Brief Review

Adipose Tissue–Derived Stem Cells
Characterization and Potential for Cardiovascular Repair

Rosalinda Madonna, Yong-Jian Geng, Raffaele De Caterina

Abstract—Experimental studies have shown that cardiac transfer of unfractionated or partially purified bone marrow cells, as well as stem cells and progenitor cells derived from the bone marrow or peripheral blood, can enhance functional recovery after an acute myocardial infarction. However, the relatively low abundance, small tissue volume, difficult accessibility, and disease-related malfunction of bone marrow–derived stem cells hamper their clinical usefulness. Numerous studies have provided evidence that stromal cells derived from the adipose tissue (adipose tissue–derived stromal cells [ADSCs]) contain a population of adult multipotent mesenchymal stem cells and endothelial progenitor cells that can differentiate into several lineages, including endothelial cells, smooth muscle cells, and cardiomyocytes. The similarities between stem cells extracted from the bone marrow and the adipose tissue suggest the potential for the adipose tissue to act as an alternative, and perhaps preferable, cell source for repairing damaged tissues, such as the ischemic or infarcted heart. We have here reviewed the medical literature describing molecular and functional characterization, differentiation, potential role, and results obtained so far using ADSCs in tissue repair, with a particular focus on the role for ADSCs in cardiovascular repair and regeneration. (Arterioscler Thromb Vasc Biol. 2009;29:1723-1729.)

Key Words: adipose tissue ■ bone marrow ■ stem cells ■ stromal cells ■ myocardial repair ■ myocardial regeneration.

Despite contemporary medical treatments, heart failure remains a major cause of morbidity and mortality in developed countries.1 Transplantation of stem or progenitor cells is a promising strategy for cardiac repair, attracting tremendous attention of basic scientists and clinicians.2 Several issues have been raised against harvesting human embryonic stem cells.3 Compared with embryonic stem cells, autologous adult stem cells do not raise any major ethical or immunologic problems. Sources of adult stem cells include the muscle, bone marrow, blood, epidermis, brain, liver, and, more recently, the adipose tissue.4 Chronologically, skeletal myoblasts were the first to be used clinically in patients with ischemic heart disease.5 Experimental studies have shown that injected myoblasts stably engraft into postinfarction scars and improve left ventricular function. Current hypotheses of mechanisms of myoblast actions include limitation of left ventricular remodeling, as well as paracrine effects determining angiogenesis, recruitment of resident quiescent cardiac cells, and extracellular matrix stabilization.6 However, the skeletal muscle, as well as the skin, brain, liver, and bone marrow, are essential organs. Cell harvesting procedures from these organs are painful and costly, and frequently associated with the risk of donor-site morbidity. For instance, bone marrow aspiration may yield low numbers of stem cells on processing, which necessitates an ex vivo expansion step to obtain sufficient cell numbers for clinical application. Therefore, research interest has increased toward alternative sources of stem cells. Adipose tissue may represent an ideal source of autologous stem cells, because it is easy to obtain with minimal patient discomfort, but yet capable of yielding cell numbers substantial enough to obviate extensive expansion in culture.4

The stem cell population derived from collagenase-digested human adipose tissue (stromal-vascular fraction [SVF]) has been shown to differentiate into multiple cell lineages, including the adipose tissue, cartilage, bone,5,7-9 skeletal muscle,10 neuronal cells,11,12 endothelial cells,13-16 cardiomyocytes,17-22 and smooth muscle cells.23-26 There is much confusion in the literature when using terms describing multipotent stem cells from the adipose tissue stroma. We refer here to the term adipose tissue–derived stromal cells (ADSCs), which identifies a plastic-adherent cell population that includes vascular (pericytes and endothelial progenitor cells/adipocyte progenitor cells (preadipocytes) and adult multipotent mesenchymal stem cells (MSCs), besides circulating blood cells, fibroblasts, endothelial cells, smooth muscle cells, and immune cells, such as macrophages and lymphocytes27 (Figure 1).
Characterization of Adipose Tissue–Derived Stromal Cells for the Presence of Endothelial Progenitors and Cardiomyocyte Lineage Differentiation

