

## NON-TECHNICAL ABSTRACT

### **A Phase I Study of the Safety of Inducible Nitric Oxide Synthase Gene Therapy for the Prevention of Intimal Hyperplasia in Arteriovenous Grafts used for Hemodialysis Access**

Patients requiring hemodialysis for end-stage renal disease experience recurrent problems with vascular access for hemodialysis. The most common vascular access is the forearm arteriovenous (AV) graft that consists of a synthetic tube placed under the skin of the forearm with one end sewn to the artery and the other sewn to the vein. This AV graft is punctured during hemodialysis. These AV grafts often fail because of a scarring process at the point where the graft is sewn to the vein. This scarring process results in narrowing of the tube and can cause clotting of the AV graft. The scar consists of overgrown smooth muscle cells, a process called intimal hyperplasia. About 50% of patients experience this problem within the first 6 months after the placement of the AV graft. The only way to treat this problem is with surgery to declot the graft and to fix the site of scarring. The hospital costs associated with vascular access complications total over \$2 billion annually.

A therapy is being developed that may prevent this scarring or intimal hyperplasia process from occurring and thereby prevent the failure of AV grafts. This therapy involves the use of gene transfer to deliver a gene called inducible nitric oxide synthase (iNOS) to the site where the synthetic tube is connected to the vein. iNOS is a protein that generates the active product nitric oxide (NO) that blocks smooth muscle cell proliferation and intimal hyperplasia. This therapy has been shown in several animal models of intimal hyperplasia to significantly reduce this scarring process.

The iNOS gene will be delivered to the vein using a virus called adenovirus. This virus is the cause of the common cold as well as other ailments. However, the form of adenovirus that is being used in this therapy is one that has been altered so that it cannot reproduce itself and cannot cause these ailments. This adenovirus has been studied in many animal models and found to be safe. The adenovirus carrying the iNOS gene (AdiNOS) will be applied to the vein of the AV graft at the time of surgical placement of the AV graft. The AdiNOS will be placed inside the segment of vein that will be connected to the graft and allowed to incubate for 30 minutes. The virus will then be removed and the graft attached to the vein.

The purpose of this proposed research study is to evaluate the safety of different doses of AdiNOS when applied to the vein-graft site in patients requiring hemodialysis. Patients selected for the study will receive a single dose of AdiNOS ranging from  $10^9$  to  $10^{11}$  particles. Approximately 5 patients will be tested with each dose with a total number of patients being treated ranging from 10-30. The follow-up for this safety study will be 12 months. The highest safe dose will then be used in efficacy studies.