We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

19

Bone Marrow Derived Pluripotent Stem Cells in Ischemic Heart Disease: Bridging the Gap Between Basic Research and Clinical Applications

Ahmed Abdel-Latif[1], Ewa Zuba-Surma[2] and Mariusz Z. Ratajczak[3]
[1]*Gill Heart Institute and Division of Cardiovascular Medicine, University of Kentucky, and Lexington VA Medical Center, Lexington, KY*
[2]*Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Cracow,*
[3]*Stem Cell Biology Institute, James Graham Brown Cancer Center, University of Louisville, Louisville, KY,*
[1,3]*USA*
[2]*Poland*

1. Introduction

The prevalence of ischemic heart disease and acute myocardial infarction (AMI) has increased to alarming rates in the United States and the western world (Roger *et al.,* 2011). Patients who survive the initial AMI suffer ischemic cardiomyopathy (ICM) which is often complicated by high mortality and poor overall prognosis (Braunwald *et al.,* 2000; McMurray *et al.,* 2005). Despite significant advances in medical therapy and revascularization strategies, the prognosis of patients with AMI and ischemic cardiomyopathy remains dismal (Levy D *et al.,* 2002; Roger VL *et al.,* 2004). The last decade has demonstrated significant progress and rapid translation of myocardial regenerative therapies particularly those utilizing stem cells isolated from adult tissues (Abdel-Latif *et al.,* 2007).

Studies examining the potential therapeutic use of bone marrow (BM)-derived cells in myocardial regeneration have overshadowed the growing evidence of innate cardiac reparatory mechanisms. Several studies have demonstrated the capability of cardiomyocytes to replenish through poorly understood innate mechanisms. Follow up of cardiac transplantation patients have demonstrated continuous replenishment of cardiomyocytes by recipient's derived cells through poorly understood mechanisms (Quaini *et al.,* 2002). There is growing evidence that BM-derived cells are responsible, at least in part, for organ chimerism including cardiomyocyte chimerism (de Weger *et al.,* 2008; Deb *et al.,* 2003). Animal studies have confirmed this to be a dynamic process responding to significant injury such as myocardial infarction and peaks in the peri-infarct zone (Hsieh *et al.,* 2007). Although this process appears to be robust enough to achieve the renewal of approximately 50% of all cardiomyocytes in the normal life span, very little is known about its underpinnings (Bergmann *et al.,* 2009).

Complex innate reparatory mechanisms are initiated by myocardial ischemia interacting with different elements of the immune system, the infarcted myocardium and bone marrow stem cells, culminating in BM-stem and progenitor cells' (SPCs) mobilization as we and others have demonstrated (Abdel-Latif *et al.,* 2010; Walter *et al.,* 2007; Wojakowski *et al.,* 2009). However, very little is known about the mechanisms and clinical significance of this mobilization. Animal studies show that mobilized BM-derived cells (BMCs) repopulate the infarct border, however the significance of this mobilization is unclear given the low rate of their differentiation into cardiomyocytes (Fukuhara *et al.,* 2005).

2. Isolation and functional characteristics of BM-derived pluripotent stem cells

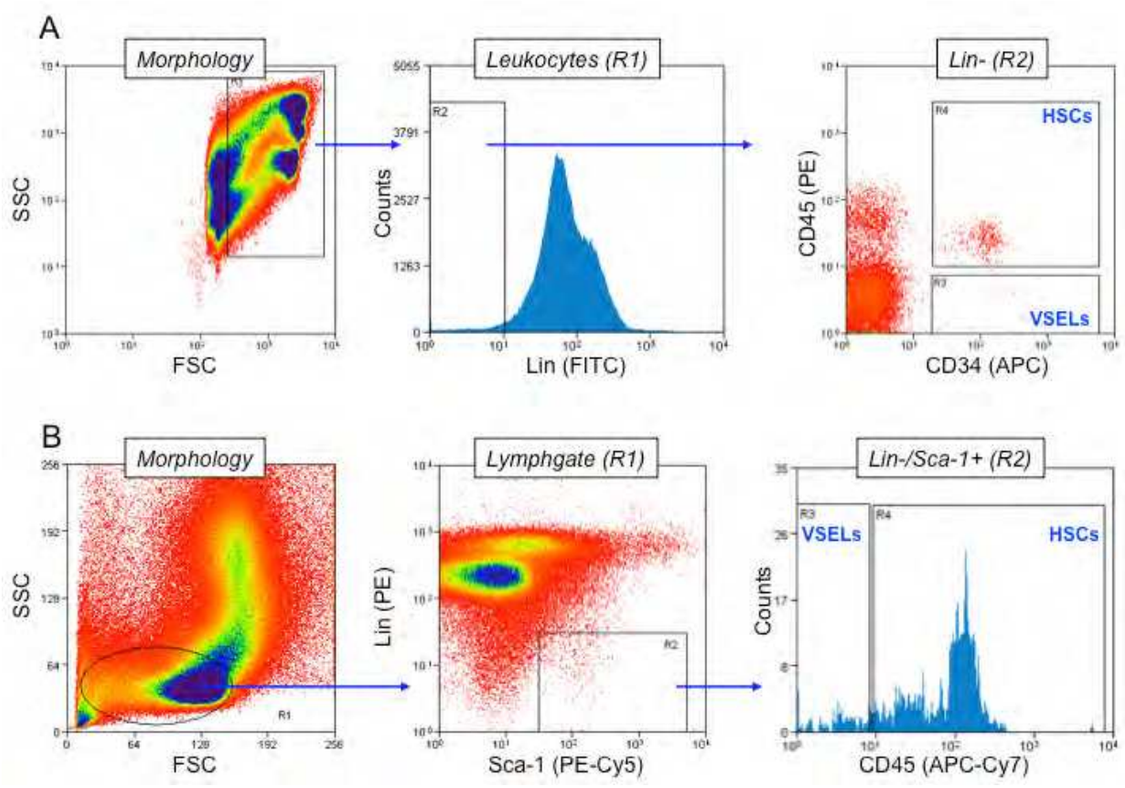
The bone marrow acts as a reservoir for a heterogeneous pool of tissue-committed and non-committed stem cells. These populations contain progenitors that aid in the chimerism and cellular turnover of different organs as well as very rare populations of pluripotent and non-committed stem cells. The old dogma that adult tissues lack pluripotent stem cells (PSCs) has been continuously challenged during the last decade through multiple studies that isolated PSCs from adult humans' and animals' tissues. These populations were distinguished based on their morphology with small cell size, large nucleus demonstrating euchromatin and large nucleus to cytoplasm ratio. Furthermore, cell surface markers as well as nuclear transcription factors, such as SSEA1/4, Oct4 and Nanog, have been deployed.

Very small embryonic like stem cells (VSELs) represent a rare yet pluripotent population of adult stem cells. They have been initially described by Dr. Ratajczak's group in the murine BM based on their expression of Sca1 (murine stem cell marker) and lack of expression of CD45 (pan–leukocytic marker) and differentiated lineage (Lin) markers (Kucia *et al.,* 2006; Zuba-Surma *et al.,* 2008). Following their isolation from murine tissues, VSELs were subsequently isolated from human BM, umbilical cord blood (CB) and peripheral blood based on the lack of expression of Lin/CD45 and the expression of the stem cell markers CD133, CXCR4 and CD34. **Figure 1** illustrates the flow cytometry protocol for identifying and isolating VSELs from murine and human samples. VSELs were further characterized using a multi-dimensional approach comprising molecular, protein and cell imaging techniques to confirm their pluripotent features (Zuba-Surma *et al.* 2008). VSELs are morphologically similar to embryonic stem cells demonstrating small diameter compared to more committed progenitors/stem cells with large nucleus containing open-type chromatin surrounded with thin rim of cytoplasm and multiple mitochondria (Zuba-Surma *et al.* 2008).

