Stem Cells to Repair the Heart
A Clinical Perspective

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"It is common sense to take a method and try it: if it fails, admit it frankly and try another. But above all, try something."
—F.D. Roosevelt

The last two decades have witnessed enormous advances in the management of acute myocardial infarction with emphasis upon prompt reperfusion therapy in conjunction with the use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and risk factor reduction as cornerstones of postdischarge management. The early and late mortality of myocardial infarction is declining, but, for several reasons, we should not become complacent. Mortality rates from randomized control trials underestimate the community mortality, in that participants in trials are highly selected. Moreover, in most countries of the world, many eligible patients do not actually receive reperfusion therapy, or if they do, it is often too late to exert a maximum benefit. Furthermore, the majority of the myocardial infarction population being elderly have a substantial mortality, and comorbidities including diabetes are on the increase. From a clinical standpoint, despite undoubted progress, there remains a large population of survivors of extensive infarctions with diminished cardiac reserve who comprise a reservoir of patients who will develop congestive heart failure with all its grim sequelaes. The concept that such patients could be treated by myocardial regeneration is logical, tantalizing, and above all, exciting. Moreover, continued progress in the basic sciences has shifted the focus from a concept more closely allied to science fiction to the realm of feasibility. Nonetheless, our expectations need to be tempered by a realistic appreciation of the hurdles to be cleared before we can claim that the new revolution in regenerative biology is truly underway.

The recent review in Circulation Research by Orlic et al is timely and, as with any good review of a controversial subject, raises many more questions than it answers and importantly outlines some of the major hurdles facing this promising field. We would like to consider several specific questions that relate directly to the feasibility of human stem cell therapy for myocardial regeneration and which we believe are of paramount importance when considering future human trials. First, is there sufficient current scientific evidence from animal and human data to support the concept of therapeutic myocardial regeneration? If so, what are the additional preclinical investigations necessary before human trials are undertaken? Second, if preclinical studies justify human investigation how should these trials be performed with regard to patient selection, nature of stem cell delivery, use of cell controls, and clinical and functional endpoints? Finally, what are the safety issues to consider when engaging in human stem cell studies. A schematic outline of the challenges facing future animal and human studies in this field is shown in the Figure.

Scientific Considerations: Role of Adult Stem Cells in the Myocardium

Animal Models
Recent studies have shown that several organs including bone marrow possess stem cells with much greater plasticity than previously envisioned. Such plasticity includes differentiation of bone marrow cells into tissue constituting all three germ layers. Nowhere has this concept of plasticity been more clearly illustrated than in myocardial regeneration with mouse models of cardiac injury. However, a disconcertingly wide variability in mouse stem cell seeding and differentiation (ranging from 0.02% to 50% of myocytes) within the heart has been reported, and hence, the physiological significance of these findings are unclear. Moreover, in murine models of bone marrow stem cell (BMSC) therapy it is extremely difficult to assess the specific effects of myocyte versus nonmyocyte (eg, endothelial cell) differentiation on the functional improvement in myocardial performance after injury. Therefore, we must be cautious in attributing benefit to a specific cell when the bone marrow contains cells of multiple lineage and phenotype, not to mention the host of potential regulatory factors released by these cells. Indeed, the whole concept of bone marrow hematopoietic stem cell (HSC) plasticity, at least recently, has been questioned by experiments that demonstrate that single labeled HSCs injected into lethally irradiated mice reconstitute peripheral blood leukocytes, but do not contribute appreciably to nonhematopoietic tissues.

These inconsistencies in basic animal data highlight evolving concepts that we are only beginning to understand. Much more intensive study is necessary in a number of larger animal models to determine the optimal stem cell type and level of myocardial recruitment required for significant physiological effects. Further information is also necessary on the homing and organ-specific differentiation signals required for various stem cells, and this includes characterization of integrin and other adhesion molecule structure/function relationships on these cells. These studies will need extensive use of cellular controls and functional endpoints including imaging modalities that are clinically...
Future challenges facing stem cell therapy for myocardial regeneration in human subjects.

appropriate and can be validated with explanted tissue analysis.

Human Studies
Similarly, there is presently significant debate over the existence of stem cells of extracardiac origin within the adult human heart with markedly variable levels of cardiomyocyte chimerism (0% to 18%) being reported in gender-mismatched cardiac allograft studies.9–11 Suggested reasons for this variability include differences in methods of detection (light versus fluorescence/confocal microscopy), study subject selection (early or late post transplantation), and confounding variables, such as the presence of inflammation and the false identification of infiltrating leukocytes as cardiomyocytes.11,12 Although most if not all of these selection and technical controversies can be addressed with further study, it is important to note that no report to date has conclusively shown a bone marrow origin for chimeric cardiomyocytes within the human heart. This creates a conceptual hurdle and technical challenge when trying to assess the therapeutic potential of bone marrow stem cell therapy for human myocardial regeneration. For instance, without knowing the contribution, if any, of human bone marrow to cardiomyocyte formation in vivo, clinical trials of these cells seem premature. The current gender mismatched hematopoietic cell transplantation models and fluorescence in situ hybridization (FISH) methods for determining stem cell plasticity in human subjects also have many limitations including an inability to exclude potentially confounding effects of pretransplant conditioning and postransplant immunosuppression therapy on progenitor cell recruitment into the adult heart. Currently, we do not have sufficiently specific bone marrow stem cell markers to allow study of stem cell activity in human hearts of nontransplanted subjects, an area that requires further investigation. However, it is likely that future intense efforts to characterize unique stem cell surface markers will make such analysis possible.

Clinical Trials: Timing and Design of Human Studies
The likelihood of clinical benefit from future human stem cell studies must significantly outweigh the risk and this consideration must be based on good science with sufficient consensus that exhaustive testing of this therapeutic paradigm has already occurred in animals both from an efficacy and toxicity perspective. Human studies should be randomized between stem cell and control therapy, double blinded to the investigator and subject, and have therapeutic endpoints that allow clinical benefit or the potential for such benefit to be clearly assessed.

The optimal model of stem cell delivery is currently unknown but catheter-based or direct surgical approaches seem the most likely to be tested in future human trials. These studies will also require specific evaluation of what represents the ideal population for investigation as many alternative medical therapies currently exist for these patients. For instance, the differentiation pathway of stem cells (scar formation, neoangiogenesis, or myocyte growth) may be determined by the local microenvironment encountered by these cells in the myocardium at the time of implantation. It is unknown at present whether stem cell therapy would be most beneficial early after infarction where significant inflammation coexists, later in the remodeling phase, or perhaps at the endstage of ischemic cardiomyopathy. Similarly, no data exist on the benefits of using myogenic versus nonmyogenic (eg, vascular progenitor) cells or whether one population of bone marrow stem cells (mesenchymal or side population) is superior to unfractionated bone marrow cells. There is also insufficient preclinical data on the long-term viability of bone marrow stem cells, their integration and differentiation characteristics in the myocardium, and the mechanism of their functional effects in vivo. Moreover, it remains unknown whether these cells can function normally when surrounded by scar tissue or whether new blood supply (angiogenesis) is a critical component of successful myogenesis.

Any future trials of stem cell therapy in humans should also include adequate control groups with use of similar lineage but nonfunctional control cells. This might be achieved by using as controls irradiated cells that are inactive and have lost their replicative capacity. Cell irradiation of lymphocyte fractions is already a well established and safe technique in blood transfusion practice.13 Such control data will be particularly important in distinguishing specific from nonspecific cellular or noncellular effects in stem cell studies using heterogeneous bone marrow preparations.

The use of surrogate endpoints is particularly appealing in clinical trials of small numbers of patients. However, the literature is replete with caveats that apply to surrogate endpoints; we should not forget trials of promising concepts such as cardiac inotropic drugs, exercise tolerance after laser myocardial revascularization, or neutrophil inhibition after myocardial infarction, where initial reasonable and logical expectations were dashed by the rigorous scrutiny of using mortality as an endpoint. Nonetheless, given that clinical studies of stem cell differentiation in the future are likely to be confined to small numbers of patients, surrogate endpoints
will have to suffice in the near term. The challenge will be for imaging modalities such as SPECT, PET, and MRI to be refined to provide scientific validation for efficacy of myocardial regeneration from a functional and structural standpoint. An important distinction needs to be emphasized, measured improvements in overall cardiac contractile function after BMSC therapy should not automatically be attributed to myocardial cell regeneration. Indeed, multiple potentially favorable contributions from other cells and factors such as vascular progenitors and cell regulatory compounds as yet unidentified may play a crucial role in improved cardiac function and these may require further investigation.

In the future, molecular imaging techniques currently being investigated in animals may also allow tracking of stem cells over time in vivo, providing an additional temporal correlation between cell longevity and clinical benefit.

Finally, two recent small nonrandomized human studies are intriguing and encouraging and demonstrate that precursor cell therapy to treat myocardial injury has already entered the clinical arena.14,15 However, for the reasons outlined above, we must be very cautious in interpreting results from such very small studies.

Safety Issues

When approaching clinical trials of stem cells in the myocardium, we should proceed cautiously because previous experience with human gene therapy studies has taught us that premature, inadequately designed clinical trials can substantially set back progress in an otherwise promising field of research. From a safety perspective, questions remain about whether adult stem cells in the heart truly undergo functional and electrical integration and whether this may have hypoxic and proarrhythmic consequences. For instance, if implanted stem cells were to differentiate into fibroblasts instead of myocytes, the consequences of increased scar formation may be worsening ventricular function and creation of an arrhythmic substrate. Moreover, even among differentiated myocytes there may be significant discordance between the structural and contractile properties as opposed to their electrophysiological characteristics. For example, the ability of these myocytes to propagate an electrical impulse in addition to myocyte refractoriness may determine the electrophysiological “milieu”—whether homogeneous or heterogeneous, with the proarrhythmic nature of the latter being well described. Consideration of the role of embryonic stem cells in myocardial regeneration is beyond our scope, but it is obvious that use of totipotent cells for in vivo therapy would represent an additional oncogenic risk as these cells are known to form teratomas in mice. Finally, the potential of adult stem cells to seed in multiple other organs must be considered when assessing the safety of systemic versus regional approaches to myocardial regeneration.

In summary, the current scientific data supports stem cell plasticity in animals and possibly in humans but much more work remains to be done in preclinical models if these initial concepts are to be translated into an effective and safe therapy in human subjects. Nonetheless, challenge creates opportunity, and in this case, the revolutionary potential of myocardial regeneration will stimulate and justify the triumphs and disappointments that will be required to eventually make this concept a clinical reality.

References


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