

SCIENTIFIC ABSTRACT

In patients in whom anti-anginal medications fail to provide sufficient symptomatic relief, additional interventions such as angioplasty or bypass surgery may be required. While both types of intervention have been shown to be effective for various types of patients, a considerable group of patients may not be candidates for either intervention due to the diffuse nature of their coronary artery disease. Moreover, there are many patients in whom recurrent narrowing and/or occlusion of bypass conduits after initially successful surgery has left the patient again symptomatic with no further angioplasty or surgical option.

Ischemic muscle represents a promising target for gene therapy with naked plasmid DNA. Intramuscular (IM) transfection of genes encoding angiogenic cytokines, particularly those which are naturally secreted by intact cells, may constitute an alternative treatment strategy for patients with extensive tissue ischemia, in whom contemporary therapies (anti-anginal medications, angioplasty, bypass surgery) have previously failed or are not feasible. This strategy is designed to promote the development of supplemental collateral blood vessels that will constitute endogenous bypass conduits around occluded native arteries, a strategy termed "therapeutic angiogenesis."

Pre-clinical animal studies from our laboratory have indeed established that IM gene transfer may be utilized to successfully accomplish therapeutic angiogenesis. More recently, Phase I clinical studies from our institution have established that IM gene transfer may be utilized to safely and successfully accomplish therapeutic angiogenesis in patients with critical limb ischemia. The notion that this concept could be extrapolated to the treatment of chronic myocardial ischemia was demonstrated in our laboratory by administering recombinant human vascular endothelial growth factor (VEGF) to a porcine animal model of chronic myocardial ischemia. Recent experiments performed in this same porcine model of myocardial ischemia have shown that direct intramyocardial gene transfer of naked plasmid DNA encoding VEGF (phVEGF₁₆₅, the identical plasmid used in our previous animal and human clinical trials) can be safely and successfully achieved via a minimally invasive chest wall incision.

The protocol outlined in this Investigational New Drug Application application has been designed as a Phase I, single site, dose escalating, open label study to determine the safety and bioactivity of direct intramyocardial gene transfer of phVEGF₁₆₅ in patients with symptomatic myocardial ischemia for the purpose of reducing angina pectoris. The secondary objective is to determine the anatomic and physiologic extent of collateral artery development in patients receiving intramyocardial phVEGF₁₆₅ gene transfer. A total of 30 adult men and women will participate in this dose-escalating study. Subjects will be eligible if they have stable exertional angina and areas of viable but underperfused myocardium and have been judged not to be optimal candidates for surgical or percutaneous revascularization. The clinical response of subjects treated in this fashion will be evaluated by serial studies performed before and after gene transfer, including dobutamine stress SPECT-sestamibi myocardial perfusion, contrast stress echocardiography, exercise treadmill testing, and selective coronary arteriography.