

# Protocol Synopsis

- TITLE:** VEGF Gene Transfer to Promote Angiogenesis in Patients with Advanced Heart Failure
- SPONSOR:** St. Elizabeth's Medical Center, 736 Cambridge St. Boston, MA. 02135
- CLINICAL CENTER:** The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195
- INVESTIGATOR:** Patrick McCarthy, M.D.
- VECTOR:** The test agent is an injectable form of plasmid DNA encoding the 165-amino acid isoform of VEGF. The cDNA to be used in this protocol encodes the 165 amino acid isoform of VEGF. The plasmid backbone into which the VEGF<sub>165</sub> cDNA has been inserted is a simple eucaryotic expression plasmid that utilizes the 763-base-pair cytomegalovirus (CMV) promoter/enhancer to drive VEGF expression. This promoter/enhancer has been used to express reporter genes in a variety of cell types and can be considered to be constitutive. Downstream from the VEGF cDNA is the SV40 polyadenylation sequence. Also included in this plasma is a fragment containing the SV40 origin of replication that includes the 72 base pair repeat, but this sequence is not functionally relevant (for autonomous replication) in the absence of SV40 T-antigen. These fragments occur in the pUC118 vector which includes an *E.coli* origin of replication and the  $\beta$ -lactamase gene for ampicillin resistance. Bulk phVEGF<sub>165</sub> contains approximately 1 mg plasmid DNA per milliliter in 0.9% sodium chloride injection USP. The active agent will be supplied in vials containing approximately 2.2 mg plasmid DNA. Placebo will consist of sodium chloride injection USP (0.9%). Each injection will be the same volume as that injected for plasmid DNA. No viral vectors or liposomes will be used to deliver the above-described plasma.
- POPULATION:** Males or Females > 21 years with diagnosis of ischemic cardiomyopathy requiring LVAD implantation.
- SAMPLE SIZE:** A total of 144 (72 patients for each of 2 study arms) patients will be recruited over a period of 4 years (the fifth year will be limited to follow-up examinations).
- TREATMENT:** The 72 patients in each arm of the study will comprise 3 cohorts, each consisting of 24 patients. Within each of these cohorts, patients will be randomized to receive phVEGF<sub>165</sub> or placebo based upon a 3:1 randomization ratio. Thus, at the completion of the study, 18 patients will have each received a given dose ( 125, 250, or 500 ug phVEGF<sub>165</sub>) and 18 patients will have received placebo. Doses will be employed in a serial dose-escalating fashion. The entire volume of the study drug will be divided and delivered in 4 intramuscular injections administered into the left ventricular wall and the distribution of the territories of the left anterior descending (2 injections), circumflex territory (1 injection), and right coronary artery distribution (1 injection).
- DURATION:** Patients will be evaluated at regular intervals for a total of 1 year following injection. Patients will continue to be followed indefinitely thereafter.
- OBJECTIVE:** Objective #1 is to evaluate the safety and impact of phVEGF<sub>165</sub> gene transfer on LV function in patients with CHF due to coronary artery disease. Objective #2 is to evaluate the safety and impact of phVEGF<sub>165</sub> gene transfer on LV function in patients with CHF due to idiopathic dilated cardiomyopathy, excluding patients with significant narrowing of the extramural coronary arteries or primary valvular heart disease. Objective #3 is to evaluate the safety and impact of phVEGF<sub>165</sub> gene transfer to allow for LVAD bridge-to-recovery (BTR) as an alternative to transplantation.
- ENDPOINTS:** While it remains entirely unproven, it is conceivable that VEGF gene transfer may promote myocardial neovascularization, and thereby lead to improvement in LV function sufficient to accomplish LVAD explantation without the need for cardiac transplantation.