

Cardiac Stem Cell Therapy: An Overview

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Abstract:

Keywords:

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Cardiovascular diseases are the major causes of mortality and morbidity throughout the world. Treatment of these diseases is often incomplete, suboptimal and far from permanent cure. One of the reasons behind this is the nature of heart as a terminally differentiated organ. Preclinical and clinical research in the last few decades has put a challenge to this conventional belief regarding the inability of regeneration of the cardiomyocytes. Embryonic, foetal and a wide range of adult stem cells have been used so far. Differentiation of adult somatic cells has led to breakthrough discovery of induced pluripotent stem cells which may be a potential solution of controversy over embryonic stem cell issue. Stem cells specially those of bone marrow origin are already being used in a limited scale to treat acute myocardial infarction, chronic myocardial ischaemia and cardiomyopathy with efficacy, feasibility and safety. Mesenchymal stem cells and adult cardiac stem cells are on the way to bedside use. skeletal myoblasts have been associated with life-threatening ventricular arrhythmia. Stem cells combined with tissue engineering have produced prosthetic tissue valves, and hope for manufacturing whole heart ex vivo in near future. However, like other rapidly evolving modalities, there are more questions than answers. Exact indications, patient selection, cell selection, timing of therapy, efficacy of repeated therapies, co-administration of growth factors, and genetic modification of stem cells are yet to be determined with precision. International community is coming forward with enthusiasm and vigor to explore the enormous potential of stem cell therapy and regenerative medicine. Future research will hopefully facilitate more versatile application of stem cells in treating the life-threatening and disabling ailments of mankind.

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Introduction:

Cardiovascular diseases are the major causes of mortality and morbidity throughout the world. The majority of them, including myocardial infarction and ischemia is associated with the irreversible loss of cardiomyocytes and vasculature. The native capacity for renewal and repair of the cardiomyocyte is incomplete. Also the available therapeutic measures to prevent left ventricular remodeling are inadequate, and the transplantation of heart as a therapeutic strategy for end-stage heart diseases is seriously jeopardized/constraint by the limited supply of donated heart. Recent developments in stem cell biology have indicated a remarkable differentiation of adult stem cells in many tissues in the body. Stem cell transplantation, to directly repopulate the injured myocardium represents a fascinating approach. In contrast to traditional pharmaceuticals, stem cell products contain viable cells as the active ingredient. Meanwhile worldwide, over 3,000

patients with ischemic heart disease have received stem cell therapy in a clinical trial setting. In favour of stem cell therapeutics there is evidence of significant human health benefit with improved quality of life and patient care.¹ However, significant problems remain especially ethical issues and the tumorigenic and arrhythmogenic potential.²

Basics of Stem Cells

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Stem cells have two

important characteristics. First, they are unspecialized cells capable of renewing themselves through **cell division**. Second, they can be induced to become tissue- or organ-specific cells by means of **differentiation**.

Stem cells are of three types: **embryonic stem cells (ESCs)**, **“somatic” or “adult” stem cells** and **induced pluripotent stem cells (iPSCs)**.

Embryonic stem cells are derived from embryos that develop in an ***in vitro* fertilization** clinic, and then donated for research purposes with informed consent of the donors. These cells can proliferate indefinitely, maintain an undifferentiated pluripotent state and differentiate into any cell type. If allowed to clump together, they form **embryoid bodies**. To generate cultures of specific types of differentiated cells, the differentiation of embryonic stem cells is controlled by changing the chemical composition of the culture medium, altering the surface of the culture dish, or modifying the cells by inserting specific genes. The process is known as **directed differentiation**.

Foetal stem cells are primitive cell types found in the organs of fetuses. The classification of fetal stem cells remains unclear and this type of stem cell is currently often grouped into an adult stem cell.

Adult stem cells are undifferentiated cells, found among differentiated cells in a tissue or organ that can renew themselves and can differentiate to yield some or all of the major specialized cell types of the tissue or organ. The primary roles of adult stem cells in a living organism are to maintain and repair the tissue in which they are found. These cells have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. In many tissues, stem cells are pericytes, residing in the outermost layer of small blood vessels.⁴

Induced pluripotent stem cells are adult cells that have been genetically reprogrammed to an embryonic stem cell-like state. **iPSCs** are capable

of generating cells characteristic of all three germ layers. Viruses and non-viral vectors can be used to introduce the reprogramming factors (usually particular genes) into adult cells. **iPSCs** may be an alternative source of pluripotent stem cells bypassing controversy over destruction of human embryo for embryonic stem cells and they will probably avoid rejection by the immune system. Recently, human **iPSCs** or fibroblasts transduced with human stemness factors have differentiated into functional myocytes.^{5,6}

