

## 2.0 DESCRIPTION OF PROPOSED RESEARCH IN NON-TECHNICAL LANGUAGE

Inflammatory arthritis, which includes rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, is a family of chronic diseases caused by the body's natural immune system attacking healthy joint tissue for unknown reasons. This causes joint inflammation, which results in joint pain and swelling, and ultimately joint destruction and disability. Inflammatory arthritis is very common in the US.

Patients with inflammatory arthritis have benefited from new medications such as Enbrel<sup>®</sup>, Remicade<sup>®</sup>, and Humira<sup>®</sup>, which are a new type of therapy to block a protein called INF- $\alpha$  (tumor necrosis factor-alpha). This protein is a key contributor to the inflammation that leads to the joint damage and bone destruction in inflammatory arthritis. These medications, which are given by injection under the skin or into the bloodstream, have led to remarkable improvement in the symptoms of inflammatory arthritis. However, some inflammatory arthritis patients have one or more joints that bother them despite these medications, or only one or two problematic joints that ordinarily don't warrant use of these medications, but are at risk for progressive joint destruction. These patients might benefit from direct injection into the joint of genes coding for proteins that block TNF- $\alpha$ . Injection of genes may be an ideal means of providing therapeutic proteins because it would require less frequent dosing, in contrast to direct injection of protein, which requires more frequent dosing, since proteins are degraded rapidly in the body.

Targeted Genetics Corporation has developed a special gene carrier, or vector, to help a gene coding for a protein that blocks TNF- $\alpha$  to get inside cells. This vector, called tgAAC94, is based on a virus called adeno-associated virus (AAV) and produces an Enbrel<sup>®</sup>-like protein. Animal tests have shown that tgAAC94 is safe in animal models and that a similar vector especially made for rats also leads to improvement of arthritic joints in a rat model of arthritis. The only adverse finding in the animal studies was a mild-to-moderate increase in joint swelling and microscopic findings of inflammation and hemorrhage at the injection site after a very frequent

repeat dose regimen of once monthly injections of the vector. The swelling went away in a few days and the inflammation and hemorrhage seen with the microscope were starting to go away by 30 days after the last dose. Dosing at monthly intervals will not be tested in humans and a second dose will be given no earlier than three months after the first dose. Many people have been infected by the naturally occurring type of AAV without realizing it, as AAV does not cause disease. Targeted Genetics Corporation is currently testing the safety of a single dose of tgAAC94 in humans in an ongoing study of 24 patients with inflammatory arthritis who are not taking TNF- $\alpha$  blockers. So far, no safety concerns have arisen.

Targeted Genetics Corporation proposes to further test the safety of tgAAC94 in a study of repeat doses of tgAAC94 in 40 patients with inflammatory arthritis who have persistent swelling in one or more joints despite treatment with strong medications. The study is divided into two segments. In the first segment, two groups of 20 patients each will be enrolled and assigned by chance to a single injection of either tgAAC94 (15 patients) or placebo (five patients). The dose of tgAAC94 will be increased between the first and second groups. In the second segment, all patients from the two groups will receive an injection of tgAAC94, even if they got placebo in the first segment, 12 to 36 weeks after the initial injection, depending on when the swelling in the injected joint is the same as or worse than it was at the beginning of the study. An independent panel of experts will oversee the study and recommend that the study be stopped if safety concerns arise.