Is stem cell therapy ready for patients?

Stem Cell Therapy for Cardiac Repair
Ready for the Next Step
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Coronary heart disease and heart failure continue to be significant burdens to healthcare systems in the Western world. In the United States alone, there are 7.1 million survivors of myocardial infarction (MI) and 4.9 million people living with congestive heart failure (CHF). Despite recent advances in medical and device therapy for heart failure, the incidence, hospitalization, and mortality rates continue to rise. After receiving a diagnosis of CHF, 1 in 5 patients will be dead within 12 months. Therefore, any new treatment modality that benefits heart failure patients has the potential to result in a dramatic improvement in health outcomes and substantial cost savings for the community.

The possibility of using stem cell–based therapies for people suffering an acute MI or living with CHF has captured the imagination of both the medical and popular communities. Since early reports in animal models 10 years ago, the stem cell field has made enormous advances in moving toward clinically applicable treatment options, and we now stand at the dawn of a new therapeutic era. An abundance of preclinical data demonstrate safety, feasibility, and efficacy, justifying the current entry into clinical trials of stem cell therapy in humans. This position, however, is extremely controversial, with some arguing that trials are premature because mechanistic insights are insufficiently addressed. Here, we argue that properly conducted rigorous clinical trials are a key and appropriate next step not only to start the long process of therapeutic development but also as an essential component in the process of understanding the scientific underpinnings of cardiac regeneration and its therapeutic utilization. The field of regenerative medicine will advance through the parallel conduct of in vitro/animal model studies and clinical trials, the latter frequently guiding the former.

The publication of Menasche et al1 describing the first patients to receive skeletal myoblasts spawned a profusion of small clinical studies investigating cellular therapy for cardiac repair. At present, a number of early clinical studies have been published and are summarized in Table 1. Several points are immediately apparent from this table. First, >400 patients have completed these published studies, yet most of them are small pilot studies that lack randomization or control groups. Second, despite the fact that several cell types have been studied using different delivery methods, the overwhelming message from all of these studies is that cell therapy is safe and feasible. In addition, the results of these studies provide encouraging, albeit preliminary, signs of efficacy. Finally, although these trials represent the currently published data, they have formed the basis for numerous larger, ongoing trials accruing more patient data (Table 2).

Mechanism of Action of Stem Cells
One of the major obstacles in progressing to large-scale clinical trials of cardiac stem cell therapy is the ongoing debate regarding the mechanism of action by which stem cell therapy leads to cardiac repair. The classic idea that provided the primary motivation for stem cell therapy is that delivery of the appropriate stem cells would repair a damaged heart via...
active myocardial regeneration resulting from transdifferentiation of the administered stem cells.\textsuperscript{4,12–14} However, new data have led to the recognition of alternative mechanisms of action (Figure 1): Exogenous stem cells may also stimulate proliferation of endogenous cardiac precursors or stem cells through neovascularization\textsuperscript{6,15} or paracrine signaling actions.\textsuperscript{16} In fact, observations in preclinical and clinical scenarios that all of these events occur allow us to generate a new concept that cellular therapy contributes to the restoration of stem cell niches, facilitating the ability of the heart to heal itself.\textsuperscript{17} Still other mechanisms are proposed: Exogenous stem cells may lead to cardiac repair via fusion of donor cells with host cardiomyocytes.\textsuperscript{18} Finally, other investigators suggest that the effects of stem cells are mediated by altering mechanical properties to strengthen the MI scar, thereby preventing deterioration in cardiac function\textsuperscript{19} (see Figure 1). This ongoing debate about mechanism fuels the case for slowing the pace of clinical trials; ie, we should not pursue work in patients until we thoroughly understand, with a high degree of scientific precision, the outcome of cell therapy in in vitro systems and animal models.\textsuperscript{9,10} We would suggest that we have reached the appropriate point in the development of cellular therapeutics to enter into the clinic; in fact, entry into the clinic is the next step that will guide our understanding of the mechanistic underpinning for effective cellular therapeutics.

### Types of Cells Contemplated for Cellular Regenerative Therapy

#### Embryonic Stem Cell

Embryonic stem (ES) cells are derived from the inner cell mass of the blastocyst-stage embryo, late in the first week after fertilization. They are considered to be pluripotent, able to give rise to many different cell lineages. For cardiac regeneration therapy, there is a growing body of knowledge from animal models regarding the steps of isolation, differentiation, and clinical application.

Human ES cells differentiate into spontaneously beating cells with a cardiomyocyte phenotype. The morphology and ultrastructure of these cells are organized with sarcomeric

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<th>TABLE 1. Clinical Studies of Stem Cell Therapy for Cardiac Repair</th>
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CPC indicates circulating progenitor cell; GCSF, granulocyte colony stimulating factor; PBMCN, peripheral blood mononuclear cell; CFR, coronary flow reserve; and LVEF, LV ejection fraction.
structures, formation of intercalated disks, desmosomes, and gap junctions, characteristic of cardiomyocytes, and they demonstrate the presence of a functional syncitium with action potential propagation. When transplanted into infarcted myocardium, ES cell–derived cardiomyocytes engraft and improve cardiac function in several rodent models. In the failing heart, in addition to replenishing cardiomyocytes by ES–derived cells, a simultaneous increase in the blood supply may be necessary for optimal and prolonged engraftment. Hence, it is of interest that ES cells differentiate to all cell lines necessary for formation of new blood vessels. Both murine and human ES cells spontaneously differentiate to form endothelial and smooth muscle cells in vitro and in vivo. To date, no human clinical studies have been initiated because of both the ethical issues surrounding access to embryos and the possibility of teratoma formation, suggested by a study injecting ES cells in skeletal muscle.

