adeno-associated vector-based product for management of familial lipoprotein lipase deficiency. The lessons learned from gene therapy in the cancer field further dictate how adenoviruses can be used effectively for management of OA.

Several strategies have been used to overcome the problems related to

adenovirus gene therapy. Adenovirus serotype 5 has several unique attributes that make it suitable for gene therapy. To circumvent the problem of cell and tissue specificity, refractory bispecific adapter molecules have allowed modification of adenovirus tropism for targeted gene transfer.⁹ The use of unconventional immunoglobulins derived from the serum of camels and alpacas provides compatibility with the cytosolic biosynthesis of adenovirus capsid proteins, thus allowing for target cell specificity and ultimately making the use of these immunoglobulins possible for adenovirus-mediated gene therapy for a specific tissue in the joint.¹⁰ Similarly, to circumvent the broad negative effects of preexisting immunity to common human serotypes of adenoviruses, researchers have developed vectors based on chimpanzee-derived adenoviruses for gene therapy.¹¹

As far as the selection of a therapeutic gene is concerned, there is no single gene that can treat OA or delay its progression; however, nuclear factor- κ B is an initial candidate for inhibition.¹² We believe that technologies, such RNA sequencing and microarray, can provide a comprehensive list of genes that are altered in disease and may qualify for therapy or provide therapeutic targets.

Great potential exists for the application of gene therapy to treat diseases such as OA. However, attention must be paid to safety, stability, cost-effectiveness, and appropriate timing of therapy. Such key considerations will guarantee approval of gene therapy products by the regulatory authorities. We believe that if gene therapy can delay joint arthroplasty (currently the only available surgical option for end-stage OA) for at least a decade, this would exert a significant impact on patients' quality of life.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 1-3 and 8-12 are level V expert opinion.

References printed in **bold type** are those published within the past 5 years.

1. Lawrence RC, Felson DT, Helmick CG, et al: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. *Arthritis Rheum* 2008;58:26-35.
2. Hootman JM, Helmick CG: Projections of US prevalence of arthritis and associated activity limitations. *Arthritis Rheum* 2006; 54:226-229.
3. Evans CH, Huard J: Gene therapy approaches to regenerating the

musculoskeletal system. *Nat Rev Rheumatol* 2015;11(4):234-242.

4. Rachakonda PS, Rai MF, Schmidt MF: Application of inflammation-responsive promoter for an in vitro arthritis model. *Arthritis Rheum* 2008;58(7):2088-2097.
5. Geurts J, Arntz OJ, Bennink MB, Joosten LA, van den Berg WB, van de Loo FA: Application of a disease-regulated promoter is a safer mode of local IL-4 gene therapy for arthritis. *Gene Ther* 2007;14 (23):1632-1638.
6. Manning K, Rachakonda PS, Rai MF, Schmidt MF: Co-expression of insulin-like growth factor-1 and interleukin-4 in an in vitro inflammatory model. *Cytokine* 2010;50(3):297-305.
7. Kim KJ, Kim HE, Lee KH, et al: Two-promoter vector is highly efficient for overproduction of protein complexes. *Protein Sci* 2004;13:1698-1703.
8. Ginn SL, Alexander IE, Edelstein ML, Abedi MR, Wixon J: Gene therapy clinical trials worldwide to 2012: An update. *J Gene Med* 2013;15(2):65-77.
9. Glasgow JN, Everts M, Curiel DT: Transductional targeting of adenovirus vectors for gene therapy. *Cancer Gene Ther* 2006;13(9):830-844.
10. Revets H, De Baetselier P, Muyldermans S: Nanobodies as novel agents for cancer therapy. *Expert Opin Biol Ther* 2005;5(1): 111-124.
11. Moffatt S, Hays J, HogenEsch H, Mittal SK: Circumvention of vector-specific neutralizing antibody response by alternating use of human and non-human adenoviruses: Implications in gene therapy. *Virology* 2000;272(1):159-167.
12. Roman-Blas JA, Jimenez SA: NF-kappaB as a potential therapeutic target in osteoarthritis and rheumatoid arthritis. *Osteoarthritis Cartilage* 2006;14(9):839-848.