

M-I (1) Scientific Abstract. Peripheral vascular disease (PVD) is the result of an imbalance between tissue blood supply and oxygen demand. The most common cause of PVD is occlusive atherosclerosis. The disease may involve one or more regions of the abdominal aorta and its branches to both lower extremities, and may progress gradually or rapidly. Diabetics are 4-5 times more likely to develop critical limb ischemia than non-diabetics. Diabetics comprise 40-60% of patients requiring peripheral bypass for limb salvage, whereas diabetics comprise only 3-5% of the general population. Fifty to sixty percent of all non-traumatic lower extremity amputations carried out in the United States are performed on the diabetic population. Diabetics tend to have more distal vascular disease than their non-diabetic counterparts, necessitating bypass grafts targeted to more distal vessel segments. The distal location of critical disease dictates that surgery is the mainstay of therapy, since catheter based techniques (angioplasty, stenting) have poor outcomes in these distal vessels. Moreover, diabetics are at significantly increased risk for limb loss despite a patent bypass graft secondary to the high incidence of large neurotrophic ulcers that do not heal despite revascularization. Thus, a more effective adjunctive measure is necessary in the treatment of diabetics with critical limb ischemia. This study is directed toward assessment of angiogenic gene therapy as an adjunct to surgical bypass distal revascularization in type I diabetes with critical limb ischemia. The angiogenic therapy will be mediated by Ad_{CU}VEGF121.1, an adenovirus gene transfer vector containing the human vascular endothelial growth factor 121 cDNA driven by the cytomegalovirus (CMV) promoter/enhancer. Based on pre-clinical data demonstrating the efficacy of AdVEGF vectors in experimental animal models of limb ischemia, and safety data using an equivalent AdVEGF vector in humans with peripheral vascular disease, this study is designed to evaluate the safety and benefit of administration of the Ad_{CU}VEGF121.1 vector to the affected limb at the time of surgery. All individuals enrolled in the study will be insulin-dependent diabetics undergoing intrapopliteal surgical bypass revascularization. To help assess the safety and preliminary efficiency of the adjunctive effect of the Ad_{CU}VEGF121.1 vector, the study is designed to be prospective, randomized and blinded with two control groups. The first control group will be administered the carbohydrate-salt vehicle used to suspend the Ad_{CU}VEGF121.1 vector and the second group will receive p_{CU}VEGF121.1, a plasmid containing the identical expression cassette as the Ad_{CU}VEGF121.1 vector (CMV promoter/enhancer driving the human VEGF 121 cDNA). A total of 60 individuals that meet the entry criteria will be randomized in a double blinded fashion into three groups of 20 individuals each. At the conclusion of the study the following two aims will be met: **(1) To evaluate the hypothesis that is safe to carry out direct intramuscular and soft tissue administration of the Ad_{CU}VEGF121.1 vector to the ischemic lower leg of individuals with insulin-dependent diabetes at the time of distal revascularization.** In addition to routine safety parameters, a variety of parameters will focus on the safety of the administration Ad_{CU}VEGF121.1 vector *per se*. **(2) To assess the hypothesis that administration of the Ad_{CU}VEGF121.1 vector as described in specific aim 1 will enhance graft patency, improve limb preservation, augment bypass graft blood flow and enhance perfusion of the lower limb.** To accomplish this, the study population will be assessed over time for the primary endpoint variables of bypass graft patency, limb preservation (preservation of the foot to at least the transmetatarsal level), and, in those with non-healing foot ulcers, the rate of wound closure. Secondary endpoint variables will include non-invasive vascular laboratory testing (duplex ultrasonography, pulse volume recordings and segmental arterial