Resident Cardiac Stem Cells

In recent years, compelling evidence has accumulated suggesting that the heart has endogenous regenerative potential.
Recent studies have isolated, from both human and murine hearts, undifferentiated cells that are clonogenic, express stem and endothelial progenitor cell (EPC) antigens/markers, and appear to have the properties of adult cardiac stem cells. These cells most likely mediate endogenous mechanisms for minor repair and for replacement of ongoing cell turnover within the adult heart. More importantly, they may represent a therapeutic target that, if enhanced, could induce cardiac self-repair.

These cells have been phenotyped using different antigenic approaches. In a seminal report published in 2003, Beltrami and colleagues separated c-kit–positive cells from the rat heart and demonstrated their clonogenicity and multipotency in vitro, as well as their capacity to participate in cardiomyocyte and blood vessel regeneration after MI. Subsequently, Oh and coworkers separated resident murine cardiac stem cells on the basis of the presence of stem cell antigen-1. They also demonstrated in vitro and in vivo myocardial differentiation of these cells and provided evidence supporting the fusion of these cells. In 2004, Messina and coworkers reported on the identification of cardiospheres, clusters of self-adherent cells that grew from cultured adult cardiac tissue derived from both human and murine hearts. These cells were shown to be clonogenic and capable of transdifferentiation in vitro, and they induced both myocardial and vascular regeneration after MI. Laugwitz and colleagues isolated a population of cardiac precursor cells from postnatal mouse hearts using isl-1 transcription factor as a cell marker. These cells are c-kit– and stem cell antigen-1–negative but are capable of differentiation into cardiomyocytes with electrical and contractile properties. Finally, Martin et al identified a side population of cells (SP cells) in the developing heart and adult heart that are capable of proliferating and differentiating into cardiac and hematopoietic lineages in vitro. These cells were identified on the basis of expressing Abcg2, an ATP-binding cassette transporter, rather than by detection of surface markers.

Cardiac stem cells can be harvested from patients and expanded ex vivo to generate large numbers of cells. A recent report by Urbanek and colleagues demonstrated that cardiac stem cells increase in number immediately after MI, but in the chronic phase, the numbers fall, and the remaining cardiac stem cells have less regenerative potential. This suggests that the left ventricular (LV) dysfunction in ischemic cardiomyopathy may be due to a defect in or deficiency of functionally competent cardiac stem cells. In addition, Mouquet et al have recently shown in an experimental study that bone marrow may represent a reservoir for cardiac stem cells and suggested that depletion of this reservoir could contribute to diminished reparative capacity.

To date, there are no clinical trials of human cardiac stem cells. However, Smith et al demonstrated that cardiospheres could be grown from human endomyocardial biopsy specimens. These cardiospheres represent an easily accessible option for autologous stem cell therapy, making the possibility of clinical testing of this approach feasible. The Specialized Centers for Cell-Based Therapy initiative of the NHLBI has funded clinical trials of cardiac stem cells that should begin in the near future.

**Skeletal Myoblasts**

Autologous skeletal myoblasts are another potential source for cardiac repair because of their biological properties and lack of ethical and immunological problems. Skeletal myoblasts or satellite cells are the reservoir of regenerative cells for skeletal muscle tissue; they have the ability for self-renewal and differentiation if muscle injury occurs. They have many desirable features as donor cells, including the ability to be amplified in an undifferentiated state in vitro and high resistance to tissue ischemia. They also have been shown to continue proliferation in vivo to a certain extent, which gives rise to a larger graft size. Satellite cells are committed solely to the myogenic lineage. Therefore, regardless of environmental influences, even if implanted into a scar made up mainly of fibroblasts, myoblasts differentiate into functional muscle cells. A growing body of experimental data and initial clinical studies has shown not only engraftment of donor cells but also improvement in global cardiac pump function. However, the exact mechanism by which they improve LV function is still debated. There may be beneficial effects of contracting noncardiac myocytes, some paracrine actions and an effect on scar strengthening to prevent LV dilatation and remodeling. The critical importance of progressing to clinical trials is underscored by the early clinical experience with skeletal myoblasts. Myoblast transfer in early studies was associated with sustained ventricular tachycardia, a life-threatening arrhythmia. This finding guided changes in future protocols involving skeletal myoblasts, which now require prophylactic cardioverter-defibrillator implantation and/or amiodarone therapy to prevent ventricular tachycardia. This protocol change resulted in less frequent clinically evident arrhythmias and is a powerful demonstration of how clinical trials are integral in guiding and refining the way in which stem cell therapy should be administered in patients. Phase II studies of skeletal myoblast therapy are presently underway.

**Human Adult Bone Marrow–Derived Stem Cells**

The observation that bone marrow elements contribute to cardiac repair in the infarcted heart served as the rationale for adult bone marrow cell therapy after MI. Jackson and coworkers transplanted wild-type mice with green fluorescent protein (GFP)–positive bone marrow and then induced MI through coronary artery ligation and reperfusion. They demonstrated that bone marrow elements contributed to cardiomyocyte and endothelial cell formation after MI by finding GFP-positive cardiomyocytes and endothelial cells. It appeared that there is an intrinsic repair mechanism for minor cardiac damage within the bone marrow but that it is not adequate to repair larger amounts of damage such as that after MI. Substantial effort has been expended to try to enhance...
this endogenous repair mechanism and use bone marrow as a potential source of stem cells for cardiac repair. Orlic and coworkers have shown that lineage-negative, c-kit-positive bone marrow-derived cells differentiate into new cardiomyocytes after MI. This regenerative therapy can be harnessed by either direct injection into the peri-infarct rim of functioning myocardium or by using chemoattractant cytokines to mobilize the cells from bone marrow. In 1 experiment, bone marrow was harvested from male mice, labeled with GFP, and injected into the peri-infarct rim of female mice. This resulted in a substantial increase in myocytes in the infarct zone, and the myocytes were of donor origin (on the basis of Y chromosome staining and GFP expression). There was a corresponding improvement in hemodynamic parameters after only 9 days.

