Cell-based myocardial repair is a 21st century approach to an intractable problem. Because the adult heart lacks a substantive pool of precursor, stem, or reserve cells, it is incapable of effective cardiomyocyte regeneration after injury or infarction. In fact, after an acute myocardial infarction, the injured myocardium becomes a non-contracting fibrous scar, which alters the workload of the surrounding myocardium. If the infarct is large enough, the remaining myocardium will ultimately deteriorate leading to congestive heart failure. Current treatment options for acute myocardial infarction and subsequent failure include medical management, cardiac transplantation, mechanical circulatory left ventricular assist devices, or other experimental attempts (artificial hearts), all of which suffer from specific limitations. In light of the limited efficacy and comorbidity of these current treatment options, alternative, additional long-term therapeutic strategies are needed. Supplying cells capable of cardiac repair is one potential new therapeutic option.

Cell-based myocardial repair

For the treatment of cardiovascular disease states ranging from heart attack to end-stage heart disease, we are developing a cell transplantation technology, ‘cellular cardiomyoplasty’ (CCM), to regenerate functioning muscle in previously infarcted, scarred or dysfunctional myocardial tissue after transplantation of myogenic cells. To date, many types of cells have been transplanted into injured myocardium, including fetal cardiomyocytes [1], autologous...
skeletal myoblasts [2–4], smooth muscle cells [5], immortalized myoblasts [6], syngeneic skeletal myoblasts [7], fibroblasts [8], adult cardiac-derived cells [9], embryonic stem cells [10], and bone marrow derived stromal [11] and stem cells [12]. Although several of these cell types may hold future promise as a therapeutic option, to date only skeletal myoblasts have been used in a safety trial as a first step toward myocardial repair [13].

**Autologous skeletal myoblasts**

Using skeletal myoblasts to repair injured heart is a straightforward, but not simple, procedure. It requires harvesting skeletal muscle, expanding cells in a laboratory, and re-injecting cells into a patient’s heart. Using self-derived (autologous) skeletal myoblasts, we are able to overcome the major limitations associated with other cell-based treatments. Most notably, we overcome the shortage of donor tissue, the need for immunosuppression, and the ethical dilemma associated with the use of allogeneic or embryonic cells. Using primary cells, rather than immortalized or totipotent stem cells, we decrease the likelihood of tumor formation after cell transplantation [14]. Using myogenic (versus non-myogenic) cells, we can potentially regenerate contractile muscle in previously infarcted heart. Finally, using relatively ischemia-resistant skeletal myoblasts rather than cardiocytes, we can obtain higher levels of cell engraftment and survival in infarcted regions of the heart, where cardiocytes would probably perish [15]. Nonetheless, myoblast CCM is not without potential limitations. For example, using autologous cells necessitates sufficient time between injury and re-injection to grow cells in the laboratory. Yet this waiting period may be in line with nature’s demands in that injecting cells too soon after an infarct seems to limit the number of cells that survive, presumably due to the inflammatory response that occurs after an injury.

There have been numerous reports of successful engraftment of autologous skeletal myoblasts into injured myocardium in multiple animal models of cardiac injury. These studies have shown that autologous skeletal myoblasts can differentiate and develop into striated cells within the damaged myocardium [2].

Four promising effects of skeletal myoblast CCM have been reported to date. The first effect was adequate survival and engraftment of myoblasts in infarcted, necrotic, or toxin-injured heart [2,16,17]. Survival and engraftment of myoblasts after single or multiple injections of varying numbers of myoblasts have also been noted [2,17]. Another effect was improved myocardial functional performance irrespective of the method used to assess function, *in vitro* (dP/dt, force transduction) or *in vivo* (sonomicrometry, echocardiography) [2,7,16,17]. Finally, myocardial performance was augmented in all animal species studied (rat, rabbit, dog, pig, sheep) [2,7,16–18] and more recently in humans [13].

These results suggest that regeneration of functional muscle after myoblast implantation could offer a valuable treatment option for injured and failing heart. Clinical trials based on these data have begun both in Europe and in the United States.

Although the pre-clinical and initial clinical data appear positive, CCM with skeletal myoblasts is not proven. Even though it is the most well-defined technique for myocardial regeneration, many important questions remain – questions that will need to be answered for any CCM technique. Probably the most important questions are those related to cell survival, integration, differentiation, and functional effect. For example, if CCM is to be viewed as a long-term solution to myocardial injury, cells must be able to survive for years in the heart. Yet the long-term fate of myoblasts is unclear. Similarly, it is not yet clear if and how myoblasts electrically integrate into the surrounding myocardium and what impact integration may have on either function or rhythmicity. Finally, there is some debate whether myoblasts improve contraction or just prevent further deterioration of the injured heart. These debates are being resolved with further research, and the future for myoblast transplantation appears promising. The understanding gained about myoblast CCM will provide a basis for developing second and third generation cells for cardiac repair.

