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Combination stem cell therapy for heart failure

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Abstract

Patients with congestive heart failure (CHF) that are not eligible for transplantation have limited therapeutic options. Stem cell therapy such as autologous bone marrow, mobilized peripheral blood, or purified cells thereof has been used clinically since 2001. To date over 1000 patients have received cellular therapy as part of randomized trials, with the general consensus being that a moderate but statistically significant benefit occurs. Therefore, one of the important next steps in the field is optimization. In this paper we discuss three ways to approach this issue: a) increasing stem cell migration to the heart; b) augmenting stem cell activity; and c) combining existing stem cell therapies to recapitulate a "therapeutic niche". We conclude by describing a case report of a heart failure patient treated with a combination stem cell protocol in an attempt to augment beneficial aspects of cord blood CD34 cells and mesenchymal-like stem cells.

Introduction

For the approximately 5 million Americans with heart failure, of which only a small proportion are eligible for transplantation, regenerative medicine is the only therapeutic hope. CHF is caused by many factors, such as poor perfusion due to atherosclerotic disease, a previous heart attack, a congenital defect, or previous viral infection, but the end result is usually similar: a self perpetuating cycle of cardiomyocyte death, inflammatory mediator release, myocardial compensatory hypertrophy, and additional cardiomyocyte death, culminating in a deterioration of ejection fraction. Numerous common themes are associated with the progression to heart failure. We will discuss below how stem cell therapy may act on these factors in a therapeutic sense.

Inhibition of Inflammatory Cascade by Mesenchymal Stem Cells

Ongoing inflammation is part of the cascade leading to heart failure. Acute inflammation occurs during infarction as a result of tissue damage, however, chronic inflammatory markers are present in both post-infarct patients, as well as ischemic heart failure patients, and patients with congenital defects. In general, a positive correlation between advanced heart failure and levels of the inflammatory marker C-reactive protein (CRP) has been reported [1,2]. While CRP elevation is conventionally seen as a marker of ongoing inflammation, produced by the liver in response to cytokines such as IL-1, IL-6, and TNF-alpha [3], it also plays an active role in cardiac deterioration through induction of endothelial dysfunction [4,5], as well as exacerbation of inflammatory processes through activation of complement [6,7]. In addition to CRP, elevated levels of inflammatory cytokines are also noted in CHF patients [8]. Inflammatory mediators are produced not only as a result of cardiomyocyte ischemia, but also stretch injury as a result of hypertrophic accommodation [9,10] and systemic activation of immune cells including T cells [11] and monocytes [12]. Functionally, inflammatory mediators induce direct apoptosis of cardiomyocytes. For example TNF-alpha is known to induce reduction of bcl-2 gene expression and activate caspase-dependent apoptosis in cardiac cells at physiological concentrations [13]. Reduction of TNF-alpha activity using soluble receptors has demonstrated beneficial effects in animal models of heart failure [14].

The importance of inflammatory stimuli in heart failure can be seen in animal models in which activators of inflammatory agents, such as toll-like receptors (TLRs) are knocked-out. Generally, TLRs particularly TLR 2 and 4, recognize endogenous "danger signals" associated with damaged tissue such as extracellular matrix degradation products [15,16], and heat shock proteins [17]. Doxorubicin induced heart failure is substantially

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attenuated in animals lacking TLR-2 [18] or TLR-4 [19]. TLR-2 knockout mice have a substantially better clinical outcome after experimental infarction, including reduction in remodeling, wall thinning, and preservation of LVEF as compared to wild-type controls [20]. Clinically, expression of TLR-4 is associated with poor prognosis in post-infarct patients [21]. Thus it appears that inflammation is associated with progression of heart failure. Supporting an "innate" immune component to heart failure are studies by Linden's group demonstrating that NKT cells play a fundamental role in reperfusion injury, and that modulation of these cells with adenosine receptor agonists results in cardioprotection [22,23].

Mesenchymal stem cells (MSC) were originally identified as "stromal cells", believed to play a role in shaping the bone marrow microenvironment where hematopoiesis occurs [24]. More recently, MSC-like populations have been isolated from a diverse range of sources such as adipose [25], heart [26], Wharton's Jelly [27], dental pulp [28], peripheral blood [29], cord blood [30], and more recently menstrual blood [31-33]. In addition to potent regenerative activities of MSC, which we will describe below, MSC have potent anti-inflammatory activities which appear to be present regardless of tissue of origin [34,35]. Mechanistically, MSC appear to suppress inflammation through secretion of anti-inflammatory cytokines such as IL-10 [36], TGF-beta [37], LIF [38], soluble HLA-G [39] and IL-1 receptor antagonist [40], expression of immune regulatory enzyme such as cycloxygenase [41] and indolamine 2,3 deoxygenase [42], and ability to induce generation of anti-inflammatory T regulatory cells [43]. The in vivo anti-inflammatory effects of MSC may be witnessed by success in treating animal models of immune mediate/inflammatory pathologies such as multiple sclerosis [44], colitis [45], graft versus host [46], rheumatoid arthritis [47], and ischemia/reperfusion injury [48]. In heart failure, administration of MSC post infarct has been demonstrated to decrease production of TNF-alpha and IL-6, but upregulate generation of the anti-inflammatory cytokine IL-10, which correlated with therapeutic benefit [49]. Clinically, MSC have demonstrated repeatedly potent therapeutic activity at suppressing graft versus host (GVHD) [50-55]. Thus one angle in which stem cell therapy may be useful for heart failure is by suppressing ongoing self-perpetuating inflammatory cascade.

Inhibition of Death/Repair

Cardiomyocyte death, either by apoptosis [56], or other types of death such as autophagy and programmed necrosis is part of the self-perpetuating cascade leading to heart failure [57,58]. Thus the manipulation of these death pathways, and upregulation of endogenous repair mechanisms in the heart could be a possible method of decreasing the progression to heart failure. For example, suppression of intracellular apoptotic pathways, as performed by transgenic expression of a dominant negative form of Mammalian sterile 20-like kinase-1 (Mst1), has been shown to inhibit post infarct remodeling [59]. Similar protective effects can be attained by transfection of anti-apoptotic genes such as IAP-2 [60], or growth factors that inhibit apoptosis [61]. ACE inhibitors have been postulate to have some beneficial effects through inhibition of cardiomyocyte apoptosis [62]. Thus one method of addressing the progression to heart failure would be identification of methods to prevent ongoing cell death.

Cell death in the heart causes some level of replacement by resident cardiac stem cells (CSC). These cells are relatively rare and are believed to respond to signals associated with damage to the myocardium. Fransioli et al generated a transgenic mouse expressing GFP under control of the c-kit promoter. Subsequent to infarct, increased proliferation of c-kit positive cells was seen in the myocardium [63]. In humans Urbanek et al examined 20 human hearts from patients who died after acute infarct, 20 hearts with chronic infarct that were transplanted, and 12 control hearts. A population of cells expressing c-kit, MDR1 and Sca-1 were seen to enter cell cycle from a basal rate of 1.5% cycling cells in controls, to 28% and 14% in acute and chronic infarcts, respectively. The cells expressing the phenotype were demonstrated to be capable of differentiating into myocyte, smooth muscle, and endothelial cell lineages [64]. Isolated CSC have been successfully expanded ex vivo and administered via the intracoronary route in rats post-infarct. Successful transmigration of the CSC across the endothelium and active regeneration of myocardium was demonstrated [65]. Thus it appears that a functional population of stem cells exists in the heart that to some extent can cause regeneration post injury.

Both HSC and MSC are capable of secreting factors that on the one hand inhibit apoptosis [66-68] and on the other hand stimulate activation of CSC [69]. For example, it was demonstrated that administration of non-fractionated bone marrow cells containing both cell populations protects against apoptosis in a doxorubin induced cardiomyopathy model [70]. Furthermore bone marrow cells are known to produce HGF [71] and IGF-1 [72], cytokines that are anti-apoptotic and activate endogenous cardiomyocyte stem cells [69]. Interestingly, production of these factors is upregulated in response to inflammatory mediators associated with heart failure such as TNF-alpha [68]. Therefore it may be possible that MSC not only migrate to injured tissue but can also "sense" inflammatory stimuli such as TNF-alpha and actually try to grade the level of their therapeutic response according to the level of damage sensed.

