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**Review**

# Stem Cell Therapy in Heart Diseases – Cell Types, Mechanisms and Improvement Strategies

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**Key Words**
Mesenchymal stem cells • Cardiovascular diseases • Cell replacement • Cardiac regeneration • Stem cell modification

**Abstract**
A large number of clinical trials have shown stem cell therapy to be a promising therapeutic approach for the treatment of cardiovascular diseases. Since the first transplantation into human patients, several stem cell types have been applied in this field, including bone marrow derived stem cells, cardiac progenitors as well as embryonic stem cells and their derivatives. However, results obtained from clinical studies are inconsistent and stem cell-based improvement of heart performance and cardiac remodeling was found to be quite limited. In order to optimize stem cell efficiency, it is crucial to elucidate the underlying mechanisms mediating the beneficial effects of stem cell transplantation. Based on these mechanisms, researchers have developed different improvement strategies to boost the potency of stem cell repair and to generate the "next generation" of stem cell therapeutics. Moreover, since cardiovascular diseases are complex disorders including several disease patterns and pathologic mechanisms it may be difficult to provide a uniform therapeutic intervention for all subgroups of patients. Therefore, future strategies should aim at more personalized SC therapies in which individual disease parameters influence the selection of optimal cell type, dosage and delivery approach.



## Introduction

Accounting for more than 3.9 million deaths a year, cardiovascular diseases (CVDs) remain the most common cause of death in Europe [1]. Despite significant advancements in pharmacological and interventional treatment options, heart diseases represent an increasingly common disorder that carries a poor long-term prognosis [2, 3]. Although current approaches improve symptoms and decelerate adverse cardiac remodeling, they

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fail to address the underlying problem of an irreversible loss of cardiac tissue.

Innovative stem cell (SC) therapies have the potential to fundamentally alter the conventional treatment of CVDs by stimulating the regeneration of injured myocardium. In 2001, first encouraging pre-clinical study results, reporting the repair of infarcted cardiac tissue and the enhancement of ventricular function, led to the rapid translation of SC therapies within the same year [4–6]. Over the last two decades, plenty of pre-clinical and early clinical trials have demonstrated the safety and feasibility of numerous SC types. However, many open questions remain to be resolved and so far, no cell therapy has been unambiguously shown to be effective for the treatment of heart diseases. As a consequence, strategies have been developed in order to improve the potency of applied SCs.

**Table 1.** Advantages and disadvantages of stem cell (SC) types used for cardiac regeneration

| Cell type | Advantages | Disadvantages |
|---|---|---|
| Skeletal myoblasts | •Easy access from autologous muscle biopsies<br>•Low ethical concerns<br>•Rapid in vitro expansion<br>•Resistant to ischemic conditions<br>•Low risk of tumorigenicity | •No transdifferentiation into functional cardiomyocytes<br>•Hazard of ventricular arrhythmias due to the lack of electromechanical coupling |
| HSCs/EPCs | •Easy access from autologous bone marrow or blood<br>•Low ethical concerns<br>•Proof of safety in clinical triaels<br>•Straightforward and standardized isolation procedures of HSCs<br>•Promotion of vasculogenesis<br>•Therapeutic secretome<br>•Low risk of tumorigenicity | •Low cell quantity<br>•Limited differentiation potential<br>•Undefined phenotype of EPCs<br>•Heterogeneous cell population<br>•Potential encouragement of inflammatory processes<br>•Inconsistent results regarding therapeutic effects |
| MSCs | •Easy access from several tissues<br>•Low ethical concerns<br>•Transplantation of autologous and allogenic cells due to low immunogenicity<br>•Proof of safety in clinical trials<br>•Rapid in vitro expansion<br>•Therapeutic secretome<br>•Beneficial immunomodulative properties<br>•Low risk of tumorigenicity | •Limited cell quantity<br>•Limited differentiation potential<br>•Undefined in situ phenotype<br>•Heterogeneous cell population<br>•Inconsistent results regarding therapeutic effects |
| CSCs | •Suitable for autologous transplantation<br>•Proof of safety in clinical trials<br>•Endogenous cardiac localization<br>•Low risk of tumorigenicity | •Limited cell quantity<br>•Access from invasive myocardial biopsies<br>•Insufficient cell characterization<br>•Contradictory results concerning cardiovascular differentiation potential |
| ESCs | •Pluripotent differentiation potential<br>•Unlimited quantity<br>•Easy generation of cell lines<br>•Allows generation of off-the-shelf cell products<br>•ESC-derived cardiomyocytes integrate electromagnetically into the host myocardium | •Difficult to generate pure and mature cardiomyocytes in large quantities<br>•Ethical concerns<br>•Risk of tumorigenicity<br>•Genomic instability<br>•Lack of availability<br>•Risk of immunologic rejection and immunosuppression required |
| iPSCs | •Pluripotent differentiation potential<br>•Low ethical concerns<br>•Suitable for autologous transplantation<br>•Easily accessible source tissue<br>•Unlimited quantity<br>•iPSC-derived cardiomyocytes integrate electromagnetically into the host myocardium | •Difficult to generate pure and mature cardiomyocytes in large quantities<br>•Risk of tumorigenicity<br>•Risk of immunologic rejection due to genomic instability<br>•Low induction efficiency<br>•Lack of standardized generation procedure |

In this review, we provide an historical overview about the different cell types that have been used in regenerative medicine to treat CVDs. Moreover, we highlight the potential mechanisms involved in SC-based cardiac repair. Since the efficiency of SC therapy is quite limited we further discuss promising improvement strategies to increase the outcome of SC transplantation.

## SC types considered for the treatment of heart disease

It has now been almost two decades since first efforts were made in cardiac SC therapy. Nowadays, several types of SCs at different developmental stages have been evaluated with respect to their cardiovascular regeneration potential (Table 1).

*Skeletal myoblasts*

In the field of cardiac regeneration, skeletal myoblasts were the first cell type to be tested both in pre-clinical and clinical trials. Myoblasts are derived from satellite cells, a progenitor cell population located under the basal lamina of skeletal muscular fibers [7]. Following muscle injury, satellite cells become mobilized, proliferate, differentiate and finally fuse into new muscle fibers [8–10]. The use of skeletal myoblasts for cardiac regeneration has been motivated due to their easy accessibility from autologous muscle biopsies, rapid *in vitro* expansion, resistance to ischemic conditions, myogenic capacity and low risk of tumorigenicity