**Cardiocytes and stem cells**

Although skeletal myoblasts appear to be the best first generation cell for use in myocardial repair, the intriguing question remaining is: what cell type will ultimately be best for myocardial repair? Cardiocytes might seem the ideal target cell at first glance. Yet several major obstacles remain to the use of these cells *in vivo*. First, for cardiocytes to be used for cell transplantation they must be readily available as a cell source. Given their inability to replicate to a significant degree *in vitro* or *in vivo*, this remains unlikely at present. Second, for cardiocytes to survive in infarcted heart, they will require a vascular supply far greater than that required for myoblast survival and one unlikely to easily be obtained in infarct. Finally, if cardiocytes are ever to contribute to myocardial function, they must align in a manner that allows them to electrically and mechanically couple to the remainder of the myocardium. At present, little or no data exist demonstrating this is possible.

Bone marrow derived stem cells have recently received attention as an ideal target for cardiac repair [11,12,19]. By their very nature, these multipotent stem cells respond to their microenvironment and develop a corresponding phenotype. This would suggest that, in normal myocardium, stem cells could become cardiocytes and integrate with surrounding host tissue. Data from several laboratories suggest this is feasible, although it appears to be a rare event [20]. But the data further suggest, as shown by Wang *et al* [11], that when injected into injured or infarcted heart stem
cells will develop characteristics of scar. Understanding this phenomenon and beginning to control it is an active area of investigation that must be better understood before stem cells per se will be a viable target for myocardial repair.

More recent data suggest that lineage negative (Lin−) c-kitPOS subpopulations of stem cells can be derived and supplied in numbers sufficient to repopulate infarcted regions of myocardium with cardiocytes and vascular structures [12]. Although this is an extremely exciting development, these data have only been obtained in the mouse heart, where the infarct size is exceedingly small. Furthermore, the functional impact of these cells has not been rigorously evaluated. Translating these initial results into larger, more physiologically relevant, models of human cardiac disease is the critical next step in evaluating stem cell contribution to cardiac repair. Taken together, these data illustrate the potential of utilizing a multipotent stem cell for cardiac repair. Unfortunately, although the idea of finding one cell that can repair injured heart is intriguing, our understanding of stem cell biology is not presently sufficient to allow us to do so.

**Challenges to CCM**

Several challenges remain if we are to successfully repair infarcted or failing myocardium with any type of cell. The majority of these challenges seem straightforward, but they are complicated by the extreme heterogeneity of cardiovascular disease. For example, the criteria for reproducible engraftment of large numbers of cells may be very different in the early post-myocardial infarction patient versus the patient with end-stage cardiac dysfunction. Similarly, the method of delivering cells (surgical versus endovascular), the concentration of cells delivered, and a host of other criteria ranging from age to co-existing disease states have to be considered as cell transplantation emerges into clinical trials. Finally, the most significant challenges to cell repair of injured myocardium evolve from our attempts to achieve more than simply halting the progression of cardiovascular deterioration. Pre-clinical data suggest that growth factors, fibroblasts or any number of cells may be able to slow or actually improve diastolic dysfunction [8,21]. Yet, if we wish to improve the contractility of the infarcted heart, we must implant cells that can electrically integrate into the heart and survive for extended periods of time. This may involve more than simply cell engraftment, and may ultimately depend on engineered grafts in which we can guarantee nutrient delivery and blood supply in an infarcted region of tissue, and protect the surrounding myocardium from mechanical remodeling and compensation secondary to these grafts. Although this is not at the forefront of myocardial repair today, it is an area that cannot be ignored.

**Conclusion**

Cell transplantation for myocardial repair has arrived. Carefully evaluating this new modality provides an opportunity to define a new era in the treatment of cardiovascular disease. Combining genomics, tissue engineering, and advanced imaging methods to define the best cell type(s), to understand the mechanism(s) of cell engraftment on function, to promote graft longevity, and to improve electromechanical graft integration is the next pre-clinical frontier. Designing clinical trials that allow us to adequately evaluate the safety and efficacy of cell transplantation in the absence of complicating adjunctive therapies is crucial [22]. Doing it improperly could relegate the field to failure before its potential is realized.

**Competing interests**

I am a consultant, board member and member of the Scientific Advisory Board for Bioheart Inc.

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