Heart disease is both common and deadly. Cardiovascular disease is a global epidemic, because it is the number 1 cause of death worldwide, and it is estimated that 1 in 3 adults in the United States have cardiovascular disease.1 Although a number of pioneering initiatives have transformed our treatment of cardiovascular disease, new therapies are required to further address the growing incidence of this deadly disease. Intense interest has focused on regenerative medicine as an emerging strategy for chronic diseases such as cardiovascular disease.

A number of human tissues, including skin,2 gut, liver,3–6 and skeletal muscle5,7 have a tremendous regenerative capacity. For example, skeletal muscle is able to completely restore its cellular architecture and function after an injury that destroys >80% of the muscle.7,8 This regenerative response lacks a fibroproliferative response (i.e., formation of scar) and is associated with restoration of the vasculature, myofibers, and extracellular matrix. Compared with skeletal muscle, the regenerative capacity of the adult heart is more limited.

Recent studies suggest that the adult heart is capable of cellular turnover and limited regeneration after injury, although the networks that govern this process are ill defined. The use of genetic mouse models and molecular biological techniques is unveiling cell populations, pathways, and extracellular cues that may direct cardiac regeneration and provide a platform for further investigation. The goal of the present review is to examine the endogenous regenerative capacity of the adult heart and highlight new experimental regenerative therapies aimed at restoring myocardial architecture and function.

**Endogenous Repair and Regeneration of the Metazoan Heart**

Previous studies have demonstrated that metazoans such as the newt and zebrafish are capable of cardiac regeneration in response to a significant injury.9–12 This myocardial regenerative response is complex, and occurs over a 2-month period. In response to a myocardial injury (amputation of 30% to 40% of the ventricular chamber), there is formation of a fibrin clot, subsequent dedifferentiation of cardiomyocytes, and recruitment of specialized cell populations, including epicardial and ventricular myocardial cell populations.11–13 Importantly, the regenerative response observed in both the newt and zebrafish lacks the formation of scar.13 These results support the notion that there is an inverse relationship between scar formation and myocardial regeneration (Figure 1). Moreover, the studies in these regenerative models have defined the role of the Notch,14,15 fibroblast growth factor 2,15,16 and retinoic acid17 signaling pathways in myocardial regeneration. Examination of these regenerative organisms and mammalian tissues that have an enhanced regenerative capacity is instructive with regard to the mechanisms and pathways that govern this repair process in response to injury.

**Endogenous Repair and Regeneration of Mammalian Tissues**

Every tissue is a product of stem cells, and evidence suggests that essentially every adult mammalian tissue harbors a stem cell or progenitor cell population that participates in the maintenance or regeneration of its host tissue(s) in response to injury (Table 1).4–7,18–30 For example, the satellite cell population occupies a niche (satellite cells are sandwiched between the basal lamina and the plasmalemma in close association with the myofibers) and resides within adult skeletal muscle.7,31 Satellite cells represent the myogenic stem cell population that is quiescent in unperturbed muscle. In response to a severe injury, the quiescent satellite cells become activated (re-enter the cell cycle); they proliferate, and in response to cellular and extracellular cues, they differentiate to form centronucleated myofibers (the hallmarks of regenerated skeletal myofibers), thus restoring the cellular architecture of the injured tissue.13 Importantly, satellite cells are capable of self-renewal, and re-establish a quiescent pool of myogenic stem cells.32,33 These studies emphasize the dynamic capacity of adult mammalian skeletal muscle to completely regenerate in response to injury. All striated muscle does not respond in a similar fashion to an injury.

**Endogenous Repair and Regeneration of the Mammalian Heart**

The neonatal mammalian heart is associated with considerable growth and cellular proliferation of cardiomyocytes...
cardiomyocyte turnover. Bergmann et al36 relied on the regeneration in response to an ischemic or nonischemic of cellular replacement of cardiomyocytes, repair, and limited mouse models have suggested that the adult heart is capable associated with modest cellular turnover.

hormonal surges, and changes that occur in extracardiac tissues. After this postnatal period, the mammalian heart is an active modeling or sculpting process that is associated with growth and modulation by hemodynamic challenges, increased apoptosis in the developing heart, which suggests an active modeling or sculpting process that is associated with growth and modulation by hemodynamic challenges, hormonal surges, and changes that occur in extracardiac tissues. After this postnatal period, the mammalian heart is associated with modest cellular turnover.

