

## Non-Technical Abstract

Rheumatoid arthritis is a common (affecting >1% of the world population) chronic disease that causes the destruction of cartilage, bone and function of joints throughout the body. Rheumatoid arthritis is a leading cause of disability and patients with rheumatoid arthritis have, on average, a shorter life span than people without rheumatoid arthritis. The available treatments for rheumatoid arthritis are not completely effective in preventing or even in slowing the progression of joint destruction which is caused in part by the growth of the lining tissue of the joints, known as synovium. Rheumatoid synovium is somewhat similar to tumor tissue in that it can proliferate, induce the formation of new blood vessels and destroy cartilage and bone. Rheumatoid synovium can also take up plasmid DNA present in the joint space and the cells undergo spontaneous transfection without the use of other components.

The aim of this proposal is to develop an experimental gene therapy that will directly target the abnormally growing rheumatoid synovium by exploiting the property of spontaneous transfection. This gene therapy will use a cellular suicide strategy. The suicide strategy will utilize an enzyme from the herpes simplex virus as the functional transgene. This enzyme, known as thymidine kinase, can convert the non-toxic drug ganciclovir to a toxic drug that can kill rheumatoid synovial cells.

We propose to inject expression plasmid DNA containing the gene for herpes simplex thymidine kinase into the knee joint of patients with active rheumatoid arthritis. Twenty four hours after injection of the plasmid DNA the study subjects will then be treated with the drug ganciclovir given by vein twice daily for a period of three days. In order to identify transfection of synovial cells patients will also undergo arthroscopy (insertion of a lighted scope) and biopsy of the synovium. These biopsy samples will be analyzed using the techniques of molecular biology for evidence of expression of the herpes simplex thymidine kinase. The biopsy specimens will also be examined under a microscope and the amount of active rheumatoid arthritis will be determined. Six weeks after the treatment, a second arthroscopy will be performed in order to obtain additional biopsy specimens. These pieces of synovial tissue will be examined under a microscope to identify any changes that may have resulted from the experimental gene therapy.

The purpose of this study is to determine the safety of the proposed experimental gene therapy, therefore it is unlikely that beneficial effects will be identified in the study subjects. The first dose of expression plasmid DNA will be 0.3 mg and subsequent study subjects will receive 1 mg, 3 mg or 10 mg of expression plasmid DNA. Two patients will be treated at each dose of expression plasmid DNA. Every subject will receive a standard dose of ganciclovir, 5 mg/kg twice daily for three days.