Introduction to a Compendium on Regenerative Cardiology

Roberto Bolli, Joshua Hare

The field of regenerative cardiology continues to evolve rapidly, requiring frequent updates. The purpose of this compendium is to provide our readers with the most recent concepts pertaining to the use of cell-based strategies for the treatment of heart disease both at the preclinical and clinical levels. The focus is on adult stem cells because embryonic stem cells (or their derivatives) are unlikely to find clinical application or to offer significant advantages compared with induced pluripotent stem cells and adult stem cells.

It is traditional for compendia published in *Circulation Research* to start with an Overview in which the Guest Editor(s) outlines the scope and significance of each article. In this case, we could not think of a better author to write the Overview than Dr Eugene Braunwald—the father of modern cardiology. His superb article distils the salient concepts and emerging paradigms in the burgeoning field of cell-based therapies and reparative cardiology and places them in the broader context of cardiovascular medicine.

The superb synthesis by Dr Braunwald is followed by a series of Reviews and a Viewpoint that address salient facets of the field, including the basic biology of new myocyte formation and cell-based therapies, paracrine mechanisms, the role of extracellular vesicles, novel techniques, such as genome editing and RNA-based therapies, bioengineering approaches, and finally, clinical trials of cell therapy in patients with cardiovascular disease. Although induced pluripotent stem cells may not find immediate clinical application as a therapy for cardiovascular disease (further work may be required to overcome technical and logistical issues), they offer great promise as a model for investigating inherited arrhythmia syndromes and testing antiarrhythmic strategies, as pointed out by Garg et al.[1] Besides cell-based strategies, the use of noncoding RNAs has emerged as a potential therapeutic approach for various cardiovascular diseases, one that does not involve administration of cells but nevertheless may lead to cardiac regeneration or repair, as discussed by Lucas et al.[2]

The picture that emerges from this compendium is very different from the views that were common only a few years ago. The most important change in the field has been the recognition that stem/progenitor cells, regardless of whether they are adult or embryonic and of the specific type, do not exhibit significant long-term engraftment in the heart and therefore act via paracrine mechanisms.[3] The paracrine factors are complex, comprising not only peptides and growth factors but also extracellular vesicles and organelles transmitted both through secretory mechanisms and hetero-cellular coupling. Other emerging ideas include the fact that cell therapy may work primarily by modifying the extracellular matrix (eg, by reducing collagen deposition) and modulating inflammation rather than by stimulating formation of new cardiac myocytes. Regardless of the mechanism of action, however, there is little doubt that cell therapy is effective in preclinical models of heart disease. Numerous studies from many laboratories have documented the ability of various types of adult progenitor/stem cells to improve left ventricular function and remodeling in a variety of animal models of ischemic cardiomyopathy, including mice, rats, and pigs.[4,5] In the clinical arena, much progress has been made in recent years: overwhelming evidence indicates that $CD34^+$ cell therapy is effective in patients with refractory angina,[6–8] and small- and medium-size clinical trials of cell therapy have produced encouraging results in the setting of chronic heart failure, which seems to be a promising target for the development of cell-based therapies.[3,9–12] Clinical data are less encouraging in the setting of acute myocardial infarction.[3,11,12] Importantly, all clinical trials have shown that administration of adult stem/progenitor cells in patients with heart disease is safe.[3] On the horizon are novel approaches, such as intravenous delivery, repetitive treatments, extracellular vesicle–based acellular therapies, cardiac patches, genome editing, and RNA-based therapies, which have the potential to revolutionize the field of regenerative cardiology.