The same group showed that mobilization of lineage-negative, c-kit+ cells with granulocyte colony-stimulating factor and stem cell factor before and after MI in mice resulted in growth of new cardiomyocytes in the infarct zone and improved ventricular function and led to substantial improvement in survival of the treated group. Endothelial and smooth muscle cells also were proliferating, but new myocyte growth predominated. However, in contrast to these findings, Murry and colleagues and Balsam and coworkers reported that lineage-negative, c-kit+ cells did not differentiate into cardiomyocytes. In the latter study, bone marrow cells transplanted into ischemic myocardium adopted hematopoietic fates rather than transdifferentiating into cardiomyocytes but were still prevented LV dilatation and dysfunction associated with postinfarction remodeling. Despite the conflicting evidence regarding the ability of bone marrow–derived cells to transdifferentiate, their efficacy in preventing remodeling has been demonstrated in many laboratories; therefore, clinical efficacy trials have progressed in parallel with ongoing mechanistic laboratory trials to determine the precise molecular mechanism by which these cells exert their beneficial effects. Kamihata et al isolated mononuclear cells from swine bone marrow and injected them into the infarct zone and peri-infarct region of pigs after MI induced by left anterior descending coronary artery ligation. This was associated with an improvement in myocardial perfusion by contrast echocardiography, increased numbers of capillaries, increased coronary collateral circulation on angiography, improved ejection fraction, and reduction in infarct size compared with controls. Of note, the endothelial lining of newly formed capillaries was derived from the donor bone marrow cells, but the fibroblasts in the fibrotic area of the infarct were not. This suggests that the microenvironment of MI is proangiogenic rather than fibrosis-inducing for this population of cells.

This evidence that precursors of both cardiomyocytes and endothelial cells exist within the mononuclear cell fraction of adult bone marrow forms the basis for the use of bone marrow mononuclear cells (BMMNCs) in clinical trials (Table 1). In just the past 3 years, BMMNC transplantation has become the most widely studied cell-based therapy for human applications (Table 1). Several studies using autologous bone marrow warrant special mention. The initial studies used intra coronary delivery of BMMNCs in the post-MI setting because animal studies demonstrate that tissue damage in MI resulted in bone marrow stem cell homing to the infarcted myocardium. In the first published human trial, Strauer et al aspirated BMMNCs and reinfused them into the infarct-related artery 7 days after MI in 10 patients and had a control group comprising 10 patients who refused the treatment. This method resulted in significantly improved myocardial perfusion and wall motion indexes. The Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) investigators randomized 59 patients after acute MI to receive intracoronary infusion of BMMNCs or ex vivo expanded circulating progenitor cells. They delivered the cells into the infarct-related artery 4 days after MI and showed improvement in LV ejection fraction from 51% to 58% (P<0.001), as well as significantly enhanced myocardial viability and regional wall motion in the infarct area. Interestingly, they were unable to show a difference between the 2 active cell treatment groups. In the BOne marOw transfer to enhance ST-elevation infarct regeneration (BOOST) trial, Wollert and coworkers randomized 60 patients after successful percutaneous coronary intervention for acute MI to receive either intracoronary BMMNCs or standard therapy. They demonstrated an improvement in LV ejection fraction of 6.7% in the treatment group and 0.7% in the control group at 6 months (P=0.0026). Taken together, these studies with control groups suggest that BMMNCs are safe and may improve cardiac function by a substantial and clinically meaningful degree following MI. However, more recently, Janssens and colleagues presented their findings that intracoronary transfer of BMMNCs failed to achieve their primary end point, improvement in global LV function. They demonstrated a significant reduction in scar size and an improvement in regional function, but there was no improvement in LV ejection fraction (P=0.36). Their patient population differed from the BOOST trial in that they were reperfused earlier and may therefore have gained only a small benefit from cell therapy because they derived maximal benefit from earlier reperfusion. In the 18-month follow-up to the BOOST study, the improvement in LV ejection fraction in the cell therapy group was sustained. However, the control group also had improved by this time, and the difference between the 2 groups was no longer significantly different. This catch-up phenomenon in the control group suggests that, rather than the effect of cell therapy being transient, cell therapy may in fact accelerate the postinfarction LV functional recovery that is achievable with standard medical therapy.

In contrast to the acute MI setting, patients with chronic ischemic cardiomyopathy are unlikely to release signals from damaged myocardium to induce stem cell homing. Therefore, an alternative approach to intracoronary infusion of cells in
Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are found in bone marrow, muscle, skin, and adipose tissue and are characterized by the potential to differentiate into any tissue of mesenchymal origin, including muscle, fibroblasts, bone, tendon, ligament, and adipose tissue. MSCs from adult bone marrow can be separated by density gradient centrifugation and adhering-cell culture in defined serum-containing medium. The cells isolated after adherence in culture are negative for CD34 and characteristically express CD29, CD44, CD71, CD90, CD45, unlike hematopoietic progenitors from bone marrow, and express markers of immature cells, including AC133, a novel hematopoietic stem cell marker not expressed on mature hematopoietic cells and certain surface markers of hematopoietic cells, and transcription factors that identify them as precursor cells. These cells have been strictly characterized by immunohistochemistry and stain positively for cardiac and endothelial specific markers, as well as gap junction proteins. Myocardial function and capillary formation are significantly increased in experimental groups treated with MSCs compared with controls. These results suggest that MSCs act by regenerating functionally effective, integrated cardiomyocytes and possibly new blood vessels. MSCs also have been injected into infarcted myocardium via a catheter-based approach in pigs, resulting in regeneration of myocardium, reduced infarct size, and improved regional and global cardiac contractile function. Importantly, the latter study used allogeneic MSCs, which did not produce evidence of rejection.

Whereas autologous cell-based therapy poses no risk of rejection, an “off the shelf” allogeneic cell product would be much more cost effective and much easier to administer and could potentially allow delivery of greater numbers of cells than autologous cell therapy. MSCs appear to avoid the problem of rejection by being hypoimmunogenic. These cells lack MHC-II and B-7 costimulatory molecule expression, thereby preventing T-cell responses, and induce a suppressive local microenvironment through the production of prostaglandins and other soluble mediators. As such, MSCs may allow allogeneic cell therapy while avoiding rejection.