Another means by which stem cells may repair the heart is through actually differentiating into new heart muscle. Reports exist of both hematopoietic [73] and mesenchymal stem cells [74,75] differentiating into cardiac-like cells, although this is controversial and some groups have reported this to be a product of cell fusion [76]. Additionally, stem cells promote angiogenesis, thus providing nutrients to ischemic areas and potentially allowing regeneration [77,78].

Currently Stem Cell Therapy Helps Heart Patients: Just Not That Well

Cardiac stem cell therapy was first described 2001 when Strauer et al reported a case in which a 46 year old patient received autologous bone marrow mononuclear cells by a percutaneous transluminal catheter placed in the infarct-related artery. 10 weeks after administration the transmural infarct area had been reduced from 24.6% to 15.7% of left ventricular circumference, while ejection fraction, cardiac index and stroke volume had increased by 20-30% [79]. A subsequent paper in the same year reported administration of similar cells in 5 patients with advanced ischemia undergoing coronary artery bypass grafting. Cells were administered intramuscularly into areas deemed ungraftable and perfusion was assessed by imaging. Specific improvement in areas injected was documented in 3 of the 5 patients. No ectopic growths or adverse effects were reported at 1 year follow-up [80]. Since these pioneering studies, cardiac stem cell therapy has been used by numerous groups for numerous conditions causing heart failure. These can be broken down into: a) inhibiting post acute myocardial infarction remodeling; b) stimulation of regeneration in chronically injured hearts and c) induction of angiogenesis in coronary artery disease. The methods of administering stem cells have included the intracoronary, epicardial, and intravenous routes. Stem cells used to date are bone marrow mononuclear cells, mobilized peripheral blood stem cells, purified CD34 or CD133 cells, autologous mesenchymal stem cells, and allogeneic bone marrow and placental mesenchymal stem cells.

To avoid detailed examination, we will discuss several meta-analysis of ongoing clinical trials performed. Abdel-Latif et al described 999 patients enrolled 18 independent controlled cardiac trials in which patients were treatment with either unseparated bone marrow cells, bone marrow mesenchymal, or mobilized peripheral blood [81]. They found that in comparison to controls, there was a statistically significant improvement in ejection fraction, reduction in infarct size and left ventricular end-systolic volume. Importantly, no safety issues or serious treatment associated adverse events were noted. In another such comprehensive review, Martin-Rendon et al focused on bone marrow therapy for post acute infarction trials. Of 13 randomized studies conducted, encompassing 811 participants, the authors of the review stated that more trials are needed to establish efficacy in terms of clinical endpoints such as death. However that authors of the review did observe a consistent improvement in LVEF, as well as trends for decrease in left ventricular end systolic and end diastolic volumes, and infarct size [82]. Two other meta-analysis of randomized trials in the area of bone marrow stem cell infusions also supported the conclusion of safety and mild but statistically significant improvement in LVEF [83,84]. These data suggest that stem cell therapy, both hematopoietic and mesenchymal have clinical effects in various types of heart failure. Theoretically the leap between these clinical trials and widespread implementation is more of a business question than a medical question. In order to postulate on the future of cardiac stem cell therapy, we will discuss several possible means of optimizing existing work.

How to Increase Stem Cell Efficacy?

Attempts at increasing efficacy of stem cells for cardiac indications have taken several avenues of investigation: increasing trafficking efficacy; enhancing plasticity of administered cells; and increasing growth factor production. Endowment of these features as been performed by gene transfection or modification of culture conditions such as exposure to cytokines or hypoxia. Another interesting approach is addition of chemotactic agents to the area of tissue injury to enhance trafficking. These approaches will be discussed below.

Making Stem Cells Home Better

Mesenchymal stem cells are known to migrate to injured tissue and hypoxic tissue through expression of receptors such as CD44 [85-87] and CXCR-4 [88], respectively. One method of increase efficacy of these cells is to increase their ability to traffic to where they are needed. This has been performed using various approaches. Cheng et al used retroviral transfection to overexpress CXCR-4 on rat bone marrow derived MSC. These cells were functionally competent as judged by similar growth profiles and differentiation ability when compared to control transfected MSC. Intravenous administration of the modified cells in a rat model of myocardial infarction led to a significant improvement in migration to the area of infarct, and LVEF, as well as decreased wall thinning and fibrosis when compared to animals receiving control MSC [89]. Although many fears exist surrounding genetically modified cells, current advances in delivery vectors have for increased safety features which may allow such modified MSC to become a clinical reality [90]. An alternative and

perhaps easier way of inducing MSC to expression CXCR-4 is simply "pulsing" them with a brief period of hypoxia [91], or exposure to cytokines such as SCF, IL-6, Flt-3 ligand, HGF and IL-3 [92].

Instead of increasing affinity of the stem cells to the chemoattractant, the other way to achieve the same result is to increase the concentration of the chemoattractant. One way is to provide an exogenous depot of angiogenic cytokines in proximity to the area where stem cell migration is desired. Tang et al administered a SDF-1 expressing plasmid into the ischemic border zone 2 weeks after induction of infarct in BALB/c mice. To determine whether the expressed chemoattractant actually caused stem cell homing, syngeneic labeled bone marrow cells were intravenously injected 3 days after SDF-1 plasmid administration. A significantly increased number of labeled cells was observed in the group receiving the plasmid, in the area whether the plasmid was injected [93]. These data suggest that it is feasible to reproduce mobilization induced by infarcts through the administration of homologous cytokines. However, the authors did not describe therapeutic benefit. In another experiment, a more clinically-translatable approach was taken. Fibrin glue, fibrinogen and thrombin mixed at the point of care, is used in surgery to control bleeding [94]. Zhang et al used pegylation technology to covalently bind recombinant SDF-1 to fibrinogen and demonstrated that subsequent to mixing with thrombin, the resultant "patch" could serve as a means of controlled release of SDF-1. The patch was placed on the infarct area of the left ventricle of mice after ligation of the left anterior descending coronary artery. In comparison to control mice receiving a fibrin patch lacking SDF-1, an increase in cells with a stem cell antigen and c-kit positive phenotype was observed in the experimental group. Additionally, at completion of experiment, an increased LVEF was observed in the treatment mice [95]. Since endogenous cardiac stem cells also express a similar phenotype [96], and cell labeling was not performed, it is difficult to determine whether the therapeutic effect was mediated by mobilization of bone marrow progenitors or cardiac resident stem cells. One interesting way of enhancing activity of such a localization of chemoattractants is to concurrently administer exogenous stem cells, or to mobilize endogenous bone marrow stem cells. In fact, the latter was performed in a study where fibroblasts expressing SDF-1 were injected into the hindlimbs of mice after femoral ligation. A synergistic induction of angiogenesis was detected when endogenous bone marrow derived stem cells were mobilized with G-CSF [97]. Other clinically used methods may be implemented to enhance stem cell trafficking. For example, erythropoietin (EPO), in addition to its well-known anti-apoptotic effects on cardiomyocytes [98], has actually been shown to stimulate responsiveness of bone marrow derived stem cells to SDF-1 when administered in vivo [99]. A recent paper described the nutraceutical Stem-Kine as the first food supplement capable of augmenting endogenous circulating stem cells, this approach may spare patients potential adverse effects associated with cytokine mobilization [100]. The procedure of transmyocardial revascularization has been demonstrated to synergize with endothelial progenitor cells for augmentation of neoangiogenesis [101], it remains an open question whether other stem cell therapies may synergize with this therapy. Combination therapies of this sort will be interesting to evaluate clinically, especially when the various components are already approved.

