Stem cells as future therapy in cardiology

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This article focuses on the key studies relevant to the clinical application of stem-cell research in cardiovascular disease. The authors also discuss current and future directions in clinical cardiovascular stem-cell research, including the potential problems and pitfalls that must be addressed to ensure the safety, as well as the efficacy, of treatment regimens in this rapidly evolving therapeutic field.

Despite major advances in the prevention, diagnosis and treatment of ischaemic heart disease (IHD) it remains the most common cause of death in the developed world. The World Health Organization predicts that IHD will eventually become the leading cause of death worldwide (World Health Organization, 2003).

The notion that endogenous human stem cells – primitive cells that as yet have no committed function, but have the potential to differentiate into specific cell types – could be used to revascularize or regenerate damaged myocardium has opened an exciting new field, which has been taken up enthusiastically by both basic and clinical cardiovascular research groups.

WHAT ARE STEM CELLS?

Stem cells are primitive cells that have the potential to differentiate into mature, specialized cells in response to appropriate signals. A totipotent stem cell can differentiate into any cell type. Pluripotent stem cells, found in the inner blastocyst 5 days post-fertilization, have the potential to differentiate into any cell type in the body other than those of the placenta and supporting structures. Human embryonic stem cells are stem cell lines that have been derived from blastocysts of 'spare' frozen embryos that had been created for in-vitro fertilization procedures but were not implanted. Human embryonic stem cells therefore provide a unique resource for study of early development, pharmacological and genetic screening and, of course, great potential for cellular transplantation therapy.

CLINICAL ISSUES OF STEM-CELL DEVELOPMENT

A number of clinical issues need to be considered before developing human embryonic stem cell treatment programmes for cardiac disease:

- How to optimize conditions for expansion and storage of cell lines?
- How to ensure regulated differentiation into target cells and control of cellular proliferation?
- How to maximize immune tolerance and choice of appropriate patient groups for therapy?

In addition, important concerns have been raised regarding the ethics of committing embryos for these purposes, despite the fact that they would otherwise have been destroyed (Gerecht-Nir et al, 2004). Others fear that the development of embryonic stem cell technology will inevitably lead to reproductive cloning. Extensive debate continues in both the scientific and lay press regarding these issues and, at present, use of embryonic stem cells for treatment of cardiac patients remains for future consideration.

RESEARCH AND THE POTENTIAL OF STEM-CELL THERAPY

A number of potentially multipotent stem-cell lines (those capable of becoming only a small number of cell lineages depending on their particular location) have been identified in peripheral blood and tissues in addition to the bone marrow of human children and adults (*Figure 1*). These include haematopoietic progenitor cells that give rise to the cellular elements involved in both vasculogenesis and haematopoiesis in the prenatal stage, and appear to show promise for cardiovascular therapeutic purposes.

Asahara et al (1997) were the first to demonstrate the ability of a subset of multipotent human stem cells (CD34+ haematopoietic progenitor cells isolated from peripheral blood) to differentiate into cells with an endothelial

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phenotype *in vitro*. These cells, which were given the name endothelial progenitor cells (EPCs), originate from bone marrow and have the ability to migrate to sites of myocardial ischaemia and incorporate into neovessels in a mouse model (Asahara et al, 1997; 1999). This work led to a paradigm shift from the previous belief that angiogenesis (growth of new vessels) occurred as a consequence of sprouting from pre-existing neighboring blood vessels and paved the way for a number of studies investigating the utility of stem cells in wound healing and tissue repair.

