Cardiovascular disease is the most significant public health problem in the industrialized and developing world. Current pharmacologic therapies have been focused on improvement of myocardial reperfusion and protection of heart tissue after acute and chronic myocardial ischemic damage. These therapies, while beneficial in managing the disease, do not effectively treat its progression.

Stem cell therapies have the potential to treat the acute and long-term progression of the disease. Recent experimental animal studies and clinical trials suggest that the transfer of stem and progenitor cells into the myocardium has a favorable impact on tissue perfusion and contractile performance. After administration of stem cells, neovascularization and myocyte formation have been noted. The underlying mechanism may be differentiation of administered stem cells, cell fusion, and/or the release of paracrine signals by injected stem cells. Recently, the mobilization of endogenous cardiac stem cells has been debated as a potential target of cardiac repair.

Embryonic stem cells (ESC) are derived from blastocysts, and adult stem cells are derived from various tissues. ESCs are pluripotent and are able to replicate indefinitely. Adult stem cells are undifferentiated cells that are found throughout the body and exist to replenish dying cells and regenerate damaged tissues. Adult or somatic stem cells include the following categories:

- mesenchymal stem/stromal cells (MSCs)
- hematopoietic stem/progenitor cells (HSCs)
- tissue-specific progenitor cells (TPSCs)
- induced pluripotent stem cells (iPSCs).

Adult stem cells are collected from either the patient to be treated (autologous source) or from a donor (allogeneic source).

In the treatment of myocardial infarct and heart failure, multiple stem cell therapies are being developed. One of the earliest potential therapies was administration of unfractionated bone marrow cells (BMCs), which contain different stem and progenitor cell populations. Other therapies involve administration of an isolated population of cells. This includes endothelial progenitor cells, CD133+ cells, mesenchymal stem cells, skeletal myoblasts, resident cardiac stem cells, and embryonic stem cells.

ESC are defined by their cell surface expression of the hematopoietic marker proteins CD133 and CD34 and the endothelial marker vascular endothelial growth factor receptor-2. In CD133+ cells, cell surface antigen CD133 is expressed on early HSCs and endothelial progenitor cells (EPCs), both of which collaborate to promote vascularization of ischemic tissues. MSCs represent a rare population of CD34- and CD133- cells present in bone marrow stroma. Skeletal myoblasts, or satellite cells, are progenitor cells that normally lie in a quiescent state under the basal membrane of mature muscular fibers. The presence of resident cardiac stem cell (CSC) population(s) capable of differentiating into cardiomyocyte or vascular lineages suggests that these cells could be used for cardiac tissue repair. Embryonic stem cells are totipotent stem cells derived from the inner cell mass of blastocysts.

In the development of a stem cell therapy for cardiovascular disease, several issues must be considered. The source, type, and methods used for culturing and/or modifying the cells will dictate the requirements for pre-clinical safety and efficacy testing. For both autologous and allogeneic-derived human stem cells, the most common species for evaluation of safety and efficacy in a cardiac ischemia model are the immune compromised rat and swine. The use of these animal disease models is instrumental in identifying and characterizing potential therapeutic effects of the cell therapy.

The Rat Model
The immune compromised rat is typically chosen for assessment of safety, engraftment, biodistribution, and efficacy of human-derived products to reduce the risk of an immune response to the cells. Cells can be injected into either healthy non-infarcted animals or animals that have undergone a myocardial ischemia reperfusion procedure. The myocardial infarct is induced by direct occlusion of the left coronary artery for a period of time, followed by reperfusion of the artery. Cell therapy administration is dictated by the proposed clinical application. The cells may be injected at the time of reperfusion or within four or five days for treatment of acute myocardial infarct.

If the proposed clinical application is treatment of heart failure, cells may be injected four to six weeks after the infarct. The most common routes of administration of the cells in the nude rat for treatment of myocardial infarct or heart failure is direct injection into the infarct and peri-infarct regions or intravenous infusion. The immune compromised rat provides a good model for assessment of the safety, engraftment, and biodistribution of the cell therapy, but it provides limited information on the efficacy of the therapy.

The Swine Model
Swine is the species of choice for evaluation of the safety and efficacy of cell therapies. The swine heart is similar to the human heart in the limited collateral circulation of the coronary vessels, the tissue response to a myocardial ischemic event, and the size of the heart. After the myocardial infarct (MI), the heart of the pig also remodels in a manner similar to the human. Recently the US FDA has been requiring cell therapies to be evaluated in the ischemic heart of the pig to evaluate both safety and efficacy.

Acute Myocardial Ischemia
An acute myocardial ischemia/reperfusion injury can be induced using multiple methodologies, but all involve occlusion of a coronary vessel (either the left anterior descending or left circumflex artery) for a specific period of time. The most common methods of occlusion of the coronary vessel are inflation of a balloon in the coronary vessel during an interventional procedure or direct “tie-off” of the vessel through a thoracotomy. At the end of the occlusion period, the balloon is deflated and removed or the tie is removed from around the vessel. Cell therapy administration is dictated by the proposed clinical application. The cells may be injected at the time of reperfusion or within four or five days for treatment of acute myocardial infarct.
Heart Failure
Heart failure can be induced using multiple methodologies, but all involve injuring the heart by changing perfusion to the muscle. The most common methods of inducing heart failure are causing an ischemia/reperfusion injury, as previously described; permanent occlusion of a coronary vessel; or infusions of microspheres that embed in the microcirculation of the heart thereby reducing blood flow. If the proposed clinical application is treatment of heart failure, cells may be injected three to six weeks after the infarct.

Cell Therapy Administration
Administration of cell therapy is also dictated by the planned clinical application. Multiple methods may be used for administration. These methods include intracoronary artery infusion, intravenous infusion, transendocardial injection, transepicardial injection, and transcoronary vein injection.

Key Study Endpoints
The study should include multiple endpoints for the evaluation of safety and efficacy. It should also include:

- An evaluation of the electrocardiogram (ECG) at the time of cell injection
- Cardiac enzyme biomarkers (Troponin I and Creatine Kinase [CK-MB]) during the first 24 hours post cell injection
- Echocardiographic evaluation of heart function and/or left ventricular hemodynamic function (PV loops)
- Clinical pathology
- Immunologic response to the cell therapy (as applicable)
- Localized tissue response to the cells at the site of injection
- Systemic tissue response.

The use of the rat and swine ischemia/reperfusion and heart failure models sheds light on the cellular and molecular mechanisms responsible for cellular therapeutic effects. Preclinical studies in these models have begun to validate the use of cell therapies as a treatment option for MI.

Contact Mark Johnson, (mark.johnson@mpiresearch.com) to further discuss your cardiovascular regenerative cell therapy research needs.

References