Revitalize Stem Cells

Once we can make sure that stem cells arrive to the site where they are needed to stimulate regeneration, how do we know that they can do this effectively? For example, we do know that in general, stem cell activity diminishes with age [102], and specifically, in patients with cardiovascular risk factors stem cell activity is additionally suppressed as compared to healthy age-matched controls [103]. There are several issues that must be taken into consideration. Perhaps, most importantly, is how do the stem cells mediate their therapeutic effects? On the one hand, people will state that adult stem cells, such as hematopoietic [104] and even in some cases mesenchymal stem cells [105], do not differentiate into functional cardiomyocytes, so therefore therapy with these cells is a futile endeavor. As we discussed above, efficacy of cardiac stem cell therapy does not rely on cell replacement but could be, and most likely is, mediated by trophic, angiogenic, anti-inflammatory and anti-apoptotic effects. Regardless of this, the concept of "revitalizing" an adult stem cell so to be able to actually replace cardiac cells is very exciting.

One method of such "revitalization" is involves making the stem cells take a more primitive, embryonic stem cell-like phenotype. It is known that the more differentiated cells become, the less plasticity they have, and the more restricted epigenetically, they become. Perhaps this was associated with the reason why DNA methyltransferase inhibitors such as 5-azacytidine were initially added to stem cells before implantation into infracted hearts [106,107]. Other agents that act epigenetically, such as the histone deacetylase inhibitor valproic acid have been demonstrated to enhance hematopoietic stem cell self renewal capacity in vitro [108,109], and have a positive effect on post infarct remodeling in vivo, although it is not clear whether stem cell activation is implicated [110]. Instead of using agents such as these that upregulate factors associated

with pluripotency such as Nanog [111], an alternative approach is to simply transfect the cells with such genes. For example Go et al transfected bone marrow derived MSC with Nanog and reported superior expansion potential and ability to differentiate as compared to control transfected cells [112]. Transfection of such "retrodifferentiation" genes is particularly exciting in light of the recent discovery that fibroblasts can be induced to pluripotency through introduction of the pluripotency genes Oct3/4, Sox2, c-Myc, and Klf4 in mice [113] and humans [114]. These "inducible pluripotent stem cells" (iPS) appear to be functional, not only by gene transcription profile, but also ability to reconstitute animals hematopoietically [115]. Theoretically, it would make sense that retrodifferentiation of an adult stem cell into an iPS would be easier than a skin fibroblast. Indeed, Kim et al demonstrated that in order to derived iPS cells from neural stem cells, only the factors Oct-4 and klf-4 or c-Myc are needed [116]. Furthermore, newer transfection methods of generating iPS through non-retroviral means have been reported, giving the possibility of generating clinically applicable therapies from these cells [117]. Unfortunately, carcinogenesis associated with the viral vectors is not the main limitation. It is known in general that ES cells are carcinogenic [118]. Additionally, the very transcriptional profile associated with cancer stem cells appears to be related to that of pluripotent cells, regardless if they are generated by iPS or from ES cells [119].

Thus one way of increasing potency of MSC-based therapy is through induction of such a "rejuvenation" unfortunately, too much rejuvenation leads to the possibility of carcinogenesis, and additionally may have implications on ability of the cells to evade immune responsiveness and/or migration to the area of injury. For example, it is known that embryonic stem cells are hypoimmunogenic, as seen by weak ability to stimulate allogeneic lymphocyte proliferation [120]. However it remains an open question whether ES cells can actively suppress ongoing immune responses as is the case with MSC both in animal models [45] and clinically [121,122]. In terms of migratory ability, it is known that functionally various adult stem cells play a protective role in the physiological response to injury. Although the effects in clinical situations are minor, there is suggestive evidence, for example in stroke patients that a correlation between endogenous stem cell mobilization and positive outcome exists [123,124]. While in cardiac infarct cases we do know that mobilization occurs [125], but correlation with infarct recovery have not been made. Regardless, the question of what stage of differentiation the best cell population is for treatment of cardiac indications remains unclear.

Stem Cell Combinations

Given that we do not know the best stage of differentiation to administer the stem cells, as well as the various drawbacks of transfection and reprogramming approaches, one possible way of advancing efficacy of stem cell therapy would be to combine various stem cell types that we know have trophic activity. One interesting combination would be the use of CD34 cells, which are primarily hematopoietic, but also angiogenic, together with allogeneic mesenchymal stem cells, which have trophic, angiogenic, and potent anti-inflammatory potential. The rationale for combining these two approaches come from several perspectives: a) after tissue injury both mesenchymal [85,126,127] and hematopoietic stem cells [128-130] are mobilized thus potentially both cells may have therapeutic synergistic activity in a physiological sense; b) In vivo MSC provide a microenvironment for CD34 stem cells both embryonically [131], and postnatally [132], in vitro MSC promote expansion of CD34 stem cells [133,134]; and c) animal models suggest synergy of function [135].

We have previously published data from an end-stage patient suffering from dilated cardiomyopathy which underwent a profound improvement in ejection fraction after receiving a combination of cord blood expanded CD34 cells and placental matrix derived mesenchymal stem cells [136]. In the current case report we describe a patient with ischemia cardiomyopathy who received a combination of allogeneic CD34 cells and endometrial regenerative cells (ERC), a MSC-like population which has previously been demonstrated to possess higher growth factor production ability as compared to control MSC cells [31], as well as in immunomodulatory and in vivo angiogenic activity [137]. Furthermore, ERC-like cells have been reported by independent groups to possess an increased propensity towards muscular [138,139] and cardiac differentiation [140], as compared with other stem cell types. Animal safety studies have demonstrated that ERC do not cause tumors in immune competent animals and actively suppress glioma growth in vivo [141]. Feasibility-based clinical investigations have demonstrated ERC do not cause abnormal growths subsequent to intrathecal or intravenous administration [142].

Case Report

Endometrial Regenerative Cells (ERC) were provided with a certificate of analysis describing purity (> 90% expression of CD90 and CD105, and < 5% expression of CD34 and CD45) and sterility (lack of adventitious contaminants). ERC and cord blood CD34 cells were generated described in our previous publications [136,143].

Patient was born January 7th, 1933. At 74 the patient presented with congestive heart failure and an ejection fraction of 25-30%. Risks associated with stem cell therapy and specifically with the combination of two stem cell products, of which neither one has been approved by the FDA, or EMEA for general use were explained to the patient in detail. After signing informed consent and being accepted by an independent oversight committee for the experimental treatment, the patient was administered ERCs. On days 1,2,3,4 and 7 the patient received intravenous administration of 3 million ERC (total number 15 million). CD34 cells were administered as follows: day 1 (4.5 million); day 2 (3 million); day 3, (2.3 × 10(5)); day 4 (1.5 million); and day 7 (1.5 million). Last injection was performed November 19th, 2007. Injection was performed by intravenous drip using USP-grade saline and autologous heat inactivated serum (10%). Injection site and general condition of the patient was monitored for 3 hours after the first administration. Before subsequent injections the injection site was examined for swelling or inflammation and the general state of the patient was examined. For all injections no evident reactions were noted.

Echocardiogram performed June 27, 2008, August 11, 2008, and Oct 1st 2009 demonstrated that the patient's ejection fraction was approximately 40%. The Minnesota Living with Heart Failure Questionnaire score dropped from 97 pretreatment to a value of 2 onFebruary 2009. Reduction of Pro-BNP was observed after treatment: Pre-treatment levels of Pro-BNP were 1946 on September 5th, 2007, 1225 on January 11, 2008, and 788.1 on Sept 28, 2009. The patient has other chemical and metabolic testing to further analyze his heart failure. Complete blood count, serum biochemistry, PSA, CEA, alpha fetoprotein, fecal occult blood test revealed no abnormalities in comparison to reference ranges. This was similar to baseline. Radiological examination of the chest PA and Lateral x-ray did not reveal any abnormalities. Physical examination of the patient, with special emphasis on the injection site revealed no masses, inflammation or abnormalities. This patient continues to do well.