ADSCs derived from the visceral and subcutaneous human adipose tissue have been recently shown to contain progenitor cells able to differentiate into mature endothelial cells and participate in blood vessel formation. Miraville et al have shown the presence of the endothelial progenitor cell (EPC) phenotype in the SVF freshly isolated from humans by flow cytometry. Cell preparations display the hematopoietic stem cell markers CD34, as well as CD133, a 130-KDa glycoprotein with unknown function that is absent on mature endothelial cells and circulating progenitor endothelial cells. Studies by Zuk et al have described the absence or low level of CD34+ cells, whereas Planat-Bernard et al reported more than 90% CD34+ cells in the SVF derived from the adipose tissue. The most likely reason for these discrepancies is that the latter investigations were performed by the use of limitedly cultured ADSCs (primary culture of 3 days with no subsequent plating). Flow cytometric analysis showed that the CD34+ cell subset is constituted of 2 populations: the CD34+/CD31− cells and the CD34+/CD31+ cells. Quantitative analysis of laser-Doppler data revealed a time-dependent increase in blood flow after the injection of CD34+/CD31− cells in the ischemic hind limb. Comparison between the angiogenic activity of the SVF from the adipose tissue with that from the bone marrow demonstrated that the administration of 1×106 SVF cells enhanced neovascularization to a similar extent as that of 1×106 bone marrow–derived mononuclear cells (BM-MNCs). Likewise, it has been found that cells positive for the kinase insert domain receptor (KDR; alternative names: vascular endothelial growth factor [VEGF] receptor-2 [VEGFR-2], protein tyrosine kinase Flik-1, CD309 antigen) isolated from cultured ADSCs featured an endothelial phenotype in the presence of VEGF.

The vascularized adipose tissue does contain other types of cells, such as pericytes, dendritic cells, macrophages, microvascular endothelial cells, and may also contain bone marrow–derived mesenchymal stem cells. Disruption of the blood supply during fat tissue isolation may result in the release of circulating bone marrow–derived mesenchymal stem cells and pericytes, known to possess the potential for multi-lineage differentiation. It is therefore plausible that ADSC-induced vessel formation and growth might also be related to the contribution of resident microvascular endothelial cells or preadipocytes through the secretion of proangiogenic factors, or through the contribution of periendothelial pericytes capable of interacting with and stabilizing endothelial networks. Based on these observations, pericytes may represent a second angiogenic precursor, resident in the adult human adipose tissue, with similar angiogenic potency to—but phenotypically distinct from—ADSCs. Recent reports have also demonstrated that human ADSCs themselves express pericyte lineage markers and exhibit perivascular functions, by showing increased migration in response to vascular endothelial growth factor (VEGF)-165 and platelet-derived growth factor (PDGF)-BB, a pericyte-like morphology around microvessels, and contributing to augmented microvascular density during angiogenesis by migrating toward vessels. These observations have supported the hypothesis that ADSCs themselves might originate from perivascular stem cells, similarly to pericytes. This hypothesis is intriguing but awaits confirmation through future studies.

ADSCs have been shown to exhibit also in vitro differentiation into the cardiomyocyte lineage. In these reports, different methods for the induction of differentiation have been used. Rangappa et al first described the appearance of beating cells on treatment of mesenchymal stem cells isolated from rabbit subcutaneous adipose tissue with 5-azacytidine. At 2 weeks, 30% of the cells aggregated and formed a ball-like structure with spontaneous contractile activity. We subsequently described the spontaneous cardiomyocyte differentiation of ADSCs from primary cultures of ADSCs isolated from murine visceral and subcutaneous adipose tissue, without any chemical treatment. In such latter protocols, the percentage of beating clones counted at 20 days ranged from 0.02% to 0.07% of the plated ADSCs. Electrophysiological studies revealed a pacemaker activity of the cells. These data...
indicate the presence of myogenic stem cells in the adipose tissue stroma.

