Clinical Potential of Adult Vascular Progenitor Cells

Arun H.S. Kumar, Noel M. Caplice

Abstract—Cell therapy to treat vascular and cardiovascular diseases has evolved over the past decade with improved understanding of progenitor cell mobilization, recruitment, and differentiation. The beneficial effects seen in several preclinical studies have prompted translation of adult vascular progenitor therapy to clinical trials. To date, progenitor cells isolated from bone marrow and peripheral blood have been tested in the context of acute myocardial infarction and chronic ischemic cardiomyopathy, with moderate benefit. This therapeutic effect occurs despite a relatively small number of injected progenitor cells and short-term residence in the target zone. Thus, indirect benefits, such as paracrine factors released from these cells, have been suggested as significant contributors to therapeutic efficacy. Several additional vascular progenitors of endothelial, smooth muscle, mesenchymal, and cardiac origin have been identified that may contribute to vasculogenesis. Indeed, a unifying paradigm for the most effective cell therapy strategies to date appears to be robust support of angiogenesis. Here we discuss a number of progenitor cells that currently show potential as cardiovascular therapeutics, either singly or in combination. We look at emerging cell types and disease targets that may be exploited for therapeutic benefit and future strategies that may maximize clinical efficacy. (Arterioscler Thromb Vasc Biol. 2010;30:1080-1087.)

Key Words: acute coronary syndromes ■ cardiovascular disease prevention ■ ischemia ■ vascular biology ■ progenitor cells ■ vascular modeling

Vascular and cardiac diseases encompass a spectrum of pathological, structural, and functional changes in the cellular architecture of blood vessels and the heart. Traditionally, the therapeutic approach to such pathologies has been pharmacological agents or surgical intervention. However, with the advent of regenerative medicine, the past decade has heralded an alternative strategy focused on cell-based therapeutics.1 For the purposes of this review, we will classify vascular progenitors as a broad category of cells that includes precursor cells in the bone marrow, circulation, and local tissues with the capacity to differentiate into endothelial cells or smooth muscle cells.2-3 Cells with vascular differentiation capacity can thus contribute to multiple aspects of therapeutic vascular and cardiac repair, including reendothelialization, device and graft passivation, tissue engineering of vascular conduits, and organ vasculogenesis and adaptive remodeling. A large number of preclinical studies support a beneficial role for adult progenitor cells in vascular and cardiac repair,3-4 and concurrently, this promise has been extended to the clinical field. To date, bone marrow mononuclear cells (BM-MNCs), endothelial progenitor cells (EPCs), and skeletal myoblasts have been evaluated in human subjects, and efficacy has been reported in acute myocardial ischemia, peripheral vascular disease, and ischemic cardiomyopathy.4-13 However, as with any nascent therapy, there remain significant technical and scientific challenges to be overcome before the full clinical potential of these cells can be realized.

Classification and Clinical Potential of Vascular Progenitor Cells

There are significant variations in the surface marker profile of each vascular progenitor cell and currently a lack of consensus on a uniform code for their classification. We therefore include in this review cells that functionally and structurally show elements of vascular ontogeny and differentiation, as well as cells that support endogenous angiogenesis in the context of preclinical and clinical studies. Based on their origin and differentiation spectrum, several adult cell types can thus be imputed with vascular progenitor potential, including BM-MNCs, mesenchymal stem cells (MSCs), skeletal myoblasts, umbilical cord or peripheral blood cells, adipose tissue–derived stem cells, EPCs, endothelial colony-forming cells, and smooth muscle progenitor cells (SPCs) (Table 1).

Established Clinical Application of Vascular Progenitor Cells

Extensive preclinical literature exists reporting the role of the vascular progenitors in treatment of acute myocardial infarction (MI), ischemia-reperfusion injuries (myocardial, renal, hindlimb, cerebral), chronic ischemic cardiomyopathy, di-
labeled cardiomyopathy, atherosclerosis, and restenosis. In addition, experimental animal models have provided evidence for a role of EPCs in postnatal vasculogenesis and hence a potential to treat complications associated with tissue ischemia. CD34+ and Flk1+ bone marrow–derived progenitor cells may contribute to tissue repair by differentiating into endothelial cells, vascular smooth muscle cells, hematopoietic cells, and possibly other cell types. CD133+ cells, which are reported to differentiate into both endothelial and smooth muscle cells, play an additional role in the remodeling of pulmonary arteries in chronic obstructive pulmonary disease.