Conclusion

Adult stem cell therapy for cardiac conditions has reached the point where new directions are needed to optimize effects. Possibilities of next-generation approaches include the use of "in vitro supercharged" cells, combinations of cells and cytokines, and of course combination of cellular therapies. Currently the use of endometrial regenerative cells as a possible substitute for bone marrow mesenchymal stem cells is being evaluated by our group including novel methods to image the cells and the changes in heart function.

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Authors' contributions

TEI, FS, FL, JPR, OC, BM, FM, EJW, MPM, DTA, ANP, and NHR performed literature review and wrote the manuscript. FS, FL, and JPR reported on the clinical case. All authors read and approved the final manuscript.

Competing interests

NHR and TEI are shareholders and management of Medistem Inc. FS, FL and JPR were employees of Cell Medicine Institutes Costa Rica, and Panama, respectively at time of manuscript submission.

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References

1. Sanchez-Lazaro IJ, Almenar L, Reganon E, Vila V, Martinez-Dolz L, Martinez-Sales V, Moro J, Aguero J, Ortiz-Martinez V, Salvador A: **Inflammatory markers in stable heart failure and their relationship with functional class.** *Int J Cardiol* 2007, **129(3)**:388-93.
2. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agara M, Olaz-Preciado F, Urbieta-Echezarreta M, Gonzalez-Arencibia C: **C-reactive protein as a predictor of improvement and readmission in heart failure.** *Eur J Heart Fail* 2002, **4**:331-336.
3. Nakou ES, Liberopoulos EN, Milionis HJ, Elisaf MS: **The role of C-reactive protein in atherosclerotic cardiovascular disease: an overview.** *Curr Vasc Pharmacol* 2008, **6**:258-270.
4. Galarraga B, Khan F, Kumar P, Pullar T, Belch JJ: **C-reactive protein: the underlying cause of microvascular dysfunction in rheumatoid arthritis.** *Rheumatology (Oxford)* 2008, **47(12)**:1780-4.
5. Nabata A, Kuroki M, Ueba H, Hashimoto S, Umemoto T, Wada H, Yasu T, Saito M, Momomura S, Kawakami M: **C-reactive protein induces endothelial cell apoptosis and matrix metalloproteinase-9 production in human mononuclear cells: Implications for the destabilization of atherosclerotic plaque.** *Atherosclerosis* 2008, **196**:129-135.
6. Griselli M, Herbert J, Hutchinson WL, Taylor KM, Sohail M, Krausz T, Pepys MB: **C-reactive protein and complement are important mediators of tissue damage in acute myocardial infarction.** *J Exp Med* 1999, **190**:1733-1740.
7. Pepys MB, Hirschfield GM, Tennent GA, Gallimore JR, Kahan MC, Bellotti V, Hawkins PN, Myers RM, Smith MD, Polara A, *et al*: **Targeting C-reactive protein for the treatment of cardiovascular disease.** *Nature* 2006, **440**:1217-1221.
8. Satoh M, Minami Y, Takahashi Y, Nakamura M: **Immune modulation: role of the inflammatory cytokine cascade in the failing human heart.** *Curr Heart Fail Rep* 2008, **5**:69-74.
9. Yokoyama T, Sekiguchi K, Tanaka T, Tomaru K, Arai M, Suzuki T, Nagai R: **Angiotensin II and mechanical stretch induce production of tumor necrosis factor in cardiac fibroblasts.** *Am J Physiol* 1999, **276**:H1968-1976.
10. Wang BW, Hung HF, Chang H, Kuan P, Shyu KG: **Mechanical stretch enhances the expression of resistin gene in cultured cardiomyocytes via tumor necrosis factor-alpha.** *Am J Physiol Heart Circ Physiol* 2007, **293**: H2305-2312.
11. Satoh S, Oyama J, Suematsu N, Kadokami T, Shimoyama N, Okutsu M, Inoue T, Sugano M, Makino N: **Increased productivity of tumor necrosis factor-alpha in helper T cells in patients with systolic heart failure.** *Int J Cardiol* 2006, **111**:405-412.
12. Conraads VM, Bosmans JM, Schuerwegh AJ, Goovaerts I, De Clerck LS, Stevens WJ, Bridts CH, Vrints CJ: **Intracellular monocyte cytokine**