[11]. A large number of research groups extensively assessed the performance of these cells for the treatment of ischemic and non-ischemic cardiomyopathies in various small and large animal models, including rodent, sheep, dog and pig [12–28]. These studies demonstrated that skeletal myoblasts are capable to differentiate into myotubes, decreased myocardial fibrosis, attenuated ventricular remodeling and improved myocardial performance. These encouraging pre-clinical results were rapidly translated into clinical trials. Thereby, several small non-randomized studies have shown an improvement in the left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class, as well as an enhanced regional wall motion after the transplantation of skeletal myoblasts [29–38]. However, in most of these studies a high incidence of ventricular arrhythmias has been detected in cell treated patients [29, 30, 32, 33, 35, 38, 39]. Subsequent investigations imply that these abnormal heart rhythms most likely result from the lack of electromechanical coupling between resident cardiomyocytes and skeletal myoblast-derived myotubes due to the absence of gap junctions [40–42]. Despite these safety concerns, randomized controlled studies have been initiated which, however, failed to show consistent beneficial effects [43–46]. In the largest randomized, placebo-controlled, double-blinded MAGIC trial (NCT00102128), the intramyocardial injection of skeletal myoblasts in patients with severe ischemic heart disease did neither improve regional nor global left ventricular (LV) function after a 6 month [43] and a 6-year follow up period [47], respectively. In addition, an increased number of early postoperative arrhythmic events was recorded following cell transplantation, although a prophylactic amiodarone therapy had been initiated [43]. Overall, based on the inconsistent therapeutic effect and the risk of arrhythmias, the focus on skeletal myoblasts for the treatment of heart diseases has diminished.

*Bone marrow (BM)-derived SCs*

BM represents a highly heterogeneous tissue, harboring numerous mature and immature cell populations. The discovery that an injury causes the recruitment of BM-derived cells to the damaged area where they contribute to tissue regeneration has introduced the field of BM-derived SC therapy [48–52]. In 2001, a pioneering study demonstrated that intramyocardially injected murine BM-derived cells improved cardiac function in a murine model of myocardial infarction (MI) [4]. Likewise, early clinical trials reported beneficial effects of BM-derived cells for the treatment of heart diseases in the same year. Thereby, the rapid clinical translation of these cells was encouraged by the easy access of self-renewing BM with low ethical concerns, the relatively large numbers of autologous cells and broad clinical experiments with BM transplantation [53].

*BM-derived mononuclear cells (MNCs)*

BM-derived MNCs are a heterogeneous population which includes a small number of hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs) and mesenchymal stromal/stem cells (MSCs), whereas the major proportion comprises cells of the hematopoietic lineage at various maturation stages [54]. In 2001, the first patient was treated by intracoronary injection of autologous MNCs isolated from BM specimens via density gradient centrifugation 6 days after MI [5]. 1 year later, results of the first controlled study showed a significantly decreased infarct region as well as an improved regional contractility and perfusion 3 month after BM-derived MNC transplantation [55]. Since patients without cell application did not display changes in these parameters, the authors postulated that beneficial effects were associated with cell-based myocardial regeneration and neovascularization [55]. To date, the regenerative capacity of BM-derived MNCs is controversial. On the one hand, a wealth of randomized, controlled clinical trials demonstrated a significantly enhanced cardiac performance after intracoronary and intramyocardial transplantation of MNCs [56–64] and on the other hand many studies failed to detect therapeutic cell effects [65–76]. Likewise, results of meta-analyses are inconsistent, either proving therapeutic effects of BM-derived MNCs by demonstrating a slight enhancement of heart functions between 2 - 5%

and an decelerated cardiac remodeling [77–81] or refuting the beneficial impact of these cell population [82].

*BM-derived HSCs and EPCs*

Adult HSCs are multipotent SCs which are mainly localized in BM and give rise to all types of blood cells from the lymphoid and myeloid lineages [83]. EPCs represent a pro-vasculogenic subpopulation of HSCs in the BM, sharing a number of cell surface markers like CD34 and CD133 [84]. In 1997, EPCs were first described by Asahara *et al.* [85], however, a proper and unambiguous molecular characterization of these cells is still lacking [86, 87]. In 2001, our group initiated the first phase I clinical trial injecting autologous BM-derived $CD133^+$ SCs into the infarcted border zone during coronary artery bypass grafting (CABG) in 6 patients [6]. 3 months after cell transplantation, 4 patients exhibited an enhanced global LVEF and 5 patients showed an improved infarcted tissue perfusion. Moreover, it was assumed that intramyocardial transplantation of BM-derived $CD133^+$ cells is safe and may induce angiogenesis. These encouraging results were confirmed in the following phase II clinical study demonstrating improved LVEF and myocardial perfusion 6 month after SC transplantation compared to the standard therapy group [88]. To date, several phase I and II clinical trials reported the safety, feasibility and beneficial effects of intramyocardially [89, 90] and intracoronary [91–95] injected BM-derived $CD133^+$ cells for the treatment of cardiac diseases. However, long term follow-up studies failed to show an improved cardiac function in SC treated patients after several years [96, 97]. In the first reported phase II/III clinical trial (CARDIO 133, NCT00462774) the scar size and regional perfusion were significantly improved following intramyocardial transplantation of $CD133^+$ SCs, nevertheless, no effects on global function and clinical symptoms were detected [98]. Similar results were obtained in our randomized, placebo-controlled, double-blinded phase III clinical trial (PERFECT, NCT00950274) where a reduction in scar size and non-viable tissue as well as an improvement of segmental myocardial perfusion was observed, while no significant difference in LVEF were detected after $CD133^+$ SC injection [99].

In addition to CD133, CD34 has been identified as a suitable single surface marker for the enrichment of human HSCs and EPCs. Early clinical trials demonstrated the safety, feasibility and potential efficacy of BM-derived $CD34^+$ cells for the treatment of cardiac diseases [100–103]. However, one of the largest randomized, controlled clinical studies failed to detect improved cardiac functions following intracoronary $CD34^+$ SC transplantation [104].

*BM-derived MSCs*

MSCs are a subset of non-hematopoietic SCs that are multipotent and plastic-adherent under culture conditions [105]. Typically, these cells are characterized by their ability to differentiate into osteoblasts, adipocytes and chondrocytes under defined *in vitro* conditions and their expression of specific cell surface markers like CD73, CD105 and CD90, while CD34, CD45, CD14, HLA-DR are lacking [106]. Notably, MSCs are considered to be immune-privileged and exhibit immunosuppressive properties, which enables their application in an allogenic setting [107]. A recent meta-analysis, including 58 pre-clinical studies, indicated an overall reduced infarct size of ~7% as well as an improved heart function of ~11% after MSC transplantation in animal models of acute myocardial infarction (AMI) and chronic ischemic cardiomyopathy (ICM) [108]. In consistence with this, Karantalis *et al.* demonstrated that the intramyocardial injection of MSCs in patients undergoing CABG reduced scar size and improved tissue perfusion as well as regional function predominantly at the site of injection [109]. However, the beneficial effects of MSCs on global cardiac function in a clinical setting remain uncertain. Several randomized controlled clinical trials showed a significantly improved LVEF after MSC transplantation [110–112], whereas others did not observe differences between SC treated and control groups [74, 113–117]. Furthermore, neither a recent meta-analysis of pre-clinical studies [118] nor comparative clinical studies [119, 120] detected significant differences of autologous versus allogeneic MSCs on cardiac function.