Characterization of Culture-Expanded Adipose Tissue–Derived Stromal Cells for Multipotency

In a nondifferentiating medium, culture-expanded cells (until passage 4) isolated from the bone marrow (bone marrow–derived stromal cells [BMSCs]) and from the adipose tissue (ADSCs) have been shown to give rise to apparently homogeneous populations with similar cell size and cell surface markers.37 Both populations were shown to express CD13, CD29 (β1-integrin), CD44, CD58, CD90, CD105 (endoglin), and CD166. SH-3, an epitope present on CD73 (ecto-5′-nucleotidase), and STRO-1, a marker for cells with multilineage potential, are also uniformly expressed by both ADSCs and BMSCs.38 However, the expression of adhesion molecules with known functions in regulating the homing or mobilization of stem cells differs between these 2 cell preparations. For example, ADSCs express CD48d (αβ integrin, which forms a heterodimer with CD29 to create very late activation antigen-4, VLA-4, the main cognate ligand for vascular cell adhesion molecule-1 [VCAM-1]–CD106 ligand), whereas cells derived from the bone marrow do not. The pattern of expression of VCAM-1 is reversed.37 Similarly, ADSCs express high levels of CD54 (intercellular adhesion molecule-1 [ICAM-1]–CD106 ligand), whereas BMSCs have very low expression of this molecule. This is an intriguing observation, given the important role of the interaction between these adhesion molecules and their ligands in regulating stem cell trafficking.37

Still, overall, the general pattern of mesenchymal lineage differentiation of ADSCs and BMSCs in nondifferentiating media is very similar. More differences have, however, been observed when cells are grown in differentiating media. In particular, in an osteogenic differentiation medium alkaline phosphatase activity is significantly greater in ADSCs compared with BMSCs, whereas mineralization is more extensive with BMSCs. Both cell populations express mRNAs specific for type-I collagen, osteocalcin, osteonectin, osteopontin, bone morphogenetic protein (BMP)-1, parathyroid hormone receptor, retinoic acid-X receptor(RXR)α, vitamin D, and core-binding factor alpha (CBFA)-1, a transcription factor that regulates multiple osteogenic genes.4 Thus, environmental factors appear to play an important role in ADSC differentiation into a given cell lineage.

Advantages of Adipose Tissue–Derived Stromal Cells Over Other Cell Sources

Studies using human bone marrow cell transplantation in ischemic patients suggest that human angiogenic cell therapy requires the administration of at least $10^7$ to $10^9$ endothelial progenitor cells (EPCs) from peripheral blood or umbilical cord, depending on the degree of stem cells purity and the delivery method. The rarity of these progenitors in peripheral blood has implications for the large amounts of patient’s blood required to achieve a proangiogenic or a proneovascularogenic effect. Such amounts are not easily available in a clinical setting. In a comparative study between peripheral blood and the adipose tissue we compared the yield of endothelial progenitor cells from these two sources.16 We found that the adipose tissue is capable of yielding a higher number of endothelial progenitor cells than peripheral blood. Furthermore, in a comparative study of BMSCs and ADSCs obtained from the same donors, De Ugarte et al demonstrated that ADSCs required approximately 5% the cell number used for marrow cells to reach initial confluence by 1 week.37 This suggests a larger proliferative potential for ADSCs, either for properties intrinsic to the cells or as the result of the higher density of stem cells within the initial population. Thus, assuming clinical equivalence, the higher proliferative activity of the adipose tissue–derived population would generate a clinically effective cell dose more rapidly than for bone marrow cells.

Recent studies have also reported on the in vivo and in vitro immunoregulatory properties of ADSCs. Independent studies from different laboratories have shown that culture-expanded human ADSCs (ie, cells beyond passage (P)0), as opposed to freshly isolated SVF cells or early-passage ADSCs, reduce their expression of surface histocompatibility antigens and no longer elicit allospecific T-cell proliferative responses.39,40 If confirmed by further independent and comprehensive testing, such differences would highlight the possibility for ADSCs, limitedly to culture-expanded cells from allogeneic healthy donors, to serve as a valuable source of stem cells for therapeutic use in older patients,41,42 or in those with malignant diseases, or obese,43 who cannot yield sufficient numbers of functional ADSCs, in alternative to autologous cells.

We cannot, however, avoid taking into account also other factors coming into play when using the adipose tissue as a stem cell source for clinical transplantation. Because the enzymatic digestion of the adipose tissue with collagenase represents a critical step in ADSC isolation, parameters such as the digestion time and enzyme activity, playing a role in the isolation procedure of primary ADSCs, may also have a significant effect on cell yield, viability, phenotype, and differentiation potential.44 In addition, the digestion process increases the risk of contamination. The challenge is to isolate the maximum possible number of functional progenitors without damaging the cell population in the process and in conformity with standards of good manufacturing practice. Careful testing of collagenase purity, lot-to-lot variation, and the purity of cell preparations from contaminants appear therefore to be mandatory before embarking in human clinical trials.