production and CD 14 expression are up-regulated in severe vs mild chronic heart failure. *J Heart Lung Transplant* 2005, **24**:854-859.
13. Haudek SB, Taffet GE, Schneider MD, Mann DL: **TNF provokes cardiomyocyte apoptosis and cardiac remodeling through activation of multiple cell death pathways.** *J Clin Invest* 2007, **117**:2692-2701.
14. Kubota T, Bounoutas GS, Miyagishima M, Kadokami T, Sanders VJ, Bruton C, Robbins PD, McTiernan CF, Feldman AM: **Soluble tumor necrosis factor receptor abrogates myocardial inflammation but not hypertrophy in cytokine-induced cardiomyopathy.** *Circulation* 2000, **101**:2518-2525.
15. Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD, Horton MR: **Hyaluronan fragments act as an endogenous danger signal by engaging TLR2.** *J Immunol* 2006, **177**:1272-1281.
16. Termeer C, Benedix F, Sleeman J, Fieber C, Voith U, Ahrens T, Miyake K, Freudenberg M, Galanos C, Simon JC: **Oligosaccharides of Hyaluronan activate dendritic cells via toll-like receptor 4.** *J Exp Med* 2002, **195**:99-111.
17. Asea A: **Heat shock proteins and toll-like receptors.** *Handb Exp Pharmacol* 2008, 111-127.
18. Nozaki N, Shishido T, Takeishi Y, Kubota I: **Modulation of doxorubicin-induced cardiac dysfunction in toll-like receptor-2-knockout mice.** *Circulation* 2004, **110**:2869-2874.
19. Riad A, Bien S, Gratz M, Escher F, Westermann D, Heimesaat MM, Bereswill S, Krieg T, Felix SB, Schultheiss HP, *et al*: **Toll-like receptor-4 deficiency attenuates doxorubicin-induced cardiomyopathy in mice.** *Eur J Heart Fail* 2008, **10**:233-243.
20. Shishido T, Nozaki N, Yamaguchi S, Shibata Y, Nitobe J, Miyamoto T, Takahashi H, Arimoto T, Maeda K, Yamakawa M, *et al*: **Toll-like receptor-2 modulates ventricular remodeling after myocardial infarction.** *Circulation* 2003, **108**:2905-2910.
21. Sheu JJ, Chang LT, Chiang CH, Youssef AA, Wu CJ, Lee FY, Yip HK: **Prognostic value of activated toll-like receptor-4 in monocytes following acute myocardial infarction.** *Int Heart J* 2008, **49**:1-11.
22. Yang Z, Linden J, Berr SS, Kron IL, Beller GA, French BA: **Timing of adenosine 2A receptor stimulation relative to reperfusion has differential effects on infarct size and cardiac function as assessed in mice by MRI.** *Am J Physiol Heart Circ Physiol* 2008, **295**:H2328-2335.
23. Yang Z, Day YJ, Toufektsian MC, Xu Y, Ramos SI, Marshall MA, French BA, Linden J: **Myocardial infarct-sparing effect of adenosine A2A receptor activation is due to its action on CD4+ T lymphocytes.** *Circulation* 2006, **114**:2056-2064.
24. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP: **Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues.** *Transplantation* 1968, **6**:230-247.
25. Zannettino AC, Paton S, Arthur A, Khor F, Itescu S, Gimble JM, Gronthos S: **Multipotential human adipose-derived stromal stem cells exhibit a perivascular phenotype in vitro and in vivo.** *J Cell Physiol* 2008, **214**:413-421.
26. Hoogduijn MJ, Crop MJ, Peeters AM, Van Osch GJ, Balk AH, Ijzermans JN, Weimar W, Baan CC: **Human heart, spleen, and perirenal fat-derived mesenchymal stem cells have immunomodulatory capacities.** *Stem Cells Dev* 2007, **16**:597-604.
27. Chao KC, Chao KF, Fu YS, Liu SH: **Islet-like clusters derived from mesenchymal stem cells in Wharton's Jelly of the human umbilical cord for transplantation to control type 1 diabetes.** *PLoS ONE* 2008, **3**:e1451.
28. Jo YY, Lee HJ, Kook SY, Choung HW, Park JY, Chung JH, Choung YH, Kim ES, Yang HC, Choung PH: **Isolation and characterization of postnatal stem cells from human dental tissues.** *Tissue Eng* 2007, **13**:767-773.
29. He Q, Wan C, Li G: **Concise review: multipotent mesenchymal stromal cells in blood.** *Stem Cells* 2007, **25**:69-77.
30. Oh W, Kim DS, Yang YS, Lee JK: **Immunological properties of umbilical cord blood-derived mesenchymal stromal cells.** *Cell Immunol* 2008.
31. Meng X, Ichim TE, Zhong J, Rogers A, Yin Z, Jackson J, Wang H, Ge W, Bogin V, Chan KW, *et al*: **Endometrial regenerative cells: a novel stem cell population.** *J Transl Med* 2007, **5**:57.
32. Hida N, Nishiyama N, Miyoshi S, Kira S, Segawa K, Uyama T, Mori T, Miyado K, Ikegami Y, Cui C, *et al*: **Novel Cardiac Precursor-Like Cells from Human Menstrual Blood-Derived Mesenchymal Cells.** *Stem Cells* 2008, **26(7)**:1695-704.
33. Patel AN, Park E, Kuzman M, Benetti F, Silva FJ, Allickson JG: **Multipotent menstrual blood stromal stem cells: isolation, characterization, and differentiation.** *Cell Transplant* 2008, **17**:303-311.
34. Le Blanc K, Ringden O: **Immunomodulation by mesenchymal stem cells and clinical experience.** *J Intern Med* 2007, **262**:509-525.
35. Keyser KA, Beagles KE, Kiem HP: **Comparison of mesenchymal stem cells from different tissues to suppress T-cell activation.** *Cell Transplant* 2007, **16**:555-562.
36. Nasef A, Chapel A, Mazurier C, Bouchet S, Lopez M, Mathieu N, Sensebe L, Zhang Y, Gorin NC, Thierry D, *et al*: **Identification of IL-10 and TGF-beta transcripts involved in the inhibition of T-lymphocyte proliferation during cell contact with human mesenchymal stem cells.** *Gene Expr* 2007, **13**:217-226.
37. Ryan JM, Barry F, Murphy JM, Mahon BP: **Interferon-gamma does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells.** *Clin Exp Immunol* 2007, **149**:353-363.
38. Nasef A, Mazurier C, Bouchet S, Francois S, Chapel A, Thierry D, Gorin NC, Fouillard L: **Leukemia inhibitory factor: Role in human mesenchymal stem cells mediated immunosuppression.** *Cell Immunol* 2008, **253**:16-22.
39. Selmani Z, Naji A, Zidi I, Favier B, Gaiffe E, Obert L, Borg C, Saas P, Tiberghien P, Rouas-Freiss N, *et al*: **Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4 +CD25highFOXP3+ regulatory T cells.** *Stem Cells* 2008, **26**:212-222.
40. Ortiz LA, Dutreil M, Fattman C, Pandey AC, Torres G, Go K, Phinney DG: **Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury.** *Proc Natl Acad Sci USA* 2007, **104**:11002-11007.
41. English K, Barry FP, Field-Corbett CP, Mahon BP: **IFN-gamma and TNF-alpha differentially regulate immunomodulation by murine mesenchymal stem cells.** *Immunol Lett* 2007, **110**:91-100.
42. Jones BJ, Brooke G, Atkinson K, McTaggart SJ: **Immunosuppression by placental indoleamine 2,3-dioxygenase: a role for mesenchymal stem cells.** *Placenta* 2007, **28**:1174-1181.
43. Casiraghi F, Azzollini N, Cassis P, Imberti B, Morigi M, Cugini D, Cavinato RA, Todeschini M, Solini S, Sonzogni A, *et al*: **Pretransplant infusion of mesenchymal stem cells prolongs the survival of a semiallogeneic heart transplant through the generation of regulatory T cells.** *J Immunol* 2008, **181**:3933-3946.
44. Kassis I, Grigoriadis N, Gowda-Kurkalli B, Mizrachi-Kol R, Ben-Hur T, Slavin S, Abramsky O, Karussis D: **Neuroprotection and immunomodulation with mesenchymal stem cells in chronic experimental autoimmune encephalomyelitis.** *Arch Neurol* 2008, **65**:753-761.
45. Parekkadan B, Tilles AW, Yarmush ML: **Bone marrow-derived mesenchymal stem cells ameliorate autoimmune enteropathy independently of regulatory T cells.** *Stem Cells* 2008, **26**:1913-1919.
46. Li H, Guo Z, Jiang X, Zhu H, Li X, Mao N: **Mesenchymal Stem Cells Alter Migratory Property of T and Dendritic Cells to Delay the Development of Murine Lethal Acute Graft-Versus-Host Disease.** *Stem Cells* 2008, **26(10)**:2531-41.
47. Augello A, Tasso R, Negrini SM, Cancedda R, Pennesi G: **Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis.** *Arthritis Rheum* 2007, **56**:1175-1186.
48. Semedo P, Wang PM, Andreucci TH, Cenedeze MA, Teixeira VP, Reis MA, Pacheco-Silva A, Camara NO: **Mesenchymal stem cells ameliorate tissue damages triggered by renal ischemia and reperfusion injury.** *Transplant Proc* 2007, **39**:421-423.
49. Du YY, Zhou SH, Zhou T, Su H, Pan HW, Du WH, Liu B, Liu QM: **Immuno-inflammatory regulation effect of mesenchymal stem cell transplantation in a rat model of myocardial infarction.** *Cytotherapy* 2008, **10**:469-478.
50. Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, Lanino E, Sundberg B, Bernardo ME, Remberger M, *et al*: **Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study.** *Lancet* 2008, **371**:1579-1586.
51. Ning H, Yang F, Jiang M, Hu L, Feng K, Zhang J, Yu Z, Li B, Xu C, Li Y, *et al*: **The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study.** *Leukemia* 2008, **22**:593-599.
52. Ball L, Bredius R, Lankester A, Schweizer J, Heuvel-Eibrink van den M, Escher H, Fibbe W, Egeler M: **Third party mesenchymal stromal cell infusions fail to induce tissue repair despite successful control of severe grade IV acute graft-versus-host disease in a child with juvenile myelo-monocytic leukemia.** *Leukemia* 2008, **22**:1256-1257.