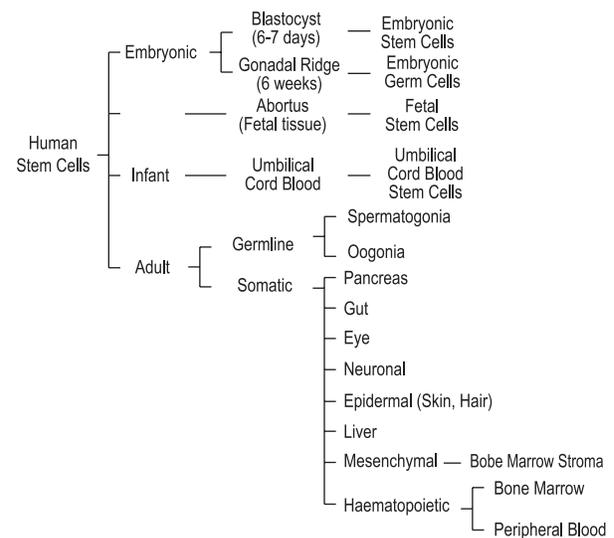


Fig.-1: Classification of stem cells.⁷

Somatic cell nuclear transfer (SCNT) or “therapeutic cloning” is a laboratory technique for creating a clonal embryo. In SCNT the nucleus of the somatic cell is inserted into an unfertilized, enucleated ovum creating a hybrid cell (Figure 2).⁷ The revolutionary application of SCNT was creation of the first animal clone Dolly the Sheep, by Ian Wilmut. The cells thus derived, have less chance of immune rejection, can be used in embryonic stem cell research, or, potentially, in regenerative medicine. However, SCNT is very resource-intensive, technologically demanding, still not ready for therapeutic use. One basic difference between SCNT and iPSC technology is that, in case of SCNT whole nucleus of a donor somatic cell is introduced into an enucleated ovum, whereas in iPSC technology, only particular gene(s) are inserted into a cell.

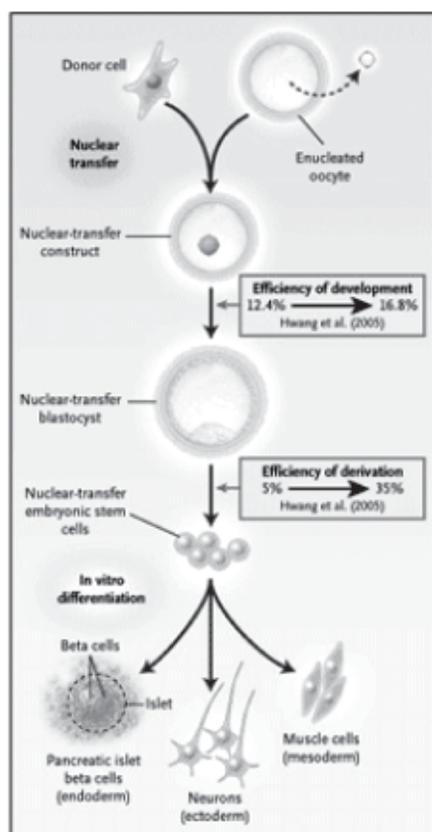


Fig.-2: Derivation of patient-specific therapeutic cells through somatic cell nuclear transfer.⁸

Stem cell therapy has the potential to dramatically change the treatment of human disease. However, bone marrow transplantation is the only established use of stem cells so far. In future, stem cells will probably be used to treat a wider variety of diseases including cardiovascular diseases, cancer, Parkinson's disease, spinal cord injuries, amyotrophic lateral sclerosis, multiple sclerosis, and muscle damage.^{9,10}

Mode of Action of Cardiac Stem Cell Therapy

Stem cells probably act via several potential mechanisms, likely involving more than one mechanism of action in a particular situation (Figure 3).

Differentiation: In this process, an unspecialized embryonic cell acquires the features of a specialized cell. Differentiation is controlled by the interaction of a cell's genes with the physical and chemical conditions outside the cell, usually through signaling pathways involving proteins embedded in the cell surface.³ Embryonic cells are

pluripotent, and can differentiate and electromechanically integrate with existing cardiomyocytes. Adult stem cells are more committed and possess a limited ability to differentiate along a specific lineage. However, resident cardiac progenitor cells are capable of producing cardiomyocytes.¹² Bone marrow and peripheral blood-derived endothelial progenitor cells can differentiate into functioning endothelium, incorporate into new blood vessels, and lead to improvement in blood flow.¹³

Transdifferentiation: The term is used to define a process by which stem cells from one tissue differentiate into cells of another tissue.³ A haemopoietic stem cell giving rise to daughter blood cells would be an example of differentiation, whereas giving rise to cardiomyocytes would be an example of transdifferentiation.¹⁴ Bone marrow progenitor cells have been shown to express cardiac specific genes and regenerate infarcted myocardium, endothelial progenitor cells can assume cardiomyogenic phenotype.^{15,16}