MSCs also have been studied clinically. Chen and colleagues randomized 69 patients after MI to receive intra-coronary autologous MSCs or placebo. They demonstrated a significant improvement in global and regional LV function and a significant reduction in the size of the perfusion defect, suggesting that MSC therapy can regenerate infarcted myocardium or protect against LV remodeling.

Currently, several studies have been published using MSCs for noncardiac disorders (see Table 3), and allogeneic MSCs are in clinical trials for myocardial regeneration in the United States under the sponsorship of Osiris Therapeutics. In addition, the Specialized Centers for Cell-Based Therapy program also plans to conduct clinical trials of MSCs for patients with CHF.

Endothelial Progenitor Cells

Cells with phenotypic and functional characteristics similar to the fetal angioblast also are present in adult human bone marrow. These cells, known as EPCs, express some, but not all, cell surface markers characteristic of mature endothelium, certain surface markers of hematopoietic cells, and transcription factors that identify them as precursor cells. In addition to endothelial cell surface markers, EPCs also express markers of immature cells, including AC133, a novel hematopoietic stem cell marker not expressed on mature endothelial cells. After MI, intravenously injected EPCs homed to the infarct region within 48 hours. At 14 days, there was a marked increase in the number of capillaries in the infarct zone and the peri-infarct rim resulting from the induction of both vasculogenesis and angiogenesis, but there

TABLE 3. Clinical Studies Using MSCs

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<td>GVHD</td>
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GVHD indicates graft-versus-host disease.
was no change in the noninfarcted regions of the heart. There was a significant reduction in collagen deposition and apoptosis of cardiomyocytes and an improvement in cardiac function on echocardiography. It appears that neovascularization induced by these cells leads to the prevention of apoptosis and LV remodeling and may lead to some degree of cardiomyocyte regeneration.

Erb and colleagues randomized patients with recanalized, chronically occluded coronary arteries to receive intracoronary progenitor cells or placebo. They mobilized bone marrow cells using granulocyte colony-stimulating factor, harvested them from peripheral blood, expanded them ex vivo, and reinfused them via the coronary artery. This treatment resulted in significant improvements in coronary flow reserve and cardiac function and a significant reduction in infarct size. Currently, clinical trials of EPC therapy for angiogenesis and myocardial regeneration are in progress that use CD34+ cells from bone marrow that are enriched for EPCs. These cells can be immunoselected from the mononuclear fraction of bone marrow (Table 2).

Umbilical Cord Blood Stem Cells

Umbilical cord blood (UCB) contains both hematopoietic stem cells and mesenchymal precursor cells. Because stem cells in UCB exist in higher numbers than in adult human blood or bone marrow, several populations of cells derived from UCB are possible sources of stem cells for cardiac repair. Kogler and colleagues have described a population of cells from human UCB called unrestricted somatic stem cells. These cells, which are fibroblastlike in appearance, adhere to culture dishes; are negative for c-kit, CD34, and CD45; and are capable of differentiating, both in vitro and in vivo, into a variety of tissues, including cardiomyocytes. Human unrestricted somatic stem cells, when delivered by direct injection at thoracotomy in immunosuppressed pigs after MI, improved perfusion and wall motion, reduced infarct scar size, and enhanced global cardiac function.

Ma et al injected human mononuclear UCB cells, a small fraction (≈1%) of which were CD34+, intravenously 1 day after MI in NOD/scid mice. The cells homed to the infarcted hearts, reduced infarct size, and enhanced neovascularization with capillary endothelial cells of both human and mouse origin. Interestingly, they found no evidence of myocytes of human origin, arguing against cardiomyogenic differentiation. In a rat model of MI, UCB CD34+ improved cardiac function when injected into the peri-infarct rim immediately after MI compared with control animals that received injection of medium.

At present, no clinical studies of UCB have been reported.

Guiding Principle for Adopting New Therapies

As outlined above, a number of promising cell types for cardiac regenerative therapy have accumulating preclinical and early clinical data supporting their potential. Nevertheless, controversy abounds as to whether ongoing clinical trials of these novel strategies are warranted. We believe that fundamental criteria supporting ongoing trials have been met. The World Medical Association in the Declaration of Helsinki has set down principles for clinician researchers to follow. These state: “In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgment it offers hope of saving life, re-establishing health or alleviating suffering.” In the case of CHF, it is clear that there are unmet needs for new treatments to save lives and alleviate suffering. Accordingly, this principle supports clinical trials of new cell-based therapies.

In assessing the possibility of adopting a new treatment into clinical practice, rigorous scientific and ethical standards must be followed. Stem cell therapy has presented us with a number of unique challenges. Not only is the optimal cell type not clear, but how to best deliver these cells also is not immediately apparent, and these questions can be addressed only by prospectively designed clinical trials. Our understanding of the exact mechanisms by which stem cells exert their beneficial effects on cardiac function has evolved substantially, initially assuming transdifferentiation as the only mode of action and subsequently expanding to include, among other possibilities, effects on strengthening the MI scar and paracrine effects. Importantly, we propose that all of these features may be important for an integrated and orchestrated mechanism of repair that involves restoring endogenous stem cell niches. Despite incomplete understanding of mechanism, many independent laboratories have consistently demonstrated the beneficial effects on cardiac function in preclinical and clinical studies. These beneficial findings cannot be ignored and ongoing clinical studies delayed on the basis of needing better understanding of the molecular underpinnings of the observed effects because these functional improvements may translate to clinical benefit for patients. These ethical and logistic issues, not encountered with most previous drug or device trials, may appear daunting. However, despite the difficulties of stem cell research, the basic tenets of clinical research still apply:

- Patient safety is paramount.
- The risk of depriving patients of a potential new therapy must be balanced against the inherent risk of testing the new therapy.

It is with these guiding principles in mind that we must decide whether stem cell therapy is ready for clinical trials.