53. Ringden O, Uzunel M, Rasmusson I, Remberger M, Sundberg B, Lonnies H, Marschall HU, Dlugosz A, Szakos A, Hassan Z, *et al*: **Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease.** *Transplantation* 2006, **81**:1390-1397.
54. Le Blanc K, Rasmusson I, Sundberg B, Gotherstrom C, Hassan M, Uzunel M, Ringden O: **Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells.** *Lancet* 2004, **363**:1439-1441.
55. Muller I, Kordowich S, Holzwarth C, Isensee G, Lang P, Neunhoeffer F, Dominici M, Greil J, Handgretinger R: **Application of multipotent mesenchymal stromal cells in pediatric patients following allogeneic stem cell transplantation.** *Blood Cells Mol Dis* 2008, **40**:25-32.
56. Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ, Schmidt U, Semigran MJ, Dec GW, Khaw BA: **Apoptosis in myocytes in end-stage heart failure.** *N Engl J Med* 1996, **335**:1182-1189.
57. Dorn GW: **Apoptotic and non-apoptotic programmed cardiomyocyte death in ventricular remodelling.** *Cardiovasc Res* 2008, **81(3)**:465-73.
58. Rodriguez M, Lucchesi BR, Schaper J: **Apoptosis in myocardial infarction.** *Ann Med* 2002, **34**:470-479.
59. Odashima M, Usui S, Takagi H, Hong C, Liu J, Yokota M, Sadoshima J: **Inhibition of endogenous Mst1 prevents apoptosis and cardiac dysfunction without affecting cardiac hypertrophy after myocardial infarction.** *Circ Res* 2007, **100**:1344-1352.
60. Chua CC, Gao J, Ho YS, Xiong Y, Xu X, Chen Z, Hamdy RC, Chua BH: **Overexpression of IAP-2 attenuates apoptosis and protects against myocardial ischemia/reperfusion injury in transgenic mice.** *Biochim Biophys Acta* 2007, **1773**:577-583.
61. Jayasankar V, Woo YJ, Bish LT, Pirolli TJ, Chatterjee S, Berry MF, Burdick J, Gardner TJ, Sweeney HL: **Gene transfer of hepatocyte growth factor attenuates postinfarction heart failure.** *Circulation* 2003, **108(Suppl 1)**: II230-236.
62. Filippatos G, Uhal BD: **Blockade of apoptosis by ACE inhibitors and angiotensin receptor antagonists.** *Curr Pharm Des* 2003, **9**:707-714.
63. Fransioli J, Bailey B, Gude NA, Cottage CT, Muraski JA, Emmanuel G, Wu W, Alvarez R, Rubio M, Ottolenghi S, *et al*: **Evolution of the c-kit-positive cell response to pathological challenge in the myocardium.** *Stem Cells* 2008, **26**:1315-1324.
64. Urbanek K, Torella D, Sheikh F, De Angelis A, Nurzynska D, Silvestri F, Beltrami CA, Bussani R, Beltrami AP, Quaini F, *et al*: **Myocardial regeneration by activation of multipotent cardiac stem cells in ischemic heart failure.** *Proceedings of the National Academy of Sciences* 2005, **102**:8692-8697.
65. Dawn B, Stein AB, Urbanek K, Rota M, Whang B, Rastaldo R, Torella D, Tang XL, Rezazadeh A, Kajstura J, *et al*: **Cardiac stem cells delivered intravascularly traverse the vessel barrier, regenerate infarcted myocardium, and improve cardiac function.** *Proc Natl Acad Sci USA* 2005, **102**:3766-3771.
66. Raffaghello L, Bianchi G, Bertolotto M, Montecucco F, Busca A, Dallegri F, Ottonello L, Pistoia V: **Human mesenchymal stem cells inhibit neutrophil apoptosis: a model for neutrophil preservation in the bone marrow niche.** *Stem Cells* 2008, **26**:151-162.
67. Mirotsou M, Zhang Z, Deb A, Zhang L, Gnecchi M, Noiseux N, Mu H, Pachori A, Dzau V: **Secreted frizzled related protein 2 (Sfrp2) is the key Akt-mesenchymal stem cell-released paracrine factor mediating myocardial survival and repair.** *Proc Natl Acad Sci USA* 2007, **104**:1643-1648.
68. Wang M, Crisostomo PR, Herring C, Meldrum KK, Meldrum DR: **Human progenitor cells from bone marrow or adipose tissue produce VEGF, HGF, IGF-I in response to TNF by a p38 MAPK-dependent mechanism.** *Am J Physiol Regul Integr Comp Physiol* 2006, **291**:R880-884.
69. Urbanek K, Rota M, Cascapera S, Bearzi C, Nascimbene A, De Angelis A, Hosoda T, Chimenti S, Baker M, Limana F, *et al*: **Cardiac stem cells possess growth factor-receptor systems that after activation regenerate the infarcted myocardium, improving ventricular function and long-term survival.** *Circ Res* 2005, **97**:663-673.
70. Li TS, Takahashi M, Ohshima M, Qin SL, Kubo M, Muramatsu K, Hamano K: **Myocardial repair achieved by the intramyocardial implantation of adult cardiomyocytes in combination with bone marrow cells.** *Cell Transplant* 2008, **17**:695-703.
71. Crisostomo PR, Wang Y, Markel TA, Wang M, Lahm T, Meldrum DR: **Human mesenchymal stem cells stimulated by TNF-alpha, LPS, or hypoxia produce growth factors by an NF kappa B- but not JNK-dependent mechanism.** *Am J Physiol Cell Physiol* 2008, **294**:C675-682.
72. Fu X, He Y, Xie C, Liu W: **Bone marrow mesenchymal stem cell transplantation improves ovarian function and structure in rats with chemotherapy-induced ovarian damage.** *Cytotherapy* 2008, **10**:353-363.
73. Zeng F, Chen MJ, Baldwin DA, Gong ZJ, Yan JB, Qian H, Wang J, Jiang X, Ren ZR, Sun D, *et al*: **Multiorgan engraftment and differentiation of human cord blood CD34+ Lin- cells in goats assessed by gene expression profiling.** *Proc Natl Acad Sci USA* 2006, **103**:7801-7806.
74. Nishiyama N, Miyoshi S, Hida N, Uyama T, Okamoto K, Ikegami Y, Miyado K, Segawa K, Terai M, Sakamoto M, *et al*: **The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro.** *Stem Cells* 2007, **25**:2017-2024.
75. Kawada H, Fujita J, Kinjo K, Matsuzaki Y, Tsuma M, Miyatake H, Muguruma Y, Tsuboi K, Itabashi Y, Ikeda Y, *et al*: **Nonhematopoietic mesenchymal stem cells can be mobilized and differentiate into cardiomyocytes after myocardial infarction.** *Blood* 2004, **104**:3581-3587.
76. Vieyra DS, Jackson KA, Goodell MA: **Plasticity and tissue regenerative potential of bone marrow-derived cells.** *Stem Cell Rev* 2005, **1**:65-69.
77. Fazel S, Cimini M, Chen L, Li S, Angoulvant D, Fedak P, Verma S, Weisel RD, Keating A, Li RK: **Cardioprotective c-kit+ cells are from the bone marrow and regulate the myocardial balance of angiogenic cytokines.** *J Clin Invest* 2006, **116**:1865-1877.
78. Kocher AA, Schuster MD, Szabolcs MJ, Takuma S, Burkhoff D, Wang J, Homma S, Edwards NM, Itescu S: **Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function.** *Nat Med* 2001, **7**:430-436.
79. Strauer BE, Brehm M, Zeus T, Gattermann N, Hernandez A, Sorg RV, Kogler G, Wernet P: **[Intracoronary, human autologous stem cell transplantation for myocardial regeneration following myocardial infarction].** *Dtsch Med Wochenschr* 2001, **126**:932-938.
80. Hamano K, Nishida M, Hirata K, Mikamo A, Li TS, Harada M, Miura T, Matsuzaki M, Esato K: **Local implantation of autologous bone marrow cells for therapeutic angiogenesis in patients with ischemic heart disease: clinical trial and preliminary results.** *Jpn Circ J* 2001, **65**:845-847.
81. Abdel-Latif A, Bolli R, Tleyjeh IM, Montori VM, Perin EC, Hornung CA, Zuba-Surma EK, Al-Mallah M, Dawn B: **Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis.** *Arch Intern Med* 2007, **167**:989-997.
82. Martin-Rendon E, Brunskill S, Doree C, Hyde C, Watt S, Mathur A, Stanworth S: **Stem cell treatment for acute myocardial infarction.** *Cochrane Database Syst Rev* 2008, CD006536.
83. Kang S, Yang YJ, Li CJ, Gao RL: **Effects of intracoronary autologous bone marrow cells on left ventricular function in acute myocardial infarction: a systematic review and meta-analysis for randomized controlled trials.** *Coron Artery Dis* 2008, **19**:327-335.
84. Zhang SN, Sun AJ, Ge JB, Yao K, Huang ZY, Wang KQ, Zou YZ: **Intracoronary autologous bone marrow stem cells transfer for patients with acute myocardial infarction: A meta-analysis of randomised controlled trials.** *Int J Cardiol* 2009, **136(2)**:178-85.
85. Herrera MB, Bussolati B, Bruno S, Morando L, Mauriello-Romanazzi G, Sanavio F, Stamenkovic I, Biancone L, Camussi G: **Exogenous mesenchymal stem cells localize to the kidney by means of CD44 following acute tubular injury.** *Kidney Int* 2007, **72**:430-441.
86. Sackstein R, Merzaban JS, Cain DW, Dagia NM, Spencer JA, Lin CP, Wohlgemuth R: **Ex vivo glycan engineering of CD44 programs human multipotent mesenchymal stromal cell trafficking to bone.** *Nat Med* 2008, **14**:181-187.
87. Zhu H, Mitsuhashi N, Klein A, Barsky LW, Weinberg K, Barr ML, Demetriou A, Wu GD: **The role of the hyaluronan receptor CD44 in mesenchymal stem cell migration in the extracellular matrix.** *Stem Cells* 2006, **24**:928-935.
88. Wang Y, Deng Y, Zhou GQ: **SDF-1alpha/CXCR4-mediated migration of systemically transplanted bone marrow stromal cells towards ischemic brain lesion in a rat model.** *Brain Res* 2008, **1195**:104-112.
89. Cheng Z, Ou L, Zhou X, Li F, Jia X, Zhang Y, Liu X, Li Y, Ward CA, Melo LG, *et al*: **Targeted migration of mesenchymal stem cells modified with CXCR4 gene to infarcted myocardium improves cardiac performance.** *Mol Ther* 2008, **16**:571-579.
90. Neschadim A, McCart JA, Keating A, Medin JA: **A roadmap to safe, efficient, and stable lentivirus-mediated gene therapy with**

hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2007, **13**:1407-1416.
91. Hung SC, Pochampally RR, Hsu SC, Sanchez C, Chen SC, Spees J, Prockop DJ: **Short-term exposure of multipotent stromal cells to low oxygen increases their expression of CX3CR1 and CXCR4 and their engraftment in vivo.** *PLoS ONE* 2007, **2**:e416.
92. Shi M, Li J, Liao L, Chen B, Li B, Chen L, Jia H, Zhao RC: **Regulation of CXCR4 expression in human mesenchymal stem cells by cytokine treatment: role in homing efficiency in NOD/SCID mice.** *Haematologica* 2007, **92**:897-904.
93. Tang YL, Qian K, Zhang YC, Shen L, Phillips MI: **Mobilizing of haematopoietic stem cells to ischemic myocardium by plasmid mediated stromal-cell-derived factor-1alpha (SDF-1alpha) treatment.** *Regul Pept* 2005, **125**:1-8.
94. Gibble JW, Ness PM: **Fibrin glue: the perfect operative sealant?** *Transfusion* 1990, **30**:741-747.
95. Zhang G, Nakamura Y, Wang X, Hu Q, Suggs LJ, Zhang J: **Controlled release of stromal cell-derived factor-1 alpha in situ increases c-kit+ cell homing to the infarcted heart.** *Tissue Eng* 2007, **13**:2063-2071.
96. Barile L, Messina E, Giacomello A, Marban E: **Endogenous cardiac stem cells.** *Prog Cardiovasc Dis* 2007, **50**:31-48.
97. Tan Y, Shao H, Eton D, Yang Z, Alonso-Diaz L, Zhang H, Schulick A, Livingstone AS, Yu H: **Stromal cell-derived factor-1 enhances pro-angiogenic effect of granulocyte-colony stimulating factor.** *Cardiovasc Res* 2007, **73**:823-832.
98. Latini R, Brines M, Fiordaliso F: **Do non-hemopoietic effects of erythropoietin play a beneficial role in heart failure?** *Heart Fail Rev* 2008, **13**:415-423.
99. Brunner S, Winogradow J, Huber BC, Zaruba MM, Fischer R, David R, Assmann G, Herbach N, Wanke R, Mueller-Hoecker J, *et al*: **Erythropoietin administration after myocardial infarction in mice attenuates ischemic cardiomyopathy associated with enhanced homing of bone marrow-derived progenitor cells via the CXCR-4/SDF-1 axis.** *FASEB J* 2008, **23(2)**:351-61.
100. Mikirova NA, Jackson JA, Hunninghake R, Kenyon J, Chan KW, Swindlehurst CA, Minev B, Patel AN, Murphy MP, Smith L, *et al*: **Circulating endothelial progenitor cells: a new approach to anti-aging medicine?** *J Transl Med* 2009, **7**:106.
101. Babin-Ebell J, Sievers HH, Charitos EI, Klein HM, Jung F, Hellberg AK, Depping R, Sier HA, Marxsen J, Stoelting S, *et al*: **Transmyocardial laser revascularization combined with intramyocardial endothelial progenitor cell transplantation in patients with intractable ischemic heart disease ineligible for conventional revascularization: preliminary results in a highly selected small patient cohort.** *Thorac Cardiovasc Surg* **58**:11-16.
102. Chambers SM, Shaw CA, Gatza C, Fisk CJ, Donehower LA, Goodell MA: **Aging hematopoietic stem cells decline in function and exhibit epigenetic dysregulation.** *PLoS Biol* 2007, **5**:e201.
103. Schmidt-Lucke C, Rossig L, Fichtlscherer S, Vasa M, Britten M, Kamper U, Dimmeler S, Zeiher AM: **Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair.** *Circulation* 2005, **111**:2981-2987.
104. Wagers AJ, Sherwood RI, Christensen JL, Weissman IL: **Little evidence for developmental plasticity of adult hematopoietic stem cells.** *Science* 2002, **297**:2256-2259.
105. Rose RA, Jiang H, Wang X, Helke S, Tsoporis JN, Gong N, Keating SC, Parker TG, Backx PH, Keating A: **Bone Marrow-Derived Mesenchymal Stromal Cells Express Cardiac-Specific Markers, Retain the Stromal Phenotype and do not Become Functional Cardiomyocytes In Vitro.** *Stem Cells* 2008, **26(11)**:2884-92.
106. Makino S, Fukuda K, Miyoshi S, Konishi F, Kodama H, Pan J, Sano M, Takahashi T, Hori S, Abe H, *et al*: **Cardiomyocytes can be generated from marrow stromal cells in vitro.** *J Clin Invest* 1999, **103**:697-705.
107. Tomita S, Li RK, Weisel RD, Mickle DA, Kim EJ, Sakai T, Jia ZQ: **Autologous transplantation of bone marrow cells improves damaged heart function.** *Circulation* 1999, **100**:II247-256.
108. De Felice L, Tatarelli C, Mascolo MG, Gregorj C, Agostini F, Fiorini R, Gelmetti V, Pascale S, Padula F, Petrucci MT, *et al*: **Histone deacetylase inhibitor valproic acid enhances the cytokine-induced expansion of human hematopoietic stem cells.** *Cancer Res* 2005, **65**:1505-1513.
109. Bug G, Gul H, Schwarz K, Pfeifer H, Kampfmann M, Zheng X, Beissert T, Boehrer S, Hoelzer D, Ottmann OG, *et al*: **Valproic acid stimulates proliferation and self-renewal of hematopoietic stem cells.** *Cancer Res* 2005, **65**:2537-2541.
110. Lee TM, Lin MS, Chang NC: **Inhibition of histone deacetylase on ventricular remodeling in infarcted rats.** *Am J Physiol Heart Circ Physiol* 2007, **293**:H968-977.
111. Hattori N, Imao Y, Nishino K, Ohgane J, Yagi S, Tanaka S, Shiota K: **Epigenetic regulation of Nanog gene in embryonic stem and trophoblast stem cells.** *Genes Cells* 2007, **12**:387-396.
112. Go MJ, Takenaka C, Ohgushi H: **Forced expression of Sox2 or Nanog in human bone marrow derived mesenchymal stem cells maintains their expansion and differentiation capabilities.** *Exp Cell Res* 2008, **314**:1147-1154.
113. Takahashi K, Yamanaka S: **Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.** *Cell* 2006, **126**:663-676.
114. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S: **Induction of pluripotent stem cells from adult human fibroblasts by defined factors.** *Cell* 2007, **131**:861-872.
115. Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, Beard C, Brambrink T, Wu LC, Townes TM, *et al*: **Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin.** *Science* 2007, **318**:1920-1923.
116. Kim JB, Zaehres H, Wu G, Gentile L, Ko K, Sebastiano V, Arauzo-Bravo MJ, Ruau D, Han DW, Zenke M, *et al*: **Pluripotent stem cells induced from adult neural stem cells by reprogramming with two factors.** *Nature* 2008, **454**:646-650.
117. Okita K, Nakagawa M, Hyenjong H, Ichisaka T, Yamanaka S: **Generation of Mouse Induced Pluripotent Stem Cells Without Viral Vectors.** *Science* 2008, **322(5903)**:949-53.
118. Yang S, Lin G, Tan YQ, Zhou D, Deng LY, Cheng DH, Luo SW, Liu TC, Zhou XY, Sun Z, *et al*: **Tumor progression of culture-adapted human embryonic stem cells during long-term culture.** *Genes Chromosomes Cancer* 2008, **47**:665-679.
119. Ben-Porath I, Thomson MW, Carey VJ, Ge R, Bell GW, Regev A, Weinberg RA: **An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors.** *Nat Genet* 2008, **40**:499-507.
120. Li L, Baroja ML, Majumdar A, Chadwick K, Rouleau A, Gallacher L, Ferber I, Lebkowski J, Martin T, Madrenas J, *et al*: **Human embryonic stem cells possess immune-privileged properties.** *Stem Cells* 2004, **22**:448-456.
121. Slavin S, Kurkalli BG, Karussis D: **The potential use of adult stem cells for the treatment of multiple sclerosis and other neurodegenerative disorders.** *Clin Neurol Neurosurg* 2008, **110(9)**:943-6.
122. von Bonin M, Stolzel F, Goedecke A, Richter K, Wuschek N, Holig K, Platzbecker U, Illmer T, Schaich M, Schetelig J, *et al*: **Treatment of refractory acute GVHD with third-party MSC expanded in platelet lysate-containing medium.** *Bone Marrow Transplant* 2008, **43(3)**:245-51.
123. Dunac A, Frelin C, Popolo-Blondeau M, Chatel M, Mahagne MH, Philip PJ: **Neurological and functional recovery in human stroke are associated with peripheral blood CD34+ cell mobilization.** *J Neurol* 2007, **254**:327-332.
124. Taguchi A, Nakagomi N, Matsuyama T, Kikuchi-Taura A, Yoshikawa H, Kasahara Y, Hirose H, Moriwaki H, Nakagomi T, Soma T, *et al*: **Circulating CD34-positive cells have prognostic value for neurologic function in patients with past cerebral infarction.** *J Cereb Blood Flow Metab* 2008, **29(1)**:34-8.
125. Grundmann F, Scheid C, Braun D, Zobel C, Reuter H, Schwinger RH, Muller-Ehmsen J: **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* 2007, **96**:621-627.
126. Herrera MB, Bussolati B, Bruno S, Fonsato V, Romanazzi GM, Camussi G: **Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury.** *Int J Mol Med* 2004, **14**:1035-1041.
127. Seebach C, Henrich D, Tewksbury R, Wilhelm K, Marzi I: **Number and proliferative capacity of human mesenchymal stem cells are modulated positively in multiple trauma patients and negatively in atrophic nonunions.** *Calcif Tissue Int* 2007, **80**:294-300.
128. Ciulla MM, Ferrero S, Gianelli U, Paliotti R, Magrini F, Braidotti P: **Direct visualization of neo-vessel formation following peripheral injection of**

bone marrow derived CD34+ cells in experimental myocardial damage. *Micron* 2007, **38**:321-322.
129. Wojakowski W, Tendera M: **Mobilization of bone marrow-derived progenitor cells in acute coronary syndromes.** *Folia Histochem Cytobiol* 2005, **43**:229-232.
130. Paczkowska E, Larysz B, Rzeuski R, Karbicka A, Jalowinski R, Kornacewicz-Jach Z, Ratajczak MZ, Machalinski B: **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* 2005, **75**:461-467.
131. Wang XY, Lan Y, He WY, Zhang L, Yao HY, Hou CM, Tong Y, Liu YL, Yang G, Liu XD, *et al*: **Identification of mesenchymal stem cells in aorta-gonad-mesonephros and yolk sac of human embryos.** *Blood* 2008, **111**:2436-2443.
132. Dexter TM: **Stromal cell associated haemopoiesis.** *J Cell Physiol Suppl* 1982, **1**:87-94.
133. Bakhshi T, Zabriskie RC, Bodie S, Kidd S, Ramin S, Paganessi LA, Gregory SA, Fung HC, Christopherson KW: **Mesenchymal stem cells from the Wharton's jelly of umbilical cord segments provide stromal support for the maintenance of cord blood hematopoietic stem cells during long-term ex vivo culture.** *Transfusion* 2008, **48(12)**:2638-44.
134. Huang GP, Pan ZJ, Jia BB, Zheng Q, Xie CG, Gu JH, McNiece IK, Wang JF: **Ex vivo expansion and transplantation of hematopoietic stem/progenitor cells supported by mesenchymal stem cells from human umbilical cord blood.** *Cell Transplant* 2007, **16**:579-585.
135. Urban VS, Kiss J, Kovacs J, Gocza E, Vas V, Monostori E, Uher F: **Mesenchymal stem cells cooperate with bone marrow cells in therapy of diabetes.** *Stem Cells* 2008, **26**:244-253.
136. Ichim TE, Solano F, Brenes R, Glenn E, Chang J, Chan K, Riordan NH: **Placental mesenchymal and cord blood stem cell therapy for dilated cardiomyopathy.** *Reprod Biomed Online* 2008, **16**:898-905.
137. Murphy MP, Wang H, Patel AN, Kambhampati S, Angle N, Chan K, Marleau AM, Pyszniak A, Carrier E, Ichim TE, *et al*: **Allogeneic endometrial regenerative cells: an "Off the shelf solution" for critical limb ischemia?** *J Transl Med* 2008, **6**:45.
138. Toyoda M, Cui C, Umezawa A: **Myogenic transdifferentiation of menstrual blood-derived cells.** *Acta Myol* 2007, **26**:176-178.
139. Cui CH, Uyama T, Miyado K, Terai M, Kyo S, Kiyono T, Umezawa A: **Menstrual blood-derived cells confer human dystrophin expression in the murine model of Duchenne muscular dystrophy via cell fusion and myogenic transdifferentiation.** *Mol Biol Cell* 2007, **18**:1586-1594.
140. Hida N, Nishiyama N, Miyoshi S, Kira S, Segawa K, Uyama T, Mori T, Miyado K, Ikegami Y, Cui C, *et al*: **Novel cardiac precursor-like cells from human menstrual blood-derived mesenchymal cells.** *Stem Cells* 2008, **26**:1695-1704.
141. Han X, Meng X, Yin Z, Rogers A, Zhong J, Rillema P, Jackson JA, Ichim TE, Minev B, Carrier E, *et al*: **Inhibition of intracranial glioma growth by endometrial regenerative cells.** *Cell Cycle* 2009, **8**:606-610.
142. Patel AN, Silva F: **Menstrual blood stromal cells: the potential for regenerative medicine.** *Regen Med* 2008, **3**:443-444.
143. Zhong Z, Patel AN, Ichim TE, Riordan NH, Wang H, Min WP, Woods EJ, Reid M, Mansilla E, Marin GH, *et al*: **Feasibility investigation of allogeneic endometrial regenerative cells.** *J Transl Med* 2009, **7**:15.

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