Introduction to *JCPT* Focused Issue on "Stem Cells and Cardiac Regenerative Medicine"

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*J CARDIOVASC PHARMACOL THER* 2014 19: 329
DOI: 10.1177/1074248414535342

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>> Version of Record - Jun 17, 2014

What is This?
Introduction to JCPT Focused Issue on “Stem Cells and Cardiac Regenerative Medicine”

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Cardiovascular diseases remain the leading cause of death in the developed world, so there has been intense recent interest in novel cell- and tissue engineering-based therapies for the cardiovascular system. Because the heart in particular has very limited endogenous capacity for repair, this organ is an especially attractive target for such approaches. Hence, in this special focused issue of the Journal of Cardiovascular Pharmacology and Therapeutics, we feature contributions by a number of thought leaders in this emerging field of cardiac regenerative medicine.

Many of these contributions emphasize pluripotent stem cell-based approaches, so it is appropriate that the first article by Yibing Qyang and colleagues introduces induced pluripotent stem cell (iPSC) technology. iPSCs are stem cells with a pluripotent phenotype akin to embryonic stem cells (ESCs), but they are generated by the reprogramming of somatic cell types, avoiding many of the ethical and political controversies that have surrounded ESCs. Qyang and his coauthors review the derivation of iPSCs, methods to guide their differentiation into the cardiovascular lineages, as well as their prospects for application in cardiac repair and in vitro disease modeling. Many of these themes are expanded on in the next article by Sean Wu and colleagues. The latter authors review cellular reprogramming as a general strategy in cardiac regenerative medicine, including the direct reprogramming of somatic cell types (eg, dermal fibroblasts) into cardiomyocytes, thereby bypassing the pluripotent state. The discovery of the latter phenomenon has sparked considerable attention in the field, but Wu and coauthors identify a number of important challenges to this approach including the inefficiency of direct reprogramming and the incomplete phenotype of the cardiomyocytes produced.

There have now been many hundreds of studies reported that examine the direct injection of candidate cell types into animal models of myocardial infarction. Klener and colleagues provide a comprehensive review of this preclinical experience to date, with a particular emphasis on comparing functional outcomes following the transplantation of cells versus noncellular biomaterials. They also discuss the pros and cons of various cell- and biomaterial-based therapies, as well as their potential mechanisms of action.

The next 2 research articles tackle 2 specific translational issues related to cell transplantation. First, because it is known that the vast majority of implanted cells are lost shortly following injection, there has been an urgent need for improved imaging modalities to noninvasively track graft cell survival and proliferation in the infarcted heart. Toward that end, Anna Naumova and colleagues use magnetic resonance imaging (MRI) to track graft cells with 2 different paramagnetic labels: exogenous iron oxide nanoparticles and genetic overexpression of ferritin. They report that although nanoparticle-labeled cells do have somewhat greater signal intensity, only ferritin tagging was able to distinguish live graft cells from dead, making it a better tool for assessing graft cell viability by MRI. In the next article, my group examined the electrical integration and arrhythmogenic potential of human ESC-derived cardiomyocytes following transplantation in a guinea pig chronic infarct model. Among other findings, we show that the extent of host–graft electrical coupling in this model is significantly lower than we had previously measured following the transplantation of comparable cells in an acute infarct model.

The final 2 articles feature tissue engineering-based approaches. First, Milica Radisic and coauthors note that, for cardiac cell grafts or engineered heart “patches” to thrive, they must develop a vascular supply sufficient for the high metabolic demands of myocardium. They describe diverse approaches to enhancing graft vascularization, ranging from delivery of proangiogenic genes or growth factors to the implantation of prevascularized engineered tissue constructs. Finally, in a forward-looking contribution, Narine Sarvazyan proposes an application for engineered cardiac tissue outside the heart. She outlines a novel therapy for chronic deep venous insufficiency in which cuffs of engineered cardiac tissue, which typically show peristaltic-type contraction in vitro, are implanted around vein segments with incompetent valves.

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