Patient Safety Is Paramount

The main issue in going forward into clinical trials is patient safety. “Primum non nocere” (first do no harm) is,
as always, our overriding concern. But how much safety data are enough to justify advancing to the next stage of clinical investigation? Autologous stem cell therapy begins with the premise that cellular repair occurs naturally in the human body and that enhancing that process should be safe. In fact, numerous animal studies have demonstrated that this is the case, with no adverse effects of cellular therapy for cardiac repair being observed; this has served as the platform for launching into human safety studies.

Several postulated safety issues about stem cell therapy were raised. There was concern regarding the intracoronary delivery route, fearing that cells administered this way may result in blockage of the coronary arteries and further damage to the myocardium. One study using autologous MSCs from dog bone marrow injected into normal coronary arteries demonstrated microinfarction in the region supplied by that artery, suggesting that these cells aggregate in vivo, leading to arterial or arteriolar obstruction. Nevertheless, intracoronary MSC therapy in human trial resulted in improved cardiac function and was safe. Differences in cell numbers or handling or delivery techniques may account for these differing clinical outcomes. A number of studies have now demonstrated safety of the intracoronary route using BMMNCs obtained by direct bone marrow aspiration and MSCs. Another theoretical safety concern was dysregulated angiogenesis or angioma formation within the myocardium seen with some angiogenic gene therapies. Could this occur with stem cell therapy designed to enhance neovascularization? Or could myogenic therapy result in the formation of myoma or myosarcoma? Tumor formation has not been reported in animal or human studies with stem cell therapy. (and substantially less) with stem cell therapy. The argument that these trials should be delayed until mechanisms are further understood will unnecessarily deprive large numbers of patients of therapeutic approaches that may improve their clinical outcome. Only clinical trials can lead to optimization of stem cell therapy with recognition of the best type of cell and the best delivery method for our patients.

Another compelling argument for initiating clinical research is that the results of these investigations often provide pivotal insights that allow a new field to advance. Several examples in cardiovascular medicine illustrate this concept. ACE inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), widely used drugs with solid mechanistic underpinning supporting their use, were both appreciated after entry into clinical practice to have pharmacological effects that extended beyond their initially intended design. The additional mechanistic effects were suggested by results obtained in clinical trials, demonstrating the important synergy between in vitro/animal studies and clinical trials conducted in parallel in guiding clinical therapies.

Regardless of the type of stem cell used in clinical trials, it is critically important to be vigilant against ex vivo contamination of the specimen. Infected or contaminated cells injected into the heart could potentially lead to devastating consequences of endocarditis and myocarditis. As such, all stem cell trial protocols should use good manufacturing practice facilities to minimize the risk of such outcomes. Rigorous follow-up also is essential after stem cell therapy to monitor for complications. Arrhythmias must be actively looked for both by continuous ECG monitoring around the time of the procedure and by ambulatory monitoring in follow-up. Additionally, patients enrolled in stem cell trials using allogeneic cells must be closely followed up for signs of allograft rejection.

A number of cells have been tested so far in preliminary trials (Table 1). More than 400 patients have been tested, and the totality of evidence from these studies supports safety of each cell therapy and the general approach. This evidence strongly supports ongoing efforts to advance to large, randomized, placebo-controlled, double-blind studies with clinical end points.

Balance of Risk
The risk of exposing patients to possible adverse outcomes of a new treatment must be weighed against the risk of depriving all patients of a new and possibly effective treatment to alleviate suffering or to prolong life. There is now sufficient preclinical and clinical data to warrant larger randomized controlled trials evaluating stem cell therapy. The argument that these trials should be delayed until mechanisms are further understood will unnecessarily deprive large numbers of patients of therapeutic approaches that may improve their clinical outcome. Only clinical trials can lead to optimization of stem cell therapy with recognition of the best type of cell and the best delivery method for our patients.
prompting substantial new basic research and the development of the coronary artery stent, which reduced but did not eliminate the incidence of restenosis. As is now well known, drug-coated stents that nearly eliminate restenosis have been developed.94 Before the publication of this seminal article, safety and feasibility data had been published on <100 patients,95–97 substantially less than the number who have been enrolled in preliminary stem cell trials. This stepwise progression to clinical trials was appropriate and timely, with patients receiving the benefits of the proven therapies, while clinical trial results guided further basic and preclinical research to eventually refine and improve these clinical therapies. We anticipate a similar iterative pathway for the development of stem cell therapy (see Figure 2).

Importantly, clinical trials do not always produce positive outcomes, yet unexpectedly negative results are often pivotal to the understanding of disease pathophysiology. For example, in the Cardiac Arrhythmia Suppression Trial (CAST), administration of antiarrhythmic drugs for asymptomatic nonsustained ventricular tachycardia after MI resulted in an excess of deaths in the treatment arms.98 No animal study had suggested that this would happen. In fact, further laboratory investigations and animal studies would have pursued a wrong path and would have wasted valuable resources. Although the outcome was unfortunate and unexpected, a properly designed prospective clinical trial discovered this deadly complication of antiarrhythmic therapy and changed future therapeutic approaches. The appropriate progression into prospective, randomized, controlled clinical trials will prevent exposing more patients to potentially dangerous therapies in uncontrolled trials or in the proliferation of delivering the therapy out of the clinical trial context.99 Additionally, the transition from preliminary studies to randomized controlled trials will demonstrate efficacy and safety of therapies that are indeed safe and effective, thereby allowing them to become incorporated into routine clinical practice. The time to take that step is now.

Clinical Trial Design

In the United States, the Food and Drug Administration (FDA) Modernization Act, section 113 (FDAMA 113), mandates the registration of all clinical trials that test effectiveness for “serious or life-threatening” conditions submitted to the FDA under investigational-new-drug applications.100 A Web-based registry, clinicaltrials.gov, was established in 2000 by the National Library of Medicine on behalf of the National Institutes of Health as a result of this law. This database permits registration of all clinical trials, including phase I studies that are not mandated to be registered; the number of registered trials has been increasing.101 The International Committee of Medical Journal Editors now demands registration of clinical trials as a prerequisite for publication.102 Currently, a number of clinical trials103–125 of stem cell therapy for cardiac repair are registered with clinicaltrials.gov; they are listed in Table 2. All of these trials are phase I or II trials rather than large phase III trials, and a number continue to be nonrandomized. We have not included trials of cytokines/growth factors alone.

Although current data do not support routine clinical use of stem cell therapy for cardiac repair, the results of preliminary studies are promising. Many treatments that improve cardiac function after MI in animal models have failed to translate into clinical benefit. A number of reasons may account for this disparity between preclinical and clinical results, but the most important difference
between the 2 situations is the complex biology and the multitude of factors in clinical situations that can never fully be replicated in experimental animal models. At some point in the discovery of any new treatment modality, only translation into clinical trials will provide the necessary data to move forward. There is also a need for ongoing basic science research in parallel to advance stem cell therapy toward clinical application.

Clinical studies of stem cell therapy should use rigorous trial designs and appropriate built-in safeguard mechanisms (Data Safety and Monitoring boards). In this regard, they should be prospective, double-blind studies with randomization on a background of best conventional therapy. Clinical trials should be designed to go beyond surrogate end points and should have adequate power to detect differences in relevant clinical end points such as survival, hospitalization, or reinfarction. Furthermore, future studies should be designed not only to assess safety and efficacy but also to gain further insight into mechanism of action of stem cells. One method of achieving this is to take advantage of state-of-the-art imaging modalities to assess myocardial function and to assess myocardial regeneration or neovascularization.126

Many issues in the burgeoning field of regenerative medicine still need to be addressed, and clinical trials will participate in a fundamental way. First, it is necessary to determine the optimal cell number required to gain maximal clinical effect; this will, in turn, guide how to access the cells (eg, bone marrow aspirate versus cytokine mobilization) and whether they need to be expanded ex vivo. Second, the optimal cell type for different patient populations remains unknown. Finally, effective delivery mechanisms must be determined and will likely be cell and/or disease specific. From these types of studies, not only will it be possible to determine whether cell therapy for cardiac repair is effective and safe in humans, but it is also probable that a great deal of mechanistic information will be derived that will guide further basic science and protocol design for subsequent clinical trials.

Conclusions

Although at this time no data support either cell-based or specific stem cell therapies as standard clinical practice for cardiac applications, there is a wealth of preclinical and early clinical data showing safety, feasibility, and early efficacy of adult cell-based therapy. Adult stem cell therapies should therefore proceed into randomized, placebo-controlled, double-blind clinical trials. The ongoing rigorously designed trials will contribute greatly to this emerging and exciting new therapeutic approach for diseases of the cardiovascular system.

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Disclosures

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Boyle et al raise several important points about the current status of stem cell therapy for cardiac repair and nicely review the results of multiple clinical trials to date. The vast majority of these trials were conducted using small numbers of patients with mixed results. Larger, recently completed, prospective, randomized, clinical trials have had similarly mixed results. Significant gaps remain with respect to our understanding of which stem cells may ultimately be the most therapeutically useful to promote cardiac tissue regeneration and how best to deliver the stem cells. Because the vast majority of stem cells do not remain within the heart, even after local injection, it is critical that better ways be developed to promote retention of the delivered cells within the heart and to be able to track and monitor the stem cells that do not remain within the heart after delivery. Other safety concerns include the progression of vascular disease and the development of arrhythmias. Do the results of the completed studies warrant initiation of larger additional clinical trials? The financial resources available for conducting stem cell research are limited. Large clinical trials, in particular, are costly. Although a significant unmet clinical need remains in patients with cardiovascular disease, we must carefully weigh how much of these resources should be devoted to additional basic research in stem cell biology and studies aimed at optimizing their therapeutic potential in animal models of cardiovascular disease versus conducting additional large clinical trials.
Cardiac Stem Cell Therapy

Need for Optimization of Efficacy and Safety Monitoring

Peter Oettgen, MD

Cardiovascular disease remains the number one cause of morbidity and mortality in the United States and Europe. In the United States alone, ≈1 million patients suffer a myocardial infarction every year, with an associated mortality of 25% at 3 years. A more sobering statistic is the fact that there are ≈5 million Americans with congestive heart failure, with an associated 20% mortality per year. This remains the case despite advances in pharmacotherapy, cardiac resynchronization therapies, and the use of implantable cardioverter-defibrillators. Some patients with end-stage congestive heart failure are considered for cardiac transplantation, but the demand for this therapeutic approach greatly outweighs the availability of donor hearts. Over the past few years, several animal studies and a few clinical trials have supported the use of stem cells as a potential therapeutic modality to address this unmet clinical need.

Type of Cells Used for Cardiac Transplantation

Several different types of cells have been used in both animal studies and patients to promote the repair of damaged myocardium. The 2 main sources of stem cells are adult stem and embryonic stem (ES) cells.

ES Cells

ES cells are derived from the inner mass of developing embryos during the blastocyst stage. Characteristic features of ES cells include their proliferative and self-renewing properties and their ability to differentiate into a wide variety of cell types, including cardiac myocytes. The major concerns with their use in human trials include the formation of teratomas when ES cells are injected into immunocompromised animals. This is particularly important because the ES cells currently available for use in humans would be of allogeneic origin and therefore would require immunosuppression. As nuclear transfer techniques improve, they will provide a way of generating an unlimited supply of histocompatible ES cells using the nuclei of cells obtained directly from the recipient patients with heart disease.

Adult Stem Cells

Bone Marrow–Derived Stem Cells

Several different types of stem cells can be isolated from adult bone marrow. Examples of some of these subpopulations of cells include hematopoietic stem cells, endothelial progenitors, and mesenchymal stem cells. Several investigators have chosen to deliver unfractionated bone marrow–derived cells, a technique that has the advantage of minimizing extensive ex vivo manipulation of the cells to isolate and expand a selected population of cells. The potential disadvantage of delivering a mixture of cells is that the percentage of cells that are therapeutically useful may be small. An alternative strategy is to isolate...
sidered in number and require ex vivo separation and expansion.

Skeletal Myoblasts
Skeletal myoblasts are a population of progenitor cells that can be isolated from skeletal muscle biopsies and expanded in vitro. These myoblasts can differentiate into myotubes and exhibit skeletal muscle phenotype after transplantation, leading to improvements in left ventricular (LV) systolic and diastolic function. However, the transplanted skeletal myocytes are not electrically coupled to surrounding cardiomyocytes and thus may lead to the development of arrhythmias.

Resident Cardiac Stem Cells
Several investigators have recently identified a population of stem cells within the myocardium that are capable of differentiating into cardiac myocytes. It has been recently reported that these cells can be harvested from cardiac biopsies. Injecting these cells in the setting of myocardial infarction can promote cardiomyocyte formation with associated improvements in systolic function. At present, these cells are limited in number and require ex vivo separation and expansion over several weeks.

Methods of Stem Cell Delivery
A major goal of cardiac stem cell therapy is to transplant enough cells into the myocardium at the site of injury or infarction to maximize restoration of function. Several different approaches are being used to deliver stem cells.

Transvascular Route
A transvascular approach is particularly well suited to treat patients with acutely infarcted and reperfused myocardium. Stem cells can be infused directly into the coronary arteries and have a greater likelihood of remaining in the injured myocardium as a result of the activation of adhesion molecules and chemokines. The advantage of an intracoronary infusion is that the cells can easily be expanded in vitro, exhibit relatively low immunogenicity, and might be particularly useful when autologous stem cells are not readily available.

Skeletal Myoblasts
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Safety Concerns
Arrhythmias
Over the past few years, some of the early-phase clinical studies have suggested the possibility of a proarrhythmic effect associated with stem cell transplantation. In 1 study, skeletal myoblasts were injected transendocardially at the time of coronary artery bypass surgery. Four patients had documented ventricular tachycardia at 11, 12, 13, and 22 days after stem cell implantation. Interestingly, these events occurred early and were not observed in treated patients later after several months of follow-up. A similar proarrhythmic effect was observed when autologous skeletal myoblasts were delivered via a transvascular route. Other studies have similarly reported an increased frequency of nonsustained ventricular tachycardia in patients treated with skeletal myoblasts, peaking 11 to 30 days after stem cell transplantation. A proposed mechanism for the increased incidence of arrhythmias is that the injected stem cells do not communicate electrically with neighboring cardiac myocytes and/or result in slowed conduction, thereby promoting reentrant arrhythmias. It has recently been suggested that skeletal myoblasts that have been genetically engineered to express gap junction protein connexin 43 exhibited decreased arrhythmogenicity. Although proarrhythmic effects have been observed predominantly in patients receiving skeletal myoblast transplantation, they also have been observed recently in 2 patients shortly after transplantation of CD133+ cells.

Restenosis, Accelerated Atherosclerosis, and Coronary Obstruction
There have been conflicting reports regarding the potential for increased restenosis after stem cell transplantation. In 1 study, a high rate of restenosis was observed after intracoronary delivery of peripheral blood stem cells mobilized with granulocyte colony-stimulating factor in the setting of myocardial infarction and stent placement. In another study, CD133+ cells were delivered via intracoronary injection in patients with acutely infarcted and reperfused myocardium.
Evidence for Tissue Regeneration

The ultimate goal of stem cell therapy is to promote cardiac tissue regeneration so that the regenerated cardiac tissue leads to improvements in cardiac function in a fashion that is synchronized with the rest of the functioning heart in the absence of proarrhythmic or other adverse effects. More recently, however, there is evidence that stem cells may lead to improvements in cardiac function that are independent of tissue regeneration. Although early studies supported the ability of bone marrow–derived mononuclear cells to differentiate into cardiac myocytes, subsequent studies failed to support these initial observations. It has been suggested that the locally injected cells can act in a paracrine fashion to improve ventricular function through the release of growth factors or other paracrine mediators. These mediators may act to directly augment systolic function, prevent apoptosis of ischemic myocardial cells, or limit injury by promoting angiogenesis. The locally injected stem cells would promote the salvage of injured myocardium rather than tissue regeneration. Additional long-term studies are needed to determine whether the improvements observed after weeks to a few months are generally sustained over longer periods of time. These paracrine effects are more likely to be useful in patients with acute myocardial ischemia or with hibernating myocardium and less likely to be beneficial in patients with chronically infarcted myocardium with significant scar formation. Significant challenges remain with regard to cardiac tissue regeneration. Future studies are needed to identify the best stem cell type to use. To promote cardiac tissue regeneration, sufficient numbers of cells will need to be delivered and maintained within the heart at the site of LV dysfunction, and the new tissue needs to be vascularized, electrically and mechanically coupled with the rest of the myocardium. The hope is that the strategies will include ways of replacing scarred or fibrotic tissue in regions of LV dysfunction. Unless autologous cells can be used to generate the cardiac tissue, potential graft rejection needs to be addressed. Real progress toward this goal will require the collaborative interaction of investigators with expertise in tissue engineering, molecular biology, electrophysiology, cardiac physiology, immunology, and vascular biology.

Recent Clinical Trials

Several small clinical studies using a variety of different cell types have shown some initial promise regarding the benefit of stem cell therapy, but these small clinical studies have several limitations. In addition to being small, some of the studies lacked adequate controls or randomization in a blinded fashion. Furthermore, some of the studies failed to assess infarct size or ventricular function before administration of the stem cells, and the follow-up period often was short.

