Till Truth Makes All Things Plain
Human Hearts and Stem Cells

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All humans develop from stem cells. Each of us also has a “rescue” system of stem cells circulating in the blood and residing in our heart (and other organs) that is intended to repair injuries. However, early after birth, the heart’s ability to regenerate itself becomes impaired. Improving our understanding of stem cells and building on the capabilities of this system may ultimately enable researchers to use cell therapy not only to repair injuries locally but also to regenerate the whole heart and other organs. Although preclinical studies provide valuable information, proof of the safety and efficacy of stem cell therapy has and will continue to come from studies in humans with cardiovascular diseases—the best model for this work. Thus, we should perform our human research of stem cell therapies as Shakespeare urged, “till truth makes all things plain” (A Midsummer Night’s Dream, Act V, sc. 1, line 128).

Multiple small-scale clinical studies examining the use of various types of cells for treating patients with cardiovascular diseases have shown that the therapy is safe and may provide clinical benefits. In patients with ischemic heart disease, transendocardial injections of autologous bone marrow–derived mononuclear cells, bone marrow–derived aldehyde dehydrogenase–bright stem cells, adipose tissue–derived mesenchymal cells (PRECISE) have been shown to be safe. Moreover, the results of these studies have revealed that these cell types may improve myocardial function, including perfusion and contractility. In addition, intracoronary infusion of autologous c-kit+ cardiac stem cells in patients with severe coronary artery disease who underwent coronary bypass surgery was shown to be safe and to improve left ventricular (LV) function and reduce infarct scar size (SCIPIO). Similarly, intracoronary infusion of cardiosphere-derived cells (a mixture of resident cardiac stem cells) obtained from endomyocardial biopsy specimens in patients with a recent, large myocardial infarction was shown to be safe and to improve LV function and decrease infarct scar mass (CADUCEUS). Larger clinical studies have also shown the safety and potential efficacy of stem cell therapy in heart disease.

In patients with acute ST-segment–elevation myocardial infarction (REPAIR-AMI), the intracoronary administration of unfractoned autologous bone marrow–derived progenitor cells improved LV ejection fraction, with the greatest gain seen in patients with the most depressed LV ejection fraction values. In a trial from the Cardiovascular Cell Therapy Research Network, transendocardial injections of autologous bone marrow–derived mononuclear cells in patients with ischemic cardiomyopathy resulted in a small but significant increase in LV ejection fraction that improved further in patients with higher percentages of CD34+ and CD133+ cells in their bone marrow samples (FOCUS-CCTRN). The therapeutic potential of CD34+ cells has also been shown in patients with refractory angina; patients treated with intramyocardial injections of autologous CD34+ cells showed a decrease in angina frequency and improvement in exercise tolerance. Although these examples suggest that stem cell therapy may be beneficial for some patients, the measurable effects have generally been modest. Thus, a better understanding of the factors that contribute to the effectiveness of cell therapy is needed.

Clinical studies of stem cell therapy in patients with ischemic cardiomyopathy have revealed several critical limitations and have raised important points. One major limitation is that human stem cells become dysfunctional with age. In addition, the ability of stem cells to replicate themselves is reduced with age, and the absolute numbers of stem cells in the bone marrow and in the circulation are reduced in older adults. Similarly, the number and effectiveness of bone marrow–derived and circulating stem cells are also reduced in patients with severe diseases and risk factors for cardiovascular disease. Therefore, the stem cells in aged individuals and patients with severe diseases may be unable to repair damage to the heart; however, the hearts of these individuals are often the ones in most need of repair. Another potentially important limitation is that the composition (ie, the cellular make-up) and potency of the transplanted cell product may have been different for each patient because of the inherent heterogeneity of products isolated from individual patients. This likely contributes to variations in the outcomes assessed. These are critical issues to consider when designing, implementing, and interpreting the results of any cell therapy trial involving patients with cardiovascular disease.