Altogether, the yield (a therapeutic dose of CD34+$^+$-enriched cells with angiogenic activity can be isolated in approximately 1-hour digestion of a limited amount of adipose tissue, without cell culture expansion) and safety from immune rejection in case of allogeneic administration from healthy donors appear major theoretical advantages of adipose tissue as an alternative to other sources of cells for myocardial repair.

Outcome Findings

The administration of cells from the adipose tissue can favorably affect revascularization in animal models of ische-
mic limb13,14,33,34,45–48 (Table 1) and can effectively improve left ventricular function in animal models of acute and chronic myocardial infarction19,20,49–54 (Table 2). Several mechanisms underlying the benefit of ADSC transplantation have been proposed to explain the recovery of the ischemic tissue after ADSCs transplantation: (1) secretion of multiple angiogenic growth factors, such as VEGF and hepatocyte growth factor (HGF), with the potential of inducing endothelial growth, migration, and tube formation33,34,46,55; (2) differentiation of transplanted ADSCs into myocytes, 17,18,20 smooth muscle cells, and endothelial cells13,14; (3) secretion of antioxidant chemicals, free radical scavengers, and chaperone/heat shock proteins at the site of ischemia.14

In this context, the study by Miyahara et al20 is of special interest, because it showed the capability of adipose tissue–derived MSCs to improve left ventricular function mainly by growth factor–mediated paracrine effects. The presence of cardiomyocytes within the MSC grafts appeared to be rare, and the authors therefore concluded that MSCs acted mainly through paracrine pathways to trigger angiogenesis.

A further mechanism by which implanted ADSCs can improve heart function is the recruitment of native cardiac resident stem or progenitor cells by paracrine mechanisms.56 ADSCs would modulate the “stem cell niche” of the host by stimulating the recruitment of endogenous stem cells to the implantation site and promoting their differentiation along the

Table 1. Adipose Tissue–Derived Stem Cell Therapy in Animal Models of Acute and Chronic Ischemic Limb

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal Model</th>
<th>Source of Adipose Tissue</th>
<th>Cell Type</th>
<th>Delivery</th>
<th>Time After Ischemia</th>
<th>Outcome Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planat-Benard et al13</td>
<td>Mouse, FA ligation</td>
<td>Subcutaneous murine AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>5 hours</td>
<td>Capillary density, DTP score</td>
</tr>
<tr>
<td>Miranville et al14</td>
<td>Mouse, FA ligation</td>
<td>Subcutaneous human AT</td>
<td>AT-derived CD34+CD31- cells</td>
<td>i.m. injection</td>
<td>24 hours</td>
<td>Capillary density, DTP score</td>
</tr>
<tr>
<td>Rehman et al33</td>
<td>Mouse, FA ligation</td>
<td>Subcutaneous human AT</td>
<td>wild-type ADSCs or VEGF-overexpressing ADSC</td>
<td>i.m. injection</td>
<td>24 hours</td>
<td>Capillary density, DTP score</td>
</tr>
<tr>
<td>Nakagami et al34</td>
<td>Mouse, FA ligation</td>
<td>Subcutaneous human AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>10 days</td>
<td>Capillary density, DTP score</td>
</tr>
<tr>
<td>Cao et al47</td>
<td>Mouse, FA ligation</td>
<td>Visceral human AT</td>
<td>At-derived KDR+/CD34+/CD31+ cells</td>
<td>i.m. injection</td>
<td>2 hours</td>
<td>Capillary density, DTP score</td>
</tr>
<tr>
<td>Sumi et al48</td>
<td>Mouse, FA ligation</td>
<td>Visceral murine AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>24 hours</td>
<td>Capillary density, DTP score</td>
</tr>
<tr>
<td>Moon et al46</td>
<td>Mouse, FA ligation</td>
<td>Subcutaneous human AT</td>
<td>AT-derived MSCs</td>
<td>i.m. injection</td>
<td>1 or 7 days</td>
<td>Capillary density, DTP score</td>
</tr>
<tr>
<td>Kondo et al48</td>
<td>Mouse, FA ligation</td>
<td>Subcutaneous murine AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>24 hours</td>
<td>Capillary density, DTP score</td>
</tr>
</tbody>
</table>

AT indicates adipose tissue; ADSCs, adipose tissue–derived stromal cells; DTP score, Doppler tissue perfusion score; i.m., intramuscular (gastrocnemius, gracilis, quadriceps muscle) injections; MSCs, mesenchymal stem cells; VEGF, vascular endothelial growth factor; FA, femoral artery.

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Table 2. Adipose Tissue–Derived Stem Cell Therapy in Acute and Chronic Animal Models of Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal Model</th>
<th>Source of Adipose Tissue</th>
<th>Cell Type</th>
<th>Delivery</th>
<th>Time After AMI</th>
<th>Outcome Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamada et al19</td>
<td>Rats, LAD ligation</td>
<td>Brown rat AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>4 weeks</td>
<td>LVEF</td>
</tr>
<tr>
<td>Miyahara et al20</td>
<td>Rats, LAD ligation</td>
<td>Subcutaneous and visceral rat AT</td>
<td>MSCs</td>
<td>i.m. injection</td>
<td>4 weeks</td>
<td>LVEF</td>
</tr>
<tr>
<td>Valina et al48</td>
<td>Pigs, LAD occlusion by AB followed by reperfusion</td>
<td>Subcutaneous porcine AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>4 weeks</td>
<td>LVEF</td>
</tr>
<tr>
<td>Zhang et al53</td>
<td>Rabbit, LAD ligation</td>
<td>Subcutaneous rabbit AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>5 weeks</td>
<td>LVEF, LVEDP</td>
</tr>
<tr>
<td>Li et al52</td>
<td>Rats, LAD ligation</td>
<td>Subcutaneous and visceral rat AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>4 weeks</td>
<td>LVEF</td>
</tr>
<tr>
<td>Schenke-Layland et al54</td>
<td>Rats, LAD ligation followed by reperfusion</td>
<td>Subcutaneous and visceral rat AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>3 months</td>
<td>LVEF, CO, LVEDV</td>
</tr>
<tr>
<td>Cai et al50</td>
<td>Rats, LAD ligation</td>
<td>Subcutaneous and visceral human AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>4 weeks</td>
<td>LVEF</td>
</tr>
<tr>
<td>Mazo et al51</td>
<td>Rats, LAD ligation</td>
<td>Subcutaneous and visceral murine AT</td>
<td>ADSCs</td>
<td>i.m. injection</td>
<td>4 weeks</td>
<td>LVEF</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending; AT, adipose tissue; ADSCs, adipose tissue–derived stromal cells; MSCs, mesenchymal stem cells; LVEF, left ventricular ejection fraction; CO, cardiac output; LVEDV, left ventricular end-diastolic volume; LVEDP, left ventricular end-diastolic pressure; AMI, acute myocardial infarction; AB, angioplasty balloon.
required lineage pathway. Excess production or degradation of the cardiac extracellular matrix (ECM) can lead to progressive ventricular dilatation and cardiac dysfunction. By determining or favoring a balance between ECM degradation and production through the secretion of growth factors, implanted cells may stabilize the ventricular scaffold and therefore exert beneficial effects on adverse remodeling\(^57\) (Figure 2). All such hypotheses need further testing.

An interesting additional possibility currently being explored is to enhance the angiogenic and myogenic effects of transplanted ADSCs by modifying them ex vivo (ie, by transection before implantation) to express one or more selected genes. Rehman et al sought to enhance the angiogenic effects of cell transplantation through the overexpression of VEGF and basic fibroblast growth factor (bFGF).\(^33\) Subsequently, Zhu et al reported that the intravenous injection of human ADSCs transfected with the gene for HGF resulted in greater angiogenesis and improved cardiac function compared with unmodified cells.\(^58\) These studies have consistently demonstrated that cell-based angiogenic gene therapy results in greater angiogenesis and functional improvement than cell transplantation alone. The promising results of these early studies need to be thoroughly confirmed before running attempts at the clinical application of this concept.