*Mobilized stem and progenitor cells*

The migration of SCs is a constant bidirectional process including SC homing and mobilization [121]. At steady state in healthy donors, the concentration of SCs in BM is much higher than in peripheral blood (PB) [122]. However, the observation that an acute MI causes a significant mobilization of circulating stem and progenitor cells indicated that these cells play a critical role for cardiac healing processes [123–126]. To date, certain factors such as granulocyte colony-stimulating factor (G-CSF) are systemically applied to stimulate an increase of stem and progenitor cells in PB [127]. Nevertheless, meta-analyses demonstrated that G-CSF treatment after AMI did not improve cardiac regeneration [128–130]. Clinical trials using G-CSF mobilized stem and progenitor cells have led to inconsistent data. Several studies showed significant therapeutic effects after intramyocardial or intracoronary injection of PB-derived MNCs [131–134] and $CD34^+$ [135–144], whereas others did not detect functional differences between SC-treated and control groups [72, 145, 146]. Nevertheless, recently published data suggested that low circulating stem and progenitor cell counts are associated with minor heart function improvement after MI [99] and contribute to the development and progression of heart failure (HF) [147].

## Adipose-derived stem and progenitor cells

In 2001, Zuk *et al.* demonstrated that adipose tissue represents an abundant source of adult SCs bearing multipotent differentiation potential [148, 149]. These adipose-derived stromal/stem cells (ASCs) exhibit properties similar to BM-derived MSCs including their plastic adherence and their ability to differentiate into osteoblasts, adipocytes and chondrocytes under certain *in vitro* conditions [150]. In addition, cultured ASCs express surface markers in common with BM-derived MSCs like CD73, CD105 and CD90, whereas CD45 is lacking [150]. However, ASCs can be distinguished from BM-derived MSCs by their expression of CD34 in early passages and the absence of CD106 [150]. The ability of these cells to significantly reduce cardiac remodeling and infarct size as well as to improve cardiac function has been demonstrated in various pre-clinical studies [151–164]. In 2012, Duckers and co-workers were the first reporting the feasibility, safety and beneficial effects, including reduced myocardial scar formation and improved perfusion, of intracoronary infused adipose tissue-derived cells in a randomized, placebo-controlled clinical trial [165]. These freshly isolated cells obtained from adipose tissue by enzymatic or non-enzymatic dissociation are also termed stroma vascular fraction (SVF) and comprise a heterogeneous mixture containing ASCs, endothelial (progenitor) cells, blood cells, pericytes and other cell types [166]. Since then, other phase I and II clinical studies confirmed the safety and usability of these cells [167–169]. However, the two largest placebo-controlled clinical trials, including 27 and 31 patients respectively, failed to detect significant changes in LV functions or volumes after the transplantation of adipose-derived cells, although an improvement in maximal oxygen consumption was observed [167, 168]. Nevertheless, the results of larger phase III clinical trials remain to be seen.

## Cardiac stem and progenitor cells

The adult heart has been traditionally considered a post-mitotic organ without significant capacity for self-renewal. However, this point of view has recently changed with the detection that the heart is capable of - albeit quite limited - cardiomyocyte turnover [170, 171]. Beltrami *et al.*, were the first who discovered self-renewing c-$Kit^+$ cells in the adult heart, able to differentiate into cardiomyocytes, endothelial cells and smooth muscle cells and to support the regeneration of injured heart tissue [172–174]. During the past decade, several different populations of cardiac stem cells (CSCs) and cardiac progenitor cells (CPCs), such as cardiosphere-derived cells (CDCs) [175–178], stem cell antigen (Sca)-$1^+$ cells [179–

181], insulin gene enhancer protein (Isl)-1$^+$ cells [182–184] and cardiac side population cells [185–187], have been found. Furthermore, various fate mapping studies indicated that resident cardiac stem and progenitor cells can contribute to adult cardiomyogenesis by direct differentiation [188–190]. Soon after the discovery of CSCs, *in vivo* experiments were initiated leading to promising results. A systemic analysis of 80 animal studies revealed an improvement of the LVEF by ~11% after application of CSCs when compared with placebo groups [191]. Surprisingly, this positive therapeutic effect of CSCs was significantly more pronounced in small animal models compared to large animal models (~12% vs. ~5% improved LVEF), while other parameters like comorbidities, cell origin and disease models did not affect the benefit of SC treatment [191]. In 2011, data from the first phase I clinical trial (SCIPIO, NCT00474461) demonstrated no mortality or CSC-related adverse events after intracoronary infusion of autologous c-Kit$^+$ CSCs in patients with ischemic cardiomyopathy [192]. The evaluation by magnetic resonance imaging (MRI) suggested an improvement of the global and regional heart function, a decrease of the infarct size and an increase of viable tissue 4 and 12 months post SC injection [193]. The benefits of CSCs were further confirmed by the CADUCEUS trial (NCT00893360) in which CDCs grown from endomyocardial biopsy tissue were delivered into patients suffering from LV dysfunction following MI [194]. Beside safety and feasibility of intracoronary SC injection, the transplantation of CDCs reduced infarct size, increased the amount of viable myocardium and improved regional contractility and regional systolic wall thickening [194, 195]. In contrast, no difference in LV function and volume could be detected between SC-treated patients and untreated control groups. In the first randomized controlled phase II clinical trial PERSEUS (NCT01829750) the absolute changes in LV function were significantly greater in CDC-treated patients than in the control group (6.4% vs. 1.3%) after 3 months [196]. Compared to baseline, beneficial SC effects, including improved ventricular functions and volumes as well as reduced HF status and cardiac fibrosis, persist even 1 year after intracoronary SC injections in patient with univentricular heart disease [196].