Recent studies that used labeling strategies and genetic mouse models have suggested that the adult heart is capable of cellular replacement of cardiomyocytes, repair, and limited regeneration in response to an ischemic or nonischemic injury. One study used radiocarbon cellular dating to examine cardiomyocyte turnover. Bergmann et al36 relied on the integration of carbon 14 into DNA as a measure of cardiomyocyte turnover in the adult heart. All organisms incorporated high concentrations of carbon 14 that were generated from nuclear bomb testing (which persisted until the 1963 Limited Nuclear Test Ban Treaty) into DNA as a measure of cardiomyocyte cellular kinetics or turnover in the adult heart. Therefore, the nuclear bomb testing and subsequent increase in atmospheric carbon 14 provided a pulse such that postnatal cellular turnover could be estimated by comparing the age of the DNA of the cardiomyocytes with the patients’ chronological age. This cellular dating technique and mathematical modeling support the notion that the adult heart is capable of cellular turnover (representing cardiomyocyte renewal) at the rate of 1% per year (although this rate decreased to 0.4% at 75 years of age).36 The results further suggested that ≈ 45% of cardiomyocytes had been generated or renewed in the 50-year-old heart since birth. These studies provide an innovative strategy to examine the cardiomyocyte turnover of the adult human heart. Issues of polyploidy and origin of the cardiomyocytes remain active areas of investigation, and further studies using similar strategies to examine cardiomyocyte turnover in distinct populations are warranted. Nevertheless, these results provide further support that the adult human heart has ongoing turnover of cardiomyocytes, and support the notion that strategies to enhance this turnover may prevent the genesis of heart failure.36

A second study used genetic mouse models to evaluate cellular kinetics in the unperturbed and postinjured heart. With use of an inducible cardiomyocyte-specific transgenic fate-mapping (MerCreMer) strategy in the mouse, cardiomyocytes were irreversibly labeled with green fluorescent protein reporter after a pulse of tamoxifen.37 In contrast, cardiac stem cells or progenitors were not genetically labeled in response to tamoxifen, because they did not express the cardiomyocyte-specific marker (myosin heavy chain 6).37 This fate-mapping strategy allowed for the measurement of cardiomyocyte turnover in the adult mouse heart. Although little to no cardiomyocyte turnover was observed in the unperturbed heart, the genetic labeling strategy after myocardial injury revealed approximately 15% of unlabeled cardiomyocytes within the border region of injured myocardium, which suggests that these cardiomyocytes had undergone cellular turnover (presumably from a progenitor or stem cell population). These genetic studies are further supported by bromodeoxyuridine incorporation studies that support the hypothesis that cardiomyocyte renewal occurs after myocardial injury (Figure 2B).38

Collectively, these and other studies support the notion that the postnatal mammalian heart is associated with cardiomyocyte renewal (cellular turnover), which is increased after injury. These results further suggest that amplification of resident or recruited stem cells or progenitors and regenerative myocardial pathways could increase endogenous myocardial repair of the acutely injured heart.

**Resident Cardiac Stem and Progenitor Cell Populations**

Previous studies have identified the contribution of stem cell and progenitor cell populations that reside in the postnatal heart

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**Table 1. Selected Examples of Somatic Adult Stem Cell Populations That Reside in Adult Mammalian Tissues**