Fusion: Fusion refers to the phenomenon where stem cells fuse with somatic cells; the resultant hybrid cells usually assume the more undifferentiated phenotype but possess some characteristics of both cell types. Bone marrow cells and circulating stem cells have been shown to fuse with cardiomyocytes with the fused hybrid cells being virtually indistinguishable from unfused cardiomyocytes.^{17,18} However, fusion of cardiomyocytes and bone marrow cells is uncommon.³

Paracrine effect: Paracrine mechanism refers to the phenomenon whereby a cell releases its secretion into the adjacent cells or surrounding tissues rather than into the blood stream. Stem cells can regulate tissue regeneration and repair through paracrine mechanisms. The transplanted cells release cytokines, growth factors and signaling proteins that induce positive effects on resident cell populations stimulating proliferation and repair within host tissue.¹⁹

Cells Used for Cardiac Stem Cell Therapy

Stem cells that have been studied in the context of cardiac regenerative medicine are embryonic, foetal, and adult stem cells. Ideal features of a stem cell population for therapy would be the

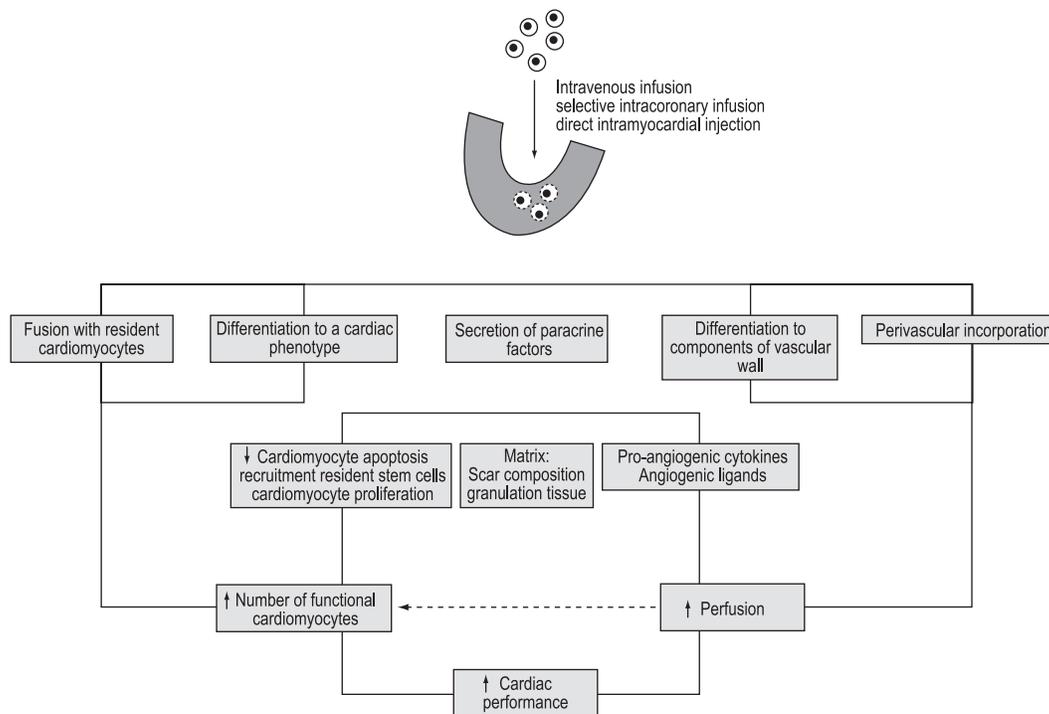


Fig.-3: Potential mechanisms through which cell therapy improves cardiac performance.¹¹

identification of a homogeneous stem cell population from an ethically uncontroversial source that exists normally *in vivo* and which could be prospectively isolated from an easily available tissue like the blood or bone marrow. Ideally, prolonged tissue culture would not be necessary and the number of cells required would be attainable within a short period of time.¹

Embryonic stem cells (ESCs): These cells are at present used for research purposes, but not for clinical application. They may be of a particular value in targeting and modifying congenital heart defects, cardiomyopathies and arrhythmias.^{20,21} They may also be more amenable to *ex vivo* engineering *via* DNA modifications. However, ethical and legal issues, potential immunorejection and tumorigenesis are the main concerns.²

Adult skeletal myoblasts (ASMs): These cells are already committed towards a myogenic fate and do not form tumors.²²⁻²⁴ Transplanted myoblasts from skeletal muscle can successfully home and engraft within a damaged myocardium, preventing progressive ventricular dilatation and improving cardiac function.²⁵⁻²⁷ Advantages include easy availability even from a small skeletal muscle

biopsy sample, and relative resistance to apoptotic damage. Lack of cardiomyogenic differentiation, inability to integrate electromechanically with the surrounding myocardium and risk of life-threatening arrhythmias are the main limitations.²⁸⁻³⁰

Bone marrow stem cells (BMC): Bone marrow contains different stem cell populations, including haemopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and multipotent adult progenitor cells (MAPCs). EPCs can promote new vessel growth, prevent cardiomyocyte apoptosis and cardiac remodeling and can transdifferentiate into cardiomyocytes.³¹⁻³³ MSCs, also called *stromal cells* have salutary effects on the postinfarct heart, differentiate into cardiomyocytes and can be used in cellular cardiomyoplasty.³⁴⁻³⁹ Advantages of adult BMCs include easy availability from autologous bone marrow aspiration, immunotolerance and compliance with ethical and legal issues.

