

M-I (2) Non-technical abstract. Peripheral vascular disease (PVD) is the result of an imbalance between tissue blood supply and oxygen demand. 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 non-diabetics comprise only 3-5% of the general population. Diabetics tend to have more distal vascular disease than their non-diabetic counterparts, necessitating bypass grafts targeted to more distal vessel segments. The choice of therapy for the treatment of PVD depends on the location and severity of disease as well as functional limitations of the individual and their accompanying medical illnesses. The invasive therapy consists of either endovascular or surgical treatment, but the intravascular approaches have limited usefulness in distal disease. The effect of diabetes on bypass graft patency has been controversial, with several series suggesting a negative impact of diabetes on graft patency. 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. An emerging strategy to combat atherosclerosis-induced limb ischemia is therapeutic angiogenesis, in which networks of newly grown blood vessels are generated in order to functionally "bypass" obstructions in the native arterial system. 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. 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 include two control groups. The first control group will be administered the carbohydrate-salt vehicle used to suspend the vector and the second group will receive p_{CU}VEGF121.1, a plasmid containing the gene itself without adenovirus. There will be 60 individuals included in this study. Of the sixty individuals, twenty (group A) will receive the Ad_{CU}VEGF121.1 vector, twenty (group B) will receive p_{CU}VEGF121.1 plasmid (gene itself without adenovirus), and twenty (group C) will receive placebo (a sugar-salt water solution) only. The distribution of vector and/or plasmid and/or placebo will be decided by chance ("flip of a coin"). At the conclusion of the study the following two aims will be met: (1) To evaluate the hypothesis that it 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; and (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.