### Embryonic stem cells (ESCs)

ESCs are derived from the inner cell mass of the blastocyst and bear the capacity of self-renewal and differentiation into cell types of all 3 germ layers (endoderm, mesoderm, ectoderm) [197]. To date, many different *in vitro* protocols have been established to induce cardiomyogenic differentiation of ESCs, although the generation of pure and mature cardiomyocytes in large quantities of is still challenging [198, 199]. In early animal studies it was suggested that the cardiac environment is sufficient to trigger the differentiation of injected ESCs into cardiomyocytes replacing injured host tissue [200, 201]. However, further *in vivo* experiments demonstrated teratoma formation after intramyocardial injection of undifferentiated ESCs [202–204]. Therefore, the focus has been placed on the development of new strategies aiming at the identification, generation and purification of ESC-derived cardiac cells. In this respect, more sophisticated pre-clinical studies showed that ESC-derived cardiomyocytes are capable to electromagnetically integrate into the host myocardium and thereby positively influence the cardiac remodeling process, diminished scar formation and improved heart function without formation of teratomas in small and large animal models [203–212]. These promising pre-clinical data have led to the initiation of the first phase I clinical trial (ESCORT, NCT02057900) in which human ESC-derived cardiac progenitors embedded into a fibrin matrix were applied to patients suffering from severe HF. For cell preparation, ESCs were first treated with bone morphogenetic protein (BMP)-2 and the fibroblast growth factor (FGF) receptor inhibitor SU-5402, afterwards cells were immunomagnetically sorted to generate a stage-specific embryonic antigen (SSEA)-1 positive population which in addition strongly expresses Isl-1 [213]. In 2015, results of the first patient were published indicating no complications such as arrhythmias or tumor formation, whereas LVEF was increased by 10% and an improvement of symptoms from

NYHA class III to I was observed [214]. Despite this positive outcome, the clinical application of ESCs and their derivatives for the treatment of CVDs is controversially discussed since the use of ESC provokes several ethical concerns [215]. Additionally, the risk of immune rejection [202, 216], genetic instability [217–219] and tumorigenic potential [197] still hampers their clinical translation.

### Induced pluripotent stem cells (iPSCs)

In 2006, Takahashi and Yamanaka were the first reporting the generation of pluripotent SCs from mouse fibroblasts by retroviral introduction of 4 defined transcription factors (c-Myc, octamer-binding transcription factor (Oct)3/4, Sox2, Kruppel-like factor (Klf)4) [220]. These, so called iPSCs, exhibited certain properties similar to murine ESCs, including their differentiation capacity, morphology and SC marker expression [220]. 1 year later, human iPSCs were established by applying the same technology to human fibroblasts [221]. Nowadays, several cardiac differentiation protocols have been developed for mouse [222–224] and human [225–228] iPSCs. However, functional analyzes of iPSC-derived cardiomyocytes revealed that these cells are immature and more related to embryonic rather than to adult cardiomyocytes [229–233]. In MI animal models it was demonstrated that transplanted cardiomyocyte-like cells generated from iPSCs are able to integrate into the host tissue as well as to improve cardiac function and alleviate adverse remodeling processes [234–240]. When compared with ESCs, patient-specific iPSCs-derived cells were thought to provide significant advantages, such as the lack of ethical issues and immune response [221, 241]. However, various studies described genomic instabilities in iPSC lines resulting either from pre-existing variations in parental adult cells or from mutations occurring during the reprogramming process and culturing time (summarized in: [242]). The unexpected finding that transplanted iPSC-derived cells possess immunogenic capabilities raised additional major concerns about the safety of iPSCs [243, 244]. To overcome these issues, new protocols have been established, minimizing the potential for mutagenesis during the reprogramming process by using non-integrating gene delivery approaches [245–250] or by introducing proteins [251, 252], modified messenger ribonucleic acids (mRNAs) [253] and microRNAs (miRs) [254, 255]. Recently, also chemically induced iPSCs have been generated by applying a cocktail of small molecules [256–258]. Despite these significant improvements, human iPSC-derived cells did not reached clinical translation for the treatment of cardiovascular diseases, yet.

### Potential mechanisms of adult SCs in cardiovascular regeneration

Investigating the mechanisms by which different SC types govern the regeneration of infarcted heart tissue is of utter importance for the development and improvement of novel SC therapeutics. The capacity of SCs to repair damaged tissue is mainly based on indirect/paracrine and direct mechanisms (Fig. 1). The latter includes the direct cardiac differentiation of injected SCs and the integration into the myocardium to compensate the loss of cardiomyocytes or endothelial cells [259]. However, data obtained from numerous *in vitro and in vivo* studies led to the conclusion that paracrine signaling is the fundamental mechanism that mediates the beneficial effects of SC therapy [260, 261].

*Direct mechanisms – (trans-)differentiation of SCs*

Initially, transplanted BM-derived SCs were thought to contribute to the functional recovery of damaged myocardial tissue by electromechanically coupling with the host myocardium after acquiring a cardiomyogenic fate and by promoting neovascularization through direct differentiation into a vascular phenotype [4, 262]. To date, the transdifferentiation capacity of adult stem and progenitor cells into cardiomyocytes within the heart is controversially

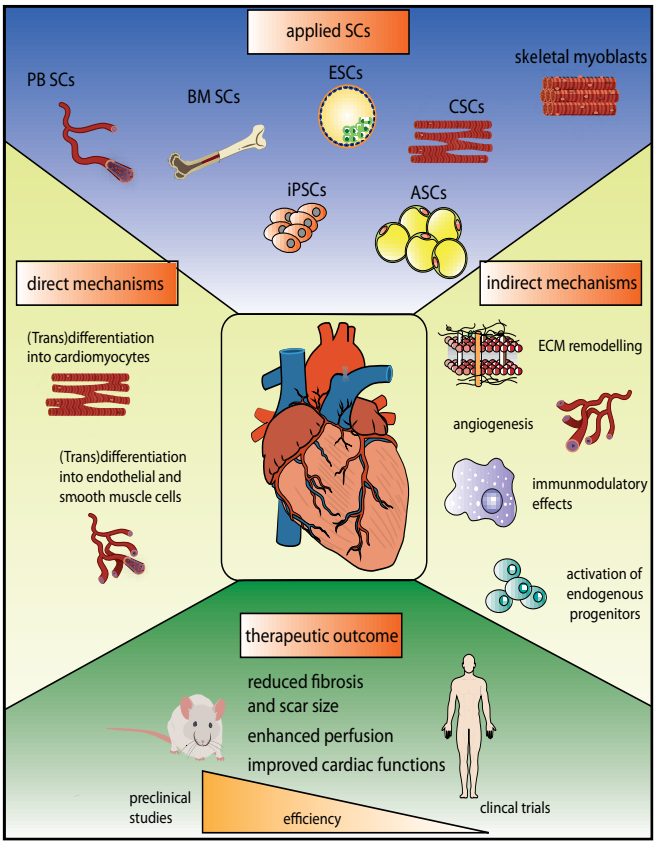


**Fig. 1.** Stem cell (SC) therapy for cardiac regeneration. Multipotent adult SCs from various tissues (bone marrow (BM), peripheral blood (PB), cardiac tissue and adipose tissue), skeletal myoblasts and pluripotent SCs (induced pluripotent SC (iPSCs), embryonic SC (ESCs)) have been applied to stimulate cardiac regeneration of the adult heart in pre-clinical and clinical studies. SCs possess the capability to differentiate into cardiomyocytes, endothelial and smoot muscle cells, supporting the regeneration process. However, numerous in vitro and in vivo data identified indirect paracrine pathways as the main mechanisms that mediate the beneficial effects of SC therapy. The release of soluble factors positively influences the remodeling of the extracellular matrix (ECM) in the injured tissue. Similarly, the formation of new blood vessels and immunmodulatory effects are stimulated by paracrine signaling of SCs. A large number of pre-clinical studies demonstrated a significant therapeutic outcome of SC treatment, including reduced fibrosis and infarction size, enhanced perfusion and improved cardiac performance. In contrast, functional data obtained in clinical trials are inconsistent and did not confirm the pronounced benefits of SCs therapy observed in various animal models. CSC: cardiac SC; ASC: adipose derived stromal/stem cells.

discussed. Indeed, several studies indicated that injected BM-derived cells adopt not only an endothelial and smooth muscle cell phenotype but also transdifferentiate into functional cardiomyocytes [263–267], while others refuted this cardiogenic potential [268–271] or indicated fusion with host cardiomyocytes as the prevalent mechanism [272–274]. Likewise, both mechanisms, transdifferentiation and cell fusion, were reported to cause the conversion of PB- and adipose tissue-derived stem and progenitor cells towards a cardiomyogenic fate *in vivo* [275–278].