Adult cardiac stem (ACS) cells: ACS cells or cardiac progenitor cells (CPCs) are the stem cells residing in the adult heart capable of differentiating into

cardiomyocytes. CPCs including *stem cell factor receptor (c-kit) positive cells, stem cell antigen-1 (Sca-1) positive cells, cardiospheres and cardioblasts* have been reported in mice, rats, dogs, and humans; they have got cardiomyogenic potential and salutary effects on ventricular function.⁴⁰⁻⁴⁵ ACS cell transplantation might be more effective than other stem cell transplantation, since cardiac stem cells may be better programmed.² However, they appear to be extremely limited in number, are difficult to identify and expand in culture², and need invasive cardiac biopsy for collection.

Other stem cells: Foetal and umbilical cord blood stem cells are primitive cell types found in the organs of fetuses and umbilical cord blood respectively. Theoretically, these cells may possess

greater plasticity than adult cells, but clinical proof is lacking.⁴⁶ Umbilical cord blood contains HSCs, MSCs and unrestricted somatic stem cells. These cells are easily obtainable from the placenta and may be cryopreserved for autologous or even allogeneic matched transplantation¹⁹, but improvement in left ventricular function is doubtful⁴⁷. Amniotic stem cells are multipotent and can differentiate in cells of adipogenic, osteogenic, myogenic, endothelial, hepatic and also neuronal lines.⁴⁸ There is still no clinical trial. Human foetal cardiomyocyte transplantation (obtained from aborted human embryos) has been successfully carried out in a rat model of myocardial infarction with good functional results.⁴⁹ Ethical issues, lack of availability, and the disadvantages of allograft transplantation apply to the foetal cell category.¹⁹

Table-I
Stem cells for cardiac regeneration therapy.^{19,46,50,51}

Cell-type	Source	Advantages	Limitations
Cardiac stem cells	Allogenic fetal, neonatal or adult heart	Electrically integrated Easily isolated Improve cardiac function Recognition of myocardial growth factors and recruitment to myocardium faster and more efficient	Poor cell growth and apoptosis Availability is low Likely immune rejection Ethical issues
Skeletal myoblast	Autologous skeletal muscle biopsy	Established phenotype Easily available Ischaemia resistant Fatigue resistant, slow-twitch fibres Excellent expansion Autologous transplantation Improves cardiac function	Electrical integration unclear Potentially arrhythmogenic Need for ex vivo expansion
Adult bone - marrow stem cells	Autologous bone marrow	Easily available Easy to grow Pluripotent Cardiomyogenic Neovascularization Immunotolerant Improves cardiac function	Limited cardiomyogenic potential New program of cell differentiation needed
Embryonic stem cells	Allogenic blastocyst (inner cell mass)	Totipotent/pluripotent Highly expandable Electrically integrated Possibly immuno-privileged Immortal <i>in vitro</i>	Ethical issues Insufficient availability Risk of tumour formation Potential for immune rejection (allogenic)
Umbilical cord blood stem cells	Umbilical cord blood of foetus or newborn	Easily available Pluripotent Cryopreservation possible	Ethical issues Allograft (at present) No clinical studies
Foetal cardiomyocytes	Allogenic fetal heart	Established phenotype	Ethical issues Allograft Insufficient availability

