Stem cells and repair of the heart

A Mathur, JF Martin

Stem-cell therapy provides the prospect of an exciting and powerful treatment to repair the heart. Although research has been undertaken in animals to analyse the safety and efficacy of this new approach, results have been inconclusive. The mechanism by which stem cells could improve cardiac function remains unclear. We describe the background to the concept of natural repair and the work that has been done to establish the role of stem cells in cardiac repair. Controversies have arisen in interpretation of experimental data. The important issues surrounding the application of stem-cell therapy to man are discussed critically. We discuss the future of this pioneering work in the setting of growing concerns about clinical studies in man without understanding the biological mechanisms involved, with the difficulties in funding this type of research.

Introduction

The discovery of pluripotent stem cells with the ability to repair adult tissue has prompted novel research into repair of the heart and blood vessels. This finding offers immense therapeutic possibilities but also problems that have never been encountered before. The use of stem cells for treatment in the heart, because of its simplicity in function and accessibility, is more advanced than in other organs. For the same reason stem-cell research has produced novel problems in biology, clinical application, ethics, funding, and organisation.

The Problem

Occlusion of arteries by atherosclerosis with or without thrombosis leads to cell death in organs. In developed populations, mortality from myocardial infarction, thrombotic cerebral infarction, and peripheral arterial disease is falling, yet morbidity from vascular disease is rising because of increased survival of patients. The increase in age of death in the population implies a future rise in mortality and morbidity from cardiovascular disease. Half the deaths in developed countries are caused by cardiovascular disease. WHO predicts that the disease will be the biggest cause of death worldwide in the near future (World Health Report, 2003 www.who.int/whr/en/). The economic costs are enormous. Extrapolation of US data to the 25 countries of the European Union indicates that in Europe the direct cost of cardiovascular disease is €473 billion and the indirect cost is €15 392 billion per year (Rynkiewicz A, Medical University, Gdansk, personal communication). Stem-cell transplantation offers the possibility of a simple and cheap way of repairing end organ damage, particularly in the heart.

Natural repair of the heart

It has been proposed that a natural system of repair exists in the body, which is overwhelmed by substantial damage.1 This suggestion has led to a re-examination of the evidence concerning cardiac regeneration and, in particular, the ability of the cardiomyocyte to divide. Previously, the cardiomyocyte was thought to be terminally differentiated.2,3 Thus, the number of cardiomyocytes at birth would only decrease with age. This traditional concept implies that the heart muscle itself has no housekeeping mechanism to repair any minor damage. This notion was supported by findings that the number of myocytes undergoing proliferation is low compared with other tissues that have high levels of cellular regenerative capacity (eg, liver). The traditional view was that myocytes responded to physiological and pathological stress by hypertrophy rather than hyperplasia. Furthermore the effects of myocardial infarction were thought to be irreversible, and improvement in left ventricular function was believed to be secondary to a process of remodelling that comprised a combination of hypertrophy and fibrosis. These ideas are challenged by recent work suggesting that large numbers of mitotic figures are present in adult hearts.4,5 However, even though a 10–60 fold increase in mitotic figures was recorded in patients dying from heart failure, the proportion of myocytes that were mitotic was low, 0·015% to 0·08%, a small and insignificant number if myocyte proliferation were to act as an effective repair mechanism.6,7 These studies might underestimate the number of cells that are dividing since the data only reflect what is happening at one instant in what is likely to be a dynamic process.

The source of dividing cells in the myocardium is also unclear. Cells might be randomly located throughout the myocardium and present from birth. However, the possibility that these dividing cells are myocytes derived from an extracardiac origin is suggested by investigations in sex-mismatched heart transplant patients. In male patients who had received female hearts, biopsies revealed the presence of cardiomyocytes carrying the Y chromosome8,9 (figure 1). Although the...
Seminar

proportion of Y chromosome positive cells with evidence of cardiac differentiation present in the female hearts varied considerably between patients, this finding showed for the first time in human beings that the heart can receive new cells from an extracardiac source. Provided that these cells can differentiate into cardiac tissue, two potential sources have been suggested. First, the cells might originate in the bone marrow, from which they could be released and engraft in the heart either as a low level process of continuing renewal or in response to injury.11–14 Second, the cells might represent a local resident cardiac stem-cell population. Evidence for the latter theory is the isolation of cells expressing a progenitor phenotype in animal heart tissue (lin-c-kit+ and Sca-1+ markers). These cells were recorded to be self-renewing, clonogenic, and multipotent. When transplanted into an animal myocardial infarction model they seemed to improve heart function. Although the “cardiac stem cells” did not express markers suggesting a haemopoietic or endothelial lineage, there is still the possibility these cells were derived from other sources such as the bone marrow.8,11,12 Another potential source of local stem cells is the epicardium, from which it has been proposed that a subset of progenitor cell is able to migrate into the myocardium and differentiate into different cardiac cell types including new blood vessels or any cell comprising the whole organ.19

The concept of self renewal is not confined to the heart but is also seen in other organs (eg, liver and bone marrow). Indeed, the tips of fingers have been found to regenerate in children.19–22 The argument that regeneration is a limited process and does not extend to complex structures involving more than one cell type is challenged by findings from a range of species, in particular amphibians (Urodeles) (figure 2). In these animals, regeneration has been shown in the brain and spinal cord,23 intestine,24 heart,25 limb,26 and lens and retina.27 This regenerative process involves cellular dedifferentiation as well as transdifferentiation and is represented in its most complex form in the total regeneration after loss of the limb and eye. Cells at the site of damage or amputation undergo dedifferentiation and are challenged by findings from a range of species, in particular amphibians (Urodeles) (figure 2). In these animals, regeneration has been shown in the brain and spinal cord, intestine, heart, limb, and lens and retina. This regenerative process involves cellular dedifferentiation as well as transdifferentiation and is represented in its most complex form in the total regeneration after loss of the limb and eye. Cells at the site of damage or amputation undergo dedifferentiation and transdifferentiation to rebuild an exact replica of the lost part. Growth factors28 and their receptors29 (FGFR-1 and FGFR-2) have been implicated in this process. The role of stem cells or progenitor cells in amphibian regeneration is unclear because of a limited supply of diagnostic antibodies to the relevant cells in this species. Therefore, whether this process is facilitated by progenitor cells of bone marrow origin remains to be seen.

Figure 1: Immunostaining and in-situ hybridisation for Y and X chromosomes in biopsy samples taken from female hearts transplanted into male patients

In A–D, blue areas show DAPI (4',6'-diamidino-2-phenylindole hydrochloride) staining of nuclei. In B–D, red dots indicate Y chromosomes, and green dots indicate X chromosomes in nuclei. (A) shows immunostaining of myocardial biopsy by α-sarcomeric actin (green area). A cardiomyocyte marked by the arrow is also shown after in-situ hybridisation in (B). Green staining surrounding nucleus in (B) is due to autofluorescence. In (C) and (D), green areas represent immunostaining for myoglobin; arrows indicate male cardiomyocytes. Asterisk in (D) indicates nucleus belonging to male non-myocyte cell.

Figure 2: Urodele limb regeneration

(A) North American red spotted newt, Notophthalmus viridescens. (B) Stages of limb regeneration in an adult newt. (Reproduced from reference 121 with permission from Springer-Verlag).
Identification of the key components in amphibian regeneration, such as the blastema (the collection of dedifferentiated cells at the site of injury) and the specialised wound epithelium provide molecular targets for potential application in human beings. A characteristic molecular signature of the blastema is the phosphorylation patterns of the protein of the retinoblastoma tumour suppressor gene. This phosphorylation pattern associated with dedifferentiation in the blastema is only seen in mammalian cells that are allowed to enter the cell cycle after transfection with viral oncogenes. Indeed, there are similarities between cells of the blastema and cancer cells. However, spontaneous tumours are rare in amphibians and application of carcinogens to cells. However, spontaneous tumours are rare in are similarities between cells of the blastema and cancer

Identification of the key components in amphibian regeneration, such as the blastema (the collection of dedifferentiated cells at the site of injury) and the specialised wound epithelium provide molecular targets for potential application in human beings. A characteristic molecular signature of the blastema is the phosphorylation patterns of the protein of the retinoblastoma tumour suppressor gene. This phosphorylation pattern associated with dedifferentiation in the blastema is only seen in mammalian cells that are allowed to enter the cell cycle after transfection with viral oncogenes. Indeed, there are similarities between cells of the blastema and cancer cells. However, spontaneous tumours are rare in amphibians and application of carcinogens to cells. However, spontaneous tumours are rare in are similarities between cells of the blastema and cancer

**Figure 3:** Possible explanations for perceived plasticity

(A) Stem cells for a specific tissue might exist in an unrelated organ. (B) Perceived plasticity might be caused by transplanted cells fusing with host cell of different lineage, leading to transfer of genetic information of transplanted cell to host-derived cell. (C) Plasticity might occur via de-differentiation and re-differentiation, as is seen in cloning or in limb regeneration in amphibians. (D) Cells with pluripotent characteristics might persist even after the initial steps of embryological development. Reproduced from reference 35 with permission from Elsevier.

Stem cells

Stem cells are defined by their ability to self-renew and to form one or more differentiated cell types. They can be categorised anatomically, functionally, or by cell surface markers, transcription factors, and the proteins they express. What distinguishes different populations of stem cells are the types of specialised cells that they generate. One clear division of the stem cell family is between those isolated from the embryo, known as embryonic stem cells, and those in adult somatic tissue known as adult stem cells. Within these categories, stem cells can be further divided according to the number of differentiated cell types they can produce. Totipotent stem cells are able to form all fully differentiated cells of the body and trophoblastic cells of the placenta. The embryo, zygote, and the immediate descendants of the first two cell divisions are the only cells considered to be totipotent.

Pluripotent stem cells can differentiate into almost all cells that arise from the three germ layers, but are unable to give rise to the placenta and supporting structures. At around 5 days after fertilisation, embryonic stem cells that form the inner cell mass of the blastocyst are considered pluripotent. Multipotent stem cells are capable of producing a small range of differentiated cell lineages appropriate to their location and are usually found in adult tissues. However, the use of the term multipotent might be somewhat redundant, since some adult stem cells, once removed from their usual location seem to transdifferentiate into cells that reflect their new environment. Stem cells with the least potential for differentiation are termed unipotent; for example, the epidermal stem cell found in the basal skin layer that only produces keratinised squames.

The embryonic stem cell has the greatest potential for organ regeneration because of the diversity and number of cell types that can be produced. However, the idea of lineage commitment has been questioned by recent findings relating to multipotent adult stem cells and the concept of plasticity in which the eventual phenotypic fate of these cells is governed by the local environment. Greater potential might persist in post-natal stem cells than previously thought (figure 3). This theory helps to explain how haemopoietic stem cells could give rise to cells from non-blood lineages such as the cardiomyocyte. An alternative explanation would suggest that these haemopoietic stem cells are contaminated with multipotent mesenchymal stem cells that have the potential to differentiate into the non-blood lineages previously described.

The debate is further complicated by the concept of cell fusion (figure 3). Rather than undergo transdifferentiation, progenitor cells could fuse with native cells to produce a hybrid that expresses both
progenitor and differentiated cell markers. Although this finding has been seen in co-cultures of tissue-derived stem cells and embryonic cell lines, considerable dispute persists with respect to its relevance. The relevance of in-vivo cell fusion in a mouse model of liver failure also has been questioned in relation to the heart since the liver already has a regenerative phenotype. There is no convincing evidence to suggest that cell fusion accounts for the potential of stem cells to regenerate into myocardium, despite the scepticism that exists over transdifferentiation.

**Stem cells in the heart**

Although the possibility of organ repair has been indicated by findings of tissue regeneration in several animal species, the concept came closer to reality with a series of reports that suggested that bone marrow derived progenitor cells were able to repair the hearts of animals that had undergone myocardial injury (figure 4). This approach allowed an autologous source of stem cells to be used thereby circumventing issues relating to the use of transgenic as well as embryonic derived tissue. In one report, a mouse model of ligature-induced myocardial infarction was used. Bone-marrow-derived cells that expressed no differentiation markers (lin-) but carried the receptor for stem-cell factor (c-kit) were injected directly into the heart; cardiac function improved. Furthermore, using immunofluorescence techniques the investigators showed that these primitive bone-marrow-derived cells had undergone a process of differentiation that led them to express various markers specific to cardiomyocytes. They concluded that locally delivered bone marrow cells were able to improve post infarct myocardial function by generating de novo myocardium. This report prompted other work suggesting that adult stem cells, in particular those derived from bone marrow, were also capable of targeting the site of myocardial injury as well as undergoing differentiation into cardiomyocytes.

These results have subsequently been challenged by new techniques that have shown that bone-marrow-derived progenitor cells undergo cellular fusion with local cells (thereby expressing a combination of markers) and therefore might undergo a much more limited process of transdifferentiation than initially thought.

More recently, researchers have used genetic techniques rather than immunofluorescence in an attempt to clarify the fate of bone marrow derived progenitor cells at the site of myocardial infarction. These experiments showed that in a mouse model of myocardial infarction, bone-marrow-derived cells underwent a very low level of transdifferentiation into cardiomyocytes and that the fate of most of these cells was to continue to differentiate along the haemopoietic lineage. These studies did establish whether engraftment of these haemopoietic cells at the infarct site led to an improvement in myocardial function. In the original study, new vessel formation at the infarct site and a subsequent increase in blood supply could have accounted for most of the improvement in left ventricular function. This suggestion is in keeping with several reports on the interaction of different cell types and the myocardium that have produced new blood vessels. The cells that have been transplanted and associated with new vessel formation and improved cardiac function include cardiomyocytes, myoblasts, and both embryonic and bone-marrow-derived stem cells.

We know little about how the fate of these transplanted stem cells might improve cardiac function, and important questions regarding the phenotype of the population of cells that develop remain to be answered. The possibilities are that progenitor cell infusion leads to: new vessel formation, new myocardial formation, or a paracrine effect. Also evidence suggests that the number of cardiac cells produced by cardiac regeneration alone is unlikely to explain the effects seen. Ultimately, the exact mechanism of potential benefit might never be discovered. Most of the controversy over the mechanism arises from the techniques that are used to track and characterise the progenitor cells in the vicinity of the infarct.
Stem cells derived from nuclear transfer with cells that are c-kit+/H11001 derived from embryonic liver are capable of regenerating myocardium with increased effectiveness compared with that reported through the use of bone-marrow-derived cells. Although this approach offers advantages over the use of embryonic stem-cell-derived tissue that provokes an immune response, it is still disadvantaged by the ethical issues related to the use of embryonic tissue. In such a prevalent disease as myocardial infarction whose treatment is an emergency, ideally we should find a therapy that is ethnically acceptable to all. Although stem cells have been used in clinical trials in man, continuing investigation of the basic mechanisms involved is needed.

Clinical studies
The initial report of an improvement in cardiac function in a mouse model of myocardial infarction treated with bone-marrow-derived progenitor cells led to a series of clinical studies in human beings. The main differences between the investigations, which were for the most part designed to test the safety of this approach, were in the choice of progenitor cell and the type of patient. They also used different end-point measurements to ascertain cardiac function (which method is best remains unclear). One of the first reports compared the effects of intracoronary injection of bone-marrow-derived progenitor cells to blood-derived progenitor cells in the context of acute anterior myocardial infarction treated by angioplasty. This interim analysis of 20 patients by Zeiher and colleagues showed that, compared with the reference group of patients, there was an improvement in left ventricular function. Cardiac function did not differ between the blood or bone-marrow-derived progenitor cells although the bone-marrow-derived population contained a substantial proportion of CD34+ haemopoietic cells compared with the blood derived fraction, which mostly contained progenitor cells expressing endothelial cell markers. Importantly, no adverse effects were reported from intracoronary injection of the autologous progenitor cells.

![Diagram](adapted from reference 123 with permission from Macmillan Publishers)

Also, in patients with acute myocardial infarction, Strauer and colleagues reported an improvement in left ventricular function including a significant reduction in infarct size after intracoronary infusion of autologous bone-marrow-derived progenitor cells. The safety and clinical improvement of the approach used in these investigations are confirmed by the work of Drexler and colleagues published in this issue of The Lancet. This study also shows an improvement in cardiac function in patients undergoing angioplasty for acute myocardial infarction who were treated with autologous bone-marrow-derived progenitor cells (see table 1 for a comparison of the studies). The control group received angioplasty and best medical practice. Comparison

![Table](See Articles page 141)

<table>
<thead>
<tr>
<th>Control group</th>
<th>Method of end-point assessment</th>
<th>End-point time (months)</th>
<th>Time to cell infusion (days)*</th>
<th>N</th>
<th>LV baseline</th>
<th>LV end point</th>
<th>Improvement</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assmus et al*</td>
<td>Historical matched</td>
<td>LVEF by ventriculography</td>
<td>4</td>
<td>4 3 (1 5)</td>
<td>Control</td>
<td>20</td>
<td>51% (10)</td>
<td>53 3% (7 9)</td>
</tr>
<tr>
<td></td>
<td>Strauer et al¶</td>
<td>Randomised to PCI</td>
<td></td>
<td></td>
<td>BMC§</td>
<td>20</td>
<td>51% (9 6)</td>
<td>60% (8 6)</td>
</tr>
<tr>
<td></td>
<td>Wollert et al¶</td>
<td>Randomised to PCI</td>
<td></td>
<td></td>
<td>Control</td>
<td>10</td>
<td>60% (7)</td>
<td>64% (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BMCM</td>
<td>10</td>
<td>57% (8)</td>
<td>62% (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>30</td>
<td>51% (3 3)</td>
<td>52% (12 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BMCM</td>
<td>30</td>
<td>50% (10)</td>
<td>56% (12 5)</td>
</tr>
</tbody>
</table>

*Time from primary interventional procedure to infusion of bone-marrow-progenitor cells. ¶Strauer et al showed no significant difference in ejection fraction between control and cell treated groups. Although each group used autologous unsorted bone marrow cells in the cell therapy group, the method of preparation varied between the studies. †p-value reflecting change relative to control group. Although each group used autologous unsorted bone marrow cells in the cell therapy group, the method of preparation varied between the studies. Data are mean (SD) unless otherwise indicated.

Table 1: Comparison of outcomes of clinical trials of infusion of autologous bone-marrow-derived progenitor cells following acute myocardial infarction
between the bone-marrow-treated and control group showed that in those patients who received progenitor cells the improvement in left ventricular function increased more than in the control group in whom a small improvement was also seen. To show the electrical stability of the myocardium after progenitor cell infusion both groups underwent electrophysiological testing with ventricular stimulation protocols. Results showing that the control and bone-marrow-cell treated groups did not differ in the ability to stimulate ventricular arrhythmia add to the safety data for the use of this approach in man. Future studies should be designed to show, using appropriate controls, that circulating cytokines alone, induced by the procedures themselves, are not responsible for the improvement in cardiac function.

Researchers have also injected autologous unfractionated progenitor cells (both circulating and bone marrow derived) into patients with acute myocardial infarction107–109 and chronic ischaemic heart failure.99,100 These studies reported an improvement in quality of life assessments and cardiac function. Route of delivery of progenitor cells varied and included intracoronary100 and direct intramyocardial injection of CD34+ enriched cells103 as well as direct intramyocardial injection of AC133+ (endothelial cell progenitors) into patients undergoing CABG104 have shown an improvement in cardiac function.

Importantly, most of these small studies have reported few side-effects. The worst side-effects reported include a mild elevation in cardiac enzymes and a non-significant increase of in-stent restenosis in a group of patients with myocardial infarction. The latter group was treated with intracoronary injection of CD34+ enriched cells110 as well as direct intramyocardial injection of AC133+ (endothelial cell progenitors) into patients undergoing CABG104 have shown an improvement in cardiac function.

The other main approach to deliver cell transplantation in man has involved the use of skeletal myoblasts. Fetal cardiomyocytes and skeletal myoblasts were transplanted into animal models of ischaemic heart failure. This improved left ventricular function.105–111 Then skeletal myoblasts (taken from autologous cells cultured from a muscle biopsy) were transplanted into the peri-infarct zone of a man undergoing bypass surgery. At 5 months, the researchers reported that the areas of the heart that had received the myoblasts had regained some functional capacity.112 Subsequently, studies in which skeletal myoblasts were injected directly into the myocardium (either at the time of CABG114 or with a percutaneous technique113) of patients with ischaemic left ventricular failure have shown an improvement in cardiac function. One major drawback to this approach is the reported increased incidence of serious ventricular dysrhythmia.113,115 The potential for myoblast treatment to produce rhythm disturbances has lead to criticism and debate as to whether these studies are premature.

A failure to explain the mechanism by which any of the methods of stem-cell transplantation leads to an improvement in cardiac function has provoked similar concerns. Chien116 suggested that more preliminary data, to elucidate the mechanism of action, are needed before these techniques are tested in patients. However, it should be remembered that most of the pharmacological agents used in the management of cardiac patients were tested in man without a full understanding of their mechanism of action. Our understanding of the beneficial effects of drugs is always provisional. Indeed, without compromising safety, it would be unreasonable to have withheld some of the major breakthroughs in the management of cardiovascular disease until a full understanding of their mechanism of action had been established. When potential clinical benefit has been shown, safety is the primary consideration that should determine further trials. An understanding of mechanism of benefit is highly desirable yet not necessary. In future, such an understanding might allow refinement of these techniques. For example, genetically engineered stem cells might be developed to target delivery of potentially beneficial agents to the heart.117

Are further trials using autologous bone marrow transplant in acute myocardial infarction justified?

The most consistent improvement in myocardial function combined with safety has come from studies using autologous bone-marrow-cell transplantation in myocardial infarction. In their studies on acute myocardial infarction Drexler,118 Strauer,119 and Zeiher120 used a preparation of bone-marrow-derived progenitor cells which was infused into the coronary artery. In all patients in these studies the cells used were autologous. Although an increase in understanding of the functioning of the heart alone is justification for research, in this case the objective was to find a new
treatment for ischaemic heart disease. The use of autologous bone marrow cells for the treatment of ischaemic heart disease would seem simple, cheap, and widely applicable if efficacy were shown. Such treatment would have the potential of relieving much human suffering and, therefore, should be applied as soon as possible. The decision on efficacy must be based upon the results of randomised, controlled, and, if possible, masked clinical trials. Such trials must take into account the fact that myocardial infarction and heart failure are treated in district general hospitals, or their equivalent, and, therefore, should use methodologies applicable to such hospitals. For example, the processing of stem cells should be done locally.

The trials so far have not been double-blind randomised controlled trials. Because of the tendency of cardiac function to improve with time after myocardial infarction, if the patient survives, controlled trials, in which the control reproduces the exact conditions of the test in the absence of the autologous bone marrow cells, are essential. They should be masked. The danger of not doing such trials is that small, uncontrolled studies, although a necessary step in the development of a new therapy, might give rise to a mosaic of unproven practices, which differ from centre to centre. Consequently, the true benefit of this novel treatment would never be fully tested.

Lack of involvement of the pharmaceutical industry

Commercial drive, controlled by government regulation, has produced most medicines used to treat ischaemic heart disease. There have been three phases in this process. Small molecules such as β blockers or calcium antagonists were developed with the pharmaceutical company owning the intellectual property in the molecule. The putative mechanism was usually understood both in-vitro and in animal models. Development was very expensive, involving much toxicology, and was heavily controlled by governmental regulatory authorities. The medical profession did most of the clinical trials involved under the control of the regulatory authorities. The medical profession was therefore in control of the situation, which gives them novel responsibilities that have to be dealt with without the drive, focus, and discipline of a commercial organisation. Toxicology is less onerous or is absent and regulations are mostly related to the preparation of cells for infusion. Of all the differences between the earlier development paradigms, the difficulty in funding large definitive, double-blind controlled trials is probably the most serious. Furthermore, there is a tendency for academic physicians to compete with each other. The formation of large co-operative teams would be helpful.

Risk benefit ratio

Evidence in this seminar suggests that further definitive clinical studies are necessary, and specifically, randomised controlled clinical trials. Whether this is justified depends on the risk benefit ratio. As shown in table 2, it would seem that the potential benefit of bone-marrow-progenitor cells in the treatment of acute myocardial infarction is not outweighed by the risk of undertaking further clinical trials. Similar risk benefit analysis should precede future clinical studies in this

<table>
<thead>
<tr>
<th>For</th>
<th>Against</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal studies</td>
<td>Models of myocardial infarction show that autologous stem-cell transplantation improves cardiac function</td>
<td>Data suggest that transplanted autologous stem cells do not become myocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In dogs, autologous stem cell transplantation leads to micro infarction</td>
</tr>
<tr>
<td>Man</td>
<td>Autologous bone marrow and peripheral blood stem cells transplanted in patients with acute myocardial infarction improves cardiac function</td>
<td>Suggestion of increased in-stent re-stenosis rate in patients with acute myocardial infarction treated with G-CSF and stem cells</td>
</tr>
</tbody>
</table>

Table 2: Are further clinical trials of autologous bone-marrow-stem cells for treatment of myocardial infarction justified?
area. As at the beginning of gene therapy studies, one
injudicious act could scuttle the whole advance.

**Conclusion**

There is evidence across species that regeneration of
tissue can occur. Both animal and human studies
suggest that stem cells capable of improving cardiac
function exist in adults. This might be part of a natural
repair process. The benefit of this novel approach to
treating cardiovascular disease should be confirmed and
optimised. Safety is the key issue. It is important that
clinical trials are designed to answer these questions.
Funding such large studies will remain a major hurdle.
Open collaboration amongst basic scientists and
clinicians around the world is crucial for these problems
to be overcome.

**Conflict of interest statement**

None declared.

**Acknowledgments**

We thank Matthew Lovell for his help in preparing this manuscript. John
Martin holds the British Heart Foundation Chair of Cardiovascular
Science at University College London and is also funded by the European
Commission and the Mary Kinross charitable trust. Anthony Mathur is
supported by the British Heart Foundation.

**References**

2. Eisenberg LM, Eisenberg CA. Adult stem cells and their cardiac
3. Soonpaa MH, Field LJ. Survey of studies examining mammalian
4. MacLellan WR, Schneider MD. Genetic dissection of cardiac growth
5. Chien KR, Olson EN. Converging pathways and principles in
6. Kajstura J, Leri A, Anversa P. Cardiomyocyte repopulation by extracardiac progenitors in
8. Laflamme MA, Myerson D, Safitz JE, Murry CE. Evidence for
cardiomyocyte repopulation by extracardiac progenitors in
10. Beltrami AP, Barlucchi L, Torella D, et al. Adult cardiac stem cells are
12. Wessels A, Perez-Pomares JM. The epicardium and epicardially
derived cells (EPDCs) as cardiac stem cells. Anat Rec 2004; 276: 43–57.
13. Douglas BS. Conservative management of guillotine amputation of
fingertip amputations with bone exposure. A comparative study
20. Cardoso MC, Leonhardt H, Nada-Ngirad B. Reversal of terminal
22. Eguchi G, Watanabe K. Elicitation of lens formation from the“ventral iris” epithelium of the newt by a carcinogenic, N-methyl-N-
23. Tsonis PA. Effects of carcinogens on regenerating and non-
26. Ozkin SH, Zon LI. Hematopoiesis and stem cells: plasticity versus
27. Anderson DJ, Gage FH, Weissman IL. Can stem cells cross lineage
30. Vassileopoulos G, Wang PR, Russell DW. Transplanted bone
32. Hawley RG, Sobieski DA. Somatic stem cell plasticity: to be or not to
33. Wagers AJ, Sherwood RI, Christensen JL, Weissman IL. Little

---

Seminar
66 Kocher AA, Schuster MD, Szabolcs MJ, et al. Neovascularization of
Hamano K, Li TS, Kobayashi T, et al. Therapeutic angiogenesis
Asahara T, Masuda H, Takahashi T, et al. Bone marrow origin of
Chien KR. Stem cells: lost in translation.
Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL,
Alvarez-Dolado M, Pardal R, Garcia-Verdugo JM, et al. Fusion of
Satomi-Kobayashi S, Kawashima S, Sakoda T, et al. Cardiac
Orlic D, Kajstura J, Chimenti S, Bodine DM, Leri A, Anversa P.
Wang JS, Shum-Tim D, Galipeau J, Chedrawy E, Eliopoulos N,
Tomita S, Li RK, Weisel RD, et al. Autologous transplantation of
Medvinsky A, Smith A. Stem cells: fusion brings down barriers.
Wells WA. Is transdifferentiation in trouble?
improves cardiac function.
ischemic myocardium by human bone-marrow-derived angioblasts
peripheral blood mononuclear cells into ischemic hibernating
angioblasts, angiogenic ligands, and cytokines.
collateral perfusion and regional function via side supply of
Ann Thorac Surg
J Am Coll Cardiol
autologous bone marrow enhances collateral perfusion and regional
Circulation
Medinsky A, Smith A. Stem cells: fusion brings down barriers.
Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human
mesenchymal stem cells differentiate to a cardiomycocyte phenotype
Wang JS, Shum-Tim D, Galipeau J, Chedrawy E, Eliopoulos N,


121 Iten LB, SV. Forelimb regeneration from different levels of amputation in the newt N. viridescens: Length, rate and stages. Wilhelm Roux Arch Dev Biol. 1973; 173: 263–82.