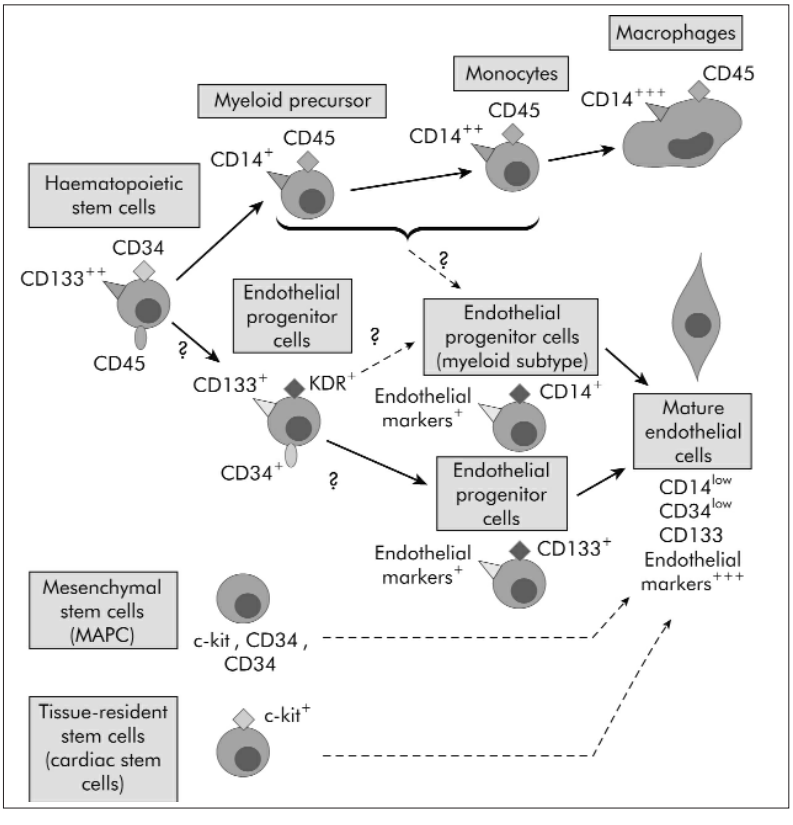
Orlic et al (2001) injected undifferentiated, lineage-negative (primitive cells with no dedicated function) bone marrow cells tagged with green fluorescent protein directly into the infarct-related area of mouse hearts after coronary artery ligation. Nine days after transplanting these bone marrow cells, newly formed myocardium occupied 68% of the infarcted portion of the ventricle; cells of donor origin were also found to express myocardial cell markers and incorporate into vascular structures. Similar results were observed in mice who had received an autologous bone marrow transfusion with and without *ex vivo* culture of the donor cells (Tomita et al, 1999). Such findings illustrate the potential of bone marrow cells to reverse the impact of coronary artery disease by creating new blood vessels and, possibly, new myocardium.

Kocher et al (2001) explored the potential of granulocyte colony stimulating factor (GCSF) to enhance bone marrow cell mobilization of a cell population which, in adult humans, expresses functional and phenotypic characteristics of endothelial precursor cells. Intravenous injection of these cells into a rat model of myocardial infarction resulted in a reduction of peri-infarct cardiac myocyte apoptosis, a reduction in collagen deposition, and long-term salvage and survival of viable myocardium. This led to a sustained improvement in cardiac contractile function. Further studies have also demonstrated improved capillary density and improved ventricular function following intracoronary (Fuchs et al, 2001) and direct intramyocardial injection (Kawamoto et al, 2003) of progenitor cells in other animal infarct models.

However, the ability of adult stem cells to differentiate into mature cardiomyocytes has been called into question by studies demonstrating that bone marrow-derived progenitor cells participate in cellular fusion processes with neighboring cells (Terada et al, 2002; Oh et al, 2003) and appear to differentiate along the haematopoietic lineage (Murry et al, 2004), suggesting a more limited capacity for transdifferentiation. Such observations raise the alternative possibility that local delivery of stem or progenitor cells exert paracrine effects that influence the repair process by modifying remodeling of the damaged ventricle, rather than by growth of new myocardium.

Clinical studies established that EPCs are mobilized during acute ischaemic events or vascular trauma in humans implicating these cells in the organization of endogenous tissue repair mechanisms (Gill et al, 2001; Shintani et al, 2001). These observations supported the hypothesis that enhancing this process in some way could improve the healing process following acute myocardial injury (*Table 1*).

Figure 1. Potential origin and differentiation of endothelial progenitor cells from haematopoietic stem cells and non-haematopoietic cells (Urbich and Dimmler, 2004)



THERAPEUTIC USE OF STEM CELLS IN CARDIOVASCULAR DISEASE

The first clinical reports of the therapeutic use of stem cells in human cardiovascular disease were published in 2001, exploiting different stem cell populations in different disease states. Strauer et al (2001) initially experimented on a 46-year-old man who had been treated with angioplasty and stenting for an anterior myocar-

dial infarction (MI). They harvested the patient's bone marrow and 6 days after infarction transfused 1.2 x 107 cells into the infarct-related artery under low pressure. After 10 weeks, the infarct-related area had decreased in size from 24.6% to 15.7% of left ventricular circumference, while ejection fraction, cardiac index and stroke volume had increased by 20–30%. A subsequent phase I clinical trial in 20 patients demonstrated an improvement in cardiac function, which persisted during a 3-month follow-up (Strauer et al, 2002).

In contrast, Menasche et al (2000, 2001) implanted skeletal myoblasts, obtained from culture of autologous muscle biopsy tissue into the peri-infarct zone of a patient undergoing surgical revascularization with subsequent improvement of cardiac function. Although further studies of autologous skeletal myoblast implantation have shown an improvement in left ventricular (LV) function, concerns have been raised regarding their pro-arrhythmic potential, which has slowed the rate of clinical development of this strategy (Menasche et al, 2000; Smits et al, 2003).

More promising results have come from two European clinical trials evaluating the effect of intra-coronary injection of autologous progenitor cells post-MI. In the TOPCARE-AMI study, Assmus et al (2002) recruited patients that had undergone percutaneous coronary intervention (PCI) for an acute myocardial infarction 4 days before. Subjects received infusion of either bone marrow or peripheral blood-derived mononuclear cells that had been cultured and were rich in cells with an endothelial phenotype into the infarct-related artery via a balloon catheter. LV function and remodelling was improved to a similar extent in patients treated with both cell types compared with controls, suggesting that either may be an appropriate therapeutic option.

In the BOOST study, Wollert et al (2004) studied 60 patients who had also undergone PCI following ST-elevation MI. Half of the subjects were randomized to receive an intracoronary infusion of bone marrow mononuclear cells 4 days post-PCI, and the remainder served as controls. Patients receiving cell therapy demonstrated an improvement in LV ejection fraction but not chamber remodelling (as measured by magnetic resonance imaging) at 6 months. Despite the early promise of these studies, a principal criticism is that a placebo effect cannot be excluded, as control patients did not undergo the cell harvesting procedures or repeat catheterization with intracoronary infusion. Nonetheless, patients tolerated the treatment well and no significant safety issues emerged from these trials. Cell therapy did not significantly affect C-reactive protein and leukocyte count in TOPCARE-AMI, which goes some way to assuaging concerns about the pro-inflammatory potential of cell therapy in the context of a recent MI. There were also no differences between the treatment and control groups in the incidence and inducibility of ventricular arrhythmias. Furthermore, clinical markers have also been reassuring despite the lack of statistical power of these trials to show a significant effect on major clinical end-points, such as mortality and recurrent MI.

Other clinical studies of autologous bone marrow-derived mononuclear cell therapy have produced encouraging results following their direct injection into the infarct border zone of patients undergoing surgical revascularization (Stamm et al, 2003; Galinanes et al, 2004), or by intramyocardial injection via a cardiac catheter delivery system in patients with chronic ischaemic heart failure (Perin et al, 2003).

FUTURE QUESTIONS

The field of stem-cell research has progressed rapidly from basic investigation to clinical ther-

TABLE 1.
Potential clinical application of stem cells

Conditions	Ischaemia	Acute coronary syndromes
		Chronic refractory angina
		Stent coating
	Heart failure	
	Valve disease*	
	Conduction system disease*	
Cell types	Bone marrow	Haemangioblasts
		Mesenchymal
		Unselected
	Peripheral blood	
	Tissue-resident side	Population (e.g. muscle)
	Embryonic stem cells*	
Cell delivery method	Intravascular	Intracoronary
		Intravenous
		Coronary sinus
	Direct injection	Catheter-based
		Surgical
	Enhanced mobilization from marrow (e.g. GCSF, EPO, VEGF)	

* = no active clinical evaluation, EPO = Erythropoietin, GCSF = Granulocyte colony stimulationg factor, VEGF = Vascular edothelial growth factor

apy, and has gained substantial momentum. However, the following practical and ethical questions need to be addressed if stem cell therapy is to be implemented successfully into routine clinical practice:

- Which cells or combination of cells should be used?
- How should the cells be harvested and prepared for delivery?
- Which cell delivery technique(s) should be used?
- How can the intrinsic capacity of the body to produce stem and progenitor cells that home to the appropriate target be enhanced?
- Which patients should receive cell therapy?

Cell type or cell combination

Perhaps the most fundamental of these questions is which cell type or combination of cells is the best therapeutic agent? This is not an easy question to answer. Stem and progenitor cells have exceptional plasticity. They are extremely sensitive to the local conditions *in vitro*. Even slight changes in the culture medium can result in their differentiation along quite different lineages and they are also able to de- and re-differentiate between different cell lineages (Mathur and Martin, 2004).

Transplanted stem cells may be able to fuse with host cells, thus making it difficult to follow the fate of individual stem cells in the cardiovascular system. Some controversy also exists about the characterization and biological potential of specific cell populations, particularly those that can be isolated and cultured from peripheral blood (Balsam, 2004). For example, peripheral blood mononuclear cells express markers of both mature monocytic and endothelial lineages when cultured under certain conditions, suggesting that they are not a true stem and/or progenitor cell population. However, these cells appear to have exceptional plasticity and are able to support therapeutic angiogenesis in animal models of ischaemia (Gulati et al, 2003; Rehman et al, 2003; Urbich et al, 2004).

The ultimate cellular fate of stem cells appears to depend on complex interactions between the individual cells and their local environment (Urbich and Dimmler, 2004). At present, there is no consensus regarding whether heterogeneous populations of bone marrow or peripheral blood mononuclear cells are most appropriate for therapy, or whether highly selected populations of the more primitive, but less abundant, CD34+ or CD133+ cells may produce better results because of their greater potential for expansion. This problem is being addressed by studying agents that promote mobilization of stem cells from the bone marrow. Granulocyte colony stimulating factor (GCSF) has generated particular interest, but erythropoietin, vascular endothelial growth factor and stromal-derived factor-1, among others, are also promising. However, questions were raised after the use of GCSF to mobilize bone-marrow cells was associated with two MIs and one cardiac death in one series of patients with advanced ischaemic heart disease (Powell et al, 2005). Although a subsequent study has suggested that GCSF administration is safe to use in patients with MI (Kang et al, 2004), it is clear that further work is needed to allay safety concerns.

The influence of local conditions on stem cell differentiation pathways remains to be determined. Although *ex vivo* expansion of stem cells has been conducted successfully, the optimal combination of growth factors, extracellular matrix components and, perhaps, as yet unidentified factors for their culture remains to be confirmed (Dimmler and Zeiher, 2004). It is important to note that statins enhance *ex vivo* stem-cell expansion by preventing telomere degeneration, thus, in a sense, keeping cells 'young' (Spyridopoulos et al, 2004). Further insights into this phenomenon and other cell-culture problems may come from interesting studies examining how stem cells manage to sustain production over the course of a lifetime without themselves becoming depleted or senescent (Dick, 2003).

There is no current consensus regarding the optimal number of cells to use, or whether better results can be obtained by rapid harvest and local delivery of bone-marrow mononuclear cells than by a more thorough selection and culture of bone marrow or peripheral blood cells. These issues are the subject of intense current research activity in both animals and humans, and will lead to a better understanding of the role and potential of specific cell types and their combination in cardiovascular disease.

Cell delivery techniques

There remain many unresolved issues regarding optimal cell delivery techniques. Numerous approaches have been studied, each with its own unique benefits and disadvantages. Intravenous infusion of cells is simple and safe, but intrinsically limited by the ability of cells to home selectively to the heart, rather than other organs, such as the lungs and spleen. Intracoronary infusion of cells is slightly more risky than the intravenous approach, but has the advantage of direct deliv-

ery to the target organ. This approach may still be limited by the ability of the cells to adhere to the coronary vascular endothelium and become incorporated into vascular or myocardial tissue. The success of intravenous and intracoronary cell delivery for cardiac repair is also likely to be dependent on the integrity of the coronary circulation supplying the region of interest, as it is difficult for cells to reach tissue that lacks an intact vasculature. This problem may be overcome by local injection of cells via an open chest or endoscopic surgical approach, or by use of specially designed injection catheters, although the procedural risks are potentially greater (Assmus et al, 2002; Stauer et al, 2002; Smits et al, 2003; Galinanes et al, 2004; Wallert et al, 2004).

The success of local delivery techniques is likely to be limited by the ability of stem cells to induce and develop their own blood supply, which is of importance when planning the injection sites. For example, cells delivered into the middle of an old scar subtended by a chronically-occluded vessel that is not amenable to revascularization are less likely to flourish than those injected into the border zone between the scar and viable myocardium. In a study of coronary bypass grafting revascularization combined with cell therapy in subjects with myocardial scar and LV dysfunction, LV functional improvement was only observed in myocardial territories that received both cell therapy and successful revascularization (Galinanes et al, 2004).

Which patients should receive cell therapy?

The issue of cell delivery route is also important when considering the type of patient that may benefit from cell therapy. At present, most clinical research activity is addressing the potential of stem-cell therapy in subjects with acute MI, chronic ischaemic LV dysfunction and those with chronic refractory myocardial ischaemia that are unsuitable for percutaneous or surgical revascularization. Eventually, stem cells may even be used to repair conduction tissue and grow new heart valves. The optimal strategies in terms of cell type(s), quantity, timing and delivery route for specific clinical conditions will be clarified as results from further studies become available.

The future: potential and limitations

The advancement of this field may be limited by a number of challenging logistical problems. For instance, there is less scope for commercialization of stem-cell therapies, which reduces the potential for funding and organizational support from pharmaceutical companies. Physicians are therefore more dependent on the support of governments, charities and philanthropy, which imparts physicians, and the wider scientific community, with greater responsibility to pioneer this new research strategy. Larger, double-blinded clinical trials are needed for the successful implementation of stem-cell therapy, and will demand high levels of collaboration between groups for their success.

This article has focused on the potential of stem cells for the treatment of established clinical cardiovascular disease. But could stem cells be used to prevent cardiovascular disease? Clear evidence has emerged showing that the number of circulating endothelial progenitor cells is decreased in those with risk factors for cardiovascular disease, but also appear to protect the vasculature from the damaging effect of exposure to risk factors (Vasa et al, 2001a; Hill et al, 2003). In addition, statins and exercise have been shown to increase the number of circulating endothelial progenitor cells, which may, in part, account for their beneficial effects on cardiovascular outcome (Vasa et al, 2001b; Rehman et al, 2004). Thus, the concept of stem cells as a vital repair mechanism for damaged endothelium has emerged as a novel paradigm that has become the subject of widespread research efforts to explore the utility of endogenous cells to prevent the development of atherosclerotic lesions.

The potential of embryonic stem cells for the treatment of cardiac disease is well recognized, although ethical and practical considerations have limited clinical application of this technology so far (Gercht-Nir et al, 2004).

CONCLUSIONS

Stem-cell research is in the forefront of translational, 'bench to bedside' scientific research. In a relatively short period of time, stem cells have shown considerable promise as a therapeutic measure in established cardiovascular disease and may also be used to harness the potential of endogenous stem cells for disease prevention.

Clinical trials into stem-cell research continue to proliferate and, although some may feel that the transition into the clinical arena has been made too quickly, the clock cannot be turned back. It is certain that the global programme will continue to gather momentum but, if the maximum benefit is to be gained from this work, it is vital that future research strategies are logical, structured, carefully coordinated, and necessary consideration is given to issues of safety. HM

Conflict of interest: none

Asahara T, Murohara T, Sullivan A et al (1997) Isolation of progenitor endothelial cells for angiogenesis. *Science* **275:** 964–7

Asahara T, Masuda H, Takahashi T et al (1999) Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. *Circ Res* **85:** 221–8

Assmus B, Shachinger V, Teupe C et al (2002) Transplantation of progenitor and regeneration enhancement on acute myocardial infarction (TOPCARE-AMI). *Circulation* **106:** 3009–17

Balsam LB, Wager AJ, Christensen JL et al (2004) Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature* **428:** 668–73

Dick JE (2003) Self-renewal writ in blood. *Nature* **423:** 231–3

Dimmeler S, Zeiher AM (2004) Wanted! The best cell for cardiac regeneration. *J Am Coll Cardiol* **44:** 464–6

Fuchs S, Baffour R, Zhou YF et al (2001) Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia. *J Am Coll Cardiol* **37**(6): 1726–32

Galinanes M, Loubani M, Davies J et al (2004) Autotransplantation of unmanipulated bone marrow into scarred myocardium is safe and enhances cardiac function in humans. *Cell Transplant* **13:** 7–13

Gerecht-Nir S, Itskovitz-Eldor J (2004) Human embryonic stem cells: a potential source for cellular therapy. *Am J Transplant* **4**(Suppl 6): 51–7

Gill M, Dias S, Hattori K et al (2001) Vascular trauma induces rapid but transient mobilization of VEGFR2+AC133+ endothelial precursor cells. *Circ Res* **88:** 167–74

Gulati R, Jevremovic D, Peterson TE et al (2003) Diverse origin and function of cells with endothelial phenotype obtained from adult human blood. *Circ Res* **93:** 1023–5

Hill JM, Zalos G, Halcox JPJ et al (2003) Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med* **348:** 593–600

Kang HJ, Kim HS, Zhang SY et al (2004) Effects of intracoronary infusion of peripheral blood stem-cells mobilized with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomized clinical trial. *Lancet* **363:** 751–6

Kawamoto A, Tkebuchava T, Yamaguchi J-I et al (2003) Intramyocardial transplantation of autologous endothelial progenitor cells for therapeutic neovascularization of myocardial ischaemia. *Circulation* **107:** 461–8

Kocher AA, Schuster MD, Szabolcs MJ et al (2001) Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat Med* **7:** 430–6

Mathur A, Martin JF (2004) Stem cells and repair of the heart. *Lancet* **364:** 183–92

Menasche P, Hagege AA, Vilquin J-T et al (2000) Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol* **41:** 1078–83

Menasche P, Hagege AA, Scorsin M et al (2001) Myoblast transplantation for heart failure. *Lancet* **357:** 279–80

Murry CE, Soonpaa MH, Reinecke H et al (2004) Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature* **428:** 664–8

Oh H, Bradfute SB, Gallardo TD et al (2003) Cardiac progenitor cells from adult myocardium: Homing, differentiation and fusion after infarction. *Proc Nat Acad Sci* (USA) **100:** 12313–18

Orlic D, Kajstura J, Chimenti S et al (2001) Bone marrow cells regenerate infarcted myocardium. *Nature* **410:** 701–5

Perin EC, Dohmann HFR, Borojevic R et al (2003) Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. *Circulation* **107:** 2294–302

Powell TM, Paul JD, Hill JM et al (2005) Granulocyte colony-stimulating factor mobilizes functional endothelial progenitor cells in patients with coronary artery disease. *Arterioscler. Thromb Vasc Biol* **25**(2): 296-301

Rehman J, Li J, Orschell CM et al (2003) Peripheral blood 'endothelial progenitor cells' are derived from monocyte/macrophages and secrete angiogenic growth factors. *Circulation* **107:** 1164–9

Rehman J, Li J, Parvathaneni L et al (2004) Exercise acutely increases circulating endothelial progenitor cells and monocyte-/macrophage-derived angiogenic cells. *J Am Coll Cardiol* **43**(12): 2314–8

Shintani S, Murohara T, Ikeda H et al (2001) Mobilization of endothelial progenitor cells in patients with acute myocardial infarction. *Circulation* **103:** 2776–9

Smits PC, van Geuns R-JM, Poldermans D et al (2003) Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischaemic heart failure: clinical experience with six-month follow-up. *J Am Coll Cardiol* **42:** 2063–9

Spyridopoulos I, Haendeler J, Urbich C et al (2004) Statins enhance migratory capacity by upregulation of the telomere repeat-binding factor (TRF2) in endothelial progenitor cells. *Circulation* **110:** 3136–42

Stamm C, Westphal B, Kleine H-D et al (2003) Autologous bone-marrow stem-cell transplantation for myocardial regeneration. *Lancet* **361:** 45–6

Strauer BE, Brehm M, Zeus T et al (2001) Myocardial regeneration after intracoronary transplantation of human autologous stem cells following acute myocardial infarction. *Dtsch med Wochenschr* **126:** 923–8

Strauer BE, Brehm M, Zeus T et al (2002) Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation* **106:** 1913–18

Terada N, Hamazaki T, Oka M et al (2002) Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. *Nature* **416:** 542–5

Tomita S, Li R-K, Weisel RD et al (1999) Autologous transplantation of bone marrow cells improved damaged heart function. *Circulation* **100:** 247II–256II

Urbich C, Dimmeler S (2004) Endothelial progenitor cells: characterization and role in vascular biology. *Circulation Research* **95:** 343–53

Urbich C, Heeschen C, Aicher A et al (2004) Relevance of monocytic features for neovascularization capacity of circulating endothelial progenitor cells. *Circulation* **110:** 3136–42

Vasa M, Fichtlsherer S, Aiser A et al (2001a) Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res* **89**(1): E1–7

Vasa M, Fichtlscherer S, Adler et al (2001b) Increase in circulating endothelial progenitor cells by statin therapy in patients with stable coronary artery disease. *Circulation* **103**(24): 2885–90

Wollert KC, Meyer GP, Lotz J et al (2004) Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomized controlled clinical trial. *Lancet* **364:** 141–8

World Health Organization (2003) *World Health Report*. WHO, Geneva. www.who.int/whr/en

KEY POINTS

- Stem cells are primitive cells that have the potential to differentiate into specific cell types in response to appropriate local stimuli.
- Embryonic stem cells, isolated from the inner blastocyst of early embryos have great potential to differentiate into multiple cell types. Extensive development of this field, in particular clinical application, has been primarily limited by ethical concerns.
- Endogenous stem cells can be isolated from bone marrow circulating blood, and are also present in most tissues as 'side-populations'.
- Studies in animal models of cardiac disease suggest that endogenous stem cells can enhance angiogenesis, vasculogenesis and myocardial repair.
- Early clinical studies have demonstrated improvement in left ventricular function in patients with ischaemic left ventricular dysfunction treated with endogenous stem-cell therapy.
- Ongoing clinical studies are addressing key questions, such as which patient groups will benefit from stem cell therapy, and what are the optimal delivery routes and techniques?