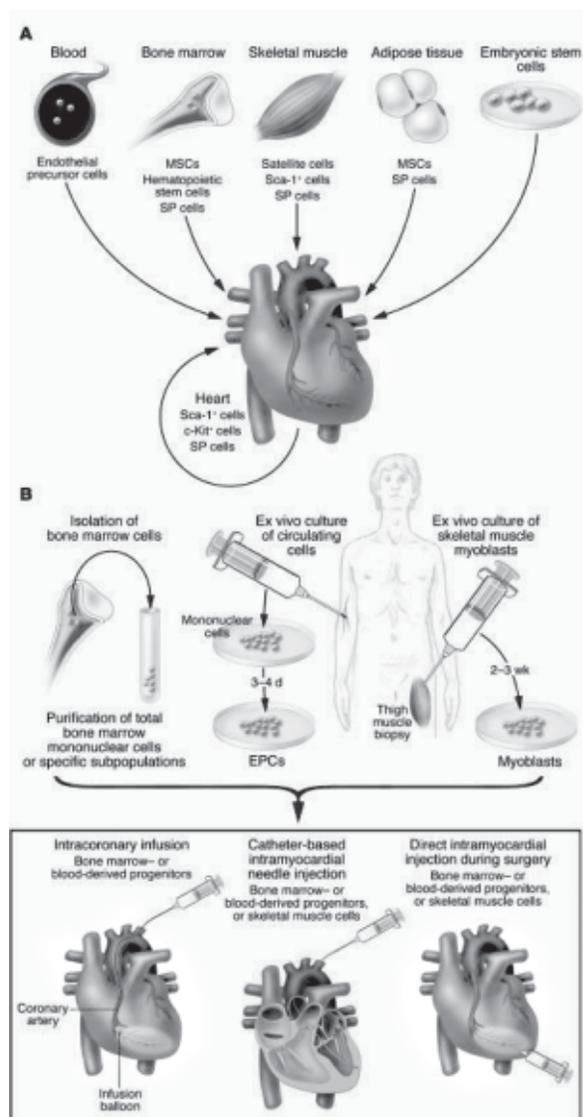


Fig.-4: Sources of cells for cardiac stem cell therapy (A), and routes of their administration (B).¹⁵

To date, the most suitable cell-line for clinical use is still unclear. In a recent head-to-head study using porcine stem cells, EPCs and MSCs increased ejection fraction to a similar extent, but the former showed more favourable effect on left ventricular remodeling.⁵² In another study, the ability of human CD34⁺ HSCs and bone marrow MSCs was compared to treat myocardial infarction in nude rats; MSCs were found more effective for the reduction of infarct size and prevention of ventricular remodeling.⁵³ Unless identification and expansion of human ACS cells in sufficient numbers is possible, or safe use of ESCs is ensured, the focus will remain on the autologous cell types

mainly from the bone marrow and the peripheral muscle.

Routes and Techniques of Stem Cell Delivery

The goal of any cell delivery strategy is to transplant sufficient numbers of cells into the myocardial region of interest and to achieve maximum retention of therapeutic cells within that area.¹¹ Currently available routes of administration include intravenous, intracoronary, and intramyocardial (the latter by transepical, transendocardial and transvenous injection)⁵²⁻⁵⁹ (Figure 4 and Table 2). Intrapericardial delivery is under investigation.

The intravenous technique involves infusion of cells through a central venous catheter. Selective intracoronary cell delivery involves cell infusion through the central lumen of an over-the-wire balloon catheter which is positioned into a coronary artery. Intramyocardial cell injection by transepical injection is performed as an adjunct to coronary artery bypass grafting (CABG). On the contrary, catheter based trans-endocardial injection of intramyocardial approach can be performed as a stand-alone procedure during cardiac catheterization. The recently introduced transvenous injection technique of intramyocardial stem cell delivery involves injection of therapeutic cells through the coronary veins into the myocardium with the use of a catheter system incorporating an ultrasound tip. The vascular approach seems generally less promising than direct intramural injection into the target myocardium.⁶⁰⁻⁶⁷ Stem cells have also been used in combination with transmyocardial and percutaneous laser revascularization to treat refractory angina or ischaemic cardiomyopathy.^{68,69} However, no single strategy has emerged as the preferred technique.

Cytokine-Based Stem Cell Therapy

In this non-invasive strategy, stem cells are not used directly, rather specific cytokines are administered to facilitate proliferation, mobilization and homing of endogenous stem cells to the area of interest e.g. injured myocardium. Granulocyte colony stimulating factor (G-CSF) has been used to mobilize bone marrow stem cells in several small trials with variable improvement in left ventricular function.⁷¹⁻⁷³ However, the safety

Table-II
*Clinical strategies for cardiac stem cell delivery.*⁵⁰

Strategies		Advantage	Disadvantage
Intravenous infusion		Simple, non-invasive Allows repetitive cell delivery	High systemic exposure Low percentage of cells enters coronary circulation Transmigration dependent on homing signals Requires large number of cells Risk of microemboli Unsuitable for occluded artery
Intracoronary infusion		Relatively simple technique Low systemic exposure Cell delivery in a specific coronary artery territory Cell delivery to myocardial regions with preserved oxygen supply	Not applicable to occluded artery Transmigration dependent on homing signals Inability to deliver cells to regions with occluded coronary artery Risk of micro-infarctions Risk of endothelial damage
Intramyocardial injection	Common features	Low systemic exposure High cell concentration in region of interest Suitable for occluded coronary artery territories	Risk for unwanted differentiation in scar tissue Risk of increased tissue heterogeneity
	Trans-epicardial	Relatively simple technique Direct visualisation of cell injections	Need for thoracotomy Mortality and morbidity of open heart surgery
	Trans-endocardial	Open heart surgery avoided Higher efficacy Short-term safety proven Clinical trials ongoing	More complex technique Need for specialized catheters and imaging technology Risk of cardiac perforation
	Transvenous (through coronary veins)	Visualisation of cell injections with echo Allows cell delivery deep in myocardium	More complex technique Inability to deliver cells in all myocardial territories Risk of damage of coronary veins
Direct epicardial patch		Needs open heart surgery Even distribution of cells Direct delivery of large amount of cells possible	Needs tissue engineering Mortality and morbidity of open heart surgery

of this approach has been questioned because of increased incidence of restenosis.⁷¹

