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REGENERATIVE MEDICINE IN CARDIOVASCULAR DISEASE: INTRODUCTION

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Although the number of deaths from cardiovascular diseases (CVDs) has steadily decreased over the last 40 years, the morbidity associated with nonfatal CVD, consequent disability, and decreased quality of life is still a huge burden on society and the leading cause of medical expenses in most developed countries. In the United States, CVD remains the number-one killer, accounting for 34% of all deaths per annum, innumerable resources, and healthcare expenditures that approach \$300 billion annually. Each year, CVD kills more people than cancer, HIV, diabetes, and trauma combined. Coronary artery disease (CAD) is accelerated by hypertension, diabetes mellitus, dyslipidemia and tobacco use; superimposed upon a genetic substrate, CAD may result in myocardial infarction (MI) and heart failure. Since the heart has limited regenerative capacity, damaged tissues are largely replaced by a collagen scar exhibiting biophysical properties that are significantly different from the original tissue. Depending on the extent of the damaged area, the presence of scar tissue may significantly impair the function of the heart and may induce life-threatening arrhythmias and aneurysms. There is clearly a need to improve the current methods for preventing CVD, limiting ischemic injury, and regenerating tissue that has been irreversibly damaged.

The treatment of postinfarction heart failure remains an elusive goal in medicine. One novel evolving therapeutic strategy for advanced ischemic heart disease is regenerative surgery, the transplantation of immature progenitor cells and microdevices into the damaged heart with the expectation that these will produce new blood vessels and cardiac muscle cells. The past decade has witnessed a surge of scientific enthusiasm for regenerative surgery that has resulted in multiple clinical trials to treat the failing human heart. Broadly speaking, cardiovascular regeneration encompasses the restoration of all circulatory functions of the damaged tissue. These include generation and coordinated conduction of electrical impulses from the pacemakers of the heart; efficient electromechanical coupling; generation of cardiac output; proper structure-function of the cardiac valves; distribution of blood flow; control of vascular resistance in response to hemodynamic, humoral, and local tissue factors; regulation of immune response and the trafficking of circulating cells; tissue trophic effects of paracrine factors elaborated by the vasculature; modulation of blood fluidity and hemostasis; permeation of nutrients and macromolecules through the systemic microvasculature; regulation of blood gases in the pulmonary circulation; and recirculation of plasma transudate by the lymphatics. As such, cardiovascular regeneration requires the coordinate efforts of scientists and clinicians with different expertise—from cell biology, engineering, and material science to mathematical modeling, cardiology, and vascular surgery.

This special issue of the *Methodist DeBakey Cardiovascular Journal* is divided into two sections: the first section reviews the current application of stem cell therapies in clinical trials, while the second section presents new interdisciplinary developments in stem cell biology, tissue engineering, molecular imaging, and computational modeling for improving the efficacy of cell-based therapies. The first contribution by Dr. Michler, at the Montefiore Medical Center of the Albert Einstein College of Medicine in New York, introduces the notion of heart regeneration via stem cell therapy and presents a detailed description of the different types of stem cells used and their effectiveness in clinical trials. In the following contribution, Drs. Sanchez, Torre-Amione, and colleagues at the Cátedra de Cardiología y Medicina Vascular of the Tecnológico de Monterrey in México and the Houston Methodist DeBakey Heart & Vascular Center review the safety of regenerative cell therapy for different cardiovascular diseases, including acute myocardial infarction, chronic ischemic myocardial dysfunction, and nonischemic dilated cardiomyopathy. The case of peripheral artery disease and its treatment with adult stem cells is described by Drs. Botham, Cooke, and colleagues at Stanford University and the Houston Methodist Research Institute, commenting on the basic mechanisms underlying the regenerative process as well as currently ongoing clinical trials. The first section of this special issue concludes with a brief update by Drs. Bruckner and Reardon on the cardiac stem cell initiative at the Houston Methodist DeBakey Heart & Vascular Center.

The new frontiers in cardiovascular regeneration are presented in the second section of this special issue, starting with two contributions by Drs. Wong, Sayed, Cooke, and collaborators addressing the challenges and clinical potential with the use of induced pluripotent stem cells for personalized therapies. Drs. Urciuolo, Netti, and associates, at the Center for Advanced Biomaterials for HealthCare of the Italian Institute of Technology in Naples, explore the use of different techniques for the ex vivo biofabrication of connective tissues and how these techniques can be translated into clinical use. Drs. Lezaic, Vrtovec, and their collaborators at the University Medical Centre of Ljubljana in Slovenia and at Stanford University describe the clinical promise of molecular imaging, mostly nuclear and magnetic resonance imaging, for monitoring stem cell homing and survival. Finally, in the closing contribution, Dr. Decuzzi from the Houston Methodist Research Institute elaborates on how the molecular imaging of stem cells and the computational modeling of cell transport within the vasculature and damaged tissue can help in optimizing stem cell-based therapies.

This special issue is intended to provide readers with a broad overview of the current clinical and preclinical research in cardiovascular regeneration via cell therapy and implantable microdevices. Readers can find additional detailed information in the original scientific works developed by this issue's contributors as well as in the cited references.

Paolo Decuzzi dedicates this special issue of the Methodist DeBakey Cardiovascular Journal to the staff and physicians of the Chest Pain Unit and Emergency Cardiology Department of the University Hospital of Bari in Italy for providing excellent care in a warm and friendly environment, under the guidance of Dr. Gianfranco Antonelli.