VSELs exhibit multiple embryonic and pluripotent surface and nuclear embryonic markers such as Oct4, SSEA1/4, Nanog, and Rex1. In vivo and in vitro studies have demonstrated the capability of VSELs to differentiate into multiple cell lines across germ lines including cardiomyocytes (Kucia *et al.* 2006).

The bone marrow harbors other multi- and pluri-potent stem cell populations such as the mesenchymal stem cells (MSC) (Hattan *et al.,* 2005; Kawada *et al.,* 2004), multipotent adult progenitor cells (MAPC) (Jiang *et al.,* 2002), and marrow-isolated multilineage inducible cells (MIAMI) (D'Ippolito *et al.,* 2004). Similar populations with cardiac differentiation potential

have been also isolated from skeletal muscle and other tissues (Abdel-Latif *et al.*, 2008a). However, it is conceivable that different investigators have isolated, using different methods, the same or very similar populations and named them differently. It is also possible that these populations at least in part contain VSELs which might explain their pluripotent potential.



Panel A: Gating strategy for isolating human cord blood (CB)-derived VSELs. Morphology of total CB-derived nucleated cells is shown on dot-plot representing FSC and SSC parameters related to cell size and granularity/ complexity, respectively. All objects larger than 2μm are enclosed in region R1 and further visualized on histogram showing the expression of markers of mature hematopoietic cells (lineage markers; Lin). Cells not expressing differentiated hematopoietic markers (Lin- in region R2) are then analyzed for CD34 and CD45 expression. VSELs are identified as CD45-/Lin-/CD34+ cells (region R3), while hematopoietic stem cells (HSCs) as CD45+/Lin-/CD34+ cells (region R4).
Panel B: Sorting of murine bone marrow (BM)-derived VSELs. Morphology of total murine BM-derived nucleated cells is shown on dot-plot presenting FSC and SSC parameters and all objects in range of 2-10μm in diameter are included in region R1. Lymphocytic cells including stem cell fraction is further analyzed for Sca-1 and differentiated hematopoietic lineages markers (Lin) expression and only Sca-1+/Lin- cells are included in region R2. Cells from this region are further seperated based on CD45 expression. Murine VSELs are distinguished as CD45-/Lin-/Sca-1+ cells (region R3), while HSCs as CD45+/Lin-/Sca-1+ cells (region R4).

Fig. 1. Strategy for flow cytometric analysis of human and murine Very Small Embryonic-Like and hematopoietic stem cells. Briefly, BM is flushed from the femurs and tibias. Nucleated cells are isolated by lysis of red blood cells and cells are then gated on based on the cell size (>2 μm). Of note, lysis is preferred for isolating VSELs rather than Ficoll gradient that we have shown to lose some of the VSELs due to their small size.

3. BM-derived pluripotent stem cells are mobilized in the peripheral circulation following myocardial ischemia in animal models and humans

Myocardial ischemia, particularly large myocardial infarction, produce multiple stimuli include various chemokines, cytokines, kinins, bioactive lipids and members of the complement cascade, that lead to the mobilization and subsequent homing of BMSPCs. Indeed, several reports have confirmed that mobilization of stem cells originating from the BM occurs in response to myocardial ischemic injury (Grundmann *et al.,* 2007; Kucia *et al.,* 2004b; Leone *et al.,* 2005; Massa *et al.,* 2005; Shintani *et al.,* 2001; Wojakowski *et al.,* 2006) and heart failure (Valgimigli *et al.,* 2004). Similar observations were noted in patients with acute neurological ischemia (Paczkowska *et al.,* 2005) and patients with extensive skin burn (Drukala *et al.,* 2011).

Stimuli responsible for the mobilization and homing of BMSCs in the setting of myocardial ischemia show similarities and differences with those involved in hematopoietic stem cells (HSCs) homing to the BM. The role of stromal cell derived factor (SDF-1) and its receptor (CXCR4) axis in the retention of hematopoietic stem/progenitor cells (HSPCs) in bone marrow is undisputed (Kucia *et al.,* 2005; Lapidot *et al.,* 2002), however, its role in the mobilization and homing of BM-SPCs to a highly proteolytic microenvironment, such as the ischemic/infarcted myocardium, is somewhat less certain. Studies have demonstrated that multiple members of the metalloproteinases (MMP) family, such as MMP2, MMP9 and MMP13, are upreagulated in the myocardium following infarction (Peterson *et al.,* 2000). The elevated levels of the MMPs contribute to the degradation of chemokines such as SDF-1 and the byproduct of this degradation acts as an inhibitor the sole SDF-1 receptor, CXCR4 (McQuibban *et al.,* 2001; McQuibban *et al.,* 2002). In support of this hypothesis, Agrawal *et al* demonstrated that the conditional deletion of CXCR4 in cardiomyocytes did not influence the recovery of left ventricular (LV) function, reduce the scar size or alter the homing of MSCs to the myocardium following myocardial infarction (Agarwal *et al.,* 2010). Thus, there is growing evidence that other mechanisms beside the SDF-1/CXCR4 axis are contributing to the mobilization and homing of BM-SPCs in AMI and other conditions (Jalili *et al.,* 2010; Ratajczak *et al.,* 2010). These data suggest an important interplay between the complement cascade, the immune system, cathelicidins, low levels of SDF-1, and sphingosine-1 phosphate (S1P) and other bioactive lipids in the mobilization and homing of HSPCs. Our preliminary data suggest that these complex interactions might be involved in the mobilization of BM-SPCs in acute myocardial ischemia as well (unpublished data). Clinically, pharmacological modulators of S1P receptors are already approved by the FDA and can be utilized to enhance BM-SPC mobilization in the setting of ischemic heart disease. Similarly, modulation of the complement cascade can be also utilized in this process similar to their role in the mobilization of HSPCs.

The first evidence for the mobilization of CD34+ mononuclear cells in AMI was demonstrated by Shintani *et al* (Shintani *et al.* 2001). The authors demonstrated successful in vitro differentiation of circulating BM-SPCs into endothelial cells that expressed CD31, VE-cadherin and the kinase insert domain receptor (KDR) (Shintani, *et al.* 2001). Leone *et al* demonstrated that the levels of circulating CD34+ cells in the setting of AMI were higher when compared to patients with mild chronic stable angina and healthy controls. The magnitude of CD34+ cell mobilization correlated with the recovery of regional and global LV function recovery as well as other functional LV parameters (Leone *et al.* 2005). Similarly,

Wojakowski *et al* demonstrated the mobilization of multiple BM-SPCs populations in patients with AMI and found significant correlation between the number of circulating CD34+ cells and plasma SDF-1 levels (Wojakowski *et al.,* 2004). In their following publication, the authors demonstrated the correlation between circulating BM-SPCs and ejection fraction at baseline and lower brain natriuretic peptide (BNP) levels (Wojakowski *et al.* 2006). Interestingly, the mobilization of BM-SPCs is reduced by the successful revascularization of the culprit vessel in acute STEMI (Müller-Ehmsen *et al.,* 2005). However, the majority of the above mentioned studies have focused on the mobilization of partially committed stem cells such as HSPCs and endothelial progenitor cells (EPCs).