<table>
<thead>
<tr>
<th>Adult Stem Cell Population</th>
<th>Niche (Tissue)</th>
<th>Derivatives</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchioalveolar stem cells</td>
<td>Lung</td>
<td>Clara- and AT2-like cells</td>
<td>18, 19</td>
</tr>
<tr>
<td>Bulge stem cells</td>
<td>Hair follicle</td>
<td>Hair follicles, sebaceous glands, and epidermis</td>
<td>20, 21</td>
</tr>
<tr>
<td>Epithelial stem cells</td>
<td>Lining of digestive tract</td>
<td>Villus columnar, mucus, enteroendocrine, and paneth cells</td>
<td>22, 23</td>
</tr>
<tr>
<td>Hematopoietic stem cells</td>
<td>Bone marrow</td>
<td>Lymphoid (B cell, T cell, natural killer cell, and lymphoid dendritic cell lineage) and myeloid (all other lineages) blood cells</td>
<td>24, 25</td>
</tr>
<tr>
<td>Neural stem cells</td>
<td>Ependymal cell layer</td>
<td>Neurons, astrocytes, and oligodendrocytes</td>
<td>26, 27</td>
</tr>
<tr>
<td>Oval cells</td>
<td>Liver</td>
<td>Hepatocytes and biliary epithelium</td>
<td>4–6</td>
</tr>
<tr>
<td>Satellite cells</td>
<td>Skeletal muscle</td>
<td>Skeletal muscle</td>
<td>7, 28, 29</td>
</tr>
</tbody>
</table>
that are capable of generating cardiomyocytes (Figure 3).39–50 Although a hierarchy of stem and progenitor cell populations has not been defined, a clonal c-kit+ cell population has been shown to generate all lineages of the heart, increase in number after myocardial injury, undergo self-renewal, and generate cardiomyocytes in a number of mammalian models (eg, rat, mouse, dog), including humans.42,43 These c-kit–expressing cells have been shown to occupy a niche within the adult heart. With immunohistochemical studies, subpopulations of c-kit–expressing cells have been identified, including those that express c-kit only versus those that coexpress c-kit with cardiac transcription factors and sarcomeric proteins. This continuum of c-kit–expressing cells (with and without cardiac specific markers) has been proposed to represent a progression of cell stages, from cardiac progenitor cell, to the committed progenitor cell, to the immature cardiomyocyte.43

An additional cell population includes cardiac side population (SP) cells that express multidrug-resistance proteins (members of the ATP-binding cassette transporter family) and are isolated by fluorescent-activated cell sorter analysis on the basis of their ability to efflux Hoechst 33342 dye.46–48 These SP cells populate the heart early during development, are resident in the adult heart, and increase in number within 3 days of cardiac injury. Using immunohistochemical techniques, these cardiac SP cells, after injury, have been shown to coexpress cardiomyocyte-specific sarcomeric proteins (which suggests that cardiac SP cells are capable of differentiating to fetal cardiomyocytes).47 Previous studies have demonstrated that members of the ABC transporter family not only serve to mark SP cells, but also play an important cytoprotective role for these stem/progenitor cells in response to oxidative stress.46 Transcriptome analysis has been useful in defining the molecular signature of cardiac SP cells that are isolated from the adult heart compared with other embryonic and somatic stem cell populations.46,47

Studies have shown that Sca1+ cells can differentiate into cardiomyocytes.44 Resident Sca1+/CD31− cardiac progenitors have been reported to increase in number and more than double 14 days after acute myocardial infarction. These cardiac Sca1+/CD31− cells were capable of differentiation to endothelial and cardiomyocyte lineages in vitro and in vivo

<table>
<thead>
<tr>
<th>Cardiac Stem/Progenitor Cell</th>
<th>Cardiomyocyte Potential</th>
<th>Proliferative Potential</th>
<th>Multipotency</th>
<th>Embryonic/Adult expression</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiospheres</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>E/A</td>
<td>39-41</td>
</tr>
<tr>
<td>c-kit+ cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>E/A</td>
<td>42-43</td>
</tr>
<tr>
<td>Sca1− cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td>44-45</td>
</tr>
<tr>
<td>SP cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>E/A</td>
<td>46-48</td>
</tr>
<tr>
<td>Isl1+ cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>E</td>
<td>49</td>
</tr>
<tr>
<td>SSEA-1+ cells</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>A</td>
<td>50</td>
</tr>
</tbody>
</table>
after delivery into the postinjured heart. The transdifferentiation of the engrafted Sca1+/CD31− cells was accompanied by a significant improvement in left ventricular systolic function compared with controls.45

Further studies, using a genetic labeling strategy (Cre-loxP technology), are warranted to fate map the c-kit−, SP−, and Sca1− expressing cell population during development and aging and after perturbations (including coronary artery ligation and pressure overload) by use of conventional and inducible genetic technologies. These fate-mapping techniques will enhance our understanding of the degree to which these cell populations contribute to the renewal of cardiomyocytes and the vasculature after injury or aging.

