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New VHUP Kitchen

Developing Gene Therapy for Equine Arthritis

Osteoarthritis is a major cause of incapacity and economic loss in animals and people. While there are multiple drugs available to alleviate the pain to some degree, the goal of researchers is to find ways to control the progression of the disease in affected joints.

There is little doubt that osteoarthritis (OA) is a consequence of both mechanical and biological events. The defining event in OA is generally agreed to be the physical deterioration of articular cartilage. Normal function of a joint demands normal articular cartilage and articular cartilage is not capable of healing when it is structurally damaged. Thus the major goal of treatment and prevention of OA is preservation of articular cartilage. This goal demands a detailed knowledge of the events involved in degradation of articular cartilage matrix and modern molecular techniques have enormously expanded understanding of these pathways.

Both degradation and synthesis of articular cartilage involve a complex interaction of cytokines, growth factors, receptors, receptor antagonists and other peptides that affect the highly specific components of cartilage matrix. All of these elements are gene products and as such there is obviously interest in both controlling and producing them by gene therapy. Gene therapy for arthritis has many attractive potential advantages.

Many of the factors controlling cartilage synthesis and degradation have potent, and often undesirable, effects in many different tissues, making their systemic use impossible. Local delivery by gene therapy might result in desirable local effects. Most of these active peptides have very short half-lives precluding effective tissue concentrations by conventional administration methods. Recombinant proteins manufactured and purified in bulk for pharmaceutical use are extraordinarily expensive and generally impractical for prolonged use. The concept of gene therapy is to make the cells residing within the joint serve as "local producers" for a desired (therapeutic) gene product.

Dr. Dean Richardson, professor and chief of surgery at New Bolton Center, is investigating gene therapy as a treatment to slow the disease progression. He is working with horses because they, like humans, commonly suffer from traumatic arthritis. A horse's joints are quite large, allowing for multiple biopsies, evaluation of joint fluid, and observation by arthroscopy.

Richardson and his colleagues investigated

the use of a retroviral vector to deliver marker genes into cultured synovial cells followed by transfer of those multiplied cells from tissue culture back into the horse. They found that the transfer worked and the engrafted cells with the marker genes expressed in the synovial lining for up to five weeks and the cells remained viable for at least six weeks.

In the second phase of the study the marker genes were replaced by potentially therapeutic genes for the interleukin 1 receptor antagonist (EcIL1Ra), a protein that specifically blocks the activity of interleukin 1, a cytokine that is one of the most important mediators of arthritic damage. It was found that the level of transferred gene product was not high enough to be truly therapeutic. Retroviral vectors are cumbersome and expensive to develop, therefore the group looked for another gene delivery method.

In the continuation of the study an adeno-associated viral vector (AAV) was used. This vector holds many advantages including its safety, an ability to infect non-dividing cells and stably integrate its genetic material. It can therefore potentially be used for direct injection. The researchers constructed an AAV into which they

inserted a marker gene coding for green fluorescent protein (GFP). These markers can be readily identified in fresh or cultured tissue.

The study demonstrated that the AAV-GFP safely infected the synovial lining and the superficial layer of intact articular cartilage and that the transferred genes were functional. The expression of the transferred genes persisted for at least six to nine weeks. It appears that delivery of genes to cells employing AAV is vastly more efficient than using a retroviral vector. There were no signs of inflammation or lameness in the horses injected with the AAV-GFP construct, even in those horses receiving multiple injections.

According to Dr. Richardson, this is the first time that it has been shown that AAV-mediated gene transfer to articular cartilage *in vivo* is feasible. The group is constructing an AAV-EcILRa to deliver therapeutic genes to the joints and will test its efficacy in the near future. The group is also working on a second therapeutic gene construct that may be valuable in inhibiting inflammatory activity in a joint as well as one containing a growth factor to help stimulate cartilage matrix production.

New VHUP Kitchen

VHUP's wards – 20 years old – are being renovated and reconfigured to enable clinicians and staff to provide even better care to the patients. As part of the renovation, a modern and more efficient kitchen was installed. The suite includes an office for **Charlotte Higgins**, nutrition nurse, and storage space for many of the special diet foods needed at VHUP. The reconfiguration and renovation of the kitchen space was made possible through the generosity of Hill's Pet Nutrition, Inc.



Dr. Kathy Michel, assistant professor of nutrition, shows some of the kitchen's features to Harcha of Hill's.



Dr. Michelle Harcha of Hill's Pet Nutrition, Inc. and Dr. Gail Smith, chair, Department of Clinical Studies, Philadelphia, cut the ribbon to the new kitchen.



Charlotte Higgins, nutrition nurse, in her office adjacent to the kitchen.