Cellular Cardiomyoplasty and Gene Delivery

Cell therapy and gene therapy are considered as “rival approaches”. Gene therapy is intended as a corrective measure which involves transgene delivery into the cell to supplement or replace a malfunctioning or attenuated gene. The expression product of the transgene restores normal function of the cells and helps to overcome the adverse effects resulting from the abnormal endogenous gene expression.^{74,75} In other cases, transgene

delivery is meant for silencing the endogenous gene involved in the disease process (i.e. inhibiting cell proliferation in the arterial wall).⁷⁶ The success of gene therapy critically depends on the efficiency of gene transfer and expression. The cell membrane of cardiomyocytes is poorly penetrable to the naked DNA plasmid.⁷⁷ So, different vectors are commonly employed to deliver therapeutic genes to the heart. In this regard, cell-based therapeutic gene delivery may be a safer alternative to viral vectors and a more efficient option as compared to non-viral approach and direct plasmid injection.⁷⁷ Combining Ang-1 delivery with

skeletal myoblast transplantation has led to myocardial angiogenesis and improvement of left ventricular contractile function.⁷⁸

Tissue Engineering

Tissue engineering applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ.⁷⁹ The concept of regenerating diseased myocardium by implantation of tissue-engineered heart muscle is an impressive approach.⁸⁰ Large, thick rings of force-generating cardiac tissue were created, stacked and stitched onto infarcted rat heart which prevented further dilatation and improved fractional shortening of the failing heart.⁸¹ The human ESCs are hopefully to be differentiating to cardiomyocytes in tissue engineered structures which may ultimately provide a better strategy for treating heart failure.⁸⁰

Stem Cells and Heart Valves

Prosthetic mechanical heart valves require lifelong anti-coagulation, and the bioprostheses suffer from limited durability.^{82,83} One potential solution may be development of biocompatible replacement heart valve by means of tissue engineering and stem cells. However, the optimal cell type, scaffold material and in vitro culture conditions for a tissue engineered heart valve still remain unknown.⁸⁴

Safety Concerns

Arrhythmogenesis, oncogenic transformation, multiorgan seeding, aberrant cell differentiation, accelerated atherosclerosis are the main safety concerns.

Arrhythmogenesis: Whether stem cells are proarrhythmic remains a subject of debate.^{85,86} Several earlier studies documented malignant ventricular arrhythmias after skeletal myoblast transplant.⁸⁷ It remains to be determined whether other cell types are proarrhythmic. The proarrhythmia is thought to arise from lack of electromechanical coupling between transplanted cells and host cardiomyocytes.^{88,89}

Oncogenic transformation: there is abundant experimental evidence of oncogenic transformation, particularly in regard to embryonic and other pluripotent stem cells.^{90,91} However,

no increase in the frequency of tumors has been shown in clinical studies.^{46,92}

Multiorgan seeding: Stem cells administered systemically seed to multiple organs including the heart, liver, spleen, and brain.⁹³ To date, this finding has not been clinically relevant.⁴⁶

Aberrant cell differentiation: Aberrant differentiation of injected stem cells into undesirable lineages is a concern. ESCs have been associated with teratoma formation, whereas unselected bone marrow stem cells and MSCs lead to intramyocardial calcification.^{94,95}

Accelerated atherosclerosis: Stem cell transplantation has been shown to form or worsen atherosclerotic plaques.^{96,97} Whether this will become an issue of clinical importance is uncertain and unlikely.⁴⁶

Microinfarcts and in-stent restenosis: Intracoronary administration of mesenchymal stem cells has been associated with microinfarctions.⁹⁸ Besides this, unexpectedly high rates of in-stent restenosis have been observed in clinical trials using G-CSF.⁷¹

Clinical Trials of Cardiac Stem-Cell Therapy

The clinical trials on cardiac stem cell therapy suffer from methodological heterogeneity, lack of standardization, un-uniform primary end-points and methods of measurement.⁹⁹ Overall, the results of the placebo-controlled trials in the setting of acute myocardial infarction, chronic coronary artery disease and chronic heart failure are promising in that they demonstrate feasibility, safety, and a modest benefit on left ventricular function.¹⁰⁰⁻¹⁰⁶

Ethical Considerations

In general, the fundamental regulatory and ethical requirements that are used in drug and other clinical trials apply equally to cell therapy.^{117,118} However, cell therapy trials

introduce new ethical issues, including the debate over the use of embryonic material for research, and the outlook differs widely at individual, socio-cultural, religious and political level. Stem cell debates have motivated and reinvigorated the pro-life movement, regarding the rights and status of the embryo as an early-aged human life. The pro-life movement believes that embryonic stem cell

Table-III
Randomized controlled trials of cardiac stem cell therapy.