For cardiac stem and progenitor cells, similar contradictory data regarding their *in vivo* cardiomyogenic differentiation capacity have been published. On the one hand, several animal studies indicated that these cells give rise to newly formed cardiomyocytes by direct differentiation [172–174, 279–282]. On the other hand, it was revealed that cardiac differentiation and cell fusion with resident cardiomyocytes occur equally following transplantation of CSCs into murine MI hearts [181]. However, frequency of cardiomyogenic transformation varied significantly between different *in vivo* studies ranging from rare to substantial [180, 187, 283, 284]. Moreover, inconclusive data were obtained regarding cell maturity, with some studies demonstrating the contractility and full maturation of newly-formed cardiomyocytes within several weeks [172, 174], while others failed to detect mature cardiomyocytes generated from transplanted c-kit$^+$ cells after years [283]. Recently, lineage tracing studies even revealed that cardiac resident c-kit$^+$ cells rarely contribute to the formation of endogenous cardiomyocyte (less than 0.03%), but predominately represent a cardiac endothelial cell population in the developing and adult heart [285, 286].

These data reveal the potential capacity of adult stem and progenitor cells to acquire a cardiovascular phenotype in the cardiac environment. However, the (trans)differentiation of

these cells is probably at a functionally insignificant level as this process is a highly inefficient and rare event [180, 270, 285].

*Paracrine signaling*

Nowadays, it is generally accepted that secretion of soluble factors is the prevailing mechanism of SC-mediated heart regeneration. Paracrine signaling enables SCs to positively influence the surrounding cardiovascular tissue by activation of several signaling pathways, independent on the establishment of functional cell-cell contacts with the host tissue [287]. Biologically active molecules like transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), stromal cell-derived factor (SDF)-1 and epidermal growth factor (EGF) can be secreted by transplanted stem and progenitor cells into the intestinal space or blood-stream [288, 289]. Thus, the release of such cytokines or extracellular vesicles is a systemic event that promotes various regenerative processes, e.g. neovascularization, reduced apoptosis of endogenous cardiomyocytes, activation of tissue intrinsic progenitor cells or recruitment of cells beneficial for tissue repair [260, 287, 290]. Beside the donor´s health status, chronological age significantly influences the characteristics of the SC´s secretome and thereby affects their potential to promote myocardial recovery [291–293].

*Neovascularization*

The formation of new blood vessels is an important part of healing processes as it enables re-supply of the damaged tissue with nutrients and oxygen. The secretome of SCs has been shown to trigger neovascularization in infarcted hearts [294, 295]. Following transplantation into a MI mouse model, human CDCs were found to release pro-angiogenic factors, including VEGF, HGF and insulin-like growth factor (IGF)-1 [175]. The authors observed a 20% enhanced neovascularization after SC injection that was attributed predominantly to paracrine signaling [175]. A recently published study further confirmed the stimulating influence of CDCs on angiogenesis in mice and identified endoglin (CD105), a co-receptor for TGF-β, as an important mediator of this paracrine-stimulated neovascularization [296]. Interestingly, Cheng *et al.* indicated that CDCs from advanced HF patients exhibited a higher paracrine expression of SDF-1 than CDCs from healthy and recently infarcted hearts [291]. As a result, transplantation of these HF CDS into infarcted mice hearts increased the proliferation rate of endogenous endothelial cells by ~30% in comparison to control CDCs [291]. Similarly, rat c-kit$^+$ CSCs significantly improved angiogenesis post MI in a paracrine manner by the secretion of VEGF [297].

Likewise, MSCs from different sources are capable to release pro-angiogenic factors contributing to the formation of new blood vessels [287, 298]. ASCs were shown to secrete VEGF, HGF and IGF-1 *in vitro* and increased the capillary density in the infarct border zone by ~28% when applied to rats [152]. Since direct endothelial differentiation of injected ASCs was very low (<1%), the authors concluded that the improved neovascularization was mainly stimulated by the paracrine release of cytokines [152]. In addition, BM-derived MSCs were demonstrated to express and release cytokines that increase capillary density [299]. The therapeutic activity of the MSC secretome was further proven by Timmers *et al.*, who intravenously injected conditioned medium of human MSCs into MI pigs [300]. After 3 weeks, animals treated with MSC conditioned media showed a significantly higher number of capillaries in the border area [300]. To unravel the underlying molecular mechanisms, overexpressing studies with MSCs were performed, indicating that GATA-4 and Akt/extracellular signal-regulated kinase (ERK) signaling are involved in the paracrine mediated stimulation of angiogenesis [287, 301]. Pre-clinical studies applying HSCs and EPCs showed a significantly enhancement of capillary density and an increase of neovascularization in the infarct scar after MI [140, 276, 302, 303]. These beneficial cell-based effects were further confirmed in phase III clinical studies reporting improved segmental myocardial perfusion as detected by cardiac MRI [98, 99]. Mechanistically, HSCs and EPCs were shown to directly integrate into the forming neovasculature as well as secrete pro-angiogenic factors, such as VEGF, basic FGF (bFGF), IGF-1, hepatocyte growth factor (HGF) and SDF-1α [84, 304].

*Immunomodulation*

Immunomodulatory properties have been well described for MSCs, which are capable to interact with cells of the innate and adaptive immune system [305]. Therefore, MSCs can influence inflammatory processes after AMI and in HF [306].

