

Protocol Synopsis

TITLE:	VEGF Gene Transfer for Diabetic Neuropathy
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CLINICAL CENTER:	St. Elizabeth's Medical Center, 736 Cambridge St. Boston, MA 02135
INVESTIGATOR:	Jeffrey M. Isner, M.D.
VECTOR:	<p>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 VEGF₁₆₅ 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 <i>E.coli</i> origin of replication and the β-lactamase gene for ampicillin resistance. Bulk phVEGF₁₆₅ 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.</p> <p>No viral vectors or liposomes will be used to deliver the above-described plasma.</p>
POPULATION:	Diabetic Males or Females > 21 years with sensory neuropathy with or without associated macrovascular disease.
SAMPLE SIZE:	A total of 192 patients will be recruited into two arms of the study (each arm consisting of 96 patients) over a period of 4 years (the fifth year will be limited to follow-up examinations).
TREATMENT:	<p>The 96 patients in each of the two arms of the study will comprise 3 cohorts, each consisting of 32 patients. Within each of these cohorts, patients will be randomized to receive phVEGF₁₆₅ or placebo based upon a 3:1 randomization ratio. Thus, at the completion of the study, 24 patients will have each received a given dose (1,2, or 4 mg phVEGF₁₆₅) and 24 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 8 intramuscular injections administered into the foot, calf muscle, or distal thigh muscle of the affected extremity. Following the initial set of injections, repeat treatment with an identical dose will be provided 2 and 4 weeks after initial treatment.</p>
DURATION:	Patients will be evaluated at regular intervals for a total of 1 year following the third injection. Patients will continue to be followed indefinitely thereafter.
OBJECTIVE:	<p>Objective #1 is to evaluate the safety and impact of phVEGF₁₆₅ gene transfer on sensory neuropathy in patients with diabetes and associated macrovascular disease involving the lower extremities.</p> <p>Objective #2 is to evaluate the safety and impact of phVEGF₁₆₅ gene transfer on sensory neuropathy in patients with diabetes without macrovascular disease involving the lower extremities.</p>
ENDPOINTS:	1) Improved sensory function.

2) In the patients with neuropathy associated with macrovascular disease, it is conceivable that in certain patients, the augmentation of collateral blood flow might be of sufficient magnitude to provide relief from rest pain, lead to resolution of a non-healing ulcer, and/or also allow the patient to walk some distance free of claudication.