Indication	Study	Patient No	Cell Type	Results
Acute myocardial infarction	BOOST ^{107,108}	30 vs. 30 controls	BMCs	<i>LVEF change</i> 6 months: +6.7% vs. +0.7% (↑6%) 18 months: +5.9% vs. +3.1% (NS)
	Jannsens et al. ⁵⁴	33 vs. 34 controls	BMCs	<i>LVEF change</i> +3.4% vs. +2.2% (NS)
	ASTAMI ¹⁰⁹	50 vs. 50 controls	BMCs	<i>LVEF change</i> +1.2% vs. +4.3% (NS); Infarct size no significant change
	MAGIC CELL-3-DES ¹¹⁰	25 vs. 25 controls	PBCs	<i>LVEF change</i> +5.5% vs. 0% (↑5.5%)
	REPAIR-AMI ¹¹¹	95 vs. 92 controls	BMCs	<i>LVEF change</i> 5.5% vs. +3.0% (↑2.5%)
	Meluzin et al. ¹¹²	44 vs. 22 controls	BMCs	<i>LVEF change</i> High: +5%; Low: +3%; Control: +2% (↑2.0%)
	REGENT ¹¹³	117 vs. 20 controls	BMC	<i>LVEF change</i> Unselected: +3%; Selected: +3%; Control: 0% (NS)
	FINCELL ¹¹⁴	40 vs. 40 controls	BMCs	<i>LVEF change</i> +7.1% vs. +1.2%
Chronic myocardial ischaemia	Losordo et al. ¹⁰⁵	18 vs. 6 controls	G-CSF mobilised PBCs	<i>Angina frequency</i> : -12.6 vs. -4.5 (↓8.1, NS) <i>SPECT perfusion score</i> : -1.5 vs. -2.2 (NS) <i>Exercise time</i> : +0.5 vs. +0.3 min (NS)
	Tse et al. PROTECT-CAD ¹⁰³	19 vs. 9 controls	BMCs	<i>Exercise time</i> : ↑53% <i>LVEF change</i> : +3.7% vs. -0.4% (↑5.4%) <i>SPECT perfusion score</i> : -0.5 vs. +2.4 (↓2.7, NS)
	Van Ramshorst et al. ¹⁰⁶	25 vs. 25 controls	BMCs	<i>SPECT perfusion score</i> : -3.4 vs. -1.1 (↓2.44) <i>LVEF change</i> : +3% vs. -1% (↑3%) <i>Exercise capacity</i> : +9W vs. +2W (↑7W)
Congestive heart failure	TOPCARE-CHD ¹¹⁵	24 (PBC), 24 (BMC) vs. 23 (controls)	PBCs or BMCs	<i>LVEF change</i> : PBC: -0.4%; BMC: +2.9%; Control: -1.2% <i>LV EDV</i> : PBC: -3%; BMC: 0%; Control: -3% (NS) <i>LV ESV</i> : PBC: -2%; BMC: +2%; Control: -1% (NS)
	MAGIC ¹¹⁶	63 vs. 34 controls	Skeletal myoblast	<i>LVEF change</i> : High dose: +5.2%, Low dose: +3.4%; Control: +4.4% (NS) <i>LV EDV (ml/m)</i> : High: -12.6, Low: -3.9, Control: +5.9 (↓12.8) <i>LV EDV (ml/m)</i> : High: -8.3, Low: -6.5, Control: -2.1 (↓8.1) ↑arrhythmia in myoblast group (NS)

Abbreviations used: BMCs, bone marrow cells; PBCs, peripheral blood cells; G-CSF, granulocyte colony stimulating factor; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NS, non-significant.