An oft-heard criticism is that cell therapy has not yet been definitely demonstrated to be effective in the treatment of heart disease. It is important to keep a historical perspective on this point. The field of cell therapy is still young (<20 years old) and has moved forward rapidly, from small, nonrandomized cohort studies in the early 2000s to large, phase 3 clinical trials. The history of medicine teaches that major advances require time—often 2 or 3 decades. Demonstrating that a novel therapy is beneficial takes many years. Clinical research typically starts with small (phase 1 or 2) trials, which are often underpowered, inconclusive, and contradictory. The issue is then resolved with larger, well-designed trials. Considering that the precise mechanism(s) of action of cell-based therapies remains unclear and that many important aspects have not yet been defined (eg, the

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optimal cell type, the optimal cell dose, the optimal route of delivery, the optimal number of treatments, etc), it is actually remarkable that the results obtained heretofore in patients with refractory angina[6–8] and heart failure[3,9–12] are encouraging, that is, that a signal for efficacy has emerged at all. The development of cell therapy is a work in progress. We are still learning how to maximize its benefits. In the end, only rigorous, properly designed, and adequately powered clinical trials will answer the question as to whether cell therapy is effective in patients with heart disease. Although the mechanism of action is unclear, cell therapy is safe,[3] and the results in refractory angina[6–8] and heart failure[3,9–12] are encouraging, as mentioned above. Therefore, while the mechanism of action is investigated at a basic level, it is important that clinical studies of cell therapy continue.[3] It would be inappropriate to withhold clinical testing of a safe and promising therapy just because we have not yet figured out how exactly it works.

As is often the case for major, disruptive advances, the progress of cell therapy has encountered many obstacles. A major one has been the bias, hostility, and nihilism of certain segments of the academic community and lay press, which have declared cell therapy to be "futile" even before conclusive clinical data are obtained and despite encouraging results in the settings of refractory angina[6–8] and chronic heart failure[3,9–12] (including randomized clinical trials that have met their primary end points, such ixCELL-DCM[9] and the CD34+ cell trials[6]). Another problem has been the proliferation of unregulated stem cell clinics that offer expensive cell-based treatments to patients using misleading, at times fraudulent, claims not based on solid clinical trial evidence. Much damage has been caused by these 2 factors. Nevertheless, despite negative bias, hostility, and nihilism, on the one hand, and unfounded or outright fraudulent claims, on the other, the broad community of investigators dedicated to the development of cell-based therapies has continued its work toward developing safe treatments with proven clinical benefits. The field has moved gradually from small observational, nonrandomized studies to medium-size phase 2 trials and now, phase 3 studies. Because of the 21st Century Cures Act and the new Food and Drug Administration Regenerative Medicine Advanced Therapy designation, it is possible that cell therapy for heart disease could be approved in the United States on the near term horizon.

Although the efficacy of cell therapy in patients remains to be definitely demonstrated, the results obtained to date are encouraging and warrant serious investigation with rigorous, well-designed phase 3 clinical trials.[3] Only these trials will definitely answer the question as to whether cell therapy has a place in the treatment of cardiovascular disease. It is important that these studies be conducted. The answer to the current uncertainty and to the apparently conflicting results of small, inconclusive, often nonrigorous clinical trials is not to stop clinical investigation; the way forward is to conduct large, rigorous trials that test the efficacy of cell-based therapies conclusively. The current situation in cell therapy is reminiscent of that in thrombolysis for acute myocardial infarction in the late 1970s and early 1980s. The first trial of streptokinase was published in 1959. Two decades later, many studies had been published with conflicting results, so that the benefits of thrombolysis were unclear. It was not until 1986 that thrombolysis was definitively shown to be beneficial in the GISSI trial. It took 27 years to demonstrate the efficacy of a treatment which is now a cornerstone in the management of acute myocardial infarction. The confusion of the late 1970s and early 1980s was not overcome by halting clinical research but by conducting a well-designed and conclusive clinical trial. The history of thrombolytic therapy for acute infarction (and of many other therapies as well) teaches a valuable lesson: patience, rigor, and reliance on objective evidence (rather than personal prejudice) are the key to move medicine forward.

Although it is not possible to cover every single aspect of a field as large and complex as regenerative cardiology, we hope that this compendium will help the readers to keep abreast of recent developments and future directions in this fascinating journey to make cardiac repair a reality.

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