Thankfully, back to basics

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The delivery of an adequate *dose* of a therapeutic agent to the targeted tissues is a fundamental tenet of pharmacologic therapy. Similar requirements should apply to biologic therapies—the use of stem cells or therapeutic genes or proteins, for example—but in the relatively new arena of myocardial drug delivery, this seemingly obvious prerequisite appears to have eluded researchers conducting innumerable experimental and even clinical studies.¹ The result of this investigational blind spot, induced by the magical thinking that dose somehow does not matter for the heart, has been the failure of many such investigations and the dismissal of otherwise potentially promising new cardiac biotherapies. Failure to “do the homework” of carefully extrapolating from preclinical pharmacokinetic studies into properly designed clinical delivery strategies may have unnecessarily subjected many trial subjects to interventions that never were likely to succeed.

Efforts to induce angiogenesis or vasculogenesis during the past 20 years have incorporated a variety of proteins, genes, and even (progenitor) cellular substrates that have been associated with native physiology.² In the studies reported in their article appearing in this issue of the *Journal*, Gaffey and colleagues³ used endothelial progenitor cells (EPCs) in their efforts to stimulate vasculogenesis. Notably, Gaffey and colleagues³ actually have paid heed to the principle of efficacious dosing. They delivered their EPCs at dosages sufficient to induce effect, with a (shear-thinning) hydrogel used to ensure adequate EPC retention in the targeted myocardial tissues. They succeeded in these efforts, demonstrating nearly a 5-fold increase in vasculogenesis after EPC-hydrogel delivery relative to that in control animals, which corresponded to a similar increase in EPC retention in the injected myocardium. Underscoring the importance of adequate delivery, they found no increase in vessel number after the administration of EPCs alone.

The elucidation by Gaffey and colleagues³ of a hyaluronic acid formulation that temporarily “liquefies” as a result of the shear stress created by injection of this solution (thereby, according to Gaffey and colleagues,³ facilitating delivery) represents an incremental innovation in cell-

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Central Message

Gaffey and colleagues used endothelial progenitor cells (EPCs) in a hyaluronic acid hydrogel to stimulate nearly a 5 times increase in vasculogenesis after EPC-hydrogel delivery relative to controls in a rat coronary ligation model, corresponding to EPC retention. Adequate (cell) dosing is an important principle frequently overlooked in cardiac biotherapies.

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based therapy. More importantly, Gaffey and colleagues³ are to be congratulated for their focus on the adequate delivery of therapeutic cells as a basis for effective therapy, which they have clearly demonstrated. It would have been interesting had they also determined whether a similar effect could have been induced by increasing the number of injected cells, because limited benefit could be ascribed to administration of hydrogel alone.

The efforts of Gaffey and colleagues³ represent one of a great number of novel therapies that have exploded onto the scene in the last several years to treat the ischemic or infarcted myocardium. Other investigators, for example, have demonstrated that hydrogel compositions “thicker” than that used by Gaffey and colleagues³ could restore myocardial wall thickness, and thereby improve wall stresses and enhance ventricular function, when injected into thinned, infarcted myocardium.^{4,5} In light of the limited impact of the hydrogel preparation reported in the current report of Gaffey and colleagues,³ it would have been interesting to have seen whether a “thicker” substrate might have enhanced the efficacy of EPC delivery in this study.

It is also interesting to note that the dramatic preservations of myocardial mass (ie, nearly a 70% diminution in fibrosis) and function (about a 50% increase in ejection fraction) seen in the current study of Gaffey and colleagues³ seem to exceed by far the extent of neovascularization induced by the injected EPCs, especially because the infarction process would likely have been completed in this coronary ligation model well before the EPC-induced neovascularity could have developed. Unless such results are (implausibly) ascribed to the rescue of at-risk border zone tissues (which in general represents <15% of overall recruitable ventricular function), it would seem that other mechanism must be in play.

As mentioned by Gaffey and colleagues,³ these data suggest that paracrine factors likely play a role in these therapeutic effects, as previously implicated in many cell-, protein-, and gene-based myocardial preservation strategies. These considerations would encourage the comparative evaluation of angiogenic mediators, such as stromal cell–derived factor, basic fibroblast growth factor 2, and vascular endothelial growth factor, that would not be subject to cell death and loss of effect in the ischemic milieu intrinsic to this clinical setting. Alternatively, angiogenic pretreatment could be used to support (endothelial progenitor) cell survival.⁶ Studies would likewise seem prudent in established infarction models, rather than the reported acute coronary ligation preparation, given that clinical focus in such an evolving infarct setting would likely be more appropriately and effectively directed toward the opening of occlusive coronary target lesions rather than the induction of the vascularization of infarcted myocardium.

The dilemma of balancing provision for the survival of exogenously implanted cells in an ischemic milieu and the tight time line of salvaging infarcting myocardium ultimately draws attention to the entirely new field of in situ cellular reprogramming as an alternative to the proposed exogenous EPC delivery strategy. Coupled with angiogenic pretreatment of scar tissue, this fascinating new bio-intervention⁷ offers the nearly unthinkable possibility of converting resident cardiac fibroblasts into induced cardiomyocytes—thus regenerating myocardium from infarcted tissue—circumventing entirely the need to ever implant exogenous cells!

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