In particular the interaction of T cells and MSCs has been investigated intensively. Several studies demonstrated that MSCs are capable to suppress the proliferation and activation and induce the apoptosis of T cells by both, a direct cell-cell contact-dependent mechanism and by releasing soluble factors like indoleamine 2, 3-dioxygenase (IDO), nitric oxide (NO), HGF, TGF-β, human leukocyte antigen class I molecule G5 (HLA-G5) and programmed cell death protein 1 (PD-1) [307–314]. Moreover, it was shown that MSCs can stimulate the generation of regulatory T (Treg) cells by their secretion of TGF-β and interleukin (IL)-10 [305, 309, 315, 316]. Treg cells promote the switch from an initial inflammatory phase to an inflammation resolution phase after AMI and thereby contribute to an improved wound healing [317, 318]. However, it was demonstrated that immunomodulatory properties of MSCs are significantly influenced by their environment [319, 320]. In response to high levels of pro-inflammatory cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF-α), MSC adopt an immune-suppressive phenotype [305]. As a result, MSCs secrete high levels of T cell suppressing factors and simultaneously express adhesion molecules and chemokines, including CXC chemokine receptor (CXCR)3 and C-C chemokine receptor type 5 (CCR5) ligands, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1), to attract T cells into their close proximity [305, 321]. Reversely, in the absence of an inflammatory environment, MSCs still produce T cell recruiting molecules but secrete only low levels of immune-suppressive factors resulting in an enhanced T cell response [319, 321, 322].

Furthermore, SCs can influence the polarization of macrophages. Initial studies reported that lymphocyte antigen 6 complex, locus C (Ly6C) high expressing monocytes/macrophages secreting large amounts of pro-inflammatory mediators such as IL-6 and TNF-α are the predominant population at the early inflammatory phase after MI, whereas $Ly6C^{low}$ monocytes/macrophages producing anti-inflammatory cytokines and growth factors including VEGF and TGF-ß are recruited in later stages [323]. Recently, co-culture experiments as well as *in vivo* studies demonstrated that MSCs and CDC are able to facilitate the shift of macrophages from an pro-inflammatory towards an anti-inflammatory phenotype which in turn can accelerate wound healing processes [324–331].

Beside the regulation of T cells and macrophages, MSCs were shown to suppress several other cells involved in the immune response including B cells [328, 332, 333], natural killer (NK) cells [334, 335], dendritic cells [336–338] and mast cells [339–341]. Conflicting results were obtained for the interaction of MSCs and neutrophils. While several studies reported that MSCs prevent apoptosis and enhance the recruitment of neutrophils [342–345], others indicated MSC-mediated limited activity and attraction of neutrophils [346, 347]. Recently, Luger *et al.* demonstrated that intravenous application of human BM-derived MSCs significantly reduced the number of NK cells and neutrophils by 25 - 50% in hearts 7 days after MI which was associated with a reduced adverse remodeling especially in mice with large infarcts [348].

In comparative analyses, ASCs were shown to secrete higher levels of immunomodulatory cytokines like IL-6, IL-8 and TGF-β *in vitro* and inhibit the differentiation of dendritic cells more efficiently than BM-derived MSCs [349, 350]. In contrast, only BM-derived MSCs reduced the cytotoxic activity of NK cell, while both, ASCs and BM-derived MSCs, decreased NK cell proliferation in a similar manner [351, 352]. However, data of other SC types are very limited and additional *in vitro* and *in vivo* studies are required to elucidate the extent of their immunomodulatory and anti-inflammatory activity.

*Recruitment of endogenous stem und progenitor cells and activation of cardiomyocyte proliferation*

SC-based therapy has the potential to activate endogenous regenerative processes, including the recruitment of resident stem and progenitor cells and the stimulation of cardiomyocyte proliferation. 2 days after injection of CDCs into infarcted mice hearts, Chimenti *et al.* observed a co-localization of endogenous c-kit$^+$ CSCs with transplanted cells [175]. In 2011, it was demonstrated that intramyocardially injected BM-derived c-kit$^+$ cells stimulate endogenous cardiogenic progenitors without evidence for transdifferentiation or fusion of cells [353]. This was further confirmed in several other studies showing the increase of c-kit$^+$ CSC within the heart tissue after MSC transplantation [354, 355]. Recently, the injection of BM-derived MNC conditioned media alone was found to significantly increase the number of circulating Sca-1$^+$ and c-kit$^+$ cells and favors the infiltration of beneficial endogenous BM-derived cells, indicating paracrine signaling as the prevailing mechanism of resident cell recruitment [356]. Furthermore, SC therapy promoted the activation of epicardium-derived cells and their differentiation into endothelial cells, smooth muscle cells and cardiomyocytes [355].

In addition to the induction of endogenous stem and progenitor cells, SC delivery can stimulate cardiomyocytes to re-enter the cell cycle. The amount of proliferating cardiomyocytes and endothelial cells was significantly elevated after MSC transplantation [354]. As these proliferating cells failed to co-express the active fragment of the Notch 1 receptor N1ICD, the authors concluded that proliferating cells did not arise from endogenous CSCs [354, 357]. An augmented proliferation rate of resident cardiomyocytes was also found in MI hearts of mice treated with trophoblast-derived SCs [358]. Quantitative analysis of immunostained heart sections demonstrated a 2-fold higher cardiomyocyte turnover in mice undergone SC therapy [358]. Interestingly, it was found that the cell cycle reentry of cardiomyocytes can also be triggered by cell fusion with hematopoietic and mesenchymal stem and progenitor cells, which highlights the potency of SC therapy for the activation and stimulation of endogenous cardiac repair [359, 360].

*Cardiac remodeling*

Cardiac remodeling is a complex process involving several molecular, cellular and interstitial changes which result in alterations of cardiac structure and function, such as adverse cardiomyocyte organization and altered extracellular matrix (ECM) homeostasis [361]. A large number of studies have given evidence that SC therapy positively influences the cardiac remodeling process after ischemic injury. The injection of c-kit$^+$ CPCs was reported to significantly reduce collagen deposition in the peri-infarcted myocardium, to increase the thickness of the infarcted LV wall and to attenuate LV hypertrophy in small animal models [283, 362, 363]. Interestingly, the observed effects were even more pronounced when the cells were delivered via multiple injections [363]. Similar beneficial alterations of adverse cardiac remodeling in rats were detected following intramyocardial delivery of MSCs. Quantitative analyses revealed a markedly higher thickness of the infarcted LV anterior wall (0.86mm vs. 0.43mm) as well as a significant lower extent of fibrosis (24.5% vs. 39.1%) in MSC-treated hearts compared to control hearts [364]. Likewise, several *in vivo* studies emphasized the therapeutic effects of SCs on the re-organization of infarcted heart tissue [282, 365–369]. Importantly, the potential of SCs to act on ECM deposition and to attenuate myocardial fibrosis was confirmed in human patients. In the PERSEUS clinical phase II trial (NCT01829750), intracoronary infusion of autologous CDCs was associated with a significant reduction of scar size, mass and volume 3 months after SC treatment [196]. Similarly, MSC treatment was found to significantly decrease endocardial length, LV sphericity index and scar thickness in patients suffering from ischemic cardiomyopathy [109, 119].

