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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Translating Stem Cell Research to Cardiac Disease Therapies

Pitfalls and Prospects for Improvement

Three sections with opinions separately and independently expressed by:
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ABSTRACT

Over the past 2 decades, there have been numerous stem cell studies focused on cardiac diseases, ranging from proof-of-concept to phase 2 trials. This series of papers focuses on the legacy of these studies and the outlook for future treatment of cardiac diseases with stem cell therapies. The first section by Drs. Rosen and Myerburg is an independent review that analyzes the basic science and translational strategies supporting the rapid advance of stem cell technology to the clinic, the philosophies behind them, trial designs, and means for going forward that may impact favorably on progress. The second and third sections were collected as responses to the initial section of this review. The commentary by Drs. Francis and Cole discusses the review by Drs. Rosen and Myerburg and details how trial outcomes can be affected by noise, poor trial design (particularly the absence of blinding), and normal human tendencies toward optimism and denial. The final, independent paper by Dr. Marbán takes a different perspective concerning the potential for positive impact of stem cell research applied to heart disease and future prospects for its clinical application. *(Compiled by the JACC editors)* (J Am Coll Cardiol 2014;64:922–37) © 2014 by the American College of Cardiology Foundation.

TRANSLATING STEM CELL RESEARCH TO THE TREATMENT OF CARDIAC DISEASE

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Over the past 5 decades, cardiovascular medicine has advanced through the melding of diverse scientific and technical concepts. Strategies for prediction, prevention, intervention, molecular genetics, and regeneration have been tested for clinical relevance and applicability by various risk profiling and clinical trial techniques. One of the more recent of these strategic concepts is regenerative therapy, which targets repair or replacement of lost or dysfunctional

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substrates. Regenerative strategies have moved rapidly to clinical application for subsets of patients, including those with heart disease, and during the past 2 decades, thousands of patients have been administered various types of stem cells in clinical cardiac disease studies ranging from proof-of-concept to phase 2 trials. These clinical cardiac applications have focused in part on patients for whom preventive and conventional intervention strategies failed to avert cellular depopulation, leading to intractable clinical consequences. However, a far broader population has received stem cells, including patients for whom traditional therapies have proven effective (1), and outcomes have been conflicting.

This paper is not intended as a thorough literature review of the field. Rather, we are analyzing the basic science and translational strategies supporting the rapid advance of stem cell technology to the clinic, the philosophies behind the strategies, the positive and negative aspects of trial designs reported, and the means for going forward that may impact favorably on progress. The analysis is provided in the context of the complex scientific, clinical, ethical, and fiscal considerations that are affected by this evolving field of interest.

THE PAST AS PROLOGUE…CARDIOVASCULAR MORBIDITY AND MORTALITY. It is useful to consider the emergence of stem cell therapy against the background of the evolution of cardiovascular disease outcomes in the past one-half century. Between the mid-20th century and the turn of the millennium, a major reduction in cardiovascular mortality (attributable to advances predating stem cell therapy) occurred in the United States and elsewhere. For example, the National Heart, Lung and Blood Institute reported a 49% reduction in age-adjusted mortality from coronary heart disease between 1950 and 1998 (2). As a mortality rate adjusted for age, this reflects prolongation of life expectancy and not necessarily an equivalent absolute reduction in total population mortality. One major contributing factor was the dramatic transition from a 30% acute myocardial infarction (AMI) death rate prior to coronary care units, to <10% with interventional therapies in the later 1990s (3), and even lower currently (4).

The reduction in AMI deaths led to a survivor cohort at risk for and characterized by the emergence of an increasing population burden of chronic heart failure. Development and refinement of various heart failure prevention and treatment strategies (none of which depend on stem cell therapy) are reflected in American Heart Association statistics revealing continued improvements in patient survival. An example is the 33% fall in death rates from heart failure and stroke between 1999 and 2009 (5). This does not argue against the potential added value of stem cell therapy for improving survival and quality of life. But, it does demand that we provide solid scientific underpinnings for incremental outcomes being suggested to the public.

DIVERGENT OPINIONS REGARDING PRESENT AND FUTURE DIRECTIONS. These advances, along with the remaining challenges and dichotomies that sometimes exist between basic and clinical research, have led to divergent viewpoints regarding advancement of cardiovascular stem cell therapies into the clinic. Such viewpoints expressed by leaders in the field were published 10 years ago (6) and are paraphrased here:

1. *"We do not…know what cell to use in any given situation…until we do, we shouldn't go forward clinically;"*
2. *"The science of clinical stem cell trials isn't sufficiently mature to warrant large-scale clinical studies;"*
3. *"The stem cell literature is too internally contradictory to provide a clear vision for going forward;"*
4. *"Patients who are dying and are desperate to live should be availed of experimental stem cell therapies;"* and
5. *"The field is sufficiently mature that within 3-5 years, stem cells will have favorably altered the clinical course of major cardiovascular disease"* (6).

We shall now revisit these viewpoints in the context of the clinical translation that has occurred during the decade since they appeared and discuss models and approaches for consideration as we move into the next decade.

"WE DO NOT KNOW WHAT CELL TO USE…" (6). There is substantial literature regarding stem cells (7–10), and a number of stem cell types described in this literature have been administered to patients. Stem cells may be pluripotent (i.e., capable of differentiating into literally any cell type in the body) or multipotent (i.e., in lineages downstream of pluripotency and destined to differentiate into more circumscribed mature cell populations). Pluripotent cells include human embryonic stem cells and induced pluripotent stem cells (7); the latter are derived from adult cells using oncogenic or nononcogenic transcription factors (11–15). Both cell types have been reprogrammed into mature lineages, including cardiac myocytes. Although both pluripotent cell types are

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

BMMC = bone marrow–derived mononuclear cell

CDC = cardiosphere-derived cell

EF = ejection fraction

LVEF = left ventricular ejection fraction

MI = myocardial infarction

MSC = mesenchymal stem cell