A Corticosteroid Gene Therapy Combination Strategy to Maximize Intramuscular-Mediated Delivery in Postischemic Myocardium

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Figure 1. (A) Direct Intramyocardial gene therapy administration. (B) Focal, non-homogenous left ventricular expression of GFP (red) following injection at 72 hours in post ischemic myocardium, magnification 4 $\times$. (C) Lower average GFP plasmid (red) transduction efficiency in control myocyte specimens, magnification 20 $\times$. (D) Significantly higher average GFP plasmid (red) transduction efficiency in combination corticosteroid treated myocyte specimens, magnification 20 $\times$.

ACHIEVING SUFFICIENT PLASMID DELIVERY is a key unresolved problem in postischemic myocardium for the latest clinical trials whose main objective is to rapidly upregulate potent regenerative mechanisms within a tight therapeutic window (i.e.,

within 48 hr). The well-documented impediments for efficient plasmid trafficking and subsequent transduction include anatomical-scale, cardiac disease-related comorbidities, and localized immune responses following the acute myocardial

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infarction event. An appreciation of delivery challenges originated from the first-in-human cardiac surgery gene therapy trial,¹ which featured direct intramuscular (IM) injection of adenovirus encoding the vascular endothelial growth factor. Long-term follow-up of this phase I trial yielded no clear evidence of efficacy, likely because of a limited, transient expression profile—but it provided an impetus for improvements in vector, target, and clinical delivery strategies. Since then, numerous regenerative trials such as the stromal cell-derived growth factor 1 have generated significant interest. These strategies seek to repair myocardium through the chemoattraction of endogenous stem cell lineages shortly after myocardial infarction.² In contrast to viral vector-mediated transgenes, these approaches offer rapid onset gene overexpression through high-dose, yet low-risk vector plasmids. The IM route is attractive for this emerging therapeutic class because of its clinical feasibility through both surgical (Fig. 1A) and catheter-based delivery techniques, but is limited by transfer inefficiency. Despite technical modifications of needle-based delivery in myocardium, these problems persist: poor retention, inconsistent performance per site, and the highly focal resultant delivery profiles. This results in the demand for more injections, thus increasing the risk for additional injury in already-compromised myocardium.³ In addition, recent trial results suggest that the predominant intracoronary infusion route may be even less efficient in patients with significant coronary disease, thus renewing interest in IM delivery. Therefore, a shift toward improvement in the delivery profile featuring clinically applicable drug combination approaches has been explored as a means to increase efficiency per injection site.⁴

A drug-gene combination therapy tested in our laboratory has generated some exciting preliminary data. In each of three ventricular zones (anterior, lateral, and posterior), we administered solumedrol (10 mg/kg/zone) versus saline (control) followed by

3.33 μ g of GFP plasmid per zone. The injections were performed immediately following left anterior descending ligation. Our hypothesis was that solumedrol pretreatment would enhance GFP expression. We expected plasmid-mediated GFP expression to be marginal 48 hr following MI because of the robust inflammatory response present at that time point. Depicted in Fig. 1B is a typical control plasmid-mediated GFP expression profile (red) in whole-mount left ventricular cross sections. When evaluating at a higher magnification (20 $\times$) across randomly selected areas, typical control cross sections with saline pretreatment ($n=4$) show less overall GFP expression (in terms of both intensity and percentage of myocytes) in the positive zones (Fig. 1C) versus those that were pretreated with solumedrol (Fig. 1D). Solumedrol is an effective nonspecific inhibitor of local inflammatory cytokines and the secretion of other mediators and chemoattractants after myocardial infarction. The effects likely enable more efficient plasmid trafficking, uptake, and subsequent expression. Future experiments to validate this concept in chronic studies are ongoing. It is anticipated that a variety of drug configuration and dosing strategies to refine this concept are warranted.

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AUTHOR DISCLOSURE

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