However, the mechanism by which SCs modulate the organization of the ECM is still under investigations. It has been suggested that matrix metalloproteinases (MMPs) might play a prominent role in reducing scar size upon SC transplantation. Administration of

MSCs in fibrotic liver or uterine tissue was associated with lower collagen deposition and significantly increased levels of MMP-9 [370, 371]. Rising levels of MMPs in tissue were also described in SC-mediated cardiac repair. In 2008, Rota *et al.* demonstrated a 10-fold higher MMP-9 activity and a significant enhanced presence of MMP-2 and MMP-14 in CPC-treated hearts than in control hearts [282]. Moreover, it was shown that the inhibition of MMPs by GM6001 counteract beneficial effects of CSC injections after MI [372]. Likewise, an enhanced MMP expression in cardiac tissue has been demonstrated for MSCs in rat models [373]. Nevertheless, it remains elusive whether the increased levels of MMPs are based on active SC secretion or generated by host cells stimulated by applied SCs. The former mechanism is supported by *in vitro* data, showing that SCs from different sources possess the capacity to release MMPs at high levels [374–376]. However, Mias *et al.* indicated that MSCs modulate the phenotype of cardiac fibroblasts *in vitro* and promoted the secretion of MMPs [364].

In addition, suppression of the TNF-signaling is an important paracrine effect by which SCs influence cardiac remodeling processes. The administration of MSCs into a murine model of inflammatory dilative cardiomyopathy inhibited the TNF/NFκB pathway in the myocardium by the release of soluble TNF receptor 1 which in turn led to ~50% reduced collagen deposition [377]. Similarly, Lee *et al.* demonstrated that the MSC-mediated secretion of the anti-inflammatory factor TNF-α-induced protein 6 was associated with a significant decline of the infarction size [378]. Surprisingly, this anti-inflammatory impact on cardiac remodeling was also stimulated by MSCs trapped in the lung following intravenous injection [378].

## Improvement strategies of SC-based therapies

Numerous pre-clinical studies have shown significant improvement in LVEF ranging from 7 – 11% after SC treatment [118, 191, 379, 380]. Moreover, a growing number of phase I and II clinical trials have proven the feasibility and safety of SC application [381]. However, data from human studies addressing functional improvement are inconsistent. Several meta-analyses and systemic reviews reported a slight but significant improvement of heart function between 2 – 4% [81, 382–391], while the first study including individual data of patients refuted beneficial SC effects [392]. Interestingly, it was revealed that many trial reports of SC-based therapies contain functional discrepancies and that trials with lower discrepancies tend do find smaller enhancements in LVEV [393].

This limited outcome of SC-based clinical trials requires the development and improvement of novel strategies to significantly enhance the efficiency of SCs for cardiac repair. Basically, 2 major concepts are available to generate the "next generation" of SC therapeutics: i) non genetic modification and ii) genetic engineering approaches. Using these techniques, numerous SC properties can be addressed, including homing, engraftment, survival, paracrine activity, angiogenic potential or differentiation capacity (Fig. 2). Moreover, the development of personalized treatment strategies could help to classify patients´ cohorts into responders vs. non-responders, thus allowing highly specific SC-based therapy depending on individual physiological and pathological criteria.

*Non-genetic SC modifications*

*Pharmacological pre-conditioning.* Pharmacological pre-conditioning represents a convenient and cost effective technique to stimulate the regenerative activity of SCs. As these cells exert their therapeutic effects on damaged tissue mainly by paracrine signaling, drug pre-treatment was applied to promote their secretion activity [394]. For example, incubation with oxytocin increased the release of cytokines in rat MSCs, including bFGF, CXCR4 and EGF [395]. As a result, these pre-conditioned MSCs were found to enhance the survival of co-cultured cardiomyocytes by ~50%. Further, *in vitro* studies described drug pre-conditioning for CDCs or human c-kit$^+$ CSCs. Inhibitors for prolyl-4-hydroxylase or cobalt protoporphyrin, an inducer of heme oxygenase 1, led to improved cell survival, increased release of cytokines

and a higher proliferation capacity [396, 397]. The potency of pharmacological pre-treatments was also confirmed in animal models of MI. Trimetazidine, an anti-ischemic drug, was applied to MSCs before transplantation into MI rat hearts, leading to a moderate improvement of cardiac performance and reduced fibrosis by 10% when compared to untreated cells [398]. *Ex vivo* pre-treatment of MSCs with the pineal hormone melatonin induced a 7-fold increase in the number of viable MSCs after intramyocardial injection resulting in an improved LVEF and a higher LV wall thickness after 2 month [364]. ASC pre-conditioning with sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor, enhanced cardiac function, reduced fibrosis, increased vascular density and stimulated the release of VEGF and bFGF when compared with non-pre-conditioned ASCs in a MI mouse model [399]. Similarly, injection of diazoxide-stimulated EPCs provoked in a 50% decreased collagen deposition in rats, which was accompanied by improved ejection fraction (EF) parameters [400]. The authors also detected a 3-fold enhancement of cell engraftment and a positive effect on blood vessel formation [400].

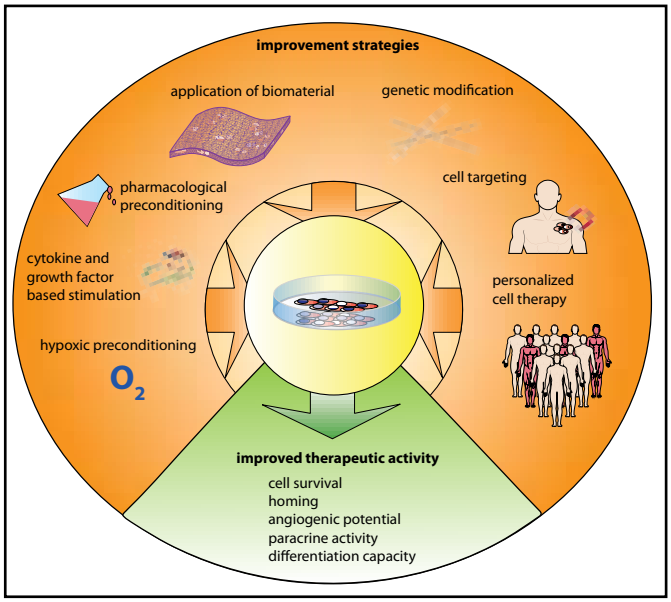


**Fig. 2.** Strategies for improving stem cell (SC) efficiency in the treatment of cardiovascular diseases. Genetic modifications are based on alterations of the cellular genome (genome editing, DNA) or on posttranscriptional gene regulation (miRNA, siRNA). Non-genetic strategies comprise pre-conditioning with environmental factors (elevated temperature, oxygen pressure), pharmacological agents and cytokines/growth factors. Moreover, the application of biomaterials, such as cell patches or biodegradable scaffolds, greatly enhance therapeutic effects of transplanted SCs. Cell targeting represents another strategy to augment SC efficiency, e.g. by labelling cells with magnetic particles. In addition to modifying transplanted SCs, proper patient selection is another novel approach to optimize SC therapy. This concept of personalized cell therapy relies on targeted therapeutic treatments, including the specific pathological characteristics of patients undergoing SC injection. These applied strategies improve cell survival and homing upon transplantation into the injured heart. Likewise, cardiovascular differentiation and stimulated angiogenic - and paracrine activity are common targets for SC improvement.