Of the various cells studied in preclinical models, at least 2 cell types, EPCs (early outgrowing colonies) and BM-MNCs, have been clinically evaluated for their benefits in acute MI, limb ischemia, and dilated cardiomyopathy. Both cell types have shown significant improvement in limb ischemia but only modest cardiovascular benefits with an approximate improvement in left ventricular ejection fraction or left ventricular (LV) contraction of 2% to 8% (see review 4). Although the therapeutic benefit of EPCs post-MI was modest in terms of left ventricular ejection fraction, it is still unclear whether this effect can be augmented by coadministration of pharmacological agents or other vascular progenitor cells. Details on EPCs and their clinical potential have recently been extensively reviewed.

On the basis of these promising outcomes, EPCs have also been investigated as diagnostic and prognostic markers. For instance, circulating EPC numbers and function were significantly reduced in patients with coronary artery disease and diabetic patients with peripheral vascular disease, and EPC levels were negatively correlated with the degree of carotid stenosis, graft vasculopathy, and tissue ischemia. Like EPCs, endothelial colony-forming cells (late outgrowing colonies) have also been evaluated for diagnostic potential. For instance, endothelial colony-forming cells have been isolated from hypertensive patients on antihypertensive medication and from patients with acute MI, but their therapeutic potential has yet to be explored. EPCs (colony-forming unit–Hill colonies) have been inversely associated with the Framingham risk score for adverse cardiovascular health outcomes in affected patients. In contrast, it is interesting to note that putative circulating progenitor cells are reported to be mobilized into peripheral blood after acute MI.

Table 1. Markers Used for Classifying Vascular Progenitor Cells

<table>
<thead>
<tr>
<th>Progenitor Cells</th>
<th>Markers</th>
<th>Differentiation Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPCs†</td>
<td>CD34+ KDR CD133+ CD146+ CD115+</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>BM-MNCs‡</td>
<td>CD34+ CD133+ CD14+ CD45+ CX3CR1+</td>
<td>Endothelial cells, smooth muscle cells, and cardiomyocytes</td>
</tr>
<tr>
<td>Skeletal myoblasts§</td>
<td>CD56+ Sca1+ Myf5+ MyoD+ Wnt 5a+ Wnt 5b+</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>BM-MNCs§</td>
<td>CD105+ CD271+ CD73+ CD44+ Str-o1+ VCAM-1+</td>
<td>Endothelial cells, smooth muscle cells, and cardiomyocytes</td>
</tr>
<tr>
<td>Adipose tissue–derived stem cells¶</td>
<td>CD34+ CD14+ CD45+ CD144+</td>
<td>Endothelial cells, smooth muscle cells, and cardiomyocytes</td>
</tr>
<tr>
<td>Endothelial colony-forming cells¶</td>
<td>CD34+ CD133+ CD115+ CD14+ CD45+ CD31+ VEGFR2+</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>SPCs†</td>
<td>CD14+ CD105+ CD45+ CD34+</td>
<td>Smooth muscle cells</td>
</tr>
<tr>
<td>Tissue-resident progenitors¶</td>
<td>CD34+</td>
<td>Endothelial cells and smooth muscle cells</td>
</tr>
</tbody>
</table>

Skeletally myoblasts have been reported to be mobilized into peripheral blood after acute MI. Specifically, the number of CD34+/AC133+/KDR+ and CD34+/CD117+/KDR+ cells was transiently higher in peripheral circulation at 2 hours after acute MI in humans and particularly in unstable/refractory angina patients. Together, these data suggest an emerging diagnostic paradigm for EPC detection in blood in the context of correlation with vascular disease burden and in the setting of complications such as MI or vascular injury.

BM-MNCs have similarly been tested for therapeutic efficacy in acute MI, as well as peripheral vascular disease. However, the outcomes with BM-MNC administration have been mixed, which may be attributed to the heterogeneous nature of these cells. To date CD34+ cells, CD133+ cells, and BM-MNCs with or without cytokine-enhanced mobilizations have been evaluated in patients with acute MI, although only a few studies have used selected BM-MNCs. Although some studies failed to observe any improvement with BM-MNC therapy, a significant improvement in LV function has been reported following bone marrow–derived CD34+ cell, CD133+ cell, or BM-MNC cell therapy (REPAIR-AMI, TOPCARE-CHD). In the TOPCARE-CHD study, BM-MNC therapy in patients (followed 6 years post-MI) resulted in significant improvement in LV ejection fraction, LV systolic volume, and ventricular contractility, whereas treatment with peripheral blood EPCs resulted in reduced LV ejection fraction, left ventricular systolic volume, and ventricular contractility. In addition to the primary benefits following cell therapy, secondary benefits, such as enhanced exercise tolerance and improved myocardial perfusion, quality-of-life score, and angina score, were also observed (Table 2). From a vascular perspective, several clinical trials of BM-MNC therapy have reported increased coronary flow reserve, which was maintained at extended follow-up. Currently, most cell therapy in patients is restricted to single dose administration, and it is still unclear whether multidosing regimens may be more successful.
<table>
<thead>
<tr>
<th>Clinical Trial (Year)</th>
<th>No. of Patients (Ages in Years)</th>
<th>Profile of Cells Injected* (No. of Cells)</th>
<th>Indications</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauer et al (2002)</td>
<td>10 (39–59)</td>
<td>BM– CD34^+ , CD34^+ MNC (28–10^6)</td>
<td>AMI</td>
<td>Decreased infarct size, LVEDV, LVESV, and LV akinetic region; increased perfusion, stroke volume, and regional contractility</td>
</tr>
<tr>
<td>TOPCARE AMI (2006, 2002)</td>
<td>204 (18–80)</td>
<td>BM– CD34^+ , CD34^+ MNC/CPC (5.5–3.9 x 10^6)</td>
<td>AMI</td>
<td>Positive ventricular remodeling; increased left ventricular contraction, myocardial viability, LVEF, regional wall motion, and coronary flow reserve; decreased LVEDV</td>
</tr>
<tr>
<td>Stamm et al (2003)</td>
<td>6 (54–75)</td>
<td>BM– CD34^+ MNC (1.5 x 10^6)</td>
<td>AMI</td>
<td>Improved global LV function and infarct tissue perfusion</td>
</tr>
<tr>
<td>Chen et al (2004)</td>
<td>69 (51–65)</td>
<td>BM– CD34^+ MNC (48–60 x 10^6)</td>
<td>AMI</td>
<td>Improved ventricular contraction, stroke volume, LVEF, and myocardial perfusion; reduced LVEDV and LVESV</td>
</tr>
<tr>
<td>MAGIC (2004)</td>
<td>10 (49–70)</td>
<td>G-CSF mobilized CD34^- MNC (7 x 10^6)</td>
<td>AMI</td>
<td>Increased LVEF; decreased LVESV; improved myocardial perfusion and exercise capacity; high rate of in-stent restenosis</td>
</tr>
<tr>
<td>Kuehne et al (2004)</td>
<td>5 (45–67)</td>
<td>BM-MNC (3.9–2.3 x 10^6)</td>
<td>AMI</td>
<td>No improvement</td>
</tr>
<tr>
<td>Ruan et al (2005)</td>
<td>9 (51–65)</td>
<td>BM– CD34^+ MNC</td>
<td>AMI</td>
<td>Improved segmental and global LV function and positive LV remodeling; reduced LVEDV and LVESV</td>
</tr>
<tr>
<td>Bartunek et al (2005)</td>
<td>19 (46–56)</td>
<td>BM– CD34^- CD14^- , CD56^+ , CD19^- , CD66b^- MNC (1.5–33.6 x 10^6)</td>
<td>AMI</td>
<td>Increased LVEF and myocardial perfusion; decreased LV volume; increased incidence of in-stent restenosis</td>
</tr>
<tr>
<td>ASTAMI (2005, 2008)</td>
<td>50 (40–75)</td>
<td>BM– CD34^+ MNC (54–10^6)</td>
<td>AMI</td>
<td>No effect on LVEF</td>
</tr>
<tr>
<td>TCT-ASTAMI (2006)</td>
<td>10 (47–69)</td>
<td>BM– CD34^+ MNC (40 x 10^6)</td>
<td>AMI</td>
<td>Increased LVEF; prevented cardiac remodeling; improved myocardial perfusion</td>
</tr>
<tr>
<td>REPAIR-AMI (2007)</td>
<td>30 (50–54)</td>
<td>BM– CD34^+ MNC (5.5–3.9 x 10^6)</td>
<td>AMI</td>
<td>Restoration of microvascular flow in infarct territory; improved ventricular conduction capacity</td>
</tr>
<tr>
<td>Li et al (2007)</td>
<td>35 (48–72)</td>
<td>G-CSF mobilized– CD34^- MNC (38.72–8.1 x 10^6)</td>
<td>AMI</td>
<td>Increased LVEF, myocardial perfusion, and wall motion score index; decreased LVESV and LVEDV</td>
</tr>
<tr>
<td>Ahmad et al (2007)</td>
<td>18</td>
<td>BM– CD34^- , CD133^- MNC</td>
<td>AMI</td>
<td>Increase LVEF, improve myocardial viability and perfusion</td>
</tr>
<tr>
<td>MYSTAR (2008)</td>
<td>60 (50–57)</td>
<td>BM– CD34^- CD133^- CD34^+ CD14^- MNC (10–200 x 10^6)</td>
<td>AMI</td>
<td>Increased global LV systolic function</td>
</tr>
<tr>
<td>HEVE (2008)</td>
<td>26 (30–75)</td>
<td>BM– CD34^- MNC (246–133 x 10^6)</td>
<td>AMI</td>
<td>Increased LVEF and systolic wall thickening; reduced infarct area; modestly increased global and regional LV function</td>
</tr>
<tr>
<td>REGENERATE (2009)</td>
<td>160 (18–75)</td>
<td>BM-MNC &amp; BM– CD34^- CD133^- CD14^- MNC (1.9–6 x 10^6)</td>
<td>AMI</td>
<td>Improvement in LVEF was observed only in patients with very poor baseline LVEF (&lt;37%)</td>
</tr>
<tr>
<td>BOOST (2004, 2009)</td>
<td>60 (42–70)</td>
<td>BM– CD34^- MNC (246–10^6)</td>
<td>STEMi</td>
<td>Enhanced systolic function at 6 but not 18 months posttherapy; reduced diastolic function; significant benefits in patients with transmural infarcts</td>
</tr>
<tr>
<td>FIRSTLINE-AMI (2005)</td>
<td>30 (18–65)</td>
<td>G-CSF therapy to mobilize CD34^- MNC (2.8 x 10^6)</td>
<td>STEMi</td>
<td>Increased LVEF, wall motion score, LV end diastolic diameter, and positive LV remodeling</td>
</tr>
<tr>
<td>Janasens et al (2008)</td>
<td>67 (18–75)</td>
<td>BM– CD34^- , CD133^- , CD117^- , CD73^+ , CD90^+ , CD105^- MNC (304–126 x 10^6)</td>
<td>STEMi</td>
<td>Improved LVEF and infarct area in patient without microvascular obstruction</td>
</tr>
<tr>
<td>Tatsumi et al (2007)</td>
<td>18 (52–69)</td>
<td>PB– CD34^- MNC (6–10^6)</td>
<td>STEMi</td>
<td>Increased LVEF, wall motion score index, and myocardial perfusion; decreased LVESV</td>
</tr>
<tr>
<td>FINCELL (2008)</td>
<td>40 (59–70)</td>
<td>BM– CD34^- MNC (2.6–10^6)</td>
<td>STEMi</td>
<td>Increased LVEF</td>
</tr>
<tr>
<td>Herbots et al (2009)</td>
<td>33 (44–68)</td>
<td>BM– CD34^- , CD133^- , CD117^- , CD73^+ , CD90^+ , CD105^- MNC (304–126 x 10^6)</td>
<td>STEMi</td>
<td>Improved regional myocardial and systolic function</td>
</tr>
<tr>
<td>IACT (2005)</td>
<td>18 (38–60)</td>
<td>BM– CD34^- CD133^- CD45^- , CD14^- MNC (15–22 x 10^6)</td>
<td>CMI</td>
<td>Reduced infarct size, increased LVEF, improved LV wall motion and infarct area oxygen uptake</td>
</tr>
<tr>
<td>TOPCARE-CHD (2006)</td>
<td>52 (18–50)</td>
<td>BM– CD34^- MNC (205–110 x 10^6)</td>
<td>CMI</td>
<td>Increased LVEF and LSVS with BM-MNC, decreased LVEF, LVSV, and contractility with PB-CPC</td>
</tr>
<tr>
<td>Tse et al (2003)</td>
<td>8 (49–72)</td>
<td>BM– CD34^- , CD3^- , CD11b^- , CD105^- , CD117^- MNC (26–212 x 10^6)</td>
<td>Severe IHD</td>
<td>Increased LVEF, wall thickening, and wall motion; improved myocardial perfusion</td>
</tr>
<tr>
<td>Losordo et al (2007)</td>
<td>24 (48–84)</td>
<td>G-CSF mobilized– CD34^- MNC (3.5–35 x 10^6)</td>
<td>Intractable angina</td>
<td>Decreased angina; increased exercise tolerance; improved myocardial perfusion; improved quality-of-life testing</td>
</tr>
<tr>
<td>Van Ramshorst et al (2009)</td>
<td>50 (56–72)</td>
<td>BM– CD34^- MNC (100–15 x 10^6)</td>
<td>Severe angina pectoris with MI</td>
<td>Increased LVEF; improved angina and quality-of-life score</td>
</tr>
</tbody>
</table>

AMI indicates acute MI; MNC, mononuclear cells; CIHD, chronic ischemic heart disease; CMI, chronic MI; CPC, circulating progenitor cells; G-CSF, granulocyte colony-stimulating factor; IHD, ischemic heart disease; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; NDC, nonischemic dilated cardiomyopathy; PB, peripheral blood; RMI, repurfused myocardial infarction; STEMi, STE-T-elevation myocardial infarction.

*Markers represent the surface profile of the cells used in these studies and do not necessarily reflect subselection.
garding a potential increased risk of arrhythmias posttreatment due to the lack of gap junction protein expression by differentiated myotubes in the early postoperative period. However, in a multicenter study, the incidence of arrhythmia was not different compared with the placebo group, and a number of myoblast trials have failed to observe any beneficial effects on the left ventricular function posttreatment. Completed and published clinical trials and the source of progenitor cells used are indicated in Table 2 and Figure 1, respectively.

Future Clinical Applications of Vascular Progenitor Cells

A number of vascular progenitor cells, including MSCs, have shown promise in the preclinical context and are on the threshold of clinical evaluation. In small animal models of MI, MSCs improved myocardial contractility, and more recently they improved vasculogenesis in a porcine model of MI. Studies in human subjects have also begun, and recent encouraging short-term safety data were reported on 30 patients with symptomatic coronary artery disease treated with autologous mesenchymal stromal cell-derived endothelial progenitor therapy. In an experimental model of myocardial injury, MSC differentiation into endothelial phenotype enhanced microvascular density and improved heart function in rats. These and other studies suggest that MSCs not only contribute paracrine factors with prosurvival and prorepair effects on myocardium but may integrate into the neovasculature having undergone multilineage differentiation. A further advantage of MSCs may be their allogeneic “off the shelf” potential, their scalability in terms of expansion, and the relatively hypoimmune response they attract on implantation. A potential disadvantage is the multidifferentiation potential of these cells and an incomplete understanding of how to direct this process toward therapeutic benefit.

Myeloid cells, although associated with inflammation, have also been evaluated for angiogenic and vasoreparative effects in preclinical models. A leukocyte population coexpressing dendritic cell and endothelial cell markers was found to infiltrate tumor and assemble neovasculature. Monocyte (CD34+/CD14-)–derived EPCs can also express a range of proangiogenic factors, such as hepatocyte growth factor, vascular endothelial growth factor, and granulocyte colony-stimulating factor, providing one mechanism whereby these cells may contribute to neangiogenesis or in-stent restenosis when implanted in vivo. Of concern is the increased incidence of in-stent restenosis, although this adverse effect was not observed in most studies. Nevertheless, in vivo integration efficiency into neovasculature and proatherogenic effects (including in-stent restenosis) of these and other bone marrow–derived cells remains unclear. Significant contributions of bone marrow–derived myeloid lineage cells toward neovascularization and reendothelialization have also been reported in transplant atherosclerosis associated with vascular injury. These cells may thus represent a double-edged sword in terms of therapeutic versus pathological angiogenesis.

Recently, smooth muscle progenitor therapy was reported to promote stable plaque phenotype in a murine model. The precise lineage of SPCs is unclear, but they may represent a myeloid precursor resident in marrow and other solid organs. c-kit-CD45- progenitor cells isolated from murine liver exhibit neovascularization capacity showing strong colony forming capacity and vascular differentiation. It is conceivable that these cells may also contribute to arteriogenesis. Systemic infusion of isolated c-kit+CD45+ progenitor cells into a model of hindlimb ischemia demonstrated potent integration of these cells in the neovasculature compared with c-kit+CD45- cells. We have shown that clonally expandable, high–proliferative potential SPCs exist in human blood, and it is conceivable that these cells could be exploited for vascular therapy.

An early promise of vascular progenitor cells relates to the field of tissue engineering, wherein endothelial and smooth muscle progenitor cells might constitute the key cellular components of ex vivo tissue-engineered vasculature. Preclinical data suggested that it was feasible to reconstitute microvascular structures with a combination of vascular progenitor cells (EPCs and SPCs). However, vascular con-
duits continue to face the same challenges that have dogged this field for decades, namely thrombogenicity, dysregulated growth, and medium- to long-term graft failure. Large vascular conduits appear to be a more feasible target, and preclinical and early clinical studies indicate successful single and combination cell seeding of synthetic vascular grafts. An alternative strategy includes mobilization of endogenous progenitors onto grafts and stents in vivo. This has been achieved using CD34 antibodies (EPC stent) and has undergone successful human safety trials. Preclinical studies have also shown benefit of physicochemical and paramagnetic approaches to augmenting EPC attachment to grafts or stents. Other cardiovascular targets for EPCs include coating of ventricular assist devices and artificial hearts. Together, these studies indicate that a number of progenitor cell types exist, with translational potential in therapies as diverse as vasculogenesis augmentation, tissue engineering, hybrid graft/device functionalization, plaque stabilization, modulation of vascular remodeling in pulmonary hypertension, and transplant atherosclerosis prevention. Emerging clinical applications of vascular progenitor cells are illustrated in Figure 2.

Strategies to Maximize Clinical Efficacy of Vascular Progenitor Cells
Numerous challenges remain to be overcome before vascular progenitor cell therapy achieves sufficiently widespread use to be competitive with current pharmacological, interventional, or surgical treatments. Currently, insufficient cells can be targeted for a sufficient time to a diseased area of the cardiovascular system to enable cellular regeneration. A significant challenge to ex vivo expansion of vascular progenitor cells is their variable replicative capacity, and thus, interest has recently focused on induced pluripotent stem cell technology to generate vascular progenitors from adult cells. Delivery of stemness-related genes (Oct-3/4, Sox2, Klf4, and c-Myc quartet) can reprogram adult somatic cells into becoming embryonic stem-like cells, with a high degree of plasticity. Recently, beneficial effects of therapy with fibroblasts transduced with human stemness factors OCT3/4, SOX2, KLF4, and c-MYC were reported in a mouse acute MI model. These transformed cells showed trilineage (cardiomyocyte, endothelial, and smooth muscle cell) differentiation in vivo. However, long-term safety issues remain to be addressed before extension of induced pluripotent stem cells to the clinic.

The mainly autologous cell approaches currently in use are also unlikely in the longer term to be either sufficiently cost effective or logistically applicable to the wider clinical community. A range of emerging paracrine growth factors/cytokines known to be secreted from vascular progenitor cells are therefore attractive as alternative therapies to cells alone. However, previous experience with single–growth factor therapies for angiogenesis more than a decade ago would suggest caution in expecting sudden therapeutic advances in this field. It is also possible that recent increased understanding of chemokine receptor signaling and endogenous progenitor mobilization may allow more tailored recruitment of specific vascular progenitor cell subtypes that favor repair over inflammation and fibrosis. We are only beginning to explore this biology, but a number of these chemokine pathways are already known, including CXCR4, CX3CR1, and CCR2, and each appears to be implicated in mobilization of different subtypes of proangiogenic cells. Whether redundancy exists in these pathways and whether specific differences in mobilization signals can be exploited to favor robust tissue repair require extensive further investigation.

Conclusion
Vascular progenitor cells show modest clinical utility in ischemic heart and peripheral vascular disease, but a number of significant challenges remain. Preclinical research suggests a burgeoning number of applications that may harness, inter
References


Clinical Potential of Adult Vascular Progenitor Cells
Arun H.S. Kumar and Noel M. Caplice

Arterioscler Thromb Vasc Biol. published online May 7, 2010;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2010/05/07/ATVBAHA.109.198895.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/