Cardiac stem cell therapy closer to reality

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Tampa, Fla. (December 27, 2007) – Since the year 2000, much has been learned about the potential for using transplanted cells in therapeutic efforts to treat varieties of cardiac disorders. With many questions remaining, the current issue of CELL TRANSPLANTATION (Vol.16 No. 9), The Proceedings of the Third Annual Conference on Cell Therapy for Cardiovascular Disease, presents research aimed at answering some of them. Eleven papers were included in this issue; the four below represent a sample.

Bench to Bedside

"Cardiac stem cell therapy involves delivering a variety of cells into hearts following myocardial infarction or chronic cardiomyopathy," says Amit N. Patel, MD, MS, director of cardiac cell therapy at the University of Pittsburgh Medical Center and lead author of an overview and introductory article, Cardiac Stem Cell Therapy from Bench to Bedside. "Many questions remain, such as what types of cells may be most efficacious. Questions about dose, delivery method, and how to follow transplanted cells once they are in the body and questions about safety issues need answers. The following studies, contribute to the growing body of data that will move cell transplantation for heart patients closer to reality."

According to Patel, special editor for this issue, suitable sources of cells for cardiac transplant will depend on the types of diseases to be treated. For acute myocardial infarction, a cell that reduces myocardial necrosis and augments vascular blood flow will be desirable. For heart failure, cells that replace or promote myogenesis, reverse apoptopic mechanisms and reactivate dormant cell processes will be useful.

"Very little data is available to guide cell dosing in clinical studies," says Patel. "Pre-clinical data suggests that there is a dose-dependent improvement in function."

Patel notes that the availability of autologous (patient self-donated) cells may fall short.

Determining optimal delivery methods raise issues not only of dose, but also of timing. Also, assessing the fate of injected cells is "critical to understanding mechanisms of action."

Will cells home to the site of injury" Labeling stem cells with durable markers will be necessary and new tracking markers may need to be developed.

Improved cell survival drugs

Adult bone marrow-derived mensenchymal stem cells (MSCs) have shown great signaling and regenerative properties when delivered to heart tissues following a myocardial infarction (MI). However, the poor survival of grafted cells has been a concern of researchers. Given the poor vascular supply after a heart attack and an active inflammatory process, grafted cells survive with difficulty. Transmyocardial revasularization (TMR), a process by which channels are created in heart tissues by laser or other means, can enhance oxygenated blood supply.

"We hypothesized that using TMR as a scar pretreatment to cell therapy might improve the microenvironment to enhance cell retention and long-term graft success," said Amit N. Patel, lead author of a study titled Improved Cell Survival in Infarcted Myocardium Using a Novel Combination Transmyocardial Laser and Cell Delivery System. "TMR may act synergistically with signaling factors to have a more potent effect on myocardial remodeling."

Patel and colleagues, who used a novel delivery system to disperse cells in the TMR-generated channels in an animal model, report significant cell survival in the TMR+Cell group versus Cells or TMR alone. The researchers speculated that there was an increase in local production of growth

factors that may have improved the survival of transplanted cells.

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Stem cells depolarize

Recent studies have suggested that there are stem cells in the heart. In this study, researchers engineered mesenchymal stem cells (MSC) to over express stromal cell-derived factor-1 (SDF-1), a chemokine.

"Our study suggests that the prolongation of SDF-1 expression at the time of an acute myocardial infarction (AMI) leads to the recruitment of what may be an endogenous stem cell in the heart," says Marc Penn, MD, PhD, director of the Skirball Laboratory for Cardiovascular Cellular Therapeutics at the Cleveland Clinic Foundation. "These cells may contribute to increased contractile function even in their immature stage."

In the study titled SDF-1 Recruits Cardiac Stem Cell Like Cells that Depolarize in Vivo, researchers concluded that there is a natural but inefficient stem cell-based repair process following an AMI that can be manipulated through the expression of key molecular pathways. The outcome of this inefficient repair can have a significant impact on the electrical and mechanical functions of the surviving myocardium.

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Grafting bioartifical myocardium for myocardial assistance

While the object of cell transplantation is to improve ventricular function, cardiac cell transplantation has had limited success because of poor graft viability and low cell retention. In a study carried out by a team of researchers from the Department of Cardiovascular Surgery, Pompidou Hospital, a matrix seeded with bone marrow cells (BMC) was grafted onto the infarcted ventricle to help support and regenerate post-ischemic lesions.

"Our study demonstrated that bone marrow cell therapy associated with the surgical implantation onto the epicardium of a cell-seeded collagen type 1 matrix prevented myocardial wall thinning, limited post-ischemic remodeling and improved diastolic function," says Juan Chachques, MD, PhD, lead author for Myocardial Assistance by Grafting a New Bioartificial Upgraded Myocardium (MAGNUM Clinical Trial): One year follow-up.

"The use of the biomaterial appears to create a micro atmosphere where both exogenous and endogenous cells find an optimal microenvironment to repair tissues and maintain low scar production," explains Chachques.

According to Chachques, the favorable effects may be attributed to several mechanisms. The BMC seeded in the collagen matrix may be incorporated into the myocardium through epicardial channels created at the injection sites. Too, the cell-seeded matrix may help prevent apoptosis.

"This biological approach is attractive because of its potential for aiding myocardial regeneration with a variety of cell types," concluded Chachques.

Those cell types include skeletal myoblasts, bone marrow-derived mensenchymal stem cells, circulating blood-derived progenitor cells, endothelial and mesothelial cells, adipose tissue stem cells and, potentially, embryonic stem cells.

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"Cardiac stem cell repair is one of the most important new areas of research today," says Cell Transplantation editor Paul Sanberg, PhD, DSc. "This special issue illustrates important new findings and the significant efforts being taken to develop these therapies and move them from the scientist's bench to the bedside where in clinical practice they can make a difference in the lives of patients."

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