As we learn the capabilities and limitations of specific stem cell populations through preclinical and clinical research, we can use this information to design more effective cell therapies. As noted above, because the patients in these clinical studies are generally older with multiple comorbidities, the stem cells isolated from them may be less potent. One promising approach that circumvents this issue is the use of allogeneic stem cells. Mesenchymal stem cells, which can be found in multiple tissues, including the bone marrow, adipose tissue, or myocardium, may not be immunologically rejected when used allogeneically; thus, mesenchymal stem cells from
youthful donors may be used to treat aging individuals with cardiovascular diseases.\textsuperscript{16,17} Indeed, transendocardial injections of allogeneic mesenchymal cells obtained from a healthy young donor seemed to be safe in patients with ischemic or nonischemic cardiomyopathy, and treatment with high cell doses improved LV remodeling and reduced rates of heart failure–associated major adverse cardiac events.\textsuperscript{16}

Another approach that could be used to improve cell therapy in older patients with multiple comorbidities is to rejuvenate the patient’s senescent stem cells. For example, the transplantation of mesenchymal stromal cells from aged mice that were induced to overexpress myocardin and telomerase reverse transcriptase resulted in improvements in cell function in a mouse model of hindlimb ischemia.\textsuperscript{18} Likewise, the ex vivo modification of senescent human cardiac progenitor cells with Pim-1 kinase has been shown to increase cellular proliferation and survival.\textsuperscript{19} Furthermore, older mouse hearts were shown to have more quiescent c-kit+ cardiac stem cells than younger hearts, but the stimulation of these cells with stem cell factor effectively reversed age-related cardiomyopathy.\textsuperscript{20}

Studies have also indicated that the efficacy of stem cell treatments may be enhanced by using specific cell combinations. In a porcine model of myocardial infarction, a combination of mesenchymal and c-kit+ stem cells improved LV function and reduced infarct size significantly more than either cell type did alone.\textsuperscript{21} The encouraging results with cardiosphere-derived cells in patients with ischemic cardiomyopathy also suggest that using a combination rather than a single type of stem cell may be more effective.\textsuperscript{4}

In summary, clinical trials assessing the use of select adult stem cells for treating patients with ischemic cardiomyopathy have produced encouraging results, suggesting that these therapies are safe and could potentially improve clinical outcomes. Based on what has been learned, we should continue our efforts to develop more effective stem cell therapies. The studies performed to date have been relatively small with limited follow-up, but the likelihood of detecting significant treatment effects may be improved by conducting larger studies with longer follow-up periods, such as the phase 3 BAMI trial (The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells [BM-MNC] on All Cause Mortality in Acute Myocardial Infarction; ClinicalTrials.gov identifier: NCT01569178), which is expected to enroll 3000 patients and follow them for 3 years. Moreover, because some patient-specific factors have been shown to be associated with improved outcomes after stem cell therapy, it may be beneficial to select more targeted study populations in future studies.

The burden on contemporary medical science is to develop cell therapies that can maximize the benefits of the body’s stem cells and enhance tissue repair by replacing endogenous stem cells or by improving their function or the bioactivity of the local niche. This investigative approach may lead to our ability to regenerate whole organs and possibly even delay the aging process. As with most medical breakthroughs, the development of successful stem cell therapies will be achieved through small, incremental improvements. Clinical trials are a vital part of this process because, ultimately, proof of the safety and efficacy of stem cell therapy for cardiovascular disease can come only from human studies. Each clinical trial can be a valuable learning experience. Insight gained from studies of patient-specific characteristics and cell therapy outcomes may lead to a better understanding of the mechanisms underlying stem cell therapy and to the development of a more personalized approach to cell therapy for heart disease. It is evident that we are on the right path of discovery in this field, and we should, therefore, have the fortitude to continue. As Shakespeare also admonished, let us not “lose the good we oft might win, by fearing to attempt” (Measure for Measure, Act I, sc. 4, lines 435 to 436).

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