We and others have demonstrated the mobilization of pluripotent stem cells (PSCs) including VSELs in the setting of myocardial ischemia (Abdel-Latif *et al.* 2010; Wojakowski *et al.* 2009). The number of circulating VSELs was highest in patients with ST-elevation myocardial infarction (STEMI), particularly in the early phases following the injury, when compared to patients with lesser degrees of ischemia such as non STEMI (NSTEMI) and those with chronic ischemic heart disease (Abdel-Latif *et al.* 2010). The mobilization of PSCs appears to be related to the extent of myocardial ischemia and the degree of myocardial damage. Moreover, the ability of patients to mobilize PSCs in the peripheral circulation in response to AMI decreases with age, reduced global LV ejection fraction (LVEF) and diabetes supporting the notion of an age/comorbidity related decline in the regenerative capacity (Abdel-Latif*, et al.* 2010; Wojakowski*, et al.* 2009). Indeed, animal models confirm the reduction of number as well as pluripotent features of BM-derived VSELs with age (Zuba-Surma *et al.* 2008). Similarly, studies have demonstrated the reduction of number as well as functional capacity of EPCs in diabetic patients (Fadini *et al.,* 2006).

The pluripotent features of mobilized VSELs, including the presence of octamer-binding transcription factor-4 (Oct4) and stage specific embryonic antigen-4 (SSEA4), were confirmed both on the RNA and protein levels. Utilizing the capabilities of the ImageStream system, we demonstrated that circulating VSELs during AMI have very similar embryonic features similar to their BM and CB counterparts including the small size (7-8 μm), large nucleus and high nuclear-to-cytoplasm ratio (**Figure 2**). Furthermore, circulating VSELs during AMI express markers of early cardiac and endothelial progenitors that suggest that the mobilization is rather specific and that circulating VSELs are destined to aid in the myocardial regeneration following injury (Abdel-Latif *et al.* 2010; Kucia *et al.* 2004b; Wojakowski *et al.* 2009).

The above evidence suggest an innate, yet poorly understood, reparatory mechanism that culminates in the mobilization of BMSCs including pluripotent and embryonic like stem cells in acute myocardial injury. This mobilization correlates with the recovery of LV function and other LV functional parameters. Therefore, mobilization of PSCs in myocardial ischemia is a relevant and clinically significant process. Future studies aiming at selective mobilization of PSCs rather than the non-selective actions of agents such as granulocyte colony stimulating factor (G-CSF) may prove beneficial in the field of myocardial regeneration.

Indeed, there is evidence that the mobilization of CXCR4+ cells in the setting of AMI is correlated with LVEF recovery as well as myocardial reperfusion when assessed with cardiac MRI in humans (Wojakowski*, et al.* 2006).

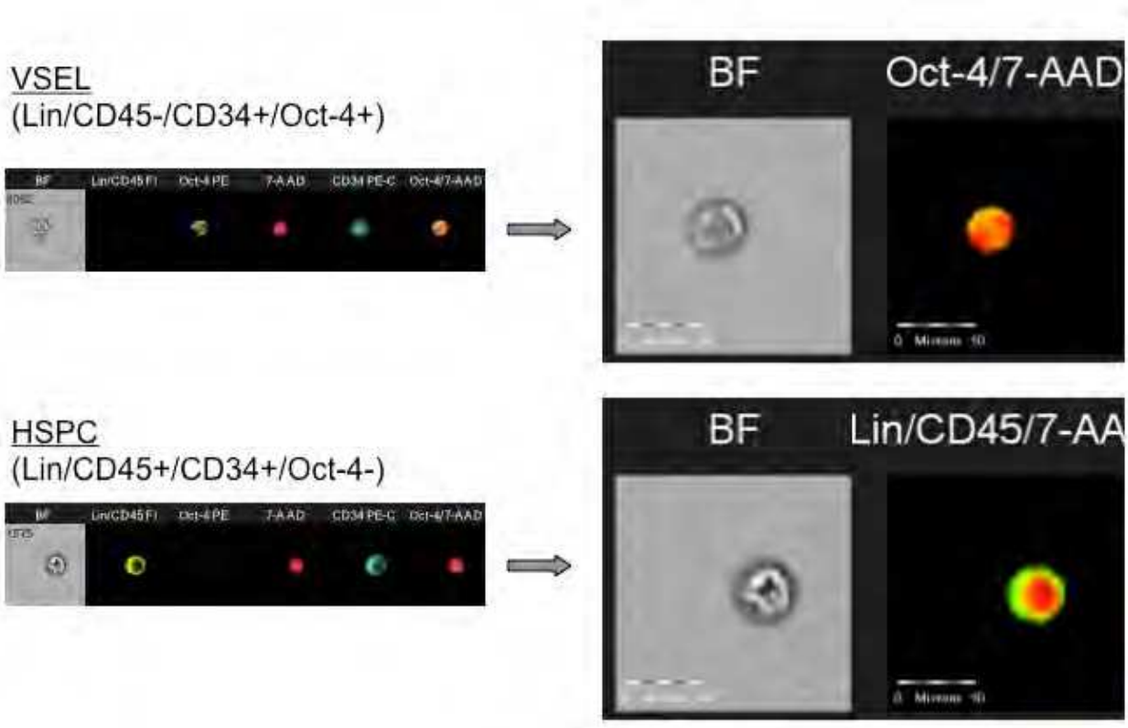


Fig. 2. Representative ImageStream images of VSEL and hematopoietic stem/ progenitor cell (HSPC) circulating in peripheral blood following acute ST-elevation myocardial infarction. Cells were stained against: 1) hematopoietic lineages markers (Lin) and CD45 to be detected in one channel (FITC, green), 2) marker of pluripotency Oct4 (PE, yellow) and 3) stem cell antigen CD34 (PE-Cy5, cyan). Nuclei are stained with 7-aminoactinomycin D (7-AAD, red). Scales represents 10 μm. VSELs are identified based on the lack of expression of both Lin and CD45 markers and positive staining for CD34 antigen and nuclear appearence of Oct-4 transcription factor (**Upper Panel**). HSCs are identified as cell expressing Lin and/ or CD45 markers as well as CD34 antigen; however, negative for Oct-4 (**Lower Panel**). BF: Bright field.

4. Therapeutic mobilization of BM-derived stem cells in myocardial regeneration

Hematologists have used the concept of BM-derived stem cell mobilization using pharmacological agents such as G-CSF for a long time. Based on the available clinical experience and safety profile of these therapies, pharmacological stem cell mobilization in the setting of AMI has gained increasing enthusiasm. Mobilized BM-SPCs are either harvested for further transplantation or allowed for spontaneous homing to the infarcted myocardium and has demonstrated various degrees of success (Engelmann *et al.,* 2006; Ince *et al.,* 2005; Zohlnhöfer *et al.,* 2006). Similar to BMCs transplantation studies, the heterogeneous methodologies of the included studies diluted the effect. The overall lack of efficacy with G-CSF BMCs mobilization in the setting of acute myocardial infarction is somewhat incongruent with the salutary effects of BMCs transplantation in humans and G-CSF therapy in animal models for myocardial regeneration.

The largest study utilizing G-CSF in the setting of acute myocardial infarction was the REVIVAL-2 trial that included 114 patients (Zohlnhöfer, *et al.* 2006). The study randomized AMI patients to 10 μg/kg of G-CSF vs. placebo and left ventricular functional parameters were assessed using cardiac MRI (CMR). The study demonstrated no significant difference in the tested parameters between patients treated with G-CSF or placebo. However, baseline characteristics in the study population showed normal or near normal LV function and therefore the expected benefit is minimal. Patient selection was a methodological flaw that plagued some of the studies that utilized G-CSF. Indeed, with careful examination of the available literature, patients with reduced LV function at baseline as well as those treated within the first 36 hours following AMI benefited the most (Abdel-Latif *et al.,* 2008b; Achilli *et al.,* 2010). On the other hand, safety concerns regarding a potentially increasing evidence of instent restenosis (Kang *et al.,* 2004) and recurrent ischemia (Hill *et al.,* 2005) have halted subsequent clinical trials. However, it is important to note that these safety concerns were not confirmed in large studies (Zohlnhöfer, *et al.* 2006) or in the cumulative meta-analyses (Abdel-Latif *et al.* 2008b).

Beyond the methodological flaws encountered in human trials, this lack of efficacy can be explained by multiple factors. While G-CSF and similar therapies mobilize a wide array of BMSPCs in the peripheral blood, homing factors may not be sufficient to guide them to the myocardial infarct zone. Indeed, the homing of c-Kit+ cells to the infarcted myocardium improved when G-CSF therapy was combined with local administration of SDF-1 (Askari *et al.,* 2003). The myocardial levels of chemoattractants peaks within 24-72 hours following injury (Kucia *et al.,* 2004a; Ma *et al.,* 2005; Wang *et al.,* 2006) and therefore delayed therapy in some human trials may have missed the homing window to the infarct zone. Similarly, the addition of Flt-3 to G-CSF therapy improved outcomes in animal models (Dawn *et al.,* 2008). Moreover, different cytokines are known to preferentially mobilize somewhat different subsets of BMCs (Hess *et al.,* 2002; Neipp *et al.,* 1998). Future studies investigating the characteristics of G-CSF-mobilized cells will be necessary to glean additional mechanistic insights in this regard.

Recently, a combined approach with stem cell mobilization and enhanced homing using therapies known to increase local SDF-1 or CXCR4 antagonists have been proposed and is currently being tested (Jujo *et al.,* 2010; Zaruba *et al.,* 2009). Going forward, the beneficial effects of BM-derived stem cell mobilization may be augmented by selective mobilization of undifferentiated BMSCs rather than differentiated inflammatory cells. It is also important to remember that some of the G-CSF arbitrated effects can be mediated by its direct effect on cardiomyocytes which are known to express G-CSF receptor (Shimoji *et al.,* 2010). G-CSF therapy may be inducing the proliferation of cardiomyocytes or the differentiation of resident cardiac stem cells. On a similar note, G-CSF therapy upregulates Akt (Ohtsuka *et al.,* 2004) and may result in reducing apoptosis of ischemic cardiomyocytes if utilized early following the acute event.

5. BM-derived stem cell transplantation for myocardial repair

The use of BM-derived cells in myocardial regeneration has moved rapidly from the basic research lab to the clinical arena. The results from these studies varied widely probably secondary to the heterogeneous methodologies used with an overall marginal benefit with

BM-derived cell transplantation compared to placebo. The majority of studies, however, utilized unselected populations of BMCs and these studies provide the longest follow-up of up to 5 years (Assmus *et al.,* 2010; Schachinger *et al.,* 2009). The underling mechanisms leading to the beneficial effect of transplanted BMCs are unclear. The observed benefits of BMCs transplantation is out of proportion of the observed rates of newly formed cardiomyocytes from BMCs' origin (Zuba-Surma *et al.,* 2011). Indeed, recent evidence suggest a primarily paracrine effect of BM-derived stem cells following their transplantation by recruiting and stimulating resident cardiac stem cells (CSCs) (Loffredo *et al.,* 2011). Furthermore, human purified CD34+ cells are a source of several growth factors including VEGF, cytokines and chemokines that may prevent apoptosis of dying cardiomyocytes and promote angiogenesis in damaged myocardium (Majka *et al.,* 2001). Cell membrane derived microvesicles or exosomes that are enriched in S1P may contribute to regeneration of myocardium and its re-vascularization (Baj-Krzyworzeka *et al.,* 2002). Hence, transplanted CD34+ cells may contribute to regeneration of damaged heart by paracrine signals and released microvesicles (Ratajczak *et al.,* 2008) and was recently confirmed by others (Sahoo *et al.,* 2011).

Long-term follow-up studies demonstrated 'catch-up phenomenon' of the placebo treated patients, thus leading to mixed results regarding the sustainability of the BMCs treatment benefit (Assmus, *et al.* 2010; Meyer *et al.,* 2009; Yousef *et al.,* 2009). The benefit of BMCs therapy is less robust among patients with chronic ischemic heart disease (IHD) (Assmus *et al.,* 2006; Strauer *et al.,* 2010). Similarly, smaller studies have demonstrated the antianginal effects of BMCs in patients with non-revascularizable severe coronary artery disease (Losordo *et al.,* 2007; Tse *et al.,* 2007).

Selected BM-derived stem cell subpopulations represent an attractive substrate for cellular therapies since they lack the inflammatory cells, which contribute to the ongoing inflammatory response at the site of myocardial infarction, contained in the unselected BMCs populations. Furthermore, highly purified stem cell populations are more likely to induce myocardial regeneration through paracrine effects or by directly differentiating into cardiomyocytes. The largest study utilizing selected BM-derived stem cell population is the REGENT study which compared selected to non-selected populations of BMCs in patients with acute ischemic heart disease and reduced LV function at baseline (Tendera *et al.,* 2009). While there were no significant differences between the groups, patients treated with selected CD34+/CXCR4+ cells showed trends of improvement in LV function when compared to controls. Other studies utilizing primitive populations of BM-SPCs such as CD133+ cells have reported improvement of LV function and perfusion (Bartunek *et al.,* 2005; Stamm *et al.,* 2004).

Nevertheless and despite the disparity in the methodologies of the conducted studies, the overall collective effect of BMCs' transplantation suggests small yet statistically significant benefit in myocardial regeneration (Abdel-Latif, *et al.* 2007; Martin-Rendon *et al.,* 2008). However, these trials have been hampered by their reliance on surrogate endpoints rather than patient important endpoints such as mortality, need for repeat revascularization, recurrent MI or re-hospitalization for congestive heart failure. While surrogate endpoints are important for mechanistic studies, patient-important endpoints are quintessential for a new therapy to achieve mainstream status.

6. Future directions

Growing evidence suggest that a multitude of BM-derived stem and pluripotent stem cells are mobilized in the peripheral blood following AMI. However, the clinical significance and the potential therapeutic use of this mobilization are still not fully understood. Circulating PSCs can be used as markers of ischemic injury in humans or as predictors of myocardial recovery following large ischemic damage. On the other hand, the therapeutic application of VSELs in myocardial regeneration has proven beneficial although the beneficial mechanisms remain elusive and are probably mainly paracrine in nature. Given the pluripotent potential of VSELs, their transplantation at smaller numbers (10,000 cells per mouse) have proven to be more beneficial than larger numbers of the more committed HSPCs (100,000 cells per mouse) indicating their greater therapeutic potential (Dawn *et al.* 2008). Current efforts directed at the ex-vivo expansion and priming of VSELs have proven to be a successful strategy in animal models and their clinical applications are pending (Dawn *et al.* 2008; Zuba-Surma, *et al.* 2011). Nuclear reprogramming has opened the door for creating patient-specific autologous pluripotent stem cells with multiple therapeutic opportunities (Takahashi *et al.*, 2006). Further studies are needed to examine the feasibility as well as the safety of inducible pluripotent stem cells (iPS) particularly their tumorigenicity and immunogenicity before they can be explored in human studies.

On the biotechnology frontier, multiple modifications of the transplanted cells (priming) and the host environment are being tested in humans to improve the efficiency of BM-SPCs' regenerative capacity. Transplanting three dimensional constructs that provide an enriched environment for the transplanted and resident stem cells are attractive modifications to the currently tested protocols [reviewed in (Mooney *et al.*, 2008)]. Similarly, the concept of multiple doses of stem cell to repair the complex process of myocardial remodeling following acute myocardial infarction is gaining traction and is very appealing. While the field of stem cell regenerative therapy for ischemic heart disease is still in its infancy, the accelerated advances in a wide array of biological and biotechnological areas have rapidly propelled the field from the bench to clinical applications.

7. Acknowledgments

Dr. Abdel-Latif is supported by the University of Kentucky Clinical and Translational Science Pilot Award and the University of Kentucky Clinical Scholar program.

Dr. Zuba-Surma is supported by the "Polish Foundation of Science" homing program grant number 2008/15.

Dr. Ratajczak is supported by NIH grant R01 CA106281, NIH R01 DK074720, and Stella and Henry Endowment.

We thank Dr. Karapetyan for her technical support for this review.

Conflict of interest: None.

8. References

Abdel-Latif A, Bolli R, Tleyjeh I, Montori V, Perin E, Hornung C, Zuba-Surma E, Al-Mallah M, and Dawn B (2007). Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med, 167:* 989-997.

Abdel-Latif A, Bolli R, Zuba-Surma EK, Tleyjeh IM, Hornung CA, and Dawn B (2008b). Granulocyte colony-stimulating factor therapy for cardiac repair after acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Am Heart J, 156*: 216-226.

Abdel-Latif A, Zuba-Surma EK, Case J, Tiwari S, Hunt G, Ranjan S, Vincent RJ, Srour EF, Bolli R, and Dawn B (2008a). TGF-beta1 enhances cardiomyogenic differentiation of skeletal muscle-derived adult primitive cells. *Basic Res Cardiol, 103*: 514-524.

Abdel-Latif A, Zuba-Surma EK, Ziada KM, Kucia M, Cohen DA, Kaplan AM, Van Zant G, Selim S, Smyth SS, and Ratajczak MZ (2010). Evidence of mobilization of pluripotent stem cells into peripheral blood of patients with myocardial ischemia. *Exp Hematol, 38: 1131-1142.*

Achilli F, Malafronte C, Lenatti L, Gentile F, Dadone V, Gibelli G, Maggiolini S, Squadroni L, Di Leo C, Burba I, Pesce M, Mircoli L, Capogrossi MC, Di Lelio A, Camisasca P, Morabito A, Colombo G, and Pompilio G (2010). Granulocyte colony-stimulating factor attenuates left ventricular remodelling after acute anterior STEMI: results of the single-blind, randomized, placebo-controlled multicentre STem cEll Mobilization in Acute Myocardial Infarction (STEM-AMI) Trial. *Eur J Heart Fail, 12*: 1111-1121.

Agarwal U, Ghalayini W, Dong F, Weber K, Zou YR, Rabbany SY, Rafii S, and Penn MS (2010). Role of cardiac myocyte CXCR4 expression in development and left ventricular remodeling after acute myocardial infarction. *Circ Res, 107*: 667-676.

Askari AT, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, Rovner A, Ellis SG, Thomas JD, DiCorleto PE, Topol EJ, and Penn MS (2003). Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. *Lancet, 362*: 697-703.

Assmus B, Honold J, Schachinger V, Britten M, Fischer-Rasokat U, Lehmann R, Teupe C, Pistorius K, Martin H, Abolmaali N, Tonn T, Dimmeler S, and Zeiher A (2006). Transcoronary transplantation of progenitor cells after myocardial infarction. *N Engl J Med, 355*: 1222-1232.

Assmus B, Rolf A, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Tillmanns H, Yu J, Corti R, Mathey DG, Hamm CW, Suselbeck T, Tonn T, Dimmeler S, Dill T, Zeiher AM, and Schachinger V (2010). Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. *Circ Heart Fail, 3*: 89-96.

Baj-Krzyworzeka M, Majka M, Pratico D, Ratajczak J, Vilaire G, Kijowski J, Reca R, Janowska-Wieczorek A, and Ratajczak MZ (2002). Platelet-derived microparticles stimulate proliferation, survival, adhesion, and chemotaxis of hematopoietic cells. *Exp Hematol, 30*: 450-459.

Bartunek J, Vanderheyden M, Vandekerckhove B, Mansour S, De Bruyne B, De Bondt P, Van Haute I, Lootens N, Heyndrickx G, and Wijns W (2005). Intracoronary injection of CD133-positive enriched bone marrow progenitor cells promotes cardiac recovery after recent myocardial infarction: feasibility and safety. *Circulation, 112*: I178-183.

Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabe-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S, and Frisen J (2009). Evidence for cardiomyocyte renewal in humans. *Science, 324*: 98-102.

Braunwald E, and Bristow M (2000). Congestive heart failure: fifty years of progress. *Circulation, 102*: IV14-IV23.

D'Ippolito G, Diabira S, Howard G, Menei P, Roos B, and Schiller P (2004). Marrow-isolated adult multilineage inducible (MIAMI) cells, a unique population of postnatal young and old human cells with extensive expansion and differentiation potential. *J Cell Sci, 117*: 2971-2981.

Dawn B, Tiwari S, Kucia MJ, Zuba-Surma EK, Guo Y, Sanganalmath SK, Abdel-Latif A, Hunt G, Vincent RJ, Taher H, Reed NJ, Ratajczak MZ, and Bolli R (2008). Transplantation of bone marrow-derived very small embryonic-like stem cells attenuates left ventricular dysfunction and remodeling after myocardial infarction. *Stem Cells, 26*: 1646-1655.

de Weger RA, Verbrugge I, Bruggink AH, van Oosterhout MM, de Souza Y, van Wichen DF, Gmelig-Meyling FH, de Jonge N, and Verdonck LF (2008). Stem cell-derived cardiomyocytes after bone marrow and heart transplantation. *Bone Marrow Transplant, 41*: 563-569.

Deb A, Wang S, Skelding KA, Miller D, Simper D, and Caplice NM (2003). Bone marrow-derived cardiomyocytes are present in adult human heart: A study of gender-mismatched bone marrow transplantation patients. *Circulation, 107*: 1247-1249.

Drukala J, Paczkowska E, Kucia M, Mlynska E, Krajewski A, Machalinski B, Madeja Z, and Ratajczak MZ (2011). Stem Cells, Including a Population of Very Small Embryonic-Like Stem Cells, are Mobilized Into Peripheral Blood in Patients After Skin Burn Injury. *Stem Cell Rev*.

Engelmann M, Theiss H, Hennig-Theiss C, Huber A, Wintersperger B, Werle-Ruedinger A, Schoenberg S, Steinbeck G, and Franz W (2006). Autologous bone marrow stem cell mobilization induced by granulocyte colony-stimulating factor after subacute ST-segment elevation myocardial infarction undergoing late revascularization: final results from the G-CSF-STEMI (Granulocyte Colony-Stimulating Factor ST-Segment Elevation Myocardial Infarction) trial. *J Am Coll Cardiol, 48*: 1712-1721.

Fadini GP, Sartore S, Schiavon M, Albiero M, Baesso I, Cabrelle A, Agostini C, and Avogaro A (2006). Diabetes impairs progenitor cell mobilisation after hindlimb ischaemia-reperfusion injury in rats. *Diabetologia, 49*: 3075-3084.

Fukuhara S, Tomita S, Nakatani T, Yutani C, and Kitamura S (2005). Endogenous bone-marrow-derived stem cells contribute only a small proportion of regenerated myocardium in the acute infarction model. *J Heart Lung Transplant, 24*: 67-72.

Grundmann F, Scheid C, Braun D, Zobel C, Reuter H, Schwinger R, and Müller-Ehmsen J (2007). Differential increase of CD34, KDR/CD34, CD133/CD34 and CD117/CD34 positive cells in peripheral blood of patients with acute myocardial infarction. *Clin Res Cardiol, 96*: 621-627.

Hattan N, Kawaguchi H, Ando K, Kuwabara E, Fujita J, Murata M, Suematsu M, Mori H, and Fukuda K (2005). Purified cardiomyocytes from bone marrow mesenchymal stem cells produce stable intracardiac grafts in mice. *Cardiovasc Res, 65*: 293-295.

Hess DA, Levac KD, Karanu FN, Rosu-Myles M, White MJ, Gallacher L, Murdoch B, Keeney M, Ottowski P, Foley R, Chin-Yee I, and Bhatia M (2002). Functional analysis of human hematopoietic repopulating cells mobilized with granulocyte colony-stimulating factor alone versus granulocyte colony-stimulating factor in combination with stem cell factor. *Blood, 100*: 869-878.

Hill JM, Syed MA, Arai AE, Powell TM, Paul JD, Zalos G, Read EJ, Khuu HM, Leitman SF, Horne M, Csako G, Dunbar CE, Waclawiw MA, and Cannon RO, 3rd (2005). Outcomes and risks of granulocyte colony-stimulating factor in patients with coronary artery disease. *J Am Coll Cardiol, 46*: 1643-1648.

Hsieh PC, Segers VF, Davis ME, MacGillivray C, Gannon J, Molkentin JD, Robbins J, and Lee RT (2007). Evidence from a genetic fate-mapping study that stem cells refresh adult mammalian cardiomyocytes after injury. *Nat Med, 13*: 970-974.

Ince H, Petzsch M, Kleine H, Eckard H, Rehders T, Burska D, Kische S, Freund M, and Nienaber C (2005). Prevention of left ventricular remodeling with granulocyte colony-stimulating factor after acute myocardial infarction: final 1-year results of the Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction by Granulocyte Colony-Stimulating Factor (FIRSTLINE-AMI) Trial. *Circulation, 112*: I73-80.

Jalili A, Shirvaikar N, Marquez-Curtis L, Qiu Y, Korol C, Lee H, Turner AR, Ratajczak MZ, and Janowska-Wieczorek A (2010). Fifth complement cascade protein (C5) cleavage fragments disrupt the SDF-1/CXCR4 axis: further evidence that innate immunity orchestrates the mobilization of hematopoietic stem/progenitor cells. *Exp Hematol, 38*: 321-332.

Jiang Y, Jahagirdar B, Reinhardt R, Schwartz R, Keene C, Ortiz-Gonzalez X, Reyes M, Lenvik T, Lund T, Blackstad M, Du J, Aldrich S, Lisberg A, Low W, Largaespada D, and Verfaillie C (2002). Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature, 418*: 41-49.

Jujo K, Hamada H, Iwakura A, Thorne T, Sekiguchi H, Clarke T, Ito A, Misener S, Tanaka T, Klyachko E, Kobayashi K, Tongers J, Roncalli J, Tsurumi Y, Hagiwara N, and Losordo DW (2010). CXCR4 blockade augments bone marrow progenitor cell recruitment to the neovasculature and reduces mortality after myocardial infarction. *Proc Natl Acad Sci U S A, 107*: 11008-11013.

Kang HJ, Kim HS, Zhang SY, Park KW, Cho HJ, Koo BK, Kim YJ, Soo Lee D, Sohn DW, Han KS, Oh BH, Lee MM, and Park YB (2004). Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial. *Lancet, 363*: 751-756.

Kawada H, Fujita J, Kinjo K, Matsuzaki Y, Tsuma M, Miyatake H, Muguruma Y, Tsuboi K, Itabashi Y, Ikeda Y, Ogawa S, Okano H, Hotta T, Ando K, and Fukuda K (2004). Nonhematopoietic mesenchymal stem cells can be mobilized and differentiate into cardiomyocytes after myocardial infarction. *Blood, 104*: 3581-3587.

Kucia M, Dawn B, Hunt G, Guo Y, Wysoczynski M, Majka M, Ratajczak J, Rezzoug F, Ildstad ST, Bolli R, and Ratajczak MZ (2004a). Cells expressing early cardiac markers reside in the bone marrow and are mobilized into the peripheral blood after myocardial infarction. *Circ Res, 95*: 1191-1199.

Kucia M, Dawn B, Hunt G, Guo Y, Wysoczynski M, Majka M, Ratajczak J, Rezzoug F, Ildstad ST, Bolli R, and Ratajczak MZ (2004b). Cells expressing early cardiac markers reside in the bone marrow and are mobilized into the peripheral blood following myocardial infarction. *Circ Res, 95*: 1191-1199.

Kucia M, Reca R, Campbell FR, Zuba-Surma E, Majka M, Ratajczak J, and Ratajczak MZ (2006). A population of very small embryonic-like (VSEL) CXCR4(+)SSEA-1(+)Oct-4+ stem cells identified in adult bone marrow. *Leukemia, 20*: 857-869.

Kucia M, Reca R, Miekus K, Wanzeck J, Wojakowski W, Janowska-Wieczorek A, Ratajczak J, and Ratajczak MZ (2005). Trafficking of normal stem cells and metastasis of cancer stem cells involve similar mechanisms: pivotal role of the SDF-1-CXCR4 axis. *Stem Cells, 23*: 879-894.

Lapidot T, and Kollet O (2002). The essential roles of the chemokine SDF-1 and its receptor CXCR4 in human stem cell homing and repopulation of transplanted immune-deficient NOD/SCID and NOD/SCID/B2m(null) mice. *Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K, 16*: 1992-2003.

Leone A, Rutella S, Bonanno G, Abbate A, Rebuzzi A, Giovannini S, Lombardi M, Galiuto L, Liuzzo G, Andreotti F, Lanza G, Contemi A, Leone G, and Crea F (2005). Mobilization of bone marrow-derived stem cells after myocardial infarction and left ventricular function. *Eur Heart J, 26*: 1196-1204.

Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, and RS. V (2002). Long-term trends in the incidence of and survival with heart failure. *N Engl J Med, 347*: 1442-1444.

Loffredo FS, Steinhauser ML, Gannon J, and Lee RT (2011). Bone marrow-derived cell therapy stimulates endogenous cardiomyocyte progenitors and promotes cardiac repair. *Cell Stem Cell, 8*: 389-398.

Losordo DW, Schatz RA, White CJ, Udelson JE, Veereshwarayya V, Durgin M, Poh KK, Weinstein R, Kearney M, Chaudhry M, Burg A, Eaton L, Heyd L, Thorne T, Shturman L, Hoffmeister P, Story K, Zak V, Dowling D, Traverse JH, Olson RE, Flanagan J, Sodano D, Murayama T, Kawamoto A, Kusano KF, Wollins J, Welt F, Shah P, Soukas P, Asahara T, and Henry TD (2007). Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. *Circulation, 115*: 3165-3172.

Ma J, Ge J, Zhang S, Sun A, Shen J, Chen L, Wang K, and Zou Y (2005). Time course of myocardial stromal cell-derived factor 1 expression and beneficial effects of intravenously administered bone marrow stem cells in rats with experimental myocardial infarction. *Basic Res Cardiol, 100*: 217-223.

Majka M, Janowska-Wieczorek A, Ratajczak J, Ehrenman K, Pietrzkowski Z, Kowalska MA, Gewirtz AM, Emerson SG, and Ratajczak MZ (2001). Numerous growth factors, cytokines, and chemokines are secreted by human CD34(+) cells, myeloblasts, erythroblasts, and megakaryoblasts and regulate normal hematopoiesis in an autocrine/paracrine manner. *Blood, 97*: 3075-3085.

Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, and Watt SM (2008). Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. *European heart journal, 29*: 1807-1818.

Massa M, Rosti V, Ferrario M, Campanelli R, Ramajoli I, Rosso R, De Ferrari G, Ferlini M, Goffredo L, Bertoletti A, Klersy C, Pecci A, Moratti R, and Tavazzi L (2005). Increased circulating hematopoietic and endothelial progenitor cells in the early phase of acute myocardial infarction. *Blood, 105*: 199-206.

McMurray J, and Pfeffer M (2005). Heart failure. *Lancet, 365*: 1877-1889.

McQuibban GA, Butler GS, Gong JH, Bendall L, Power C, Clark-Lewis I, and Overall CM (2001). Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1. *The Journal of biological chemistry, 276*: 43503-43508.

McQuibban GA, Gong JH, Wong JP, Wallace JL, Clark-Lewis I, and Overall CM (2002). Matrix metalloproteinase processing of monocyte chemoattractant proteins generates CC chemokine receptor antagonists with anti-inflammatory properties in vivo. *Blood, 100*: 1160-1167.

Meyer GP, Wollert KC, Lotz J, Pirr J, Rager U, Lippolt P, Hahn A, Fichtner S, Schaefer A, Arseniev L, Ganser A, and Drexler H (2009). Intracoronary bone marrow cell

transfer after myocardial infarction: 5-year follow-up from the randomized-controlled BOOST trial. *European heart journal, 30*: 2978-2984.

Mooney DJ, and Vandenburgh H (2008). Cell delivery mechanisms for tissue repair. *Cell Stem Cell, 2*: 205-213.

Müller-Ehmsen J, Scheid C, Grundmann F, Hirsch I, Turan G, Tossios P, Mehlhorn U, and Schwinger R (2005). The mobilization of CD34 positive mononuclear cells after myocardial infarction is abolished by revascularization of the culprit vessel. *Int J Cardiol, 103*: 7-11.

Neipp M, Zorina T, Domenick MA, Exner BG, and Ildstad ST (1998). Effect of FLT3 ligand and granulocyte colony-stimulating factor on expansion and mobilization of facilitating cells and hematopoietic stem cells in mice: kinetics and repopulating potential. *Blood, 92*: 3177-3188.

Ohtsuka M, Takano H, Zou Y, Toko H, Akazawa H, Qin Y, Suzuki M, Hasegawa H, Nakaya H, and Komuro I (2004). Cytokine therapy prevents left ventricular remodeling and dysfunction after myocardial infarction through neovascularization. *The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 18*: 851-853.

Paczkowska E, Larysz B, Rzeuski R, Karbicka A, Jałowiński R, Kornacewicz-Jach Z, Ratajczak M, and Machaliński B (2005). Human hematopoietic stem/progenitor-enriched CD34(+) cells are mobilized into peripheral blood during stress related to ischemic stroke or acute myocardial infarction. *Eur J Haematol, 75*: 461-467.

Peterson JT, Li H, Dillon L, and Bryant JW (2000). Evolution of matrix metalloprotease and tissue inhibitor expression during heart failure progression in the infarcted rat. *Cardiovascular research, 46*: 307-315.

Quaini F, Urbanek K, Beltrami AP, Finato N, Beltrami CA, Nadal-Ginard B, Kajstura J, Leri A, and Anversa P (2002). Chimerism of the transplanted heart. *N Engl J Med, 346*: 5-15.

Ratajczak MZ, Lee H, Wysoczynski M, Wan W, Marlicz W, Laughlin MJ, Kucia M, Janowska-Wieczorek A, and Ratajczak J (2010). Novel insight into stem cell mobilization-plasma sphingosine-1-phosphate is a major chemoattractant that directs the egress of hematopoietic stem progenitor cells from the bone marrow and its level in peripheral blood increases during mobilization due to activation of complement cascade/membrane attack complex. *Leukemia, 24*: 976-985.

Ratajczak MZ, Zuba-Surma EK, Shin DM, Ratajczak J, and Kucia M (2008). Very small embryonic-like (VSEL) stem cells in adult organs and their potential role in rejuvenation of tissues and longevity. *Exp Gerontol, 43*: 1009-1017.

Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, and SJ. J (2004). Trends in heart failure incidence and survival in a community-based population. *JAMA, 292*: 344-350.

Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, and Wylie-Rosett J (2011). Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation, 123*: e18-e209.

Sahoo S, Klychko E, Thorne T, Misener S, Schultz KM, Millay M, Ito A, Liu T, Kamide C, Agarwal H, Perlman H, Qin G, Kishore R, and Losordo DW (2011). Exosomes From Human CD34+ Stem Cells Mediate Their Proangiogenic Paracrine Activity. *Circ Res*.

Schachinger V, Assmus B, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Yu J, Corti R, Mathey DG, Hamm CW, Tonn T, Dimmeler S, and Zeiher AM (2009). Intracoronary infusion of bone marrow-derived mononuclear cells abrogates adverse left ventricular remodelling post-acute myocardial infarction: insights from the reinfusion of enriched progenitor cells and infarct remodelling in acute myocardial infarction (REPAIR-AMI) trial. *Eur J Heart Fail, 11*: 973-979.

Shimoji K, Yuasa S, Onizuka T, Hattori F, Tanaka T, Hara M, Ohno Y, Chen H, Egasgira T, Seki T, Yae K, Koshimizu U, Ogawa S, and Fukuda K (2010). G-CSF promotes the proliferation of developing cardiomyocytes in vivo and in derivation from ESCs and iPSCs. *Cell Stem Cell, 6*: 227-237.

Shintani S, Murohara T, Ikeda H, Ueno T, Honma T, Katoh A, Sasaki K, Shimada T, Oike Y, and Imaizumi T (2001). Mobilization of endothelial progenitor cells in patients with acute myocardial infarction. *Circulation, 103*: 2776-2779.

Stamm C, Kleine HD, Westphal B, Petzsch M, Kittner C, Nienaber CA, Freund M, and Steinhoff G (2004). CABG and bone marrow stem cell transplantation after myocardial infarction. *Thorac Cardiovasc Surg, 52*: 152-158.

Strauer BE, Yousef M, and Schannwell CM (2010). The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heARt failure: the STAR-heart study. *Eur J Heart Fail, 12*: 721-729.

Takahashi K, and Yamanaka S (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell, 126*: 663-676.

Tendera M, Wojakowski W, Ruzyllo W, Chojnowska L, Kepka C, Tracz W, Musialek P, Piwowarska W, Nessler J, Buszman P, Grajek S, Breborowicz P, Majka M, and Ratajczak MZ (2009). Intracoronary infusion of bone marrow-derived selected CD34+CXCR4+ cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) Trial. *European heart journal, 30*: 1313-1321.

Tse HF, Thambar S, Kwong YL, Rowlings P, Bellamy G, McCrohon J, Thomas P, Bastian B, Chan JK, Lo G, Ho CL, Chan WS, Kwong RY, Parker A, Hauser TH, Chan J, Fong DY, and Lau CP (2007). Prospective randomized trial of direct endomyocardial implantation of bone marrow cells for treatment of severe coronary artery diseases (PROTECT-CAD trial). *European heart journal, 28*: 2998-3005.

Valgimigli M, Rigolin G, Fucili A, Porta M, Soukhomovskaia O, Malagutti P, Bugli A, Bragotti L, Francolini G, Mauro E, Castoldi G, and Ferrari R (2004). CD34+ and endothelial progenitor cells in patients with various degrees of congestive heart failure. *Circulation, 110*: 1209-1212.

Walter DH, Rochwalsky U, Reinhold J, Seeger F, Aicher A, Urbich C, Spyridopoulos I, Chun J, Brinkmann V, Keul P, Levkau B, Zeiher AM, Dimmeler S, and Haendeler J (2007). Sphingosine-1-phosphate stimulates the functional capacity of progenitor cells by activation of the CXCR4-dependent signaling pathway via the S1P3 receptor. *Arterioscler Thromb Vasc Biol, 27*: 275-282.

Wang Y, Haider H, Ahmad N, Zhang D, and Ashraf M (2006). Evidence for ischemia induced host-derived bone marrow cell mobilization into cardiac allografts. *Journal of molecular and cellular cardiology, 41*: 478-487.

Wojakowski W, Tendera M, Kucia M, Zuba-Surma E, Paczkowska E, Ciosek J, Halasa M, Krol M, Kazmierski M, Buszman P, Ochala A, Ratajczak J, Machalinski B, and Ratajczak MZ (2009). Mobilization of bone marrow-derived Oct-4+ SSEA-4+ very small embryonic-like stem cells in patients with acute myocardial infarction. *J Am Coll Cardiol, 53*: 1-9.

Wojakowski W, Tendera M, Michałowska A, Majka M, Kucia M, Maślankiewicz K, Wyderka R, Ochała A, and Ratajczak M (2004). Mobilization of CD34/CXCR4+, CD34/CD117+, c-met+ stem cells, and mononuclear cells expressing early cardiac, muscle, and endothelial markers into peripheral blood in patients with acute myocardial infarction. *Circulation, 110*: 3213-3220.

Wojakowski W, Tendera M, Zebzda A, Michalowska A, Majka M, Kucia M, Maslankiewicz K, Wyderka R, Król M, Ochala A, Kozakiewicz K, and Ratajczak M (2006). Mobilization of CD34(+), CD117(+), CXCR4(+), c-met(+) stem cells is correlated with left ventricular ejection fraction and plasma NT-proBNP levels in patients with acute myocardial infarction. *Eur Heart J, 27*: 283-289.

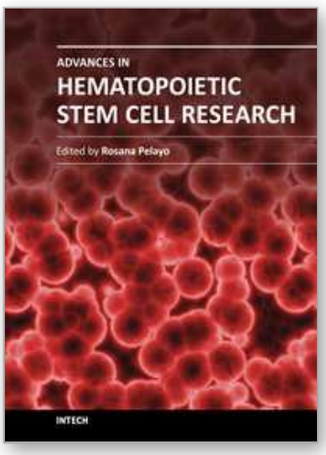
Yousef M, Schannwell CM, Kostering M, Zeus T, Brehm M, and Strauer BE (2009). The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. *Journal of the American College of Cardiology, 53*: 2262-2269.

Zaruba MM, Theiss HD, Vallaster M, Mehl U, Brunner S, David R, Fischer R, Krieg L, Hirsch E, Huber B, Nathan P, Israel L, Imhof A, Herbach N, Assmann G, Wanke R, Mueller-Hoecker J, Steinbeck G, and Franz WM (2009). Synergy between CD26/DPP-IV inhibition and G-CSF improves cardiac function after acute myocardial infarction. *Cell Stem Cell, 4*: 313-323.

Zohlnhöfer D, Ott I, Mehilli J, Schömig K, Michalk F, Ibrahim T, Meisetschläger G, von Wedel J, Bollwein H, Seyfarth M, Dirschinger J, Schmitt C, Schwaiger M, Kastrati A, Schömig A, and Investigators. R- (2006). Stem cell mobilization by granulocyte colony-stimulating factor in patients with acute myocardial infarction: a randomized controlled trial. *JAMA, 295*: 1003-1010.

Zuba-Surma EK, Guo Y, Taher H, Sanganalmath SK, Hunt G, Vincent RJ, Kucia M, Abdel-Latif A, Tang XL, Ratajczak MZ, Dawn B, and Bolli R (2011). Transplantation of expanded bone marrow-derived very small embryonic-like stem cells (VSEL-SCs) improves left ventricular function and remodelling after myocardial infarction. *Journal of cellular and molecular medicine, 15*: 1319-1328.

Zuba-Surma EK, Kucia M, Abdel-Latif A, Dawn B, Hall B, Singh R, Lillard JW, Jr., and Ratajczak MZ (2008). Morphological characterization of very small embryonic-like stem cells (VSELs) by ImageStream system analysis. *J Cell Mol Med, 12*: 292-303.



Advances in Hematopoietic Stem Cell Research
Edited by Dr. Rosana Pelayo

ISBN 978-953-307-930-1
Hard cover, 464 pages
Publisher InTech
Published online 27, January, 2012
Published in print edition January, 2012

This book provides a comprehensive overview in our understanding of the biology and therapeutic potential of hematopoietic stem cells, and is aimed at those engaged in stem cell research: undergraduate and postgraduate science students, investigators and clinicians. Starting from fundamental principles in hematopoiesis, Advances in Hematopoietic Stem Cell Research assemble a wealth of information relevant to central mechanisms that may regulate differentiation, and expansion of hematopoietic stem cells in normal conditions and during disease.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen