Editorial Comment

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Time Is Like a Clock in My Heart: Implications for Stem Cell Delivery after Myocardial Infarction

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For more than 2 decades, advances in cardiovascular medicine have trended toward the early detection and treatment of ischemic heart disease. New biomarkers, imaging modalities, and educational campaigns now target at-risk patients for primary prevention. Improved drugs, devices, and healthcare delivery systems speed the reperfusion of thrombosed arteries. Nonetheless, some patients still miss this early detection and treatment window, presenting either late to outlying centers or with pathophysiologic barriers to reperfusion. This missed opportunity may then be followed by scarring, negative remodeling, and heart failure.

Stem cell therapy may change the trajectory of such patients, but it may also require a change in our traditional thinking about optimal treatment timing. While myocardial infarction survivors with systolic dysfunction may benefit from early and ongoing medical therapy with antiplatelets, β-blockers, ACE inhibitors, aldosterone antagonists, and statins, stem cell therapy may be effective only within a narrow time frame. Stem cell survival may be compromised early after infarction by inflammation, microvascular obstruction, and reperfusion injury. Stem cell homing may be compromised late after infarction by scar formation and cytokine downregulation. Identification of the optimal time for stem cell delivery thus represents a critical piece in the overall cardiac stem cell therapy puzzle [1].

In a recent issue of *Cardiology*, Dr. ter Horst [2] reviews the knowns and unknowns of stem cell timing. We already know that repair after myocardial infarction follows a natural history with prescribed times for intrinsic progenitor cell mobilization [3] and cytokine/growth factor expression [2, table 1]. We already know that extrinsic stem cell delivery at different times following myocardial infarction yields different outcomes in preclinical [4] and clinical studies [2, table 2]. What we don't know is how best to apply this knowledge to provide optimal stem cell therapy.

In the adjacent table 1, we propose a framework to discuss the implications of stem cell timing and stem cell characteristics for the overall goals of stem cell therapy after myocardial infarction. Extrinsic stem cell delivery may occur either coincident with or distinct from the natural peak in mobilization of intrinsic stem cells of similar lineage. In addition, the pool of cells delivered at any given time may be enriched for specific lineages via cell sorting and expansion techniques or enhanced by hypoxic preconditioning, biological or chemical pretreatment, or gene transfer.

These methodological choices imply different goals of therapy. In the most straightforward scenario, a pool of cells enriched for a specific lineage is delivered coincident with the natural peak in circulating levels of that cell lineage in order to augment the natural healing process (sce-

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Table 1. Goals of stem cell therapy after myocardial infarction implied by the timing of stem cell delivery and characteristics of donor cells

		Timing of extrinsic stem cell delivery	
		Coincident with peak intrinsic stem cell mobilization	Distinct from peak intrinsic stem cell mobilization
Extrinsic stem cell characteristics	Enriched	(A) augment healing	(B) extend healing
	Enhanced	(C) augment and improve healing	(D) extend and improve healing

nario A). Alternatively, the same pool of cells is delivered at an earlier or later time point in order to extend the healing process (scenario B). Scenario A benefits from our faith in the purposeful construction of the human body, whereby myocardial engraftment, survival, and proliferative factors are expressed in harmony with cognate receptors on circulating cells. Scenario B suggests the possibility that beneficial myocardial receptors may be expressed but underoccupied before or after the peak mobilization of their associated cellular targets.

This is the level of complexity of all past and present clinical trials of stem cell therapy after myocardial infarction [5]. Whether by intent or by happenstance, published reports describe scenario A or B or span both, without a prespecified comparison. Post hoc analyses such as those summarized by Dr. ter Horst [2] form our current knowledge base concerning therapeutic timing. Thus far, the delivery of bone marrow-derived stem cells within 24 h of reperfusion has failed to show benefit [6], indicating that earlier is not always better. Improved outcomes at later time points [2, table 2] are consistent with observed fluctuations in circulating levels of native progenitor cell lineages between 3 and 28 days after myocardial infarction [3].

Within this window, 3 ongoing, multicenter, randomized, controlled trials aim to identify the optimal time for the delivery of bone marrow mononuclear cells after myocardial infarction. The NIH Cardiovascular Cell Therapy Research Network's (CCTRN) TIME trial (http://www.cctrn.org) will compare an early time point of 3 days after infarction to an intermediate time point of 7 days after infarction [7]. A related study called LateTIME will focus on a late time point of 2–3 weeks after infarction using an otherwise identical protocol [8]. The SWISS-AMI study will compare an intermediate time point of 5–7 days after infarction to a late time point of 3–4 weeks after infarction [9]. While these studies may clarify the optimal time for the delivery of bone marrow mononuclear cells, similar time comparator studies may be required for other cell types and other cell preparations.

Stem cells with enhanced functionality, conferred ex vivo by hypoxic preconditioning, biological or chemical pretreatment, or gene transfer, delivered coincidently with the natural mobilization of intrinsic stem cells of similar lineage may not only increase the total number of stem cells available for myocardial repair but also improve the engraftment, survival, and cardioprotective activities of both donor and host cells (scenario C). When delivered at a time otherwise unfavorable for intrinsic stem cell-mediated repair mechanisms, enhanced stem cells may additionally extend the window of opportunity for myocardial repair by providing the necessary paracrine factors [10, 11] to allow healing at a time when more deleterious processes might otherwise dominate (scenario D). Indeed, if scenario A represents the goal of current clinical trials, scenario D certainly represents where we will want to be going in the coming years.

To this end, it is imperative that we identify those factors that define the window of opportunity for stem cell-mediated repair after myocardial infarction. A catalog of relevant cytokines is provided in the accompanying article by Dr. ter Horst [2, table 1]. Of these, several have been used successfully in rodent models of cell-based gene therapy after myocardial infarction, including homing factors such as stromal cell-derived factor-1 (SDF-1) [12] and vascular endothelial growth factor [13] as well as cell surface markers such as SDF-1's binding partner chemokine (c-x-c motif) receptor 4 (CXCR4) [14] and monocyte chemotactic protein-3's (MCP-3) binding partner chemokine (c-c motif) receptor 1 (CCR1) [15]. These examples demonstrate that cytokine-overexpressing donor cells may provide trophic support to injured myocardium while improving donor and host cell homing. Chemokine receptor-overexpressing donor cells may allow for stem cell retention in injured myocardium at time points with

a mismatch between myocardial chemokine expression and host stem cell chemokine receptor expression. Together, such strategies may open the temporal window of opportunity for myocardial repair.

The scale-up of enhanced stem cell technologies from mouse to man will be challenging. Although the fundamental biology of myocardial repair is remarkably similar across species, the time course of myocardial repair after infarction is different. Genes that are upregulated within days of a murine myocardial infarction may not be upregulated until weeks after a human myocardial infarction [2, table 1]. Difficult decisions will need to be made. Should stem cells modified to overexpress proteins be delivered in synchrony with the peak native expression (scenario C) or when the corresponding native proteins are lacking but their matching binding partners are maximal (scenario D)? Are the time courses employed in preclinical models helpful in making this decision? The answers to these and other time-critical questions will need to be agreed upon before committing resources to advanced clinical trials. Nevertheless, with continued research, we are confident that stem cell therapy will ultimately reduce the morbidity and mortality of patients with cardiovascular disease.

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