Moreover, drug-mediated activation or inhibition of pathways can modify SC physiology relevant for cardiac regeneration. Selective activation of Rap-1 dependent signaling improves the survival and adhesion capacity of MSCs [401]. Quantitative analysis of cardiac repair revealed that these drug-treated MSCs reduced the fibrotic area by 40% and significantly improved EF and endsystolic value [401]. Likewise, stimulation of the cannabinoid receptor type 2 of ASCs before injection was found to restore cardiac function and counteract adverse tissue remodeling in mice [402]. The observed enhanced regenerative ability of SCs was suggested to be based on an increased paracrine activity and resistance to oxidative stress [402].

In addition, pharmacological compounds have been applied to promote cardiac programming of cells by interfering with important developmentally relevant pathways [403, 404]. For instance, Protze *et al.* developed a transgene-independent method for the generation of pacemaker-like cells from human pluripotent SCs by applying several small

molecules, like the FGF signaling inhibitor PD-173074 and the activing/nodal/TGF-β signaling inhibitor SB431542, for stage-specific manipulation of signaling pathways [405]. Furthermore, several other compounds were identified to boost cardiac programming of pluripotent SC, such as the Wnt signaling activator CHIR-9902, the Rho kinase inhibitor Y-27632 as well as the Wnt signaling inhibitors IWR1 IWP2 and IWP4 [406–409].

*Cytokine and growth factor-based pre-conditioning.* In addition to pharmacological agents, growth factors and cytokines can be utilized to modify SC activity prior administration to damaged hearts. As reported by Pasha and co-workers, pre-incubation of MSCs with SDF-1 induced a profound increase of their homing ability and pro-angiogenetic properties [410]. The assessment of cardiac function and LV remodeling showed that the EF was improved by 75% and 50% less fibrotic tissue was detected within the infarct region in the SDF-1-treated MSC group [410]. Likewise, pre-treatment of BM-derived Sca-1$^+$ SCs with IGF-1 improves cell survival and engraftment in the myocardium, leading to increased blood vessel density, reduced infarction size and improved LVEF in an AMI model [411]. Enhancement of the therapeutic activity of MSCs was also achieved by pre-conditioning with TGF-α. This positive impact on the regenerative abilities of MSCs was assumed to rely on upregulation of VEGF in stimulated MSCs [412]. Additionally, cytokines and growth factors are involved in cell fate determination and thus can be used to induce lineage-specification of SCs to generate cardiopoietic progenitors prior cell transplantation - a concept that has been proven to be beneficial in animal models [413, 414]. In the clinical trial C-CURE (NCT00810238), MSCs were exposed to a cardiogenic cocktail (TGF-β, FGF-2, BMP-4, cardiotrophin, α-thrombin) triggering the differentiation towards cardiac lineage [415]. Injection of these primed MSCs was shown to be safe for the treatment of chronic HF [415]. Moreover, 21 patients receiving lineage-specified SCs demonstrated improved LVEF and 6-min walk distance when compared to 15 patients receiving standard of care alone [415]. However, in the larger phase III clinical trial CHART-1 (NCT01768702) no difference was found in primary efficacy endpoints between cardiopoietic cell treatment and control group [416] albeit post hoc analysis revealed an cell-mediated reverse remodeling at 1 year follow-up [417].

*Pre-conditioning with environmental factors.* Numerous studies have proven that pre-conditioning at low oxygen levels can stimulate intrinsic cell defense mechanisms, leading to improved cell survival and positive effects on SC efficiency [394, 418, 419]. For example, CDC sheets subjected to hypoxic conditions markedly increase angiogenesis by 25% in the infarction border zone and significantly reduce collagen deposition in mice [420]. Similarly, hypoxic pre-conditioning of different SC types resulted in a higher therapeutic activity, including improved SC engraftment, migration to infarcted tissue and heart function [421–426]. This enhancement of SC potency induced by lower oxygen concentration mainly relies on the up-regulation of pro-survival and pro-angiogenic factors, such as hypoxia-inducible factor (HIF)-1, angiopoietin (Ang)-1, VEGF, erythropoietin EPO)) as well as in increased CXCR-4 expression [422, 425, 426].

In addition, heat shock pre-treatment was shown to significantly improve the survival of BM-derived Sca-1$^+$ SCs *in vitro* and *in vivo* which was mainly mediated by the heat shock protein (HSP) 70 [427]. Moreover, heat shock pre-treated cells improved global heart function after MI and efficiently reduced cardiomyocyte apoptosis likely by the secretion of heat shock factor (HSF) 1-enriched exosomes [427]. Similarly, short-time exposure of MSCs to elevated temperatures induced the expression of HSPs and decreased apoptotic rates [428, 429].

*Application of biomaterials.* Biomaterials are 3-dimensional polymeric scaffolds that have been engineered to protect cells against harsh environments and to prevent substantial cell loss after transplantation. The usage of injectable scaffolds forming a temporary ECM such as fibrin [430–432], matrigel [433], chitosan [434] and synthetic hydrogels [435, 436] improved SC engraftment and survival and led to an increase of cardiac performance. Biocompatible

cell patches represent another approach to successfully improve the therapeutic outcome of SC transplantation and to avoid the shortcoming of needle injection. In numerous studies collagen and fibrin patches seeded with SCs were applied to the injured heart resulting in beneficial effects on heart function [160, 437–440]. Currently, the feasibility of fibrin patch generation embedding cardiac-committed progenitors and its efficacy on cardiac regeneration are investigated in the phase I clinical trial ESCORT (NCT02057900). Recently, Ichihara *et al.* demonstrated that epicardial coating with MSCs incorporated in an self-assembling peptide hydrogel significantly enhanced global cardiac function and decreased ventricular dilatation compared to intramyocardially injected MSCs in rat models of AMI and ischemic cardiomyopathy [441]. Moreover, these authors indicated a significant greater survival of donor cells (50% vs. 20% after 3 days) and detected an upregulation of repair-related genes including HIF-1α, IL-10, IGF-1 and SDF-1 in the myocardium [441]. Similar regenerative effects were obtained for epicardial delivery of 3-layerd ASC sheets produced by culturing cells on temperature-sensitive dishes [442]. Gaetani *et al.* reported that epicardial application of CPCs in a 3D-printed gelatin/hyaluronic acid patch supported the long-term cell engraftment, significantly reduced adverse remodeling and improved cardