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REVIEW

Optimizing stem cells for cardiac repair: Current status and new frontiers in regenerative cardiology

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Abstract

Cell therapy has the potential to improve healing of ischemic heart, repopulate injured myocardium and restore cardiac function. The tremendous hope and potential of stem cell therapy is well understood, yet recent trials involving cell therapy for cardiovascular diseases have yielded mixed results with inconsistent data thereby readdressing controversies and unresolved questions regarding stem cell efficacy for ischemic cardiac disease treatment. These controversies are believed to arise by the lack of uniformity of the clinical trial methodologies, uncertainty regarding the underlying reparative mechanisms of stem cells, questions concerning the most appropriate cell population to use, the proper delivery method and timing in relation to the moment of infarction, as well as the poor stem cell survival and engraftment especially in a diseased microenvironment which is collectively acknowledged as a major hindrance to any form of cell therapy. Indeed, the microenvironment of the failing heart exhibits pathological hypoxic, oxidative and inflammatory stressors impairing the survival of transplanted cells. Therefore, in order to observe any significant therapeutic benefit there is a need to increase resilience of stem cells to death in the transplant microenvironment while preserving or better yet improving their reparative functionality. Although stem cell differentiation into cardiomyocytes has been observed in some instance, the prevailing reparative benefits are afforded through paracrine mechanisms that promote angiogenesis, cell survival, transdifferentiate host cells and modulate immune responses. Therefore, to maximize their reparative functionality, *ex vivo* manipulation of stem cells through physical, genetic and pharmacological means have shown promise to enable cells to thrive in the post-ischemic transplant microenvironment. In the present work, we will overview the current status of stem cell therapy for ischemic heart disease, discuss the most recurring cell populations employed, the mechanisms by which stem cells deliver a therapeutic benefit and

strategies that have been used to optimize and increase survival and functionality of stem cells including *ex vivo* preconditioning with drugs and a novel "pharmaco-optimizer" as well as genetic modifications.

Key words: Stem cell; Regenerative medicine; Cellular cardiomyoplasty; Preconditioning; Myocardial infarction; Heart failure; Viability; Paracrine activity; Transplantation; Pharmaco-optimizer

Core tip: Cell therapy has the potential to improve healing of the ischemic heart, to repopulate injured myocardium and restore cardiac function in ischemic and non-ischemic cardiomyopathy. However, one of the biggest impediments lessening clinical effectiveness of cell therapy is the poor viability, retention and functionality of transplanted cells. This review looks as various stem cell *ex vivo* preconditioning and reprogramming methods aimed at enhancing the therapeutic potential of stem cells for heart failure treatment.

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STEM CELL THERAPY FOR ISCHEMIC HEART DISEASE

Considering the elevated morbidity and mortality of ischemic heart diseases, there is a pressing need to develop new therapeutic solutions to reduce ventricular remodeling, improve cardiac function and prevent development of heart failure (HF) following myocardial infarction (MI). For many of the patients, heart transplantation is a last resort option and its use is limited due to the scarcity of available donors. Therefore, myocardial stem cell therapy or cellular cardiomyoplasty is an approach that aims at inducing neoangiogenesis and even generating new functional myocardium. Many preclinical studies have involved transplanting cells in the border region of the infarcted myocardium to improve vascular supply, increase or preserve cardiomyocytes and repair damaged ones, and based on many positive findings, cell therapy has long been proposed as a potential treatment for HF[1-3]. However, recent clinical trials have reported much less remarkable results with meta-analyses indicating a mean increase in ejection fraction (EF) of approximately 3% to < 6%, with better results in patients with low EF, or if cell infusion is delayed at least 5 d after MI[4-7]. Randomized trials have also shown that the composite end point of death, infarction, revascularization, is significantly decreased at 12 mo, others have reported sustained benefits up to 5 years with reduced death and infarct size, improved myocardial perfusion and global cardiac function, whereas some have not found any profound long-term clinical benefit thereby advocating for cautious optimism in regards to cell therapy[5,8-10].

Clearly evidence shows there is much room for improvement that can only be achieved through the fundamental understanding of the stem cell biology and mechanisms for the therapeutic benefit afforded by these cells. We now understand that only a small portion of cells are retained in the myocardium and that their paracrine activity will promote cardiac repair through production of anti-inflammatory, pro-survival and angiogenic factors[11]. Indeed studies have shown that injection of stem cell conditioned media rich in these factors improve cardiac repair in HF models[12]. These factors are able to attenuate tissue injury, inhibit fibrotic remodeling, stimulate recruitment of endogenous stem cells and reduce oxidative stress[13]. Therefore, cell therapy can be viewed as providing cellular units releasing paracrine mediators to promote a beneficial effect[14]. This is true of course only if the cells are retained long enough and remain viable in the transplant environment for this to occur.

STEM CELLS USED IN REGENERATIVE MEDICINE

Stem cells possess the capacity for prolonged proliferation, multilineage differentiation as well as trophic functions which enables tissue and organ repair[15-17]. Cell types used for cardiac repair include unfractionated bone marrow cells (BMCs) and mononuclear cells, mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), skeletal myoblasts (SkMbs), cardiac progenitor cells (CPCs), fetal cardiomyocytes, and embryonic stem cells (ESCs)[18-20]. Each cell type has its advantages and disadvantages for cell therapy applications. Therapeutic injection of stem cells into a host requires accurate cell selection based on differentiation potential, relative ease of isolation, availability in large quantities, *in vitro* expansion[21,22]. These cells are isolated from various sources. For instance, SkMbs are isolated by skeletal muscle biopsies and expanded *in vitro*. EPCs have shown the greatest potential for angiogenesis[23], can be isolated from the blood. Resident cardiac stem cells or cardiospheres could be isolated from biopsies, clonally expanded *in vitro* and differentiated into cardiomyocytes[24]. Bone marrow contains a heterogeneous cell population that includes differentiated cells and stem cells, such as HSCs, MSCs and EPCs. Due to its relative ease of accessibility and processing, as well as its ability to transdifferentiate into myocardial or vascular cells, BMCs have been readily used in clinical trials. However, contradictory benefits have been reported mainly since

either unfractionated or sub-populations of BMCs with or without *in vitro* culture steps have been employed in various studies[25,26].

MSC

MSCs are one of the best candidates for heart disease cell therapy due to their easy isolation, rapid expansion and safety[27]. MSCs retain their growth potential over several passages[28,29] and have the ability to differentiate into osteoblasts, chondrocytes, myocytes, fibroblasts, adipocytes and other mesenchymal phenotypes *in vitro* and *in vivo*[28,30-32]. In addition, MSCs are also immune-privileged because they express low levels of MHC Ⅱ compared with MHC Ⅰ[33]. They display immunosuppressive effects allowing successful allogenic transplantation. Many reports have shown improved recovery of ventricular function following MI with transplantation of MSCs in animal models[34] as well as an improvement in cardiac function and infarct size in human trials[29,35-38].

The safety and feasibility of intra-coronary MSC infusion and intra-myocardial delivery during coronary bypass grafting in post-MI patients has been demonstrated[33,39]. However, MSC-based therapy has the fatal limitation of poor viability of MSCs after cell transplantation[31]. Only approximately 5% of transplanted MSCs survive for 14 d in the infarcted porcine heart[40], whereas survival rate of human MSCs transplanted in an uninjured mouse heart is less than 0.5% at 4 d[31]. Similar results were obtained from studies using different cell types. For instance, about 7% of SkMb, 15% of smooth muscle cells, and 6% of unfractionated BMCs survived at 3 d to 1 wk in infarcted animal hearts[41-43]. Consequently, cell viability is likely a common barrier for any cell therapy approach for MI.

HEMATOPOIETIC AND ENDOTHELIAL PRECURSOR STEM CELLS

HSCs count for perhaps as few as 1:10000 bone-marrow cells and are known for their positivity for the CD34 cell surface marker. EPCs also residing in the bone marrow, have originally been defined by their expression of the CD133, CD34, and the vascular endothelial growth factor receptor-2 (VEGFR-2) markers. CD133 or prominin-1 is a highly conserved stem cell glycoprotein antigen described as marker for identification of early immature EPCs[44]. $CD133^+$ cells migrate upon gradients of vascular endothelial growth factor (VEGF) and stromal-derived factor (SDF) *in vitro* and *in vivo*[45-47]. $CD133^+$ cells *in vitro* differentiate into endothelial cells and release paracrine angiogenic cytokines. Differentiated $CD133^+$ are capable of inducing capillary tubes *in vitro*[46,48-51] and several clinical trials have reported promising effects following infusion or direct intramyocardial injection of autologous $CD133^+$ cells into ischemic hearts[52-56].

TRANSPLANT CELL DEATH IN THE INFARCTED HEART

One of the prime challenges of stem cell therapy consists in the survival, retention and differentiation of cells delivered in the harsh microenvironment of diseased tissues or organs[31,57-59]. Poor retention and survival of transplanted cells in the heart which can decrease to 39% at 1 h following injection as seen in human studies[60-64] or reach at most 21% in animal models following intramyocardial injection[65,66], further decrease exponentially thereafter due to apoptosis[31,57,67,68]. The increased cell death is swayed by various inflammatory response mediators, mechanical injury, hypoxia and ischemia-reperfusion stressors, and influenced as well by the donor cell source and quality[69]. Indeed, the cause of death of implanted cells may begin during the preparation step where MSCs for example, which are normally grown attached, are prepared in suspension in order to be injected. The loss of matrix attachments causes programmed cell death called "anoikis"[69-73]. Adhesion of cells to the matrix predominantly *via* integrin molecules represses apoptotic signaling, whereas detachment has the opposite effect. This effect is compounded by the hostile microenvironment of diseased myocardium which includes deprivation of nutrients and oxygen, upregulation of inflammatory mediators and low pH leading to poor transplant survival[70,74,75]. Moreover, myocardial injury generates an inflammatory response involving neutrophils and macrophages[76] which themselves produce inflammatory cytokines and reactive oxygen species (ROS) that may intensify the inflammatory response and anoikis signals and lead to cell death as well[77-79]. Indeed, co-injection of SkMbs with the ROS scavenger superoxide dismutase (CuZn-SOD) increases graft survival[43].

MECHANISMS OF INFARCT REPAIR BY STEM CELLS: PARACRINE MODULATION OF ISCHEMIC ENVIRONMENT

Several studies have shown that recruitment of endogenous stem cells or their delivery to injury sites results in structural regeneration and functional improvement[80]. While the original thesis regarding the beneficial mechanism pointed to stem cells and their differentiation within the host myocardium, we now understand that few if no exogenously administered cells engraft and differentiate[81-84]. It is rather the paracrine biomolecules produced by stem cells which account for the bulk of observed functional repair and these molecules also reduce cell death in cardiomyocytes and other populations thereby benefiting the diseased host tissue[85-89]. Stem cells secrete an array of cytokines, growth factors and extracellular

matrix (ECM) components that act in an autocrine or paracrine manner. Cytokines are signaling and immune-modulating agents involved in cellular communication, whereas chemokines also produced by stem cells are involved in chemotaxis, while growth factors stimulate cell growth, proliferation and differentiation. Moreover, antioxidants, anti-apoptotic, anti-inflammatory or immunosuppressive molecules also secreted by stem cells can protect the cellular niche and transplant microenvironment from damaging mediators such as ROS. Finally, angiogenic and antifibrotic factors secreted by stem cells are responsible for tissue repair. In view of the numerous bioactive molecules produced and secreted by stem cells, current research using transcriptomic and proteomic technologies is poised at identifying the precise beneficial mediators and developing ways to harness these powerful pathways and mechanisms of repair[80,90-94].

The cardioprotective panel of stem cell secreted factors include bFGF/FGF-2, IL-1β, IL-10, PDGF, VEGF, HGF, IGF-1, SDF-1, thymosin-β4, Wnt5a, Ang-1 and Ang-2, MIP-1, EPO and PDGF[21,85-89,95]. FGF-2 reduces ischemia-induced myocardial apoptosis, cell death and arrhythmias, and stimulates increased expression of anti-apoptotic Bcl-2[96,97]. HGF, bFGF, Ang-1 and -2, and VEGF secreted by BMMSCs lead to augmented vascular density and blood flow in the ischemic heart[91,98,99], whereas SDF-1, IGF-1, HGF facilitate circulating progenitor cell recruitment to injury sites thereby promoting repair and regeneration[100-103]. Stem cells also secrete ECM components including collagens, TGF-β, matrix metalloproteinases (MMPs) and tissue-derived inhibitors (TIMPs) that inhibit fibrosis[104-106] and may thereby benefit cardiac tissue remodeling post-MI.

STRATEGIES TO ENHANCE STEM CELL SURVIVAL

It is clear that the injected stem cells must survive and thrive in the injured or diseased transplant environment for any significant repair to occur. Acute cardiac ischemia results in a hypoxic and inflammatory microenvironment which makes it extremely difficult for the injured area to be functionally repaired[107-109]. Consequently the injected cells will need to be tolerant of these deleterious conditions[110-113]. For this, *ex vivo* manipulation of cells has been used to overcome cell survival issues as well as to enhance metabolic characteristics in order to confer cells with a powerful advantage in the critical early days after transplantation. Preconditioning, or pre-treating and reprograming cells by physical/environmental, pharmacological, genetic manipulations or with cytokine and growth factor treatments has shown great potential to prime cells to withstand the rigors of the transplant microenvironment post-ischemia and maximize the cells' biological and functional properties. In addition, there are strategies to modify the transplant environment through immune modulation and even by increasing cell retention with bio-scaffolds.

PRECONDITIONING STEM CELLS USING PHYSICAL/ENVIRONMENTAL CHALLENGES

Beneficial effect of preconditioning was first demonstrated by treating healthy heart with intermittent cycles of non-lethal ischemia followed by reperfusion. This manipulation protected the myocardium from a subsequent important ischemic episode[114]. Subsequently, various strategies including hypoxic, oxidative and thermal conditioning challenges have been studied in an attempt to improve stem cell survival[115-118]. Low oxygen culture conditions (0.5% O_2 for 24 h) have been shown to trigger survival pathways in MSCs before their engraftment *in vivo*[119]. MSCs exposed to hypoxia *in vitro* showed upregulation of Bcl-2 and Bcl-XL survival genes, promoting reduced infarct size and enhanced cardiac function[119]. Hypoxia preconditioning also increases *in vitro* expression of antiapoptotic genes such as Akt and eNOS[81,88,116]. Hypoxia treated cells show significantly improved survival post-engraftment in the infarcted heart[119]. Also, during ischemic preconditioning, hypoxia inducible factor-1α (HIF-1α), a master regulator of genes responsible for low oxygen survival signaling[119-121], stimulates the transcription of VEGF and erythrogenin that increase cellular oxygen availability by promoting angiogenesis and erythropoiesis[122,123]. In addition to VEGF, temporary exposure to hypoxia increases expression of many growth factors including bFGF, HGF, IGF-1, and thymosin-β4[124,125] which are implicated in cell mobilisation and apoptosis.

In addition to promoting pro-survival and cytoprotective effects, hypoxic preconditioning supports cells to preserve their stemness and promote their differentiation and proliferation potential post-engraftment[116,126-129]. Furthermore, BMMSCs exposed to anoxic conditions and transplanted into infarcted myocardium have been shown to exert increased protective effects on cardiomyocytes[130]. Thus, hypoxic treatment may lead to enhanced donor and host cell survival in ischemic environments and provide functional benefits.

Burst exposure to low levels of oxidative stress *in vitro* also increases stem cell viability as seen for example by the exposure of CPCs *in vitro* to low concentration of H_2O_2 prior to implantation in ischemic rat hearts[131]. Similarly, NPCs exposed to non-cytotoxic low dose treatment of H_2O_2 demonstrated improved resistance to lethal oxidative stress[132], and MSCs preconditioned with H_2O_2 and transplanted in the ischemic heart display increased viability and functional improvement[133].

Heat shock treatment is also an interesting approach to enhance cell survival. Heat shock protein (HSP) generation can be achieved by exposing cells to elevated temperatures (39 ℃ to 45 ℃). Thermal shock

of primary cardiomyocytes has been shown to result in increased expression of HSP70 thereby protecting the cells from *in vitro* and *in vivo* oxidant stress[134,135]. Transplantation of human ESC-derived cardiomyocytes treated by 30 to 60 min of 43 ℃ heat upregulates HSPs such as HSP60, 70, and 90 has been shown to improve graft functionality in a rat model of MI injury[136,137]. Exposing MSCs to elevated temperature (43 ℃) also induces secretion of HSPs, including HSP27 and HSP70[138] which may contribute to increased cell survival. Similarly, culture of CPCs at 42 ℃ has been shown to reduce apoptosis, increase functionality, and reduce fibrosis of mouse ischemic myocardium[139]. Considering the role of HSPs in cell protection and immune modulation, thermal conditioning represents an easy and effective means of increasing cell viability, retention and consequently improving stem cell graft function.

PRECONDITIONING STEM CELLS WITH DRUGS

The effectiveness of preconditioning on cell viability and function can also be achieved by pharmacological treatments[118]. Other than the initiation of survival signaling, treating cells with conditioning mimetics causes release of growth factors and cytokines that exert protective and angiomyogenic effects. Preconditioned cells show greater release of growth factors including VEGF, Ang-1, SDF-1α, HGF, and IGF[118]. Several drugs including mitochondrial potassium channel openers that promote influx of K^+ through ATP-sensitive K^+ channels (mitoKATP) are useful agents altering the apoptotic cascade by preventing cytochrome c release[140-143]. Pinacidil or Diazoxide, well-known non-selective mitoKATP channel openers have been demonstrated to suppress apoptosis[144-146]. SkMbs and BMMSCs treated with Diazoxide demonstrated increased cell survival in ischemic environment, and increased secretion of Ang-1, bFGF, HGF and VEGF by preconditioning was proposed to augment angiomyogenesis[146,147].

HMG CoA reductase inhibitors (Statins) appear promising in blocking apoptosis, prolonging stem cell survival and improving organ repair. Treatment with atorvastatin for example enhances cell survival and differentiation into cardiomyocytes, decreases the infarcted area, promotes angiogenesis, and reverses the ventricular remodeling processes[148]. Also, *ex vivo* statin treatment has been shown to prevent impairment of the functionality of EPCs *in vitro* as well as the loss of telomere repeat-binding factor 2, whose expression is reduced in end-stage human HF, and functions to prevent cells from entering in apoptosis or senescence[149,150]. A recent review provides encouraging basis for the use of statins to increase the number and/or function of MSCs and EPCs for cell therapy[151].

Preconditioning cells with naturally occurring hormones such as Oxytocin (OT) or its synthetic analog drug (Pitocin) is another means for stem cell optimization. Indeed, OT preconditioning of various cell types makes them resistant to oxidative stress[152], and primes stem cell differentiation into cardiomyocytes[153] and vascular cells[154]. MSC express a functional OT receptor which mediates glucose uptake[155] and cell differentiation[156] it has been shown that OT modulates gene expression for adhesion molecules and MMPs involved in cellular migration[154,157,158]. Our group showed that OT treated MSC respond with rapid calcium mobilization and upregulation of the protective pAkt and pErk1/2 proteins. Functional analyses revealed the involvement of these kinase pathways in cell proliferation, migration, and protection against apoptotic effects of hypoxia and serum starvation. OT preconditioning increased upregulation of genes with angiogenic, anti-apoptotic and cardiac anti-remodeling properties such as HSP27, HSP32, HSP70, VEGF, thrombospondin, TIMPs and MMPs, and co-culture of cardiomyocytes with OT-preconditioned MSC reduced apoptosis[159].

Various other classes of drugs and chemicals have also shown potential for use as stem cell *ex vivo* conditioning agents. Treatment of BMMSCs with trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine), an anti-ischemic drug for angina treatment has been shown to increase cell viability in response to oxidative stress[160]. Also, treatment of rat BMMSCs with β-mercaptoethanol was shown to upregulate HSP72 resulting in improved resistance to oxidative injury[161] Also, the pan caspase inhibitor ZVAD-fmk has been shown to increase engraftment of HSC during intrabone marrow transplantation procedure in allogeneic mice[162]. This said, one has to be mindful of the balance between enhancing stem cell survival and enabling unintended carcinogenic effects when selecting compounds in the development of stem cell conditioning agents.

Finally, a means to favor stem cell differentiation would constitute an interesting pharmacological conditioning method for improving graft function. Small molecules such as 5-Azacytidine, a DNA demethylating agent[32], have been shown to prime cardiac differentiation in MSCs. Other molecules including the HSP90 inhibitor Geldanamycin[163], the kinase inhibitor Imatinib Mesylate[164] and the proteasome inhibitor Bortezomid[165] have been shown to instruct stem cell commitment to various lineages.

A NOVEL STEM CELL PHARMACO-OPTIMIZER

Stem cell "pharmaco-optimization" as we term it, is the process of contacting stem cells *ex vivo* with drugs in order to enhance their innate therapeutic qualities and develop a desirable phenotypic profile with enhanced cellular functions and viability favored in the context of stem cell therapy.

Celastrol is an antioxidant molecule extracted from the root of a vine (*Tripterygium wilfordii*) which has showed beneficial effects in the treatment of various diseases including cancer, neurodegenerative diseases, autoimmune diseases, and inflammatory conditions[166-171]. We are the first to report Celastrol's efficacy as a potent infarct sparing agent[172] and we propose its use as a stem cell pharmaco-optimizer considering in part Celastrol's targeting and activation of two very potent cellular defence mechanisms: The heat shock response (HSR) and the antioxidant response (AR). HSR leads to cell protection against various physiological stresses[173,174] *via* activation of HSP. HSR is regulated at the transcriptional level by the activation of heat shock factors with heat shock factor 1 (HSF1) being the master switch for HSP expression[174]. The AR is mediated by the transcription factor nuclear factor (erythroid-derived 2)-like 2 (NRF2). NRF2 is a key controller of the redox homeostatic gene regulatory network including antioxidant proteins and phase Ⅱ enzymes such as glutathione *S*-transferase, heme oxygenase 1 (HO1), NADPH-quinone oxidoreductase 1, superoxide dismutase 1-3 (SOD1-3), catalase (CAT), thioredoxin, glutathione peroxidase (GPx), and non-enzymatic antioxidants such as glutathione which exert protective, antioxidant, and anti-inflammatory effects[173-176]. Under homeostatic conditions, HSF1 is bound and silenced by its natural repressor HSP90 chaperone, and NRF2 is similarly repressed by KEAP1 (Kelch-like ECH-associated protein1). During oxidative and electrophilic stress (ROS increase), NRF2 is liberated from KEAP1 and binds to antioxidant response elements in the promoter region of genes including HO-1. Similarly, during cellular stress, HSF1 translocates to the nucleus where it binds to heat shock elements as a phosphorylated-trimer and drives the transcriptional activity of HSPs[177].

Briefly, Celastrol targets the interaction between HSP90 and its essential cofactors (*i.e.*, Cdc37)[178], and through HSP90 functional inhibition, Celastrol promotes HSF1 release and HSR activation. Similarly, through a ROS/KEAP1/NRF2 pathway Celastrol activates the AR[179]. Together, Celastrol activates the two evolutionary conserved cellular protective mechanisms as detailed above and is able to stimulate a powerful endogenous protective effect that could be harnessed to increase viability and therapeutic efficiency of stem cells.

PRECONDITIONING STEM CELLS WITH GROWTH FACTORS AND CYTOKINES

Pre-treating stem cells with growth factor (GF) is a simple and safe strategy to improve cellular survival, proliferation and differentiation. For example, preconditioning EPCs by culturing them in medium supplemented with VEGF, activates Akt and significantly reduces apoptosis in a dose-dependent manner[180]. Also, by exploiting the SDF-1/CXCR4 ligand/receptor interaction which modulates cell growth, proliferation, survival, migration and transcriptional activation[21,181-184], SDF-1 can be used as a preconditioning chemokine[185]. Indeed, treatment with recombinant SDF-1 enhanced vascular density and survival of cells under anoxic condition *in vitro* and following engraftment in the infarcted heart[185]. Also, it has been shown that IGF-1 preconditioning of bone marrow-derived Sca-1$^+$ cells upregulates connexin 43 which improves survival and integration of cells with host myocytes[186]. The anti-apoptotic effects of IGF-1 are mediated by IGF-1/IGF-1R ligand/receptor interaction which involves PI3K/Akt and MAPK/Erk1/2 activation, whereas knockdown of connexin 43 rescinds cell viability to hypoxia *in vitro* and *in vivo* in the infarcted heart.

An additional strategy may consist of preconditioning cells with anti-inflammatory cytokines such as interleukin-10 (IL-10) which promotes multiple effects including down-regulation of Th1 cytokines such as IL-2, IFN-γ, TNF-α, and increase expression of the cell survival gene Bcl-2 thereby increasing stem cell survival[187]. It also has been demonstrated *in vitro* and *in vivo* that in the presence of IFN-γ, MSCs suppress T-cells and graft *vs* host disease[188-190].

EX VIVO GENETIC OPTIMIZATION OF STEM CELLS

Survival, differentiation and angiogenesis as targets

Stem cells are excellent vehicles for therapeutic gene delivery and can be genetically engineered for gene overexpression. Transgenes can encode for a myriad of beneficial factors including angiogenic and chemoattractant factors, anti-apoptotic proteins and growth factor(s) of interest[181,191-193] and serve as a continuous source for these to mediate sustained intracrine, autocrine, and paracrine effects. Indeed, molecules secreted by transgene-modified MSCs may have different therapeutic profiles compared with normal MSCs. For example, transformation of stem cells to overexpress IGF-1 promotes donor cell survival, engraftment, and differentiation in cardiac cell therapy[194-196]. IGF-1 induces expression of the pro-survival genes PI3-kinase, Akt, Bcl-xL and SDF-1 which is a potent chemoattractant of stem cells. Indeed, IGF-1 transformed MSC improve EF and fractional shortening in an infarct model[197]. Cells have also been manipulated to overexpress Ang-1, HGF, VEGF and MyoD for post-MI myocardial repair. Results show increased cell engraftment, angiogenesis and commitment to the myogenic lineage in the ischemic region[100,198-205]. Indeed, any therapeutic approach aimed at increasing vascularization within the ischaemic heart tissue will improve functional repair and recovery of the infarcted myocardium. One of the key proteins is VEGF whose overexpression will promote a strong pro-angiogenic signal. VEGF has been shown to promote endothelial cell survival[206,207], and myocardial transfer of VEGF-transfected MSCs lead to better improvement of myocardial perfusion and heart function following

ischemia[192,208]. Studies evaluating other angiogenic and myogenic genes with various VEGF isoforms, PDGF and TGF-β1, have also suggested enhancement of cell therapy efficacy[209]. VEGF is itself regulated by the transcription factor HIF-1α which plays a critical role in the stabilization of VEGF transcription during hypoxia[210,211]. Therefore, HIF-1α overexpression has also been evaluated as an means to optimize BMMSCs for increased VEGF expression[212].

Stem and progenitor cells have also been engineered to survive and engraft more effectively in hostile environments[213,214]. Transfection of MSCs with growth factors such as bFGF shows increased survival in hypoxic conditions. These transformed cells also improve neovascularization compared to non-transformed MSCs[215]. Interestingly, Akt-modified BMMSCs exhibit resilience to apoptosis through secretion of growth factors such as bFGF, HGF, IGF-1 and VEGF, as well as secreted frizzled-related protein 2 (Sfrp2) which exerts a beneficial effect on the infarcted heart post-engraftment by antagonizing pro-apoptotic properties of Wnt3a. Together, secretion of these factors known to exert pro-angiogenetic, cardioprotective and inotropic actions[125] is increased under hypoxic conditions[81,125,216]. Transplantation of Akt-modified BMMSCs in the infarcted myocardium safeguards surviving myocardium for up to 2 wk post-MI at least in part through paracrine actions[217]. In another study, MSCs overexpressing Akt with Ang-1 provide long-term therapeutic benefits for preventing apoptosis in an ischemic heart up to three months after initial transplantation[218]. This said, it is interesting to note that medium from BMMSCs overexpressing Akt cultured under hypoxic conditions show an increase of many beneficial molecules including VEGF, FGF-2, HGF, IGF-1, and TB4, and trigger an increase in contractile response of cultured rat cardiomyocytes as well as improves ventricular function in a rat infarction model[125]. In addition to Akt overexpression, BMMSCs have been engineered with anti-apoptotic genes such as Bcl-2 and HO-1. Bcl-2 overexpression in BMMSC decrease apoptosis of BMMSCs and increases VEGF secretion and capillary density in the infarct border zone thereby increasing functional recovery in ischemic myocardium[124]. HO-1 exerts potent antioxidant and cytoprotective activity in the ischemic environment[219,220]. HO-1 transfected MSCs are resistant to apoptosis and inflammatory injury and display improved tolerance to ischemia-reoxygenation injury harsh transplant microenvironments[221]. Another opportunity to enhance transplanted cell survival in the damaged heart is to transfect them with recombinant HSPs, that represents a family of inducible and constitutively expressed proteins responsible for potent increase in cell tolerance to environmental stress including ischemia, hypoxia, oxidative injury, heat stress, and ischemia-reperfusion injury[222]. Indeed, cells transfected with HSP encoding genes, namely HSP70, are protected from ischemic injury *in vitro* and *in vivo*[223-226].

In order to procure a holistic coverage of survival and growth effects, combination treatment of stem and progenitor cells can be achieved prior to their transplantation. As mentioned, combined overexpression of Akt and Ang-1 has been attempted in MSC. Ang-1, a potent modulator of vascular development activates survival signaling[227-229], and co-expression with Akt was shown to be more effective for cytoprotection in the context of lethal anoxia[230]. Simultaneous over-expression of Akt and Ang-1 in MSC transplanted in infarcted rat heart conferred better engraftment, and cells were able to adopt myogenic and endothelial phenotypes. Combination treatments may also be more ambitious by including various components such as a collagen matrix (matrigel) to increase retention and prevent anoikis, Bcl-xL and Cyclosporine A to block mitochondrial death pathways, an inducer of mitoKATP channel opening such as Pinacidil or Diazoxide to mimic ischemic conditioning, a caspase inhibitor such as zVAD-fmk and IGF-1 to activate Akt pathways as previously described[136].

Adhesion as a target

Adhesion is necessary for cell survival and is a key factor for MSC differentiation. Disruption of cell-ECM contact with trypsinization may facilitate apoptosis once cells are transplanted. Therefore, over-expression of adhesion molecules may enhance cell retention and improve viability. For example, tissue transglutaminase (tTG) over-expression in MSC leads to increased survival *via* an integrin-dependent mechanism[231]. tTG also acts as a coreceptor for fibronectin (Fn)[232,233] and enhances adhesion by bridging integrins and Fn or by mediating formation of ternary complexes[234]. Compared to simple MSC transplantation, tTG transformed MSCs have been shown to better restore cardiac function of infarcted myocardium[231]. Also, transfection of the integrin-linked kinase (ILK), a 59-kDa Ser/Thr kinase that binds to the cytoplasmic domain of β-integrin and participates in cell adhesion, growth, and ECM assembly, activates Erk and Akt phosphorylation which play important roles in cell survival during hypoxia[77,235-238]. Transplantation of ILK-MSCs has been shown to further reduce infarct size, improve left ventricle function and increase microvessel density[239].

Stem cell rejuvenation as a target

Increasing evidence supports the concept of senescence affecting tissue resident stem cells and diminishing regenerative capacity of organs[240-242]. Cellular senescence is induced by multitude of stressors including hypoxia and oxidative conditions[243-245] which reduces the cell's proliferative, differentiation and metabolic potential, and upregulates apoptotic markers[246-255]. At the genomic level, aging appears associated with increase in p53-associated genes in addition to modulation of telomere, mitochondrial and apoptotic process[255,256]. These age related changes limit the

ability of stem cells to secrete angiogenic factors thereby reducing their regenerative potential. It has been shown that MSCs from old patients are less effective in preventing ventricular remodelling and inducing new vessel formation post-MI[248]. Old donors exhibit reduced tolerance to ischemia and decreased transplant survival within ischemic muscle[251]. Similarly, older recipients have a diminished therapeutic response to receiving stem cells from donors of any age[251,254]. To overcome these effects related to cellular senescence, many strategies are being developed as recently reviewed[257]. In this regard, modifications to improve regenerative capacity have been sought[30,81,258,259] and include genetic modification of human CPCs with Pim-1, a pro-survival downstream effector of cytokine signalling pathways[260] including Akt[261], in order to improve cellular metabolic activity[262]. The WNT/β-catenin pathway has also been studied as a potential target for MSC rejuvenation[263]. While increasing age is associated with reduced MSC proliferation, differentiation capacity and WNT/β-catenin signalling, lithium treatment which increases β-catenin bioavailability restores the impaired function of these cells[257].

CONCLUSION

The use of stem cells to regenerate heart muscle has revolutionized the clinical practice for ischemic heart disease treatment. While safety and feasibility of cell therapy has been demonstrated in experimental and clinical studies, and the technology is making its way from bench to bedside, in order to reap the full regenerative potential afforded by stem cells, there is a necessity to develop the tools and the understanding required to ameliorate clinical efficacy. Most importantly, in order to harness the full therapeutic potential of these cells for cell therapy or any regenerative medicine application, optimization of cell viability, retention and functionality are of utmost importance. As summarized here, many groups are currently investigating various avenues of stem cell optimization. These methods include cell preconditioning using environmental stressors, genetic manipulations to enhance survival pathways, increase angiogenesis and cell adhesion, as well as preconditioning methodologies involving *ex vivo* stimulation of stem cells with growth hormones, cytokines and pharmacological agents such as statins and conditioning mimetics. The latter pharmacological method may be one of the safest, quickest, most reproducible, reliable and readily transferable method to the clinic used for producing optimized cell populations for patients. It is also foreseeable that in order to further enhance the therapeutic quality of these cells, multiple cellular pathways and effectors may be targeted, drug cocktails may be developed, or even conditioned cells may be combined with hydrogel technologies to encapsulate cells in a favorable environment to further promote retention, limit anoikis and facilitate cell-cell and cell-matrix interactions. All of these upcoming advances in stem cell optimization will greatly benefit patients and the promising field of regenerative medicine in the coming years.

REFERENCES

1 **Chiu RC**, Zibaitis A, Kao RL. Cellular cardiomyoplasty: myocardial regeneration with satellite cell implantation. *Ann Thorac Surg* 1995; **60**: 12-18 [PMID: 7598572]

2 **Li RK**, Jia ZQ, Weisel RD, Mickle DA, Zhang J, Mohabeer MK, Rao V, Ivanov J. Cardiomyocyte transplantation improves heart function. *Ann Thorac Surg* 1996; **62**: 654-660; discussion 660-661 [PMID: 8783989]

3 **Scorsin M**, Hagege AA, Dolizy I, Marotte F, Mirochnik N, Copin H, Barnoux M, le Bert M, Samuel JL, Rappaport L, Menasché P. Can cellular transplantation improve function in doxorubicin-induced heart failure? *Circulation* 1998; **98**: II151-II155; discussion II155-II156 [PMID: 9852897]

4 **Martin-Rendon E**, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM. Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. *Eur Heart J* 2008; **29**: 1807-1818 [PMID: 18523058 DOI: 10.1093/eurheartj/ehn220]

5 **Fisher SA**, Doree C, Mathur A, Martin-Rendon E. Meta-analysis of cell therapy trials for patients with heart failure. *Circ Res* 2015; **116**: 1361-1377 [PMID: 25632038 DOI: 10.1161/CIRCRESAHA.116.304386]

6 **Mills JS**, Rao SV. REPAIR-AMI: stem cells for acute myocardial infarction. *Future Cardiol* 2007; **3**: 137-140 [PMID: 19804241 DOI: 10.2217/14796678.3.2.137]

7 **Drexler H**, Meyer GP, Wollert KC. Bone-marrow-derived cell transfer after ST-elevation myocardial infarction: lessons from the BOOST trial. *Nat Clin Pract Cardiovasc Med* 2006; **3** Suppl 1: S65-S68 [PMID: 16501634 DOI: 10.1038/ncpcardio0407]

8 **Rangappa S**, Makkar R, Forrester J. Review article: current status of myocardial regeneration: new cell sources and new strategies. *J Cardiovasc Pharmacol Ther* 2010; **15**: 338-343 [PMID: 21098418 DOI: 10.1177/1074248410376382]

9 **Yousef M**, Schannwell CM, Köstering M, Zeus T, Brehm M, Strauer BE. The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. *J Am Coll Cardiol* 2009; **53**: 2262-2269 [PMID: 19520249 DOI: 10.1016/j.jacc.2009.02.051]

10 **Janssens S**, Dubois C, Bogaert J, Theunissen K, Deroose C, Desmet W, Kalantzi M, Herbots L, Sinnaeve P, Dens J, Maertens J, Rademakers F, Dymarkowski S, Gheysens O, Van Cleemput J, Bormans G, Nuyts J, Belmans A, Mortelmans L, Boogaerts M, Van de Werf F. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Lancet* 2006; **367**: 113-121 [PMID: 16413875 DOI: 10.1016/S0140-6736(05)67861-0]

11 **Gnecchi M**, Zhang Z, Ni A, Dzau VJ. Paracrine mechanisms in adult stem cell signaling and therapy. *Circ Res* 2008; **103**: 1204-1219 [PMID: 19028920 DOI: 10.1161/CIRCRESAHA.108.176826]

12 **Shabbir A**, Zisa D, Suzuki G, Lee T. Heart failure therapy mediated by the trophic activities of bone marrow mesenchymal stem cells: a noninvasive therapeutic regimen. *Am J Physiol Heart Circ Physiol* 2009; **296**: H1888-H1897 [PMID: 19395555 DOI: 10.1152/ajpheart.00186.2009]

13 **Lin H**, Shabbir A, Molnar M, Yang J, Marion S, Canty JM, Lee T. Adenoviral expression of vascular endothelial growth factor splice variants differentially regulate bone marrow-derived mesenchymal stem cells. *J Cell Physiol* 2008; **216**: 458-468 [PMID: 18288639 DOI: 10.1002/jcp.21414]

14 **Ziegelhoeffer T**, Fernandez B, Kostin S, Heil M, Voswinckel R, Helisch A, Schaper W. Bone marrow-derived cells do not incorporate into the adult growing vasculature. *Circ Res* 2004; **94**: 230-238 [PMID: 14656934 DOI: 10.1161/01.RES.0000110419.50982.1C]

15 **Pourrajab F**, Babaei Zarch M, Baghi Yazdi M, Rahimi Zarchi A, Vakili Zarch A. Application of stem cell/growth factor system, as a multimodal therapy approach in regenerative medicine to improve cell therapy yields. *Int J Cardiol* 2014; **173**: 12-19 [PMID: 24612559 DOI: 10.1016/j.ijcard.2014.02.006]

16 **Wollert KC**, Drexler H. Cell therapy for the treatment of coronary heart disease: a critical appraisal. *Nat Rev Cardiol* 2010; **7**: 204-215 [PMID: 20177405 DOI: 10.1038/nrcardio.2010.1]

17 **Xu C**. Differentiation and enrichment of cardiomyocytes from human pluripotent stem cells. *J Mol Cell Cardiol* 2012; **52**: 1203-1212 [PMID: 22484618 DOI: 10.1016/j.yjmcc.2012.03.012]

18 **Melo LG**, Pachori AS, Kong D, Gnecchi M, Wang K, Pratt RE, Dzau VJ. Molecular and cell-based therapies for protection, rescue, and repair of ischemic myocardium: reasons for cautious optimism. *Circulation* 2004; **109**: 2386-2393 [PMID: 15159329 DOI: 10.1161/01.CIR.0000128597.37025.00]

19 **Vertesaljai M**, Piroth Z, Fontos G, Andreka G, Font G, Szantho G, Lueff S, Reti M, Masszi T, Ablonczy L, Juhasz ED, Simor T, Turner MS, Andreka P. Drugs, gene transfer, signaling factors: a bench to bedside approach to myocardial stem cell therapy. *Heart Fail Rev* 2008; **13**: 227-244 [PMID: 17668319 DOI: 10.1007/s10741-007-9047-9]

20 **Laflamme MA**, Murry CE. Regenerating the heart. *Nat Biotechnol* 2005; **23**: 845-856 [PMID: 16003373 DOI: 10.1038/nbt1117]

21 **Chen L**, Tredget EE, Wu PY, Wu Y. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. *PLoS One* 2008; **3**: e1886 [PMID: 18382669 DOI: 10.1371/journal.pone.0001886]

22 **Luttun A**, Carmeliet P. De novo vasculogenesis in the heart. *Cardiovasc Res* 2003; **58**: 378-389 [PMID: 12757872]

23 **Asahara T**, Kawamoto A. Endothelial progenitor cells for postnatal vasculogenesis. *Am J Physiol Cell Physiol* 2004; **287**: C572-C579 [PMID: 15308462 DOI: 10.1152/ajpcell.00330.2003]

24 **Smith RR**, Barile L, Cho HC, Leppo MK, Hare JM, Messina E, Giacomello A, Abraham MR, Marbán E. Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens. *Circulation* 2007; **115**: 896-908 [PMID: 17283259 DOI: 10.1161/CIRCULATIONAHA.106.655209]

25 **Murry CE**, Field LJ, Menasché P. Cell-based cardiac repair: reflections at the 10-year point. *Circulation* 2005; **112**: 3174-3183 [PMID: 16286608 DOI: 10.1161/CIRCULATIONAHA.105.546218]

26 **Seeger FH**, Tonn T, Krzossok N, Zeiher AM, Dimmeler S. Cell isolation procedures matter: a comparison of different isolation protocols of bone marrow mononuclear cells used for cell therapy in patients with acute myocardial infarction. *Eur Heart J* 2007; **28**: 766-772 [PMID: 17298974 DOI: 10.1093/eurheartj/ehl509]

27 **Kumar S**, Chanda D, Ponnazhagan S. Therapeutic potential of genetically modified mesenchymal stem cells. *Gene Ther* 2008; **15**: 711-715 [PMID: 18356815 DOI: 10.1038/gt.2008.35]

28 **Graf T**. Differentiation plasticity of hematopoietic cells. *Blood* 2002; **99**: 3089-3101 [PMID: 11964270]

29 **Bartholomew A**, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, Hardy W, Devine S, Ucker D, Deans R, Moseley A, Hoffman R. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. *Exp Hematol* 2002; **30**: 42-48 [PMID: 11823036]

30 **Mangi AA**, Noiseux N, Kong D, He H, Rezvani M, Ingwall JS, Dzau VJ. Mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infarcted hearts. *Nat Med* 2003; **9**: 1195-1201 [PMID: 12910262 DOI: 10.1038/nm912]

31 **Toma C**, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation* 2002; **105**: 93-98 [PMID: 11772882]

32 **Makino S**, Fukuda K, Miyoshi S, Konishi F, Kodama H, Pan J, Sano M, Takahashi T, Hori S, Abe H, Hata J, Umezawa A, Ogawa S. Cardiomyocytes can be generated from marrow stromal cells in vitro. *J Clin Invest* 1999; **103**: 697-705 [PMID: 10074487 DOI: 10.1172/JCI5298]

33 **Schuleri KH**, Boyle AJ, Hare JM. Mesenchymal stem cells for cardiac regenerative therapy. *Handb Exp Pharmacol* 2007; **(180)**: 195-218 [PMID: 17554510 DOI: 10.1007/978-3-540-68976-8_9]

34 **Orlic D**, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Bone marrow cells regenerate infarcted myocardium. *Nature* 2001; **410**: 701-705 [PMID: 11287958 DOI: 10.1038/35070587]

35 **Heldman AW**, DiFede DL, Fishman JE, Zambrano JP, Trachtenberg BH, Karantalis V, Mushtaq M, Williams AR, Suncion VY, McNiece IK, Ghersin E, Soto V, Lopera G, Miki R, Willens H, Hendel R, Mitrani R, Pattany P, Feigenbaum G, Oskouei B, Byrnes J, Lowery MH, Sierra J, Pujol MV, Delgado C, Gonzalez PJ, Rodriguez JE, Bagno LL, Rouy D, Altman P, Foo CW, da Silva J, Anderson E, Schwarz R, Mendizabal A, Hare JM. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. *JAMA* 2014; **311**: 62-73 [PMID: 24247587 DOI: 10.1001/jama.2013.282909]

36 **Chen S**, Liu Z, Tian N, Zhang J, Yei F, Duan B, Zhu Z, Lin S, Kwan TW. Intracoronary transplantation of autologous bone marrow mesenchymal stem cells for ischemic cardiomyopathy due to isolated chronic occluded left anterior descending artery. *J Invasive Cardiol* 2006; **18**: 552-556 [PMID: 17090821]

37 **Shake JG**, Gruber PJ, Baumgartner WA, Senechal G, Meyers J, Redmond JM, Pittenger MF, Martin BJ. Mesenchymal stem cell implantation in a swine myocardial infarct model: engraftment and functional effects. *Ann Thorac Surg* 2002; **73**: 1919-1225; discussion 1926 [PMID: 12078791]

38 **Chen SL**, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, Zhang JJ, Chunhua RZ, Liao LM, Lin S, Sun JP. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol* 2004; **94**: 92-95 [PMID: 15219514 DOI: 10.1016/j.amjcard.2004.03.034]

39 **Katritsis DG**, Sotiropoulou PA, Karvouni E, Karabinos I, Korovesis S, Perez SA, Voridis EM, Papamichail M. Transcoronary transplantation of autologous mesenchymal stem cells and endothelial progenitors into infarcted human myocardium. *Catheter Cardiovasc Interv* 2005; **65**: 321-329 [PMID: 15954106 DOI: 10.1002/ccd.20406]

40 **Freyman T**, Polin G, Osman H, Crary J, Lu M, Cheng L, Palasis M, Wilensky RL. A quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial infarction. *Eur Heart J* 2006; **27**: 1114-1122 [PMID: 16510464 DOI: 10.1093/eurheartj/ehi818]

41 **Sadek HA**, Martin CM, Latif SS, Garry MG, Garry DJ. Bone-marrow-derived side population cells for myocardial regeneration. *J Cardiovasc Transl Res* 2009; **2**: 173-181 [PMID: 20559985 DOI: 10.1007/s12265-009-9090-0]

42 **Nakamura Y**, Yasuda T, Weisel RD, Li RK. Enhanced cell transplantation: preventing apoptosis increases cell survival and ventricular function. *Am J Physiol Heart Circ Physiol* 2006; **291**: H939-H947 [PMID: 16582022 DOI: 10.1152/ajpheart.00155.2006]

43 **Suzuki K**, Murtuza B, Beauchamp JR, Smolenski RT, Varela-Carver A, Fukushima S, Coppen SR, Partridge TA, Yacoub MH. Dynamics and mediators of acute graft attrition after myoblast transplantation to the heart. *FASEB J* 2004; **18**: 1153-1155 [PMID: 15155562 DOI: 10.1096/fj.03-1308fje]

44 **Gehling UM**, Ergün S, Schumacher U, Wagener C, Pantel K, Otte M, Schuch G, Schafhausen P, Mende T, Kilic N, Kluge K, Schäfer B, Hossfeld DK, Fiedler W. In vitro differentiation of endothelial cells from AC133-positive progenitor cells. *Blood* 2000; **95**: 3106-3112 [PMID: 10807776]

45 **Donndorf P**, Useini D, Lux CA, Vollmar B, Delyagina E, Laupheimer M, Kaminski A, Steinhoff G. Analyzing migratory properties of human CD133(+) stem cells in vivo after intraoperative sternal bone marrow isolation. *Cell Transplant* 2013; **22**: 1627-1635 [PMID: 23051098 DOI: 10.3727/096368912X657729]

46 **Zhang Y**, Wong S, Laflèche J, Crowe S, Mesana TG, Suuronen EJ, Ruel M. In vitro functional comparison of therapeutically relevant human vasculogenic progenitor cells used for cardiac cell therapy. *J Thorac Cardiovasc Surg* 2010; **140**: 216-224, 224.e1- e4 [PMID:

20167338 DOI: 10.1016/j.jtcvs.2009.11.016]
47 **Peichev M**, Naiyer AJ, Pereira D, Zhu Z, Lane WJ, Williams M, Oz MC, Hicklin DJ, Witte L, Moore MA, Rafii S. Expression of VEGFR-2 and AC133 by circulating human CD34(+) cells identifies a population of functional endothelial precursors. *Blood* 2000; **95**: 952-958 [PMID: 10648408]
48 **Suuronen EJ**, Veinot JP, Wong S, Kapila V, Price J, Griffith M, Mesana TG, Ruel M. Tissue-engineered injectable collagen-based matrices for improved cell delivery and vascularization of ischemic tissue using CD133+ progenitors expanded from the peripheral blood. *Circulation* 2006; **114**: I138-I144 [PMID: 16820563 DOI: 10.1161/CIRCULATIONAHA.105.001081]
49 **Senegaglia AC**, Brofman PR, Aita CA, Dallagiovanna B, Rebelatto CL, Hansen P, Barchiki F, Krieger MA. In vitro formation of capillary tubules from human umbilical cord blood cells with perspectives for therapeutic application. *Rev Bras Cir Cardiovasc* 2008; **23**: 467-473 [PMID: 19229416]
50 **Ma N**, Ladilov Y, Moebius JM, Ong L, Piechaczek C, Dávid A, Kaminski A, Choi YH, Li W, Egger D, Stamm C, Steinhoff G. Intramyocardial delivery of human CD133+ cells in a SCID mouse cryoinjury model: Bone marrow vs. cord blood-derived cells. *Cardiovasc Res* 2006; **71**: 158-169 [PMID: 16730684 DOI: 10.1016/j.cardiores.2006.03.020]
51 **Bonanno G**, Mariotti A, Procoli A, Corallo M, Rutella S, Pessina G, Scambia G, Mancuso S, Pierelli L. Human cord blood CD133+ cells immunoselected by a clinical-grade apparatus differentiate in vitro into endothelial- and cardiomyocyte-like cells. *Transfusion* 2007; **47**: 280-289 [PMID: 17302775 DOI: 10.1111/j.1537-2995.2007.01104.x]
52 **Forcillo J**, Stevens LM, Mansour S, Prieto I, Salem R, Baron C, Roy DC, Larose E, Masckauchan D, Noiseux N. Implantation of CD133+ stem cells in patients undergoing coronary bypass surgery: IMPACT-CABG pilot trial. *Can J Cardiol* 2013; **29**: 441-447 [PMID: 23265095 DOI: 10.1016/j.cjca.2012.08.009]
53 **Forcillo J**, Stevens LM, Mansour S, Prieto I, Roy DC, Noiseux N. IMPACT-CABG Trial: Implantation of CD133(+) Stem Cells in Patients Undergoing Coronary Bypass Surgery-Presentation of the First Treated Patient. *Case Rep Transplant* 2011; **2011**: 685394 [PMID: 23213603 DOI: 10.1155/2011/685394]
54 **Mansour S**, Roy DC, Bouchard V, Stevens LM, Gobeil F, Rivard A, Leclerc G, Reeves F, Noiseux N. One-Year Safety Analysis of the COMPARE-AMI Trial: Comparison of Intracoronary Injection of CD133 Bone Marrow Stem Cells to Placebo in Patients after Acute Myocardial Infarction and Left Ventricular Dysfunction. *Bone Marrow Res* 2011; **2011**: 385124 [PMID: 22046562 DOI: 10.1155/2011/385124]
55 **Mansour S**, Roy DC, Bouchard V, Nguyen BK, Stevens LM, Gobeil F, Rivard A, Leclerc G, Reeves F, Noiseux N. COMPARE-AMI trial: comparison of intracoronary injection of CD133+ bone marrow stem cells to placebo in patients after acute myocardial infarction and left ventricular dysfunction: study rationale and design. *J Cardiovasc Transl Res* 2010; **3**: 153-159 [PMID: 20560029 DOI: 10.1007/s12265-009-9145-2]
56 **Mansour S**, Roy DC, Lemieux B, Ouellet C, Stevens LM, Noiseux N. Stem cell therapy for the broken heart: mini-organ transplantation. *Transplant Proc* 2009; **41**: 3353-3357 [PMID: 19857748 DOI: 10.1016/j.transproceed.2009.08.033]
57 **Pagani FD**, DerSimonian H, Zawadzka A, Wetzel K, Edge AS, Jacoby DB, Dinsmore JH, Wright S, Aretz TH, Eisen HJ, Aaronson KD. Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation. *J Am Coll Cardiol* 2003; **41**: 879-888 [PMID: 12628737]
58 **Müller-Ehmsen J**, Whittaker P, Kloner RA, Dow JS, Sakoda T, Long TI, Laird PW, Kedes L. Survival and development of neonatal rat cardiomyocytes transplanted into adult myocardium. *J Mol Cell Cardiol* 2002; **34**: 107-116 [PMID: 11851351 DOI: 10.1006/jmcc.2001.1491]
59 **Shi RZ**, Li QP. Improving outcome of transplanted mesenchymal stem cells for ischemic heart disease. *Biochem Biophys Res Commun* 2008; **376**: 247-250 [PMID: 18789897 DOI: 10.1016/j.bbrc.2008.09.004]
60 **Hofmann M**, Wollert KC, Meyer GP, Menke A, Arseniev L, Hertenstein B, Ganser A, Knapp WH, Drexler H. Monitoring of bone marrow cell homing into the infarcted human myocardium. *Circulation* 2005; **111**: 2198-2202 [PMID: 15851598 DOI: 10.1161/01.CIR.0000163546.27639.AA]
61 **Goussetis E**, Manginas A, Koutelou M, Peristeri I, Theodosaki M, Kollaros N, Leontiadis E, Theodorakos A, Paterakis G, Karatasakis G, Cokkinos DV, Graphakos S. Intracoronary infusion of CD133+ and CD133-CD34+ selected autologous bone marrow progenitor cells in patients with chronic ischemic cardiomyopathy: cell isolation, adherence to the infarcted area, and body distribution. *Stem Cells* 2006; **24**: 2279-2283 [PMID: 16794269 DOI: 10.1634/stemcells.2005-0589]
62 **Schächinger V**, Aicher A, Döbert N, Röver R, Diener J, Fichtlscherer S, Assmus B, Seeger FH, Menzel C, Brenner W, Dimmeler S, Zeiher AM. Pilot trial on determinants of progenitor cell recruitment to the infarcted human myocardium. *Circulation* 2008; **118**: 1425-1432 [PMID: 18794392 DOI: 10.1161/CIRCULATIONAHA.108.777102]
63 **Blocklet D**, Toungouz M, Berkenboom G, Lambermont M, Unger P, Preumont N, Stoupel E, Egrise D, Degaute JP, Goldman M, Goldman S. Myocardial homing of nonmobilized peripheral-blood CD34+ cells after intracoronary injection. *Stem Cells* 2006; **24**: 333-336 [PMID: 16223854 DOI: 10.1634/stemcells.2005-0201]
64 **Kang WJ**, Kang HJ, Kim HS, Chung JK, Lee MC, Lee DS. Tissue distribution of 18F-FDG-labeled peripheral hematopoietic stem cells after intracoronary administration in patients with myocardial infarction. *J Nucl Med* 2006; **47**: 1295-1301 [PMID: 16883008]
65 **Tossios P**, Krausgrill B, Schmidt M, Fischer T, Halbach M, Fries JW, Fahnenstich S, Frommolt P, Heppelmann I, Schmidt A, Schomäcker K, Fischer JH, Bloch W, Mehlhorn U, Schwinger RH, Müller-Ehmsen J. Role of balloon occlusion for mononuclear bone marrow cell deposition after intracoronary injection in pigs with reperfused myocardial infarction. *Eur Heart J* 2008; **29**: 1911-1921 [PMID: 18544545 DOI: 10.1093/eurheartj/ehn218]
66 **Hou D**, Youssef EA, Brinton TJ, Zhang P, Rogers P, Price ET, Yeung AC, Johnstone BH, Yock PG, March KL. Radiolabeled cell distribution after intramyocardial, intracoronary, and interstitial retrograde coronary venous delivery: implications for current clinical trials. *Circulation* 2005; **112**: I150-I156 [PMID: 16159808 DOI: 10.1161/CIRCULATIONAHA.104.526749]
67 **Leiker M**, Suzuki G, Iyer VS, Canty JM, Lee T. Assessment of a nuclear affinity labeling method for tracking implanted mesenchymal stem cells. *Cell Transplant* 2008; **17**: 911-922 [PMID: 19069634]
68 **Zhang M**, Methot D, Poppa V, Fujio Y, Walsh K, Murry CE. Cardiomyocyte grafting for cardiac repair: graft cell death and anti-death strategies. *J Mol Cell Cardiol* 2001; **33**: 907-921 [PMID: 11343414 DOI: 10.1006/jmcc.2001.1367]
69 **Hodgetts SI**, Beilharz MW, Scalzo AA, Grounds MD. Why do cultured transplanted myoblasts die in vivo? DNA quantification shows enhanced survival of donor male myoblasts in host mice depleted of CD4+ and CD8+ cells or Nk1.1+ cells. *Cell Transplant* 2000; **9**: 489-502 [PMID: 11038066]
70 **Mylotte LA**, Duffy AM, Murphy M, O'Brien T, Samali A, Barry F, Szegezdi E. Metabolic flexibility permits mesenchymal stem cell survival in an ischemic environment. *Stem Cells* 2008; **26**: 1325-1336 [PMID: 18308942 DOI: 10.1634/stemcells.2007-1072]
71 **Chiarugi P**, Giannoni E. Anoikis: a necessary death program for anchorage-dependent cells. *Biochem Pharmacol* 2008; **76**: 1352-1364 [PMID: 18708031 DOI: 10.1016/j.bcp.2008.07.023]
72 **Michel JB**. Anoikis in the cardiovascular system: known and unknown extracellular mediators. *Arterioscler Thromb Vasc Biol* 2003; **23**: 2146-2154 [PMID: 14551156 DOI: 10.1161/01.ATV.0000099882.52647.E4]
73 **Ingber DE**. Mechanical signaling and the cellular response to extracellular matrix in angiogenesis and cardiovascular physiology. *Circ Res* 2002; **91**: 877-887 [PMID: 12433832]
74 **Guo J**, Lin GS, Bao CY, Hu ZM, Hu MY. Anti-inflammation

role for mesenchymal stem cells transplantation in myocardial infarction. *Inflammation* 2007; **30**: 97-104 [PMID: 17497204 DOI: 10.1007/s10753-007-9025-3]

75 **Singer AJ**, Clark RA. Cutaneous wound healing. *N Engl J Med* 1999; **341**: 738-746 [PMID: 10471461 DOI: 10.1056/NEJM199909023411006]

76 **Frangogiannis NG**. Targeting the inflammatory response in healing myocardial infarcts. *Curr Med Chem* 2006; **13**: 1877-1893 [PMID: 16842199]

77 **Sáenz-Morales D**, Conde E, Escribese MM, García-Martos M, Alegre L, Blanco-Sánchez I, García-Bermejo ML. ERK1/2 mediates cytoskeleton and focal adhesion impairment in proximal epithelial cells after renal ischemia. *Cell Physiol Biochem* 2009; **23**: 285-294 [PMID: 19471096 DOI: 10.1159/000218175]

78 **Zhu WG**, Li S, Lin LQ, Yan H, Fu T, Zhu JH. Vascular oxidative stress increases dendritic cell adhesion and transmigration induced by homocysteine. *Cell Immunol* 2009; **254**: 110-116 [PMID: 18809175 DOI: 10.1016/j.cellimm.2008.08.001]

79 **Pelegrin P**, Surprenant A. Dynamics of macrophage polarization reveal new mechanism to inhibit IL-1beta release through pyrophosphates. *EMBO J* 2009; **28**: 2114-2127 [PMID: 19536133 DOI: 10.1038/emboj.2009.163]

80 **Baraniak PR**, McDevitt TC. Stem cell paracrine actions and tissue regeneration. *Regen Med* 2010; **5**: 121-143 [PMID: 20017699 DOI: 10.2217/rme.09.74]

81 **Noiseux N**, Gnecchi M, Lopez-Ilasaca M, Zhang L, Solomon SD, Deb A, Dzau VJ, Pratt RE. Mesenchymal stem cells overexpressing Akt dramatically repair infarcted myocardium and improve cardiac function despite infrequent cellular fusion or differentiation. *Mol Ther* 2006; **14**: 840-850 [PMID: 16965940 DOI: 10.1016/j.ymthe.2006.05.016]

82 **Murry CE**, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M, Pasumarthi KB, Virag JI, Bartelmez SH, Poppa V, Bradford G, Dowell JD, Williams DA, Field LJ. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature* 2004; **428**: 664-668 [PMID: 15034593 DOI: 10.1038/nature02446]

83 **Balsam LB**, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature* 2004; **428**: 668-673 [PMID: 15034594 DOI: 10.1038/nature02460]

84 **Perez-Ilzarbe M**, Agbulut O, Pelacho B, Ciorba C, San Jose-Eneriz E, Desnos M, Hagège AA, Aranda P, Andreu EJ, Menasché P, Prósper F. Characterization of the paracrine effects of human skeletal myoblasts transplanted in infarcted myocardium. *Eur J Heart Fail* 2008; **10**: 1065-1072 [PMID: 18805052 DOI: 10.1016/j.ejheart.2008.08.002]

85 **Korf-Klingebiel M**, Kempf T, Sauer T, Brinkmann E, Fischer P, Meyer GP, Ganser A, Drexler H, Wollert KC. Bone marrow cells are a rich source of growth factors and cytokines: implications for cell therapy trials after myocardial infarction. *Eur Heart J* 2008; **29**: 2851-2858 [PMID: 18953051 DOI: 10.1093/eurheartj/ehn456]

86 **Kubal C**, Sheth K, Nadal-Ginard B, Galiñanes M. Bone marrow cells have a potent anti-ischemic effect against myocardial cell death in humans. *J Thorac Cardiovasc Surg* 2006; **132**: 1112-1118 [PMID: 17059931 DOI: 10.1016/j.jtcvs.2006.06.028]

87 **Xu M**, Uemura R, Dai Y, Wang Y, Pasha Z, Ashraf M. In vitro and in vivo effects of bone marrow stem cells on cardiac structure and function. *J Mol Cell Cardiol* 2007; **42**: 441-448 [PMID: 17187821 DOI: 10.1016/j.yjmcc.2006.10.009]

88 **Uemura R**, Xu M, Ahmad N, Ashraf M. Bone marrow stem cells prevent left ventricular remodeling of ischemic heart through paracrine signaling. *Circ Res* 2006; **98**: 1414-1421 [PMID: 16690882 DOI: 10.1161/01.RES.0000225952.61196.39]

89 **Takahashi M**, Li TS, Suzuki R, Kobayashi T, Ito H, Ikeda Y, Matsuzaki M, Hamano K. Cytokines produced by bone marrow cells can contribute to functional improvement of the infarcted heart by protecting cardiomyocytes from ischemic injury. *Am J Physiol Heart Circ Physiol* 2006; **291**: H886-H893 [PMID: 16603697 DOI: 10.1152/ajpheart.00142.2006]

90 **Liu CH**, Hwang SM. Cytokine interactions in mesenchymal stem cells from cord blood. *Cytokine* 2005; **32**: 270-279 [PMID: 16377203 DOI: 10.1016/j.cyto.2005.11.003]

91 **Schinköthe T**, Bloch W, Schmidt A. In vitro secreting profile of human mesenchymal stem cells. *Stem Cells Dev* 2008; **17**: 199-206 [PMID: 18208373 DOI: 10.1089/scd.2007.0175]

92 **Sarojini H**, Estrada R, Lu H, Dekova S, Lee MJ, Gray RD, Wang E. PEDF from mouse mesenchymal stem cell secretome attracts fibroblasts. *J Cell Biochem* 2008; **104**: 1793-1802 [PMID: 18348263 DOI: 10.1002/jcb.21748]

93 **Caplan AI**. Why are MSCs therapeutic? New data: new insight. *J Pathol* 2009; **217**: 318-324 [PMID: 19023885 DOI: 10.1002/path.2469]

94 **Kilroy GE**, Foster SJ, Wu X, Ruiz J, Sherwood S, Heifetz A, Ludlow JW, Stricker DM, Potiny S, Green P, Halvorsen YD, Cheatham B, Storms RW, Gimble JM. Cytokine profile of human adipose-derived stem cells: expression of angiogenic, hematopoietic, and pro-inflammatory factors. *J Cell Physiol* 2007; **212**: 702-709 [PMID: 17477371 DOI: 10.1002/jcp.21068]

95 **Pallante BA**, Duignan I, Okin D, Chin A, Bressan MC, Mikawa T, Edelberg JM. Bone marrow Oct3/4+ cells differentiate into cardiac myocytes via age-dependent paracrine mechanisms. *Circ Res* 2007; **100**: e1- e11 [PMID: 17122441 DOI: 10.1161/01.RES.0000253487.02398.85]

96 **Xie Z**, Koyama T, Suzuki J, Fujii Y, Togashi H, Sawa H, Nagashima K. Coronary reperfusion following ischemia: different expression of bcl-2 and bax proteins, and cardiomyocyte apoptosis. *Jpn Heart J* 2001; **42**: 759-770 [PMID: 11933925]

97 **Nishida S**, Nagamine H, Tanaka Y, Watanabe G. Protective effect of basic fibroblast growth factor against myocyte death and arrhythmias in acute myocardial infarction in rats. *Circ J* 2003; **67**: 334-339 [PMID: 12655165]

98 **Schenke-Layland K**, Strem BM, Jordan MC, Deemedio MT, Hedrick MH, Roos KP, Fraser JK, Maclellan WR. Adipose tissue-derived cells improve cardiac function following myocardial infarction. *J Surg Res* 2009; **153**: 217-223 [PMID: 18694573 DOI: 10.1016/j.jss.2008.03.019]

99 **Estrada R**, Li N, Sarojini H, An J, Lee MJ, Wang E. Secretome from mesenchymal stem cells induces angiogenesis via Cyr61. *J Cell Physiol* 2009; **219**: 563-571 [PMID: 19170074 DOI: 10.1002/jcp.21701]

100 **Askari AT**, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, Rovner A, Ellis SG, Thomas JD, DiCorleto PE, Topol EJ, Penn MS. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. *Lancet* 2003; **362**: 697-703 [PMID: 12957092 DOI: 10.1016/S0140-6736(03)14232-8]

101 **Neuss S**, Becher E, Wöltje M, Tietze L, Jahnen-Dechent W. Functional expression of HGF and HGF receptor/c-met in adult human mesenchymal stem cells suggests a role in cell mobilization, tissue repair, and wound healing. *Stem Cells* 2004; **22**: 405-414 [PMID: 15153617 DOI: 10.1634/stemcells.22-3-405]

102 **Mourkioti F**, Rosenthal N. IGF-1, inflammation and stem cells: interactions during muscle regeneration. *Trends Immunol* 2005; **26**: 535-542 [PMID: 16109502 DOI: 10.1016/j.it.2005.08.002]

103 **Linke A**, Müller P, Nurzynska D, Casarsa C, Torella D, Nascimbene A, Castaldo C, Cascapera S, Böhm M, Quaini F, Urbanek K, Leri A, Hintze TH, Kajstura J, Anversa P. Stem cells in the dog heart are self-renewing, clonogenic, and multipotent and regenerate infarcted myocardium, improving cardiac function. *Proc Natl Acad Sci USA* 2005; **102**: 8966-8971 [PMID: 15951423 DOI: 10.1073/pnas.0502678102]

104 **Xu X**, Xu Z, Xu Y, Cui G. Effects of mesenchymal stem cell transplantation on extracellular matrix after myocardial infarction in rats. *Coron Artery Dis* 2005; **16**: 245-255 [PMID: 15915077]

105 **Ohnishi S**, Sumiyoshi H, Kitamura S, Nagaya N. Mesenchymal stem cells attenuate cardiac fibroblast proliferation and collagen synthesis through paracrine actions. *FEBS Lett* 2007; **581**: 3961-3966 [PMID: 17662720 DOI: 10.1016/j.febslet.2007.07.028]

106 **Ohnishi S**, Yasuda T, Kitamura S, Nagaya N. Effect of hypoxia on

gene expression of bone marrow-derived mesenchymal stem cells and mononuclear cells. *Stem Cells* 2007; **25**: 1166-1177 [PMID: 17289933 DOI: 10.1634/stemcells.2006-0347]

107 **Yu Y**, Fukuda N, Yao EH, Matsumoto T, Kobayashi N, Suzuki R, Tahira Y, Ueno T, Matsumoto K. Effects of an ARB on endothelial progenitor cell function and cardiovascular oxidation in hypertension. *Am J Hypertens* 2008; **21**: 72-77 [PMID: 18091747 DOI: 10.1038/ajh.2007.5]

108 **Krupnick AS**, Kreisel D, Riha M, Balsara KR, Rosengard BR. Myocardial tissue engineering and regeneration as a therapeutic alternative to transplantation. *Curr Top Microbiol Immunol* 2004; **280**: 139-164 [PMID: 14594210]

109 **Brehm M**, Stanske B, Strauer BE. Therapeutic potential of stem cells in elderly patients with cardiovascular disease. *Exp Gerontol* 2008; **43**: 1024-1032 [PMID: 18845234 DOI: 10.1016/j.exger.2008.09.008]

110 **Yamada S**, Nelson TJ, Behfar A, Crespo-Diaz RJ, Fraidenraich D, Terzic A. Stem cell transplant into preimplantation embryo yields myocardial infarction-resistant adult phenotype. *Stem Cells* 2009; **27**: 1697-1705 [PMID: 19544428 DOI: 10.1002/stem.116]

111 **Seidel M**, Borczyńska A, Rozwadowska N, Kurpisz M. Cell-based therapy for heart failure: skeletal myoblasts. *Cell Transplant* 2009; **18**: 695-707 [PMID: 19500482 DOI: 10.3727/096368909X470810]

112 **LaPar DJ**, Kron IL, Yang Z. Stem cell therapy for ischemic heart disease: where are we? *Curr Opin Organ Transplant* 2009; **14**: 79-84 [PMID: 19337151 DOI: 10.1097/MOT.0b013e328320d2e2]

113 **Boudoulas KD**, Hatzopoulos AK. Cardiac repair and regeneration: the Rubik's cube of cell therapy for heart disease. *Dis Model Mech* 2009; **2**: 344-358 [PMID: 19553696 DOI: 10.1242/dmm.000240]

114 **Murry CE**, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124-1136 [PMID: 3769170]

115 **Tang YL**, Zhu W, Cheng M, Chen L, Zhang J, Sun T, Kishore R, Phillips MI, Losordo DW, Qin G. Hypoxic preconditioning enhances the benefit of cardiac progenitor cell therapy for treatment of myocardial infarction by inducing CXCR4 expression. *Circ Res* 2009; **104**: 1209-1216 [PMID: 19407239 DOI: 10.1161/CIRCRESAHA.109.197723]

116 **Rosová I**, Dao M, Capoccia B, Link D, Nolta JA. Hypoxic preconditioning results in increased motility and improved therapeutic potential of human mesenchymal stem cells. *Stem Cells* 2008; **26**: 2173-2182 [PMID: 18511601 DOI: 10.1634/stemcells.2007-1104]

117 **Kubo M**, Li TS, Suzuki R, Shirasawa B, Morikage N, Ohshima M, Qin SL, Hamano K. Hypoxic preconditioning increases survival and angiogenic potency of peripheral blood mononuclear cells via oxidative stress resistance. *Am J Physiol Heart Circ Physiol* 2008; **294**: H590-H595 [PMID: 18156196 DOI: 10.1152/ajpheart.00856.2007]

118 **Haider HKh**, Ashraf M. Preconditioning and stem cell survival. *J Cardiovasc Transl Res* 2010; **3**: 89-102 [PMID: 20560023 DOI: 10.1007/s12265-009-9161-2]

119 **Hu X**, Yu SP, Fraser JL, Lu Z, Ogle ME, Wang JA, Wei L. Transplantation of hypoxia-preconditioned mesenchymal stem cells improves infarcted heart function via enhanced survival of implanted cells and angiogenesis. *J Thorac Cardiovasc Surg* 2008; **135**: 799-808 [PMID: 18374759 DOI: 10.1016/j.jtcvs.2007.07.071]

120 **Yuan G**, Nanduri J, Khan S, Semenza GL, Prabhakar NR. Induction of HIF-1alpha expression by intermittent hypoxia: involvement of NADPH oxidase, Ca2+ signaling, prolyl hydroxylases, and mTOR. *J Cell Physiol* 2008; **217**: 674-685 [PMID: 18651560 DOI: 10.1002/jcp.21537]

121 **Nanduri J**, Yuan G, Kumar GK, Semenza GL, Prabhakar NR. Transcriptional responses to intermittent hypoxia. *Respir Physiol Neurobiol* 2008; **164**: 277-281 [PMID: 18692603 DOI: 10.1016/j.resp.2008.07.006]

122 **Chau CH**, Clavijo CA, Deng HT, Zhang Q, Kim KJ, Qiu Y, Le AD, Ann DK. Etk/Bmx mediates expression of stress-induced adaptive genes VEGF, PAI-1, and iNOS via multiple signaling cascades in different cell systems. *Am J Physiol Cell Physiol* 2005; **289**: C444-C454 [PMID: 15788485 DOI: 10.1152/ajpcell.00410.2004]

123 **Cipolleschi MG**, D'Ippolito G, Bernabei PA, Caporale R, Nannini R, Mariani M, Fabbiani M, Rossi-Ferrini P, Olivotto M, Dello Sbarba P. Severe hypoxia enhances the formation of erythroid bursts from human cord blood cells and the maintenance of BFU-E in vitro. *Exp Hematol* 1997; **25**: 1187-1194 [PMID: 9328456]

124 **Li W**, Ma N, Ong LL, Nesselmann C, Klopsch C, Ladilov Y, Furlani D, Piechaczek C, Moebius JM, Lützow K, Lendlein A, Stamm C, Li RK, Steinhoff G. Bcl-2 engineered MSCs inhibited apoptosis and improved heart function. *Stem Cells* 2007; **25**: 2118-2127 [PMID: 17478584 DOI: 10.1634/stemcells.2006-0771]

125 **Gnecchi M**, He H, Noiseux N, Liang OD, Zhang L, Morello F, Mu H, Melo LG, Pratt RE, Ingwall JS, Dzau VJ. Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement. *FASEB J* 2006; **20**: 661-669 [PMID: 16581974 DOI: 10.1096/fj.05-5211com]

126 **Theus MH**, Wei L, Cui L, Francis K, Hu X, Keogh C, Yu SP. In vitro hypoxic preconditioning of embryonic stem cells as a strategy of promoting cell survival and functional benefits after transplantation into the ischemic rat brain. *Exp Neurol* 2008; **210**: 656-670 [PMID: 18279854 DOI: 10.1016/j.expneurol.2007.12.020]

127 **Heads RJ**, Yellon DM, Latchman DS. Differential cytoprotection against heat stress or hypoxia following expression of specific stress protein genes in myogenic cells. *J Mol Cell Cardiol* 1995; **27**: 1669-1678 [PMID: 8523429]

128 **Das R**, Jahr H, van Osch GJ, Farrell E. The role of hypoxia in bone marrow-derived mesenchymal stem cells: considerations for regenerative medicine approaches. *Tissue Eng Part B Rev* 2010; **16**: 159-168 [PMID: 19698058 DOI: 10.1089/ten.TEB.2009.0296]

129 **Akita T**, Murohara T, Ikeda H, Sasaki K, Shimada T, Egami K, Imaizumi T. Hypoxic preconditioning augments efficacy of human endothelial progenitor cells for therapeutic neovascularization. *Lab Invest* 2003; **83**: 65-73 [PMID: 12533687]

130 **He A**, Jiang Y, Gui C, Sun Y, Li J, Wang JA. The antiapoptotic effect of mesenchymal stem cell transplantation on ischemic myocardium is enhanced by anoxic preconditioning. *Can J Cardiol* 2009; **25**: 353-358 [PMID: 19536376]

131 **Pendergrass KD**, Boopathy AV, Seshadri G, Maiellaro-Rafferty K, Che PL, Brown ME, Davis ME. Acute preconditioning of cardiac progenitor cells with hydrogen peroxide enhances angiogenic pathways following ischemia-reperfusion injury. *Stem Cells Dev* 2013; **22**: 2414-2424 [PMID: 23544670 DOI: 10.1089/scd.2012.0673]

132 **Sharma RK**, Zhou Q, Netland PA. Effect of oxidative preconditioning on neural progenitor cells. *Brain Res* 2008; **1243**: 19-26 [PMID: 18761002 DOI: 10.1016/j.brainres.2008.08.025]

133 **Zhang J**, Chen GH, Wang YW, Zhao J, Duan HF, Liao LM, Zhang XZ, Chen YD, Chen H. Hydrogen peroxide preconditioning enhances the therapeutic efficacy of Wharton's Jelly mesenchymal stem cells after myocardial infarction. *Chin Med J* (Engl) 2012; **125**: 3472-3478 [PMID: 23044308]

134 **Su CY**, Chong KY, Chen J, Ryter S, Khardori R, Lai CC. A physiologically relevant hyperthermia selectively activates constitutive hsp70 in H9c2 cardiac myoblasts and confers oxidative protection. *J Mol Cell Cardiol* 1999; **31**: 845-855 [PMID: 10329212 DOI: 10.1006/jmcc.1998.0923]

135 **Haider HKh**, Ashraf M. Strategies to promote donor cell survival: combining preconditioning approach with stem cell transplantation. *J Mol Cell Cardiol* 2008; **45**: 554-566 [PMID: 18561945 DOI: 10.1016/j.yjmcc.2008.05.004]

136 **Laflamme MA**, Chen KY, Naumova AV, Muskheli V, Fugate JA, Dupras SK, Reinecke H, Xu C, Hassanipour M, Police S, O'Sullivan C, Collins L, Chen Y, Minami E, Gill EA, Ueno S, Yuan C, Gold J, Murry CE. Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts. *Nat Biotechnol* 2007; **25**: 1015-1024 [PMID: 17721512 DOI: 10.1038/nbt1327]

137 **Laflamme MA**, Gold J, Xu C, Hassanipour M, Rosler E, Police S, Muskheli V, Murry CE. Formation of human myocardium in the rat heart from human embryonic stem cells. *Am J Pathol*

2005; **167**: 663-671 [PMID: 16127147 DOI: 10.1016/S0002-9440(10)62041-X]
138 **Moloney TC**, Hoban DB, Barry FP, Howard L, Dowd E. Kinetics of thermally induced heat shock protein 27 and 70 expression by bone marrow-derived mesenchymal stem cells. *Protein Sci* 2012; **21**: 904-909 [PMID: 22505291 DOI: 10.1002/pro.2077]
139 **Feng Y**, Huang W, Meng W, Jegga AG, Wang Y, Cai W, Kim HW, Pasha Z, Wen Z, Rao F, Modi RM, Yu X, Ashraf M. Heat shock improves Sca-1+ stem cell survival and directs ischemic cardiomyocytes toward a prosurvival phenotype via exosomal transfer: a critical role for HSF1/miR-34a/HSP70 pathway. *Stem Cells* 2014; **32**: 462-472 [PMID: 24123326 DOI: 10.1002/stem.1571]
140 **Kis B**, Nagy K, Snipes JA, Rajapakse NC, Horiguchi T, Grover GJ, Busija DW. The mitochondrial K(ATP) channel opener BMS-191095 induces neuronal preconditioning. *Neuroreport* 2004; **15**: 345-349 [PMID: 15076766]
141 **Sato T**, Li Y, Saito T, Nakaya H. Minoxidil opens mitochondrial K(ATP) channels and confers cardioprotection. *Br J Pharmacol* 2004; **141**: 360-366 [PMID: 14691056 DOI: 10.1038/sj.bjp.0705613]
142 **Kicińska A**, Szewczyk A. Protective effects of the potassium channel opener-diazoxide against injury in neonatal rat ventricular myocytes. *Gen Physiol Biophys* 2003; **22**: 383-395 [PMID: 14986888]
143 **Busija DW**, Katakam P, Rajapakse NC, Kis B, Grover G, Domoki F, Bari F. Effects of ATP-sensitive potassium channel activators diazoxide and BMS-191095 on membrane potential and reactive oxygen species production in isolated piglet mitochondria. *Brain Res Bull* 2005; **66**: 85-90 [PMID: 15982523 DOI: 10.1016/j.brainresbull.2005.03.022]
144 **Rajapakse N**, Kis B, Horiguchi T, Snipes J, Busija D. Diazoxide pretreatment induces delayed preconditioning in astrocytes against oxygen glucose deprivation and hydrogen peroxide-induced toxicity. *J Neurosci Res* 2003; **73**: 206-214 [PMID: 12836163 DOI: 10.1002/jnr.10657]
145 **O'Sullivan JC**, Yao XL, Alam H, McCabe JT. Diazoxide, as a postconditioning and delayed preconditioning trigger, increases HSP25 and HSP70 in the central nervous system following combined cerebral stroke and hemorrhagic shock. *J Neurotrauma* 2007; **24**: 532-546 [PMID: 17402858 DOI: 10.1089/neu.2006.0128]
146 **Niagara MI**, Haider HKh, Jiang S, Ashraf M. Pharmacologically preconditioned skeletal myoblasts are resistant to oxidative stress and promote angiomyogenesis via release of paracrine factors in the infarcted heart. *Circ Res* 2007; **100**: 545-555 [PMID: 17234963 DOI: 10.1161/01.RES.0000258460.41160.ef]
147 **Ahmad N**, Wang Y, Haider KH, Wang B, Pasha Z, Uzun O, Ashraf M. Cardiac protection by mitoKATP channels is dependent on Akt translocation from cytosol to mitochondria during late preconditioning. *Am J Physiol Heart Circ Physiol* 2006; **290**: H2402-H2408 [PMID: 16687609 DOI: 10.1152/ajpheart.00737.2005]
148 **Yang YJ**, Qian HY, Huang J, Geng YJ, Gao RL, Dou KF, Yang GS, Li JJ, Shen R, He ZX, Lu MJ, Zhao SH. Atorvastatin treatment improves survival and effects of implanted mesenchymal stem cells in post-infarct swine hearts. *Eur Heart J* 2008; **29**: 1578-1590 [PMID: 18456710 DOI: 10.1093/eurheartj/ehn167]
149 **Assmus B**, Urbich C, Aicher A, Hofmann WK, Haendeler J, Rössig L, Spyridopoulos I, Zeiher AM, Dimmeler S. HMG-CoA reductase inhibitors reduce senescence and increase proliferation of endothelial progenitor cells via regulation of cell cycle regulatory genes. *Circ Res* 2003; **92**: 1049-1055 [PMID: 12676819 DOI: 10.1161/01.RES.0000070067.64040.7C]
150 **Spyridopoulos I**, Haendeler J, Urbich C, Brummendorf TH, Oh H, Schneider MD, Zeiher AM, Dimmeler S. Statins enhance migratory capacity by upregulation of the telomere repeat-binding factor TRF2 in endothelial progenitor cells. *Circulation* 2004; **110**: 3136-3142 [PMID: 15520325 DOI: 10.1161/01.CIR.0000142866.50300.EB]
151 **Park A**, Barrera-Ramirez J, Ranasinghe I, Pilon S, Sy R, Fergusson D, Allan DS. Use of Statins to Augment Progenitor Cell Function in Preclinical and Clinical Studies of Regenerative Therapy: a Systematic Review. *Stem Cell Rev* 2016; **12**: 327-339 [PMID: 26873165 DOI: 10.1007/s12015-016-9647-7]
152 **Szeto A**, Nation DA, Mendez AJ, Dominguez-Bendala J, Brooks LG, Schneiderman N, McCabe PM. Oxytocin attenuates NADPH-dependent superoxide activity and IL-6 secretion in macrophages and vascular cells. *Am J Physiol Endocrinol Metab* 2008; **295**: E1495-E1501 [PMID: 18940936 DOI: 10.1152/ajpendo.90718.2008]
153 **Paquin J**, Danalache BA, Jankowski M, McCann SM, Gutkowska J. Oxytocin induces differentiation of P19 embryonic stem cells to cardiomyocytes. *Proc Natl Acad Sci USA* 2002; **99**: 9550-9555 [PMID: 12093924 DOI: 10.1073/pnas.152302499]
154 **Cattaneo MG**, Lucci G, Vicentini LM. Oxytocin stimulates in vitro angiogenesis via a Pyk-2/Src-dependent mechanism. *Exp Cell Res* 2009; **315**: 3210-3219 [PMID: 19563802 DOI: 10.1016/j.yexcr.2009.06.022]
155 **Florian M**, Jankowski M, Gutkowska J. Oxytocin increases glucose uptake in neonatal rat cardiomyocytes. *Endocrinology* 2010; **151**: 482-491 [PMID: 20008042 DOI: 10.1210/en.2009-0624]
156 **Elabd C**, Basillais A, Beaupied H, Breuil V, Wagner N, Scheideler M, Zaragosi LE, Massiéra F, Lemichez E, Trajanoski Z, Carle G, Euller-Ziegler L, Ailhaud G, Benhamou CL, Dani C, Amri EZ. Oxytocin controls differentiation of human mesenchymal stem cells and reverses osteoporosis. *Stem Cells* 2008; **26**: 2399-2407 [PMID: 18583541 DOI: 10.1634/stemcells.2008-0127]
157 **Cattaneo MG**, Chini B, Vicentini LM. Oxytocin stimulates migration and invasion in human endothelial cells. *Br J Pharmacol* 2008; **153**: 728-736 [PMID: 18059319 DOI: 10.1038/sj.bjp.0707609]
158 **Cassoni P**, Marrocco T, Bussolati B, Allia E, Munaron L, Sapino A, Bussolati G. Oxytocin induces proliferation and migration in immortalized human dermal microvascular endothelial cells and human breast tumor-derived endothelial cells. *Mol Cancer Res* 2006; **4**: 351-359 [PMID: 16778082 DOI: 10.1158/1541-7786.MCR-06-0024]
159 **Noiseux N**, Borie M, Desnoyers A, Menaouar A, Stevens LM, Mansour S, Danalache BA, Roy DC, Jankowski M, Gutkowska J. Preconditioning of stem cells by oxytocin to improve their therapeutic potential. *Endocrinology* 2012; **153**: 5361-5372 [PMID: 23024264 DOI: 10.1210/en.2012-1402]
160 **Wisel S**, Khan M, Kuppusamy ML, Mohan IK, Chacko SM, Rivera BK, Sun BC, Hideg K, Kuppusamy P. Pharmacological preconditioning of mesenchymal stem cells with trimetazidine (1-[2,3,4-trimethoxybenzyl]piperazine) protects hypoxic cells against oxidative stress and enhances recovery of myocardial function in infarcted heart through Bcl-2 expression. *J Pharmacol Exp Ther* 2009; **329**: 543-550 [PMID: 19218529 DOI: 10.1124/jpet.109.150839]
161 **Cízková D**, Rosocha J, Vanický I, Radonák J, Gálik J, Cízek M. Induction of mesenchymal stem cells leads to HSP72 synthesis and higher resistance to oxidative stress. *Neurochem Res* 2006; **31**: 1011-1020 [PMID: 16865557 DOI: 10.1007/s11064-006-9107-x]
162 **Imai Y**, Adachi Y, Shi M, Shima C, Yanai S, Okigaki M, Yamashima T, Kaneko K, Ikehara S. Caspase inhibitor ZVAD-fmk facilitates engraftment of donor hematopoietic stem cells in intra-bone marrow-bone marrow transplantation. *Stem Cells Dev* 2010; **19**: 461-468 [PMID: 19686047 DOI: 10.1089/scd.2009.0251]
163 **Yun BG**, Matts RL. Differential effects of Hsp90 inhibition on protein kinases regulating signal transduction pathways required for myoblast differentiation. *Exp Cell Res* 2005; **307**: 212-223 [PMID: 15922741 DOI: 10.1016/j.yexcr.2005.03.003]
164 **Xaymardan M**, Cimini M, Fazel S, Weisel RD, Lu WY, Martin U, Harvey RP, Li RK. c-Kit function is necessary for in vitro myogenic differentiation of bone marrow hematopoietic cells. *Stem Cells* 2009; **27**: 1911-1920 [PMID: 19544423 DOI: 10.1002/stem.106]
165 **Roussel M**, Moreau P, Huynh A, Mary JY, Danho C, Caillot D, Hulin C, Fruchart C, Marit G, Pégourié B, Lenain P, Araujo C, Kolb B, Randriamalala E, Royer B, Stoppa AM, Dib M, Dorvaux V, Garderet L, Mathiot C, Avet-Loiseau H, Harousseau JL, Attal M. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone

du Myelome (IFM). *Blood* 2010; **115**: 32-37 [PMID: 19884643 DOI: 10.1182/blood-2009-06-229658]
166 **Pinna GF**, Fiorucci M, Reimund JM, Taquet N, Arondel Y, Muller CD. Celastrol inhibits pro-inflammatory cytokine secretion in Crohn's disease biopsies. *Biochem Biophys Res Commun* 2004; **322**: 778-786 [PMID: 15336532 DOI: 10.1016/j.bbrc.2004.07.186]
167 **Li H**, Zhang YY, Huang XY, Sun YN, Jia YF, Li D. Beneficial effect of tripterine on systemic lupus erythematosus induced by active chromatin in BALB/c mice. *Eur J Pharmacol* 2005; **512**: 231-237 [PMID: 15840409 DOI: 10.1016/j.ejphar.2005.02.030]
168 **Li H**, Zhang YY, Tan HW, Jia YF, Li D. Therapeutic effect of tripterine on adjuvant arthritis in rats. *J Ethnopharmacol* 2008; **118**: 479-484 [PMID: 18577440 DOI: 10.1016/j.jep.2008.05.028]
169 **Allison AC**, Cacabelos R, Lombardi VR, Alvarez XA, Vigo C. Celastrol, a potent antioxidant and anti-inflammatory drug, as a possible treatment for Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; **25**: 1341-1357 [PMID: 11513350]
170 **Yang H**, Chen D, Cui QC, Yuan X, Dou QP. Celastrol, a triterpene extracted from the Chinese «Thunder of God Vine,» is a potent proteasome inhibitor and suppresses human prostate cancer growth in nude mice. *Cancer Res* 2006; **66**: 4758-4765 [PMID: 16651429 DOI: 10.1158/0008-5472.CAN-05-4529]
171 **Zhang T**, Hamza A, Cao X, Wang B, Yu S, Zhan CG, Sun D. A novel Hsp90 inhibitor to disrupt Hsp90/Cdc37 complex against pancreatic cancer cells. *Mol Cancer Ther* 2008; **7**: 162-170 [PMID: 18202019 DOI: 10.1158/1535-7163.MCT-07-0484]
172 **Der Sarkissian S**, Cailhier JF, Borie M, Stevens LM, Gaboury L, Mansour S, Hamet P, Noiseux N. Celastrol protects ischaemic myocardium through a heat shock response with up-regulation of haeme oxygenase-1. *Br J Pharmacol* 2014; **171**: 5265-5279 [PMID: 25041185 DOI: 10.1111/bph.12838]
173 **Jeong WS**, Jun M, Kong AN. Nrf2: a potential molecular target for cancer chemoprevention by natural compounds. *Antioxid Redox Signal* 2006; **8**: 99-106 [PMID: 16487042 DOI: 10.1089/ars.2006.8.99]
174 **Zhang M**, An C, Gao Y, Leak RK, Chen J, Zhang F. Emerging roles of Nrf2 and phase II antioxidant enzymes in neuroprotection. *Prog Neurobiol* 2013; **100**: 30-47 [PMID: 23025925 DOI: 10.1016/j.pneurobio.2012.09.003]
175 **Biswas C**, Shah N, Muthu M, La P, Fernando AP, Sengupta S, Yang G, Dennery PA. Nuclear heme oxygenase-1 (HO-1) modulates subcellular distribution and activation of Nrf2, impacting metabolic and anti-oxidant defenses. *J Biol Chem* 2014; **289**: 26882-26894 [PMID: 25107906 DOI: 10.1074/jbc.M114.567685]
176 **Li N**, Alam J, Venkatesan MI, Eiguren-Fernandez A, Schmitz D, Di Stefano E, Slaughter N, Killeen E, Wang X, Huang A, Wang M, Miguel AH, Cho A, Sioutas C, Nel AE. Nrf2 is a key transcription factor that regulates antioxidant defense in macrophages and epithelial cells: protecting against the proinflammatory and oxidizing effects of diesel exhaust chemicals. *J Immunol* 2004; **173**: 3467-3481 [PMID: 15322212]
177 **Baird NA**, Turnbull DW, Johnson EA. Induction of the heat shock pathway during hypoxia requires regulation of heat shock factor by hypoxia-inducible factor-1. *J Biol Chem* 2006; **281**: 38675-38681 [PMID: 17040902 DOI: 10.1074/jbc.M608013200]
178 **Zhang T**, Li Y, Yu Y, Zou P, Jiang Y, Sun D. Characterization of celastrol to inhibit hsp90 and cdc37 interaction. *J Biol Chem* 2009; **284**: 35381-35389 [PMID: 19858214 DOI: 10.1074/jbc.M109.051532]
179 **Seo WY**, Goh AR, Ju SM, Song HY, Kwon DJ, Jun JG, Kim BC, Choi SY, Park J. Celastrol induces expression of heme oxygenase-1 through ROS/Nrf2/ARE signaling in the HaCaT cells. *Biochem Biophys Res Commun* 2011; **407**: 535-540 [PMID: 21414301 DOI: 10.1016/j.bbrc.2011.03.053]
180 **Shintani S**, Kusano K, Ii M, Iwakura A, Heyd L, Curry C, Wecker A, Gavin M, Ma H, Kearney M, Silver M, Thorne T, Murohara T, Losordo DW. Synergistic effect of combined intramyocardial CD34+ cells and VEGF2 gene therapy after MI. *Nat Clin Pract Cardiovasc Med* 2006; **3** Suppl 1: S123-S128 [PMID: 16501618 DOI: 10.1038/ncpcardio0430]
181 **Elmadbouh I**, Haider HKh, Jiang S, Idris NM, Lu G, Ashraf M. Ex vivo delivered stromal cell-derived factor-1alpha promotes stem cell homing and induces angiomyogenesis in the infarcted myocardium. *J Mol Cell Cardiol* 2007; **42**: 792-803 [PMID: 17350033 DOI: 10.1016/j.yjmcc.2007.02.001]
182 **Lataillade JJ**, Domenech J, Le Bousse-Kerdilès MC. Stromal cell-derived factor-1 (SDF-1)CXCR4 couple plays multiple roles on haematopoietic progenitors at the border between the old cytokine and new chemokine worlds: survival, cell cycling and trafficking. *Eur Cytokine Netw* 2004; **15**: 177-188 [PMID: 15542441]
183 **Shyu WC**, Lin SZ, Yen PS, Su CY, Chen DC, Wang HJ, Li H. Stromal cell-derived factor-1 alpha promotes neuroprotection, angiogenesis, and mobilization/homing of bone marrow-derived cells in stroke rats. *J Pharmacol Exp Ther* 2008; **324**: 834-849 [PMID: 18029549 DOI: 10.1124/jpet.107.127746]
184 **Zemani F**, Silvestre JS, Fauvel-Lafeve F, Bruel A, Vilar J, Bieche I, Laurendeau I, Galy-Fauroux I, Fischer AM, Boisson-Vidal C. Ex vivo priming of endothelial progenitor cells with SDF-1 before transplantation could increase their proangiogenic potential. *Arterioscler Thromb Vasc Biol* 2008; **28**: 644-650 [PMID: 18239152 DOI: 10.1161/ATVBAHA.107.160044]
185 **Pasha Z**, Wang Y, Sheikh R, Zhang D, Zhao T, Ashraf M. Preconditioning enhances cell survival and differentiation of stem cells during transplantation in infarcted myocardium. *Cardiovasc Res* 2008; **77**: 134-142 [PMID: 18006467 DOI: 10.1093/cvr/cvm025]
186 **Lu G**, Haider HK, Jiang S, Ashraf M. Sca-1+ stem cell survival and engraftment in the infarcted heart: dual role for preconditioning-induced connexin-43. *Circulation* 2009; **119**: 2587-2596 [PMID: 19414636 DOI: 10.1161/CIRCULATIONAHA.108.827691]
187 **Weber-Nordt RM**, Henschler R, Schott E, Wehinger J, Behringer D, Mertelsmann R, Finke J. Interleukin-10 increases Bcl-2 expression and survival in primary human CD34+ hematopoietic progenitor cells. *Blood* 1996; **88**: 2549-2558 [PMID: 8839847]
188 **Polchert D**, Sobinsky J, Douglas G, Kidd M, Moadsiri A, Reina E, Genrich K, Mehrotra S, Setty S, Smith B, Bartholomew A. IFN-gamma activation of mesenchymal stem cells for treatment and prevention of graft versus host disease. *Eur J Immunol* 2008; **38**: 1745-1755 [PMID: 18493986 DOI: 10.1002/eji.200738129]
189 **Ren G**, Zhang L, Zhao X, Xu G, Zhang Y, Roberts AI, Zhao RC, Shi Y. Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. *Cell Stem Cell* 2008; **2**: 141-150 [PMID: 18371435 DOI: 10.1016/j.stem.2007.11.014]
190 **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 [PMID: 17507101 DOI: 10.1016/j.imlet.2007.04.001]
191 **Dzau VJ**, Gnecchi M, Pachori AS. Enhancing stem cell therapy through genetic modification. *J Am Coll Cardiol* 2005; **46**: 1351-1353 [PMID: 16198854 DOI: 10.1016/j.jacc.2005.07.023]
192 **Matsumoto R**, Omura T, Yoshiyama M, Hayashi T, Inamoto S, Koh KR, Ohta K, Izumi Y, Nakamura Y, Akioka K, Kitaura Y, Takeuchi K, Yoshikawa J. Vascular endothelial growth factor-expressing mesenchymal stem cell transplantation for the treatment of acute myocardial infarction. *Arterioscler Thromb Vasc Biol* 2005; **25**: 1168-1173 [PMID: 15831811 DOI: 10.1161/01.ATV.0000165696.25680.ce]
193 **Yau TM**, Kim C, Ng D, Li G, Zhang Y, Weisel RD, Li RK. Increasing transplanted cell survival with cell-based angiogenic gene therapy. *Ann Thorac Surg* 2005; **80**: 1779-1786 [PMID: 16242455 DOI: 10.1016/j.athoracsur.2005.04.079]
194 **Kanemitsu N**, Tambara K, Premaratne GU, Kimura Y, Tomita S, Kawamura T, Hasegawa K, Tabata Y, Komeda M. Insulin-like growth factor-1 enhances the efficacy of myoblast transplantation with its multiple functions in the chronic myocardial infarction rat model. *J Heart Lung Transplant* 2006; **25**: 1253-1262 [PMID: 17045939 DOI: 10.1016/j.healun.2006.05.012]
195 **Kofidis T**, de Bruin JL, Yamane T, Balsam LB, Lebl DR, Swijnenburg RJ, Tanaka M, Weissman IL, Robbins RC. Insulin-like

growth factor promotes engraftment, differentiation, and functional improvement after transfer of embryonic stem cells for myocardial restoration. *Stem Cells* 2004; **22**: 1239-1245 [PMID: 15579642 DOI: 10.1634/stemcells.2004-0127]

196 **Liu TB**, Fedak PW, Weisel RD, Yasuda T, Kiani G, Mickle DA, Jia ZQ, Li RK. Enhanced IGF-1 expression improves smooth muscle cell engraftment after cell transplantation. *Am J Physiol Heart Circ Physiol* 2004; **287**: H2840-H2849 [PMID: 15331370 DOI: 10.1152/ajpheart.00439.2004]

197 **Haider HKh**, Jiang S, Idris NM, Ashraf M. IGF-1-overexpressing mesenchymal stem cells accelerate bone marrow stem cell mobilization via paracrine activation of SDF-1alpha/CXCR4 signaling to promote myocardial repair. *Circ Res* 2008; **103**: 1300-1308 [PMID: 18948617 DOI: 10.1161/CIRCRESAHA.108.186742]

198 **Duan HF**, Wu CT, Wu DL, Lu Y, Liu HJ, Ha XQ, Zhang QW, Wang H, Jia XX, Wang LS. Treatment of myocardial ischemia with bone marrow-derived mesenchymal stem cells overexpressing hepatocyte growth factor. *Mol Ther* 2003; **8**: 467-474 [PMID: 12946320]

199 **Hattan N**, Warltier D, Gu W, Kolz C, Chilian WM, Weihrauch D. Autologous vascular smooth muscle cell-based myocardial gene therapy to induce coronary collateral growth. *Am J Physiol Heart Circ Physiol* 2004; **287**: H488-H493 [PMID: 15277192 DOI: 10.1152/ajpheart.00145.2004]

200 **Miyagawa S**, Sawa Y, Taketani S, Kawaguchi N, Nakamura T, Matsuura N, Matsuda H. Myocardial regeneration therapy for heart failure: hepatocyte growth factor enhances the effect of cellular cardiomyoplasty. *Circulation* 2002; **105**: 2556-2561 [PMID: 12034665]

201 **Murry CE**, Kay MA, Bartosek T, Hauschka SD, Schwartz SM. Muscle differentiation during repair of myocardial necrosis in rats via gene transfer with MyoD. *J Clin Invest* 1996; **98**: 2209-2217 [PMID: 8941636 DOI: 10.1172/JCI119030]

202 **Payne TR**, Oshima H, Okada M, Momoi N, Tobita K, Keller BB, Peng H, Huard J. A relationship between vascular endothelial growth factor, angiogenesis, and cardiac repair after muscle stem cell transplantation into ischemic hearts. *J Am Coll Cardiol* 2007; **50**: 1677-1684 [PMID: 17950150 DOI: 10.1016/j.jacc.2007.04.100]

203 **Yau TM**, Fung K, Weisel RD, Fujii T, Mickle DA, Li RK. Enhanced myocardial angiogenesis by gene transfer with transplanted cells. *Circulation* 2001; **104**: I218-I222 [PMID: 11568059]

204 **Yau TM**, Li G, Weisel RD, Reheman A, Jia ZQ, Mickle DA, Li RK. Vascular endothelial growth factor transgene expression in cell-transplanted hearts. *J Thorac Cardiovasc Surg* 2004; **127**: 1180-1187 [PMID: 15052220 DOI: 10.1016/j.jtcvs.2003.09.052]

205 **Zhang M**, Mal N, Kiedrowski M, Chacko M, Askari AT, Popovic ZB, Koc ON, Penn MS. SDF-1 expression by mesenchymal stem cells results in trophic support of cardiac myocytes after myocardial infarction. *FASEB J* 2007; **21**: 3197-3207 [PMID: 17496162 DOI: 10.1096/fj.06-6558com]

206 **Gerber HP**, Dixit V, Ferrara N. Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. *J Biol Chem* 1998; **273**: 13313-13316 [PMID: 9582377]

207 **Das H**, George JC, Joseph M, Das M, Abdulhameed N, Blitz A, Khan M, Sakthivel R, Mao HQ, Hoit BD, Kuppusamy P, Pompili VJ. Stem cell therapy with overexpressed VEGF and PDGF genes improves cardiac function in a rat infarct model. *PLoS One* 2009; **4**: e7325 [PMID: 19809493 DOI: 10.1371/journal.pone.0007325]

208 **Markel TA**, Wang Y, Herrmann JL, Crisostomo PR, Wang M, Novotny NM, Herring CM, Tan J, Lahm T, Meldrum DR. VEGF is critical for stem cell-mediated cardioprotection and a crucial paracrine factor for defining the age threshold in adult and neonatal stem cell function. *Am J Physiol Heart Circ Physiol* 2008; **295**: H2308-H2314 [PMID: 18849336 DOI: 10.1152/ajpheart.00565.2008]

209 **Haider HK**, Elmadbouh I, Jean-Baptiste M, Ashraf M. Nonviral vector gene modification of stem cells for myocardial repair. *Mol Med* 2008; **14**: 79-86 [PMID: 17985003 DOI: 10.2119/2007-00092.Haider]

210 **Liu LX**, Lu H, Luo Y, Date T, Belanger AJ, Vincent KA, Akita GY, Goldberg M, Cheng SH, Gregory RJ, Jiang C. Stabilization of vascular endothelial growth factor mRNA by hypoxia-inducible factor 1. *Biochem Biophys Res Commun* 2002; **291**: 908-914 [PMID: 11866451 DOI: 10.1006/bbrc.2002.6551]

211 **Zou D**, Zhang Z, He J, Zhang K, Ye D, Han W, Zhou J, Wang Y, Li Q, Liu X, Zhang X, Wang S, Hu J, Zhu C, Zhang W, zhou Y, Fu H, Huang Y, Jiang X. Blood vessel formation in the tissue-engineered bone with the constitutively active form of HIF-1α mediated BMSCs. *Biomaterials* 2012; **33**: 2097-2108 [PMID: 22172336 DOI: 10.1016/j.biomaterials.2011.11.053]

212 **Razban V**, Lotfi AS, Soleimani M, Ahmadi H, Massumi M, Khajeh S, Ghaedi M, Arjmand S, Najavand S, Khoshdel A. HIF-1α Overexpression Induces Angiogenesis in Mesenchymal Stem Cells. *Biores Open Access* 2012; **1**: 174-183 [PMID: 23514846 DOI: 10.1089/biores.2012.9905]

213 **Phillips MI**, Tang YL. Genetic modification of stem cells for transplantation. *Adv Drug Deliv Rev* 2008; **60**: 160-172 [PMID: 18031863 DOI: 10.1016/j.addr.2007.08.035]

214 **Chachques JC**, Trainini JC, Lago N, Cortes-Morichetti M, Schussler O, Carpentier A. Myocardial Assistance by Grafting a New Bioartificial Upgraded Myocardium (MAGNUM trial): clinical feasibility study. *Ann Thorac Surg* 2008; **85**: 901-908 [PMID: 18291168 DOI: 10.1016/j.athoracsur.2007.10.052]

215 **Song H**, Kwon K, Lim S, Kang SM, Ko YG, Xu Z, Chung JH, Kim BS, Lee H, Joung B, Park S, Choi D, Jang Y, Chung NS, Yoo KJ, Hwang KC. Transfection of mesenchymal stem cells with the FGF-2 gene improves their survival under hypoxic conditions. *Mol Cells* 2005; **19**: 402-407 [PMID: 15995358]

216 **Gnecchi M**, He H, Liang OD, Melo LG, Morello F, Mu H, Noiseux N, Zhang L, Pratt RE, Ingwall JS, Dzau VJ. Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. *Nat Med* 2005; **11**: 367-368 [PMID: 15812508 DOI: 10.1038/nm0405-367]

217 **Gnecchi M**, He H, Melo LG, Noiseaux N, Morello F, de Boer RA, Zhang L, Pratt RE, Dzau VJ, Ingwall JS. Early beneficial effects of bone marrow-derived mesenchymal stem cells overexpressing Akt on cardiac metabolism after myocardial infarction. *Stem Cells* 2009; **27**: 971-979 [PMID: 19353525 DOI: 10.1002/stem.12]

218 **Shujia J**, Haider HK, Idris NM, Lu G, Ashraf M. Stable therapeutic effects of mesenchymal stem cell-based multiple gene delivery for cardiac repair. *Cardiovasc Res* 2008; **77**: 525-533 [PMID: 18032392 DOI: 10.1093/cvr/cvm077]