Results of recent randomized clinical trials evaluating the therapeutic effect of administering bone marrow–derived mononuclear cells via intracoronary injection at the time of myocardial infarction have recently been reported (Table). Results of these studies have been mixed. The primary end point of these studies was LV ejection fraction. The administration of stem cells in 2 studies, BOne marrOw transfer to...
Randomized Clinical Trials of Stem Cell Therapy for MI

<table>
<thead>
<tr>
<th>Study</th>
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<th>Cell Type/Treatment</th>
<th>Mode of Delivery</th>
<th>End Point</th>
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<td>BMMNCs</td>
<td>Intracoronary</td>
<td>LV ejection fraction</td>
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<td>G-CSF</td>
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<td>LV systolic wall thickening</td>
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</table>

BMMNCs indicates bone marrow mononuclear cells; G-CSF, granulocyte colony-stimulating factor; and STEMMI, Stem Cells in Myocardial Infarction.

*LV ejection fraction was higher in the control group.

enhance ST-elevation infarct regeneration (BOOST) and Reinfusion of Enriched Progenitor cells And Infarct Remodelling in Acute Myocardial Infarction (REPAIR-AMI), resulted in significant increases in LV ejection fraction.35,36 The differences in ejection fraction of the treated and control groups at 6 months in the BOOST trial were 56.7% and 52.0%; in the REPAIR-AMI treated and control groups, the differences were 54% versus 50%. In contrast, in the study by Janssens et al.,37 no difference between control and treated groups was observed, and in the Autologous Stem cell Transplantation in Acute Myocardial Infarction (ASTAMI) trial, the LV ejection fraction was higher in the control group.36,38 The cause of these differences is unclear but may relate to how the cells were prepared before delivery or to the fact that the baseline ejection fractions at the time of myocardial infarction were only mildly diminished. There are ongoing additional randomized trials. BOOST-II will enroll 200 patients with large myocardial infarctions and depressed ejection fractions to receive bone marrow–derived mononuclear cells or placebo. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial will evaluate the effect of autologous skeletal muscle myoblasts in patients with chronic heart failure who are undergoing coronary bypass and defibrillator implantation.

One attractive alternative to delivering autologous stem cells via local injection is to identify the mechanisms by which stem cells are recruited to the heart and try to augment mobilization of stem cells, particularly in the setting of acute infarction. Small clinical studies suggested that cytokines such as granulocyte colony-stimulating factor could promote the mobilization of bone marrow–derived stem cells in the setting of myocardial infarction, leading to improvements in myocardial function.39,40 The advantage of this approach is that the cells are autologous and can be mobilized via systemic injections of granulocyte colony-stimulating factor. Two larger randomized trials, consisting of 78 and 114 patients, similarly used granulocyte colony-stimulating factor to mobilize stem cells in the setting of myocardial infarction.41,42 Unfortunately, neither of these studies demonstrated a significant benefit with respect to cardiac function after 6 months. Furthermore, another smaller study in which intracoronary injections of stem cells isolated after stimulation with granulocyte colony-stimulating factor were administered in the setting of myocardial infarction resulted in an increased rate of restenosis.21

Conclusions

Stem cells remain a highly promising therapeutic modality that could address the large, unmet clinical need of treating patients throughout the world with significant cardiac dysfunction that cannot be adequately treated with conventional therapeutic approaches or cardiac transplantation because of the limited availability of this resource. On the basis of the mixed results of more recent larger clinical trials, we should err on the side of caution before committing precious resources to conduct additional large clinical trials. Several questions need to be addressed. First, have we identified which stem cell type to use? Second, have we determined the mechanisms by which stem cells promote myocardial function or repair? At present, there is limited evidence to support that stem cells used thus far in patients promote significant cardiac tissue regeneration. Third, can the stem cell be retained efficiently within the heart? Finally, can clinical trials be done in such a way that important safety issues will be adequately addressed? What methods will be used to monitor the development of life-threatening arrhythmias and to track injected stem cells throughout the body? Because the financial resources available for clinical and basic stem cell research are not unlimited and because of the high cost associated with conducting larger clinical trials, it is particularly important that we address the aforementioned questions before proceeding with larger clinical trials. It is clear that additional basic research is needed to optimize ways to promote cardiac tissue regeneration, to improve methods by which delivered stem cells will remain in the heart, and to optimize the way in which stem cells are tracked after delivery.

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References
Response to Oettgen

Andrew J. Boyle, MBBS, PhD; Steven P. Schulman, MD; Joshua M. Hare, MD

We agree with Dr Oettgen on many issues surrounding cell therapy. Preclinical studies demonstrate considerable promise for many cell types to effect cardiac repair, yet the initial promise from small animal work is far more difficult to demonstrate in humans. Moreover, early clinical trials of skeletal myoblasts and granulocyte colony-stimulating factor have discovered unexpected side effects not apparent in animal models. These rigorously designed early clinical studies and their unanticipated findings have now guided not only the design of next phase of clinical studies but also the future of basic and animal studies. Most importantly, we agree that understanding the mechanistic underpinnings of cell-based therapy is essential. Our area of fundamental disagreement relates to the role of the clinical trial in advancing the burgeoning field of cell-based therapy. We believe that these trials must proceed but must be conducted by responsible investigators concerned with patient safety and committed to incorporating mechanistic studies into the trials. Clinical development of any new therapy begins with a phase I study aimed at proving safety, and major trials contain independent Data Safety and Monitoring boards. Every detail regarding the mechanism of action of these cells cannot be appropriately determined in animal models because, by definition, that which happens in controlled animal experiments may not translate into humans, who are much more heterogeneous and have many comorbidities that affect responsiveness to novel therapies. There exists, by necessity, a synergy between basic science and clinical research. An incomplete understanding of molecular/cellular mechanisms should not halt the progression of clinical trials; quite the opposite is the case. The success or failure of clinical trials guides future basic science research, which, in turn, informs future clinical trials to achieve improvements in health outcomes for patients.
Stem Cell Therapy for Cardiac Repair: Ready for the Next Step
Andrew J. Boyle, Steven P. Schulman and Joshua M. Hare

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