Peripheral vascular disease (PVD) affects approximately 12 million Americans and is associated with significant morbidity and mortality. Patients with advanced PVD who are poor candidates for revascularization have 6-month amputation and mortality rates as high as 40% and 20%, respectively. JVS-100 is comprised of non-viral DNA plasmid engineered to transiently express non-modified human Stromal Cell-Derived Factor-1 (SDF-1). SDF-1 is a chemoattractant of endogenous organ specific and bone marrow derived stem cells and progenitor cells to the site of tissue damage, which promotes tissue preservation and blood vessel development. Re-stimulating SDF-1 expression by gene transfer into ischemic muscle has a high therapeutic potential for treatment of ischemic disease because it has the potential to regenerate vasculature and repair in organs damaged by ischemia. We have previously demonstrated that injection of JVS-100 into pigs with heart failure due to myocardial infarction increased cardiac vessel density and improved cardiac function through 90 days post-treatment. We hypothesized that the vasculogenic and stem cell homing properties of SDF-1 could also provide therapeutic benefit in PVD. In this study, we tested the safety and efficacy of JVS-100 delivery to ischemic limbs in an established rabbit PVD model.

Methods

JVS-100 delivery to ischemic limbs in an established rabbit PVD model. A. Image of luciferase expression in ischemic rat leg 3 days post-injection. B. Time course of mid dose (2 mg/ml) JVS-100 in ischemic limbs of rabbit at baseline (A) and 30 and 60 days post-injection with JVS-100. Efficacy was measured by % change in angiographic score compared to control at 30 and 60 days post-injection. In vivo bioluminescence demonstrated pDNA expression in normal rabbit hind limb. Normal Adult New Zealand white rabbits were injected at 6 sites with up to 8 mg of the luciferase version of JVS-100 (100 micrograms of luciferase DNA/0.5 ml) into an awake rabbit. Animals were allowed to recover for 10 days, then anesthetized and directly injected with 1.0, 2.0 or 4 mg/ml of the luciferase version of JVS-100 (vector backbone with luciferase cDNA) into the hindlimb. In vivo bioluminescence was measured after injection of 125 mg/kg using the Xenogen imaging system for 3 minute exposure.

Results

JVS-100 Peak expression in muscle 3-8 days post-injection

JVS-100 vector expression 3 days post-injection to rabbit hind limb

JVS-100 increases angiographic score in ischemic rabbit hindlimbs

Hypothesis: Direct injection of JVS-100 to increase SDF-1 expression in a rabbit model of hind limb ischemia will increase blood flow.

Summary and Conclusions

• JVS-100 vector expresses functional SDF-1 which induces MSC migration
• Peak SDF-1 expression occurs 3 days post muscle injection
• 8 injections of 1 or 2 mg/ml JVS-100 induced therapeutic benefit
• JVS-100 increased angiographic score 30 and 60 days post-injection (p < 0.05 at 60 days)
• Direct injection of JVS-100 improves angiogenesis in rabbits with CLI.

This data has led to the initiation of a Phase II clinical trial evaluating JVS-100 safety and efficacy after delivery to Rutherford Class 4 and 5 patients with critical limb ischemia.

Proposed Clinical Program in CLI

JVS-100 Phase IIa Study allowed under US IND for treatment of Critical Limb Ischemia (CLI):

• 48 subject, double-blind, placebo controlled trial
• Single dose escalation, 4 cohorts
• Rutherford Class 4 & 5
• Safety and efficacy assessments with 12 month follow-up
• Safety Endpoints: Adverse Events, ECG, PE/Vitals, Labs
• Efficacy Endpoints: Amputations, survival , ulcer healing

Rutherford class, VAS,QOL,TBI,VAS,QOL,ABI,TBI,TcP02

References