219 **Melo LG**, Agrawal R, Zhang L, Rezvani M, Mangi AA, Ehsan A, Griese DP, Dell'Acqua G, Mann MJ, Oyama J, Yet SF, Layne MD, Perrella MA, Dzau VJ. Gene therapy strategy for long-term myocardial protection using adeno-associated virus-mediated delivery of heme oxygenase gene. *Circulation* 2002; **105**: 602-607 [PMID: 11827926]

220 **Vulapalli SR**, Chen Z, Chua BH, Wang T, Liang CS. Cardioselective overexpression of HO-1 prevents I/R-induced cardiac dysfunction and apoptosis. *Am J Physiol Heart Circ Physiol* 2002; **283**: H688-H694 [PMID: 12124217 DOI: 10.1152/ajpheart.00133.2002]

221 **Tang YL**, Tang Y, Zhang YC, Qian K, Shen L, Phillips MI. Improved graft mesenchymal stem cell survival in ischemic heart with a hypoxia-regulated heme oxygenase-1 vector. *J Am Coll Cardiol* 2005; **46**: 1339-1350 [PMID: 16198853 DOI: 10.1016/j.jacc.2005.05.079]

222 **Snoeckx LH**, Cornelussen RN, Van Nieuwenhoven FA, Reneman RS, Van Der Vusse GJ. Heat shock proteins and cardiovascular pathophysiology. *Physiol Rev* 2001; **81**: 1461-1497 [PMID: 11581494]

223 **Hutter MM**, Sievers RE, Barbosa V, Wolfe CL. Heat-shock protein induction in rat hearts. A direct correlation between the amount of heat-shock protein induced and the degree of myocardial protection. *Circulation* 1994; **89**: 355-360 [PMID: 8281669]

224 **Jayakumar J**, Suzuki K, Khan M, Smolenski RT, Farrell A, Latif N, Raisky O, Abunasra H, Sammut IA, Murtuza B, Amrani M, Yacoub MH. Gene therapy for myocardial protection: transfection of donor hearts with heat shock protein 70 gene protects cardiac function

against ischemia-reperfusion injury. *Circulation* 2000; **102**: III302-III306 [PMID: 11082405]

225 **Okubo S**, Wildner O, Shah MR, Chelliah JC, Hess ML, Kukreja RC. Gene transfer of heat-shock protein 70 reduces infarct size in vivo after ischemia/reperfusion in the rabbit heart. *Circulation* 2001; **103**: 877-881 [PMID: 11171798]

226 **Kabakov AE**, Budagova KR, Bryantsev AL, Latchman DS. Heat shock protein 70 or heat shock protein 27 overexpressed in human endothelial cells during posthypoxic reoxygenation can protect from delayed apoptosis. *Cell Stress Chaperones* 2003; **8**: 335-347 [PMID: 15115286]

227 **Kim I**, Kim HG, Moon SO, Chae SW, So JN, Koh KN, Ahn BC, Koh GY. Angiopoietin-1 induces endothelial cell sprouting through the activation of focal adhesion kinase and plasmin secretion. *Circ Res* 2000; **86**: 952-959 [PMID: 10807867]

228 **DeBusk LM**, Hallahan DE, Lin PC. Akt is a major angiogenic mediator downstream of the Ang1/Tie2 signaling pathway. *Exp Cell Res* 2004; **298**: 167-177 [PMID: 15242771 DOI: 10.1016/j.yexcr.2004.04.013]

229 **Asahara T**, Chen D, Takahashi T, Fujikawa K, Kearney M, Magner M, Yancopoulos GD, Isner JM. Tie2 receptor ligands, angiopoietin-1 and angiopoietin-2, modulate VEGF-induced postnatal neovascularization. *Circ Res* 1998; **83**: 233-240 [PMID: 9710115]

230 **Jiang S**, Haider HKh, Idris NM, Salim A, Ashraf M. Supportive interaction between cell survival signaling and angiocompetent factors enhances donor cell survival and promotes angiomyogenesis for cardiac repair. *Circ Res* 2006; **99**: 776-784 [PMID: 16960098 DOI: 10.1161/01.RES.0000244687.97719.4f]

231 **Song H**, Chang W, Lim S, Seo HS, Shim CY, Park S, Yoo KJ, Kim BS, Min BH, Lee H, Jang Y, Chung N, Hwang KC. Tissue transglutaminase is essential for integrin-mediated survival of bone marrow-derived mesenchymal stem cells. *Stem Cells* 2007; **25**: 1431-1438 [PMID: 17347495 DOI: 10.1634/stemcells.2006-0467]

232 **Persad S**, Attwell S, Gray V, Mawji N, Deng JT, Leung D, Yan J, Sanghera J, Walsh MP, Dedhar S. Regulation of protein kinase B/Akt-serine 473 phosphorylation by integrin-linked kinase: critical roles for kinase activity and amino acids arginine 211 and serine 343. *J Biol Chem* 2001; **276**: 27462-27469 [PMID: 11313365 DOI: 10.1074/jbc.M102940200]

233 **Akimov SS**, Krylov D, Fleischman LF, Belkin AM. Tissue transglutaminase is an integrin-binding adhesion coreceptor for fibronectin. *J Cell Biol* 2000; **148**: 825-838 [PMID: 10684262]

234 **Jiang Y**, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, Reyes M, Lenvik T, Lund T, Blackstad M, Du J, Aldrich S, Lisberg A, Low WC, Largaespada DA, Verfaillie CM. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 2002; **418**: 41-49 [PMID: 12077603 DOI: 10.1038/nature00870]

235 **Schwartz MA**, Schaller MD, Ginsberg MH. Integrins: emerging paradigms of signal transduction. *Annu Rev Cell Dev Biol* 1995; **11**: 549-599 [PMID: 8689569 DOI: 10.1146/annurev.cb.11.1-10195.003001]

236 **Clark EA**, Brugge JS. Integrins and signal transduction pathways: the road taken. *Science* 1995; **268**: 233-239 [PMID: 7716514]

237 **White DE**, Cardiff RD, Dedhar S, Muller WJ. Mammary epithelial-specific expression of the integrin-linked kinase (ILK) results in the induction of mammary gland hyperplasias and tumors in transgenic mice. *Oncogene* 2001; **20**: 7064-7072 [PMID: 11704830 DOI: 10.1038/sj.onc.1204910]

238 **Cho HJ**, Youn SW, Cheon SI, Kim TY, Hur J, Zhang SY, Lee SP, Park KW, Lee MM, Choi YS, Park YB, Kim HS. Regulation of endothelial cell and endothelial progenitor cell survival and vasculogenesis by integrin-linked kinase. *Arterioscler Thromb Vasc Biol* 2005; **25**: 1154-1160 [PMID: 15802621 DOI: 10.1161/01.ATV.0000164312.20008.93]

239 **Song H**, Song BW, Cha MJ, Choi IG, Hwang KC. Modification of mesenchymal stem cells for cardiac regeneration. *Expert Opin Biol Ther* 2010; **10**: 309-319 [PMID: 20132054 DOI: 10.1517/14712590903455997]

240 **Conboy IM**, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature* 2005; **433**: 760-764 [PMID: 15716955 DOI: 10.1038/nature03260]

241 **Sharpless NE**, DePinho RA. How stem cells age and why this makes us grow old. *Nat Rev Mol Cell Biol* 2007; **8**: 703-713 [PMID: 17717515 DOI: 10.1038/nrm2241]

242 **Chimenti C**, Kajstura J, Torella D, Urbanek K, Heleniak H, Colussi C, Di Meglio F, Nadal-Ginard B, Frustaci A, Leri A, Maseri A, Anversa P. Senescence and death of primitive cells and myocytes lead to premature cardiac aging and heart failure. *Circ Res* 2003; **93**: 604-613 [PMID: 12958145 DOI: 10.1161/01.RES.0000093985.76901.AF]

243 **Mohyeldin A**, Garzón-Muvdi T, Quiñones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. *Cell Stem Cell* 2010; **7**: 150-161 [PMID: 20682444 DOI: 10.1016/j.stem.2010.07.007]

244 **Sanada F**, Kim J, Czarna A, Chan NY, Signore S, Ogórek B, Isobe K, Wybieralska E, Borghetti G, Pesapane A, Sorrentino A, Mangano E, Cappetta D, Mangiaracina C, Ricciardi M, Cimini M, Ifedigbo E, Perrella MA, Goichberg P, Choi AM, Kajstura J, Hosoda T, Rota M, Anversa P, Leri A. c-Kit-positive cardiac stem cells nested in hypoxic niches are activated by stem cell factor reversing the aging myopathy. *Circ Res* 2014; **114**: 41-55 [PMID: 24170267 DOI: 10.1161/CIRCRESAHA.114.302500]

245 **Hekimi S**, Guarente L. Genetics and the specificity of the aging process. *Science* 2003; **299**: 1351-1354 [PMID: 12610295 DOI: 10.1126/science.1082358]

246 **Kajstura J**, Gurusamy N, Ogórek B, Goichberg P, Clavo-Rondon C, Hosoda T, D'Amario D, Bardelli S, Beltrami AP, Cesselli D, Bussani R, del Monte F, Quaini F, Rota M, Beltrami CA, Buchholz BA, Leri A, Anversa P. Myocyte turnover in the aging human heart. *Circ Res* 2010; **107**: 1374-1386 [PMID: 21088285 DOI: 10.1161/CIRCRESAHA.110.231498]

247 **Chidgey A**, Dudakov J, Seach N, Boyd R. Impact of niche aging on thymic regeneration and immune reconstitution. *Semin Immunol* 2007; **19**: 331-340 [PMID: 18024073 DOI: 10.1016/j.smim.2007.10.006]

248 **Fan M**, Chen W, Liu W, Du GQ, Jiang SL, Tian WC, Sun L, Li RK, Tian H. The effect of age on the efficacy of human mesenchymal stem cell transplantation after a myocardial infarction. *Rejuvenation Res* 2010; **13**: 429-438 [PMID: 20583954 DOI: 10.1089/rej.2009.0986]

249 **Kan CD**, Li SH, Weisel RD, Zhang S, Li RK. Recipient age determines the cardiac functional improvement achieved by skeletal myoblast transplantation. *J Am Coll Cardiol* 2007; **50**: 1086-1092 [PMID: 17825720 DOI: 10.1016/j.jacc.2007.06.009]

250 **Zhang H**, Fazel S, Tian H, Mickle DA, Weisel RD, Fujii T, Li RK. Increasing donor age adversely impacts beneficial effects of bone marrow but not smooth muscle myocardial cell therapy. *Am J Physiol Heart Circ Physiol* 2005; **289**: H2089-H2096 [PMID: 16219813 DOI: 10.1152/ajpheart.00019.2005]

251 **Zhuo Y**, Li SH, Chen MS, Wu J, Kinkaid HY, Fazel S, Weisel RD, Li RK. Aging impairs the angiogenic response to ischemic injury and the activity of implanted cells: combined consequences for cell therapy in older recipients. *J Thorac Cardiovasc Surg* 2010; **139**: 1286-1294, 1294.e1-e2 [PMID: 19931095 DOI: 10.1016/j.jtcvs.2009.08.052]

252 **Dimmeler S**, Leri A. Aging and disease as modifiers of efficacy of cell therapy. *Circ Res* 2008; **102**: 1319-1330 [PMID: 18535269 DOI: 10.1161/CIRCRESAHA.108.175943]

253 **Cesselli D**, Beltrami AP, D'Aurizio F, Marcon P, Bergamin N, Toffoletto B, Pandolfi M, Puppato E, Marino L, Signore S, Livi U, Verardo R, Piazza S, Marchionni L, Fiorini C, Schneider C, Hosoda T, Rota M, Kajstura J, Anversa P, Beltrami CA, Leri A. Effects of age and heart failure on human cardiac stem cell function. *Am J Pathol* 2011; **179**: 349-366 [PMID: 21703415 DOI: 10.1016/j.ajpath.2011.03.036]

254 **Li SH**, Sun Z, Brunt KR, Shi X, Chen MS, Weisel RD, Li RK. Reconstitution of aged bone marrow with young cells repopulates cardiac-resident bone marrow-derived progenitor cells and prevents

cardiac dysfunction after a myocardial infarction. *Eur Heart J* 2013; **34**: 1157-1167 [PMID: 22507976 DOI: 10.1093/eurheartj/ehs072]

255 **Sahin E**, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. *Nature* 2010; **464**: 520-528 [PMID: 20336134 DOI: 10.1038/nature08982]

256 **Edwards MG**, Anderson RM, Yuan M, Kendziorski CM, Weindruch R, Prolla TA. Gene expression profiling of aging reveals activation of a p53-mediated transcriptional program. *BMC Genomics* 2007; **8**: 80 [PMID: 17381838 DOI: 10.1186/1471-2164-8-80]

257 **Ludke A**, Li RK, Weisel RD. The rejuvenation of aged stem cells for cardiac repair. *Can J Cardiol* 2014; **30**: 1299-1306 [PMID: 25092405 DOI: 10.1016/j.cjca.2014.03.021]

258 **Mohsin S**, Khan M, Nguyen J, Alkatib M, Siddiqi S, Hariharan N, Wallach K, Monsanto M, Gude N, Dembitsky W, Sussman MA. Rejuvenation of human cardiac progenitor cells with Pim-1 kinase. *Circ Res* 2013; **113**: 1169-1179 [PMID: 24044948 DOI: 10.1161/CIRCRESAHA.113.302302]

259 **Mohsin S**, Khan M, Toko H, Bailey B, Cottage CT, Wallach K, Nag D, Lee A, Siddiqi S, Lan F, Fischer KM, Gude N, Quijada P, Avitabile D, Truffa S, Collins B, Dembitsky W, Wu JC, Sussman MA. Human cardiac progenitor cells engineered with Pim-I kinase enhance myocardial repair. *J Am Coll Cardiol* 2012; **60**: 1278-1287 [PMID: 22841153 DOI: 10.1016/j.jacc.2012.04.047]

260 **Bachmann M**, Möröy T. The serine/threonine kinase Pim-1. *Int J Biochem Cell Biol* 2005; **37**: 726-730 [PMID: 15694833 DOI: 10.1016/j.biocel.2004.11.005]

261 **Muraski JA**, Rota M, Misao Y, Fransioli J, Cottage C, Gude N, Esposito G, Delucchi F, Arcarese M, Alvarez R, Siddiqi S, Emmanuel GN, Wu W, Fischer K, Martindale JJ, Glembotski CC, Leri A, Kajstura J, Magnuson N, Berns A, Beretta RM, Houser SR, Schaefer EM, Anversa P, Sussman MA. Pim-1 regulates cardiomyocyte survival downstream of Akt. *Nat Med* 2007; **13**: 1467-1475 [PMID: 18037896 DOI: 10.1038/nm1671]

262 **Borillo GA**, Mason M, Quijada P, Völkers M, Cottage C, McGregor M, Din S, Fischer K, Gude N, Avitabile D, Barlow S, Alvarez R, Truffa S, Whittaker R, Glassy MS, Gustafsson AB, Miyamoto S, Glembotski CC, Gottlieb RA, Brown JH, Sussman MA. Pim-1 kinase protects mitochondrial integrity in cardiomyocytes. *Circ Res* 2010; **106**: 1265-1274 [PMID: 20203306 DOI: 10.1161/CIRCRESAHA.109.212035]

263 **Brunt KR**, Zhang Y, Mihic A, Li M, Li SH, Xue P, Zhang W, Basmaji S, Tsang K, Weisel RD, Yau TM, Li RK. Role of WNT/β-catenin signaling in rejuvenating myogenic differentiation of aged mesenchymal stem cells from cardiac patients. *Am J Pathol* 2012; **181**: 2067-2078 [PMID: 23026201 DOI: 10.1016/j.ajpath.2012.08.021]

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