Other cell populations that may represent a cardiac stem cell pool, progenitors (such as transit amplifying cells), or other stem cell populations that are capable of generating cardiomyocytes include endothelial progenitor cells,53,54 mesenchymal stem cells,55,56 CD34+ cells,57,58 myofibroblasts, and others that have been reported to participate in cardiomyocyte renewal and regeneration. Studies support the notion that these cell populations form cardiomyocytes under permissive conditions.

Cardiac progenitors that are obtained from adult hearts (after an endomyocardial biopsy) coalesce in culture to form a 3-dimensional spherical structure, termed a cardiosphere. Two independent laboratories have generated cardiospheres from both mouse and human biopsy specimens of adult hearts. These cardiospheres (up to 150 µm in size) have a tremendous proliferative capacity (generating more than 1 million cardiospheres in a 1-month period), and are capable of forming differentiated contractile cardiomyocytes.39,40 Cardiospheres also represent a heterogeneous cell population with a cortex of c-kit− expressing proliferating cells and a mantle of differentiated cardiomyocytes.39,40 Delivery of cardiospheres as a graft after myocardial injury resulted in improved cardiac function in rodent models, and limited clinical trials are in progress to evaluate these autologous cell preparations in patients. It is unclear whether cardiospheres are derivatives of a resident cardiac stem/progenitor cell population or whether they represent reprogramming of cardiomyocytes (dedifferentiation) or progenitor cell populations. Moreover, a recent study demonstrated that transplantation of cardiosphere-derived cells into the postinjured pig model further induced repair and regeneration by endogenous cardiac progenitors.41

A complementary cell population to the resident cardiac stem/progenitor cell population is the reprogrammed induced pluripotent stem cell population. These induced pluripotent stem cells have been derived from somatic cells such as skin fibroblasts through forced gene expression (Oct3/4, Sox2, c-Myc, and Klf4 versus OCT4, SOX2, NANOG, and LIN28) in mouse59,60 and humans.61,62 These induced pluripotent stem cells have been shown to mirror embryonic stem cells with regard to their proliferative capacity, pluripotency, chimera formation, teratoma formation, and capacity to differentiate to all germ-layer derivatives. Recent studies suggest that reprogramming is possible without genetic alteration of the somatic cell. In addition to these initiatives, the use of chemical genetics and exposure of cells to small molecules may be sufficient to direct somatic or stem cells to a cardiovascular fate.63,64 An alternative reprogramming strategy is to decipher the pathways or factors that will directly convert somatic cells (fibroblasts) to cardiomyocytes, thus bypassing the pluripotent state. An example of this strategy includes the forced expression of 3 developmental transcription factors (Tbx5, Gata4, and Mef2c) to reprogram murine cardiac fibroblasts into cardiomyocyte-like cells that are similar to neonatal cardiomyocytes.65 These results provide a proof of concept and rationale for future studies aimed at reprogramming human cardiac fibroblasts to a cardiomyocyte fate. This field is rapidly evolving, and will provide a platform for disease-specific stem cell populations and personalized stem cell populations, as well as cell sources for pharmacogenetics studies.

**Cell Therapy for Chronic Diseases**

The delivery of allogeneic or autologous cellular populations for the treatment of chronic diseases has been used for more than 40 years. Since the world’s first and second successful bone marrow transplantations in 1968 at the University of Minnesota, this cellular therapy has been used to treat an array of diseases, including solid tumors, mucopolysaccharidoses, and hematologic cancers.66 In total, more than 50 000 patients worldwide receive this life-saving therapy each year.67 Bone marrow transplantation provides the rationale and the feasibility for using cellular therapeutic strategies for the treatment of terminal diseases such as cardiovascular disease and heart failure.

**Cell Therapy for Cardiovascular Disease**

Although bone marrow transplantation has been used successfully to treat terminal diseases, certain challenges need to be overcome to translate the use of cellular therapy to other tissues such as the heart. For example, the heart is unlike the bone marrow in that it has a highly structured cellular architecture that is electrically and functionally synchronized to produce more than 2 billion heart beats in a lifetime. Furthermore, the working load of the heart is constantly changing and responding to local and systemic stimuli. These hemodynamic challenges provide both permissive and reproductive challenges for the use of cell therapy. Third, the geometric shape of the heart adapts in response to injury, scar, and hemodynamic demand, among other things, as remodeling promotes the change from a prolate ellipse to a spherical shape due to hemodynamic load. Collectively, these challenges are balanced with the increasing prevalence of cardiovascular disease, decreasing donors for heart transplantation (the only definitive therapy for advanced heart failure), and a need to develop new therapies for this patient population.

Because bone marrow transplantation has been an effective therapy for human diseases, studies were undertaken to examine the capacity of unfractionated bone marrow mononuclear cells (which contain hematopoietic stem cells) to transdifferentiate to a cardiomyocyte fate and improve the functional performance of the injured heart. Using genetic labeling strategies, studies demonstrated either significant, limited, or no ability of labeled bone marrow mononucleated cells or stem cells to generate cardiomyocytes after delivery.
used cell therapy for the treatment of cardiovascular disease demonstrated positive results fueled the design of clinical trials that varied in their findings. The variability of the results, the preclinical studies that demonstrated a functional improvement in response to the delivery of hematopoietic stem cells, unfractonated bone marrow mononuclear cells, and other cell populations (including fibroblasts, skeletal myoblasts, mesenchymal stem cells, endothelial progenitors, and cord stem cells). Despite the variability of the results, the preclinical studies that demonstrated positive results fueled the design of clinical trials that used cell therapy for the treatment of cardiovascular disease.

### Table 2. Results of Selected Cell Therapy Trials in Patients With Ischemic Cardiomyopathies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Subjects</th>
<th>Design</th>
<th>Patients</th>
<th>Type of Cells</th>
<th>Mode of Delivery</th>
<th>Follow-Up</th>
<th>Parameters Measured</th>
<th>Modality</th>
<th>Improvement</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOP CARE-AMI</td>
<td>59</td>
<td>Randomized</td>
<td>AMI</td>
<td>Circulating progenitor cells vs BM mononuclear cells</td>
<td>IC</td>
<td>12 mo</td>
<td>LV function, LV EDV</td>
<td>MRI</td>
<td>All parameters improved</td>
<td>74</td>
</tr>
<tr>
<td>REPAIR-AMI</td>
<td>60</td>
<td>Randomized</td>
<td>STEMI</td>
<td>BM mononuclear cells</td>
<td>IC</td>
<td>18 mo</td>
<td>LVEF</td>
<td>MRI</td>
<td>No change</td>
<td>75</td>
</tr>
<tr>
<td>REPAIR-AMI</td>
<td>57</td>
<td>Randomized</td>
<td>STEMI</td>
<td>BM mononuclear cells</td>
<td>IC</td>
<td>12 mo</td>
<td>LV EDV, LV ESV</td>
<td>MRI</td>
<td>Improvement in LVEF, LV EDV, and LV ESV</td>
<td>75</td>
</tr>
<tr>
<td>ASTAMI</td>
<td>100</td>
<td>Randomized</td>
<td>STEMI</td>
<td>BM mononuclear cells</td>
<td>IC</td>
<td>3 y</td>
<td>LV function, LV EDV</td>
<td>MRI</td>
<td>No change in LVEF or infarct size; slight improvement in exercise capacity</td>
<td>77</td>
</tr>
<tr>
<td>MAGIC</td>
<td>120</td>
<td>Randomized</td>
<td>CABG</td>
<td>Autologous myoblasts</td>
<td>IM</td>
<td>6 mo</td>
<td>LVEF, LV EDV, LV ESV</td>
<td>Echo</td>
<td>No change in LVEF; improvement in LV EDV and LV ESV with high dose</td>
<td>78</td>
</tr>
</tbody>
</table>

TOPCARE-AMI indicates Transplantation of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction; AMI, acute myocardial infarction; BM, bone marrow; IC, intracoronary; LV, left ventricle; ESV, end-systolic volume; MRI, magnetic resonance imaging; echo, echocardiograph; BOOST, Bone marrow transfer to enhance ST-elevation infarct regeneration; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; REPAIR-AMI, Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction; EDV, end-diastolic volume; ASTAMI, Autologous Stem cell Transplantation in Acute Myocardial Infarction; MAGIC, Myoblast Autologous Grafting in Ischemic Cardiomyopathy; IM, intramuscular; and CABG, coronary artery bypass surgery.

A majority of the cardiovascular cell therapy clinical trials have used autologous cell populations (the exception is the use of allogeneic mesenchymal stem cells), which obviate immunologic mediated cellular rejection. The mode of delivery primarily has been intracoronary, but has also included intramyocardial and endocardial routes. The initial nonrandomized studies delivered bone marrow mononuclear cells (intracoronary route) 7 days after percutaneous revascularization and observed no significant change in function (left ventricular ejection fraction) compared with controls 3 months after delivery. TOPCARE-AMI (Transplantation of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction) was the first randomized clinical trial; it compared 2 different cell populations (peripherally derived stem cells versus mononucleated bone marrow cells) 5 days after percutaneous coronary intervention. At 1 year after cell delivery, there was a decrease in infarct area in both patient populations. The first randomized, controlled study (n=60) was the BOOST trial (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration), which delivered bone marrow mononucleated cells (intracoronary route) 5 days after percutaneous coronary intervention. Although left ventricular ejection fraction improved in those patients who received cell therapy at 6 months compared with control subjects, no significant differences were noted at 18 months after delivery. In contrast, the larger REPAIR-AMI (Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction) trial (n=204) was a randomized, controlled study that reported a modest improvement of left ventricular ejection fraction as measured by ventriculography in patients who received intracoronary delivery of bone marrow mononucleated cells 5 days after percutaneous coronary intervention at 4- and 12-month follow-up compared with control subjects.

The ASTAMI (Autologous Stem cell Transplantation in Acute Myocardial Infarction) trial (n=100) also examined the efficacy of intracoronary delivery of autologous bone marrow mononuclear cells 6 days after percutaneous coronary intervention and observed no significant change in left ventricular ejection fraction between experimental and control groups at 3 years after intervention. Potential side effects associated with cell therapy include arrhythmogenesis, tumorigenesis, myocardial injury, infection (bacterial or viral pathogens), or immunologic responses. One example of the side effects associated with the delivery of autologous human skeletal myoblasts includes the genesis of ventricular arrhythmias and the need for implantable cardioverter defibrillator support. Another possible side effect is the immunologic response to the cardiac delivery of allogeneic cell sources. Although these complications are possible, very few side effects have been observed in clinical trials performed in the United States and in Europe.

Collectively, these clinical trials support the conclusion that cell therapy for cardiovascular disease is relatively safe; it may modulate remodeling and may yield a modest improvement in cardiac function (Table 2). Many of these clinical studies used ejection fraction as the only end point for...
the efficacy of these cell transfer studies, which may be insufficient. Other primary or secondary end points for future studies may include exercise tolerance, infarct size, 5-year survival rate, or progression to heart failure (New York Heart Association stages I through IV). Furthermore, future studies aimed at a mechanistic understanding of cell therapy for heart disease will be important for the advancement of this field.

