

**Public Lecture by Dr. H. Kirk Hammond**  
**Gene Transfer for Angina**  
**January 16, 2002 at 6:00 p.m. in the Garren Auditorium, Basic Science Building**  
**Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD**

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Increased new blood vessel formation in the heart could potentially benefit patients with angina (myocardial ischemia). In a pig model of stable stress-induced myocardial ischemia, intracoronary injection of adenovirus vectors encoding a variety of angiogenic genes resulted in protein expression of the transferred gene in the heart. Two weeks after gene transfer, abnormalities in stress-induced function and blood flow in the heart were improved. Animals that received a recombinant adenovirus encoding a reporter gene with no angiogenic potential showed no improvement in blood flow or function. Data acquisition and analysis were conducted blinded to treatment group. Favorable effects on blood flow and function persisted for at least 12-weeks. Transgene presence and expression were detected in heart from animals that received the transgene, but were not detected in extracardiac tissues as determined by PCR and immunoblotting at doses up to  $2 \times 10^{11}$  vp. Intracoronary delivery of  $10^{12}$  vp is associated with detectable virus DNA in liver, lung, and spleen (PCR) but no transgene expression was evident in extracardiac sites. There was no inflammation in the heart or other organs, and no increase in anti-adenovirus antibody was found after intracoronary injection. Second injections of adenovirus can be delivered with no decrement in efficacy, and without deleterious sequelae. The virus can be delivered even in the setting of a high neutralizing antibody to human adenovirus and still retain its efficacy. These data document successful amelioration of abnormalities in myocardial blood flow and function following *in vivo* gene transfer of a variety of growth factor genes.

Based on these studies, a multicenter Phase 1 / Phase 2 clinical trial was initiated to determine whether intracoronary delivery of a recombinant, replication-incompetent, human adenovirus-5 encoding human fibroblast growth factor-4 (FGF-4) is safe and effective for treating patients with *angina*. The trial was a blinded, prospective, placebo-controlled dose-escalation study that enrolled patients with stable exertional *angina*, normal ventricular function, and at least one open native vessel. End points included safety parameters and treadmill testing. There were no serious adverse events related to product administration, and a dose was identified that increased treadmill duration 4 weeks after gene transfer, a primary endpoint of the study. Increase in treadmill time was comparable to that achieved using CABG or angioplasty. Pivotal worldwide clinical trials were recently initiated using two doses identified in this initial trial.