

SECTION 1

SCIENTIFIC ABSTRACT

There are thirteen million adults in the United States alone with symptomatic coronary artery disease. Antianginal drugs, the initial management of patients with stable angina, act by reducing myocardial oxygen demand or by increasing blood flow to the ischemic myocardium. Revascularization procedures are often necessary and consist of angioplasty (with or without stents) or coronary artery bypass graft (CABG) surgery. 400,000 angioplasty procedures and nearly 500,000 coronary bypass graft procedures were performed in the U.S. in 1996. Despite the increasing use of stents, restenosis remains a significant problem following angioplasty. Morbidity and high cost are significant disadvantages of CABG surgery. At the present time transmyocardial laser revascularization procedure requires surgery.

The healthy human heart lacks native collateral vessels, but these (collateral vessels) may form in response to myocardial ischemia. These collaterals are, in most cases, insufficient to meet increased blood flow required during stress. The process of coronary collateral vessel formation in response to ischemia is not well understood. Angiogenic proteins have been shown to be expressed in ischemic regions of the heart, possibly originating from myocytes. The initial event in new vessel formation probably involves mitosis of capillary endothelial cells. There is, up to now, no approved therapy that will stimulate new blood vessel formation.

Using an ameroid ischemia model, Giordano et al performed gene transfer by an intracoronary delivery of a recombinant adenovirus expressing human fibroblast growth factor-5 in pigs. The results of this study indicate an improvement in regional LV function and blood flow to the ischemic area. Two weeks after intracoronary injection, there was also evidence of angiogenesis. This improvement was sustained at 12 weeks. A similar benefit in LV function and perfusion to the ischemic area was also seen with FGF4 gene transfer. Successful transgene transfer, expression and biological activity of the transgene product were demonstrated.

Two weeks after intracoronary injection of the recombinant adenovirus, Giordano et al were unable to detect viral DNA in liver, retina or skeletal muscle using polymerase chain reactions (PCR), despite the presence of transgene DNA in the myocardium. Pulmonary artery blood drawn during intracoronary injection of the recombinant virus contained less than 1.5% of the virus injected into the coronary artery. There was no evidence of myocardial inflammation, necrosis or fibrosis. The results of the above study demonstrate the effectiveness and safety of adenovirus-mediated angiogenic gene therapy in pigs.

The pig model of myocardial ischemia closely mimics the clinical situation in man. Both pigs and humans are devoid of native collateral vessels in the healthy heart. However, in response to myocardial ischemia, collateral blood vessels develop, but in those patients that remain symptomatic the collateral vessels fail to meet the need for enhanced blood flow during stress. This clinical situation is mimicked by the pig model of myocardial ischemia. Collaterals develop, but are inadequate to meet myocardial demands during pacing induced stress.

The proposed clinical development will test whether gene transfer with human adenovirus-5 FGF-4 gene (Ad5 FGF-4) in patients with exertional angina will augment collateral blood flow and relieve myocardial ischemia.

The gene product is an E1 A/B deleted human adenovirus serotype 5 with hFGF-4 insert driven by the CMV promoter. The gene product will be diluted with normal saline prior to administration.

The gene product will be administered by (once only) intracoronary injections in the left (left anterior descending and circumflex) and right coronary arteries. Sixty percent (60%) of the dose will be injected into the left coronary system and 40% of the dose in the right coronary system.

Patients with stable angina will be evaluated in the initial study in the clinical program. Clinical studies will be initiated to provide evidence that the gene product (by enhancing collateral formation) increases myocardial perfusion to ischemic areas, reduces stress-related myocardial ischemia and relieves angina. The studies will evaluate whether the above clinical benefit can be brought about without significant risks from adenoviral infections, neovascular growth or oncogenesis. Once developed, collateral vessels should remain patent. Therefore, the clinical benefit from gene therapy should persist long-term.

Adenovirus mediated angiogenic gene therapy with Ad5 FGF-4 is indicated for the long-term management of patients with stable angina.

The first clinical study (Study 97166), which is an ascending dose, randomized, double-blind, placebo-controlled, Phase 1 / Phase 2 study will be undertaken in patients with stable angina who can exercise on a treadmill for at least 3 minutes. Assessments will include safety, exercise time, time to onset of angina, time to ≥ 1 mm ST segment depression on the 12-lead ECG during treadmill exercise, left ventricular wall motion abnormalities during peak stress and left ventricular ejection fraction.

The lowest dose (3.2×10^8 viral particles) will be evaluated first. Safety will be confirmed in each of the first two patients receiving active medication in each dose group before proceeding with recruiting the remaining patients in the dose group. The safety of each of the dose groups will be confirmed based on the observations up to 2 weeks before proceeding to the higher group. The subsequent doses planned are 10^9 , 3.2×10^9 , 10^{10} , 3.2×10^{10} and 10^{11} viral particles. In each dose group, there will be 9 patients allocated to the gene product and 3 patients to placebo (vehicle). Prior to entry, patients will be carefully screened to exclude malignancy. Potential risks from adenoviral infections (heart, liver), extracardiac angiogenesis and from cardiac catheterization will be looked for carefully, during periodic observations for up to 3 months. A further follow-up will be undertaken at 6 and 12 months to assess the clinical status of study patients. Appropriate precautions will be taken to protect personnel likely to be exposed to the viral product.

The highest dose of the gene product administered will not exceed the highest dose safely used in the pig studies. Details of study design, conduct, potential risks and precautions can be seen in Study Protocol #97166.

Study 97166 will start in the first quarter of 1998 in up to 10 centers in the U.S. Recruitment and 3-month follow-up will be completed in approximately 18 months. The number and nature of subsequent clinical study(ies) will depend on the results of Study 97166 and subsequent discussions with the FDA/CBER.