

**M-I (1) Scientific Abstract.** Cardiovascular disease is the single leading cause of mortality in the United States, responsible for the deaths of two out of every five Americans, with a total of nearly one million deaths annually. Coronary artery disease describes a broad spectrum of ischemic syndromes that may evolve from atherosclerosis, thrombosis, and/or vasospasm. Current therapies include pharmacologic interventions and surgical therapy by mechanical revascularization using percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG) or transmyocardial laser revascularization (TMR). The identification of specific biologic mediators of angiogenesis make it possible to consider "therapeutic angiogenesis," where angiogenic molecules can be employed to develop new vascular networks to circumvent the ischemic consequences of atherosclerosis occluding the arterial system. The most specific of the known angiogenic indicators is vascular endothelial growth factor (VEGF). The focus of this protocol is to determine the safety/toxicity and biologic efficacy of the delivery of VEGF cDNA directly into the myocardium of individuals with life threatening coronary artery disease in conjunction with coronary artery bypass surgery. The protocol will use a vector similar to the Ad vector which has been safely administered to the myocardium of 31 individuals, including 25 individuals at the same or higher doses that is intended to use in the present study (RAC 9711-221 and RAC 9806-258). The vector to be used is a E1<sup>-</sup> and E3<sup>-</sup> adenovirus gene transfer vector expressing vascular endothelial growth factor under cytomegalovirus early/intermediate promoter/enhancer. The study will involve 50 individuals, each with clinically significant coronary artery disease, who, in the opinion of their cardiologist, are optimal candidates for coronary artery bypass grafting but not for percutaneous coronary intervention (i.e., balloon, stent, atherectomy). The study population that meet the inclusion/exclusion criteria will be randomized in a blinded fashion into two groups of 25 individuals each. One group will receive Ad<sub>CU</sub>VEGF121.1 vector and the other will receive placebo (a salt-carbohydrate solution in which vector will be diluted). Following administration of the Ad<sub>CU</sub>VEGF121.1 vector into the heart there will be an assessment of exercise tolerance and myocardial function and perfusion by using a <sup>99m</sup>Tc-sestamibi single photon emission computerized tomography (SPECT) scan. At the conclusion of the study, the following objectives will be met: (1) to determine the safety/toxicity of direct administration of the vector Ad<sub>CU</sub>VEGF121.1 to the ischemic myocardium; (2) to assess whether direct administration of Ad<sub>CU</sub>VEGF121.1 to the myocardium will induce growth of collateral blood vessels, improve coronary blood flow and improve cardiac function in the region of ischemia in individuals with coronary artery disease undergoing CABG.