research instrumentalizes and violates the sanctity of life and is tantamount to murder. Both Baptist and Catholic Churches oppose human ESC research but support research with adult stem cells. In USA, both the Clinton and Bush administrations were against the use of the federal government fund in

human ESC research that directly destroys embryos. On the other hand, private funding in such research was unrestricted. On March 9, 2009, President Barack Obama removed certain restrictions on federal funding for research involving new human ESC lines, but the funding

remains prohibited for (1) the creation of a human embryo for research purposes; or (2) research in which a human embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero. In Europe, Austria, Denmark, France, Germany, and Ireland do not allow the production of embryonic stem cell lines, but the same is permitted in Finland, Greece, the Netherlands, Sweden, and the United Kingdom.¹¹⁹ Regarding ethical issues, destruction of human embryo can be avoided by adoption of recently described alternative method of collection of stem cells without damaging the embryo, use of somatic cell nuclear transfer (SCNT), use of iPSCs and preferential use of human adult stem cells or cell lines. Other issues concerning stem cell research and therapy include those of ownership of cell lines, intellectual property, patents, collection of blood in minors (i.e., umbilical cord blood donations), and the potential effect of conflict of interest on research study recruitment and analysis of results.¹²⁰⁻¹²² To bring about uniformity in stem cell research and therapeutics, the International Stem Cell Forum (ISCF) and the International Society for Stem Cell Research (ISSCR) were established.⁸ In addition to the publication of the Guidelines for the Conduct of Human Embryonic Stem Cell Research in December 2006, the ISSCR recently published its Guidelines for the Clinical Translation of Stem Cells.¹²³ In the USA, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) regulate stem cell research and therapeutics. Many of the advertised stem cell treatments on the Internet are not evidence-based.¹²⁴ Patients must be protected from stem cells therapy without definitive proof of efficacy and safety.¹²⁵

Current Status and Future Perspectives

Cardiovascular stem cell therapy has brought about enormous therapeutic potential to ischaemic heart disease, heart failure and cardiomyopathy. Given the promising scientific findings, early results of clinical trials, and unmet clinical needs, cardiac cell therapy is being rapidly translated from the bench to the bedside.¹²⁶ In general, the use of adult stem cells is closer to the clinic. Bone marrow stem cell therapy appears to be safe, effective and feasible in acute MI, as well as, in chronic ischemic

conditions, but the same cannot be concluded about skeletal muscle stem cells. Trials with MSCs are still too early to certify about safety.¹³ Right now, no attempt should be made to use ESCs and iPSCs to treat cardiovascular problems clinically.⁵⁰

Ethical issues still remain a great concern in regard to stem cell research and therapeutics. Alternative approaches are being sought to avoid destruction of human embryo. Adoption of safe method of stem cell collection without damaging the embryo, use of umbilical cord blood stem cells, application of SCNT or iPSCs and preferential use of cell lines or adult stem cells are the possible approaches.

Questions about patient selection, cell selection, timing of therapy, efficacy of repeated therapies, co-administration of growth factors, and genetic modification of stem cells remain unanswered still now.^{11,13} Finally, it remains to be assessed whether cell therapy may reduce cardiovascular morbidity and mortality.¹¹

Different countries around the Globe are taking national initiatives of their own with hopes of making stem cell therapy and regenerative medicine a reality for themselves. In the USA, to achieve the aggressive goal of tissues on demand within 20 years, recently the Federal Initiative for Regenerative Medicine (FIRM) has been proposed.¹²⁷ It has been hoped that within 5 years complex skin, cartilage, bone, and blood vessel products; within 10 years organ patches; and within 20 years full organ regeneration would potentially be available.¹²⁷ The European Union (EU) formulates a regenerative medicine strategy for their own.¹²⁸ A total of 436 tissue-engineering related companies currently exist in the EU, with 40 percent located in the United Kingdom and Germany.¹²⁷ The Japanese government has committed resources to the city of Kobe in the Kansai region of Japan under the Kobe Medical Industry Development Project, one of the key components of which is cell therapy and regenerative medicine research.^{129,130} Other notable foreign efforts include Australia, which boasts a growing regenerative medicine industry, and China, which has committed a \$1 billion initial investment towards establishing regenerative medicine research.¹³¹ There are over three dozen research institutes, hospitals, and firms involved in stem cell research in India. In 2007, the Indian

Council of Medical Research and the Department of Biotechnology published a guideline for stem cell research.¹³² A National Apex Committee for Stem Cell Research is going to be formed to prescribe stringent procedures for sourcing and use of stem cells by research institutions in the country.

Conclusions:

Stem cell therapy or regenerative medicine is the vanguard of 21st century healthcare. It has brought about revolutionary changes in conventional therapeutics, including treatment of major acute and chronic cardiovascular diseases. Beyond pharmacological and mechanical interventions the new paradigm of stem cell therapy hopes for permanent 'cure' of the lost tissues and function. Preclinical and subsequent clinical research has indicated safety and feasibility of using this modality at bedside. However, uncertainties still prevail over many aspects of stem cell therapy. Unscrupulous handling of this delicate weapon may cause more harm than good. Only unbiased, knowledge-based and judicious application of stem cells can alleviate mortality and morbidity from cardiovascular diseases to a large extent. Needless to say, the next evolution of medical technology is now in sight, and has the potential to become reality in short time.

Conflict of Interest - None.

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