

Non-technical Abstract

Rheumatoid Arthritis (RA) is a chronic, crippling disease which remains incurable and, in many cases, poorly treatable. The primary sites of disease are the joints where inflammation and tissue destruction lead to pain and disability. Chronic RA is also associated with a lower life expectancy. Because the medical control of RA remains inadequate joint replacement surgery remains the only reasonable option for many patients. We propose to break this stalemate by developing gene therapies for RA and other diseases of joints. Our basic strategy is to deliver therapeutic genes to a tissue known as the synovium, which lines all moveable joints. Once the genes are incorporated into the cells of the synovium (synoviocytes), these cells synthesize and secrete into the joint the anti-arthritis proteins encoded by the genes. In this manner, the joint now becomes the site of synthesis of its own anti-arthritis proteins.

For the past five years we have been developing methods for delivering genes to joints, using the rabbit knee as a model system. This joint is approximately the same size as the human knuckle joint to be used in this clinical trial. Synovial tissue is surgically removed from the rabbits' knee joint and the synoviocytes grown outside the animal where the genes of interest are then transferred to the cells using a harmless, modified virus. The genetically modified cells are injected back into the knee joints of the donor rabbits where they continue to produce the proteins encoded by the transferred genes for several weeks. We have failed to find any toxicity associated with this procedure.

We have devoted considerable attention to using a replication-defective retrovirus to deliver a gene encoding a potentially antiarthritis protein called the "interleukin-1 receptor antagonist protein" (IRAP). IRAP protein is presently in human phase II clinical trials for the treatment of arthritis, where it is proving to be non-toxic and of some benefit. We have successfully removed samples of synovium from rabbits' knees, grown the cells contained within these samples and used the virus to incorporate the IRAP gene into the chromosomes of the rabbit synoviocytes. These genetically modified cells are then injected back into the knees of the recipient rabbits, where IRAP production continues for several weeks. This process provides protection against arthritis in these knees.

We now propose to extend these methods to a human trial. Synovial tissue will be removed from human, rheumatoid joints at the time of scheduled joint replacement surgery. Cells will be grown outside the body in nutrient medium and infected with a modified retrovirus which not only carries the IRAP gene but also, as an additional safety measure, a gene encoding a viral protein known as "thymidine kinase" (tk). This renders the cells sensitive to the anti-viral agent ganciclovir, so that they may be easily eradicated if necessary. Modified cells will be injected into selected rheumatoid knuckle joints one week prior to normal, scheduled surgery to remove these joints and replace them with artificial joints. This provides a huge safety margin because the joints into which the genetically modified cells have been introduced will later be surgically removed during scheduled joint replacement procedures. Removal of the knuckle joints will remove all the experimental material, leaving the patient otherwise unaltered.

At the time of surgery tissue will be retrieved and analyzed for the presence and expression of the transferred genes, and evidence of a biological response to IRAP. Patients will be monitored periodically after surgery and their blood cells tested for the presence of viral sequences.

This trial represents a crucial first step towards the development of a safe, effective gene treatment for human RA.