**Paracrine Hypothesis and Myocardial Regeneration**

An increasing number of studies suggest that cell therapy may also be associated with a bystander effect through the release of cytokines, antiapoptotic factors, or growth factors that may improve cardiac function. For example, studies suggest that transplanted cells release paracrine factors that decrease programmed cell death (thereby limiting the remodeling process), promote angiogenesis, or enhance myocardial regeneration mediated by the endogenous cardiac stem cell/progenitor cells that are resident in the adult heart.82,83 Alternatively, small molecules or growth factors such as neuregulin-1 may induce cell cycle reentry and division of differentiated cardiomyocytes.84 Increasing evidence supports the hypothesis that paracrine factors or the delivery of small molecules may promote myocardial repair and regeneration.

**Gaps in Knowledge and Challenges for the Future**

To further examine these mechanistic questions and accelerate cell-based therapies for cardiovascular disease, the National Heart, Lung, and Blood Institute funded the Cardiovascular Cell Therapy Research Network (CCTRN), which includes investigators at 5 institutions across the United States.85 This network, and other ongoing trials, will need to collaborate with bench investigators to define the patient population that benefits from cell therapy (eg, ischemic versus nonischemic dilated cardiomyopathy), the optimal cell population (eg, autologous versus allogeneic versus endothelial progenitor cells, skeletal muscle satellite cells, bone marrow mononuclear cells, CD34+ cells, mesenchymal stem cells, or cardiospheres), mode of delivery (eg, intracoronary, intravenous, or intramyocardial), cell preparation (cultured and possibly reprogrammed versus freshly isolated cells), numbers of cells delivered, site of delivery (eg, infarct-related artery, border region of injured myocardium, distant ventricular delivery, or atrium), mechanisms of action of cell therapy (paracrine effect to limit apoptosis, promote neovascularization, promote myocardial regeneration, or limit fibroproliferative response), and the role of multiple or serial interventions with cell delivery. These studies will further benefit from the design of Food and Drug Administration–approved cell-labeling strategies that will allow for the detection of single cells by use of imaging technologies. Moreover, cell therapy studies performed in combination with patches or scaffolds and ventricular assist devices used as a bridge to heart transplantation will allow histological analyses of the explanted heart at the time of transplantation. These technologies will provide new mechanistic insight regarding the use of cellular therapy for treatment of cardiac failure.

To complement these clinical trials, the National Heart, Lung, and Blood Institute established the NHLBI Progenitor Cell Biology Consortium, which is a collaborative network for the exchange of reagents and acceleration of discoveries related to stem cell and progenitor cell biology.86 One of the goals of this consortium is to gain an understanding of the mechanisms that direct stem and progenitor cells to a cardiac fate. Importantly, this network will provide an infrastructure for the field and will address issues including but not limited to the following:

- The definition of a hierarchy of somatic and progenitor cells that reside in the adult heart.
- The definition of transcriptional networks, epigenetic networks, and microRNA networks that direct stem cells toward a cardiac fate.
- The provision of protocols for stem/progenitor cellular characterization and cardiomyocyte differentiation pathways.
- The establishment of nonviral strategies to reprogram somatic cells to cardiomyocytes or induced pluripotent stem cells.
- The establishment of fate-mapping strategies to define the contribution of selected stem/progenitor cell populations to the cardiac lineage during development and after myocardial injury.
- Comparison of specific cardiac and hematopoietic stem/progenitor cells by fluorescent-activated cell sorter, transcriptional, microRNA, functional, or epigenetic analyses.

Together, these translational and basic science networks of investigators facilitate communication and collaborations. They further provide an infrastructure that supports ongoing and future discoveries that are intended to lead to new therapies for heart disease.

In summary, the field of cardiac regeneration has exploded with interest and opportunities. Although significant advances have energized the field, further studies will be necessary to provide additional mechanisms and insights into the possibility of identifying the key(s) that will promote myocardial repair, whether the strategy relies on the endogenous repair program of the heart or the use of a cell-delivery program. Although neither the endogenous repair program nor the cell therapy programs are ready for prime time, they will serve as a platform that will launch the field forward. Collaboration and exchange of data through professional networks should amplify and accelerate the science to move the field toward effective therapies.

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**Disclosures**

Dr Garry is an Established Investigator of the American Heart Association.
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Tara L. Rasmussen, Ganesh Raveendran, Jianyi Zhang and Daniel J. Garry

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