Despite several unsettled mechanistic issues, the (still relatively modest, in our opinion) bulk of animal studies has been deemed convincing enough for some researchers to justify a move toward clinical applications. The first human studies started in 2007, with 2 now ongoing trials, APOLLO and PRECISE (registered at www.clinicaltrials.gov). The APOLLO (AdiPOse-Derived Stem ceLLs in the Treatment of Patients With ST-Elevation myOcardial Infarction), and the PRECISE (A Randomized Clinical Trial of adiPose-deRived stEm & Regenerative Cells In the Treatment of Patients With Non revaScularizable ischEmic Myocardium) studies are both prospective, double-blind, randomized, placebo-controlled, phase-I trials, currently in the recruiting phase. The primary and secondary outcomes of both studies are safety (determined by the rate of major adverse cardiac and cerebral events [MACCE]) and feasibility. For the APOLLO trial, inclusion criteria are: (1) clinical symptoms consistent with acute myocardial infarction for a minimum of 2 and a maximum of 12 hours from onset to a percutaneous coronary intervention (PCI), and unresponsive to nitroglycerin; (2) a successful revascularization of the culprit lesion in the major epicardial vessel; (3) an area of hypoperfusion corresponding to the culprit lesion; (4) left ventricular ejection fraction in a range between 30\% and 50\% at the time of successful revascularization; and (5) the ability to undergo liposuction. For the PRECISE trial inclusion criteria are: (1) coronary artery disease not amenable to any type of revascularization (percutaneous or surgical) in the target area; (2) hemodynamic stability; and (3) the ability to undergo liposuction.

Certainly more clinical studies are needed to demonstrate the long-term efficacy of this approach.

**Perspectives and Open Questions**

Although several studies have provided in vitro and in vivo evidence that ADSCs contain a population of adult multipotent mesenchymal stem cells with therapeutical potential for repairing damaged cardiac tissues, a number of fundamental points need to be addressed before this approach can be proposed clinically. Because the majority of patients with acute myocardial infarction undergo spontaneous or therapeutic reperfusion, the ability of ADSCs to improve cardiac function should be tested in an infarcted reperfused myocardium. The literature is replete with examples of therapies that work in the presence of a permanent coronary occlusion. Consequently, it is of utmost importance to determine whether ADSCs are effective when coronary occlusion is followed by reperfusion, an event that dramatically alters the milieu of the myocardial interstitium and of the myocardium itself. Second, improvement in left ventricular function has been shown when stem cells are injected intramyocardially in the perinfarcted area. Clinically, the most practical route for ADSC administration is the intravascular (intracoronary) delivery, but only a limited number of studies have explored this modality of administration. A recent study by Valina et al has shown that the intracoronary administration of ADSCs into the acutely infarcted myocardium allows ADSCs to transdifferentiate into endothelial and vascular smooth muscle cells, leading to an improvement of left ventricular function, remodeling, and perfusion in a porcine model.\(^49\)
These observations have been confirmed in subsequent studies, showing that, after injection into the perifascialed region, the administration of these cells improves left ventricular ejection fraction, with postmortem evidence of reduced fibrosis and increased angiogenesis. Other investigators have demonstrated substantial improvement of left ventricular ejection fraction in a chronic rat model of myocardial infarction after the intramyocardial injection of ADSCs. The main mechanism whereby ADSCs improve cardiac function (differentiation into cardiac cells versus fusion versus paracrine effects on preexisting cells) remains poorly understood, and the advantage of using total unFractionated ADSCs compared with purified populations of ADSCs, such as the CD34⁺-purified ADSCs, remains to be determined. Although it is tempting to jump on clinical application, we advocate much more experimental work in animal models. Large animal models of myocardial infarction, such as in swine, exist, closely resemble human disease, but are laborious and expensive. Yet such models should guide to the proper selection of cell types, timing, and mode of delivery before running the risk of throwing this entire promising area of research into discredit for premature clinical trials.

**Source of Funding**

This work was supported by the Italian Ministry of Research and Scientific Research through funding to the Center of Excellence on Research into discredit for premature clinical trials. Proper selection of cell types, timing, and mode of delivery before running the risk of throwing this entire promising area of research into discredit for premature clinical trials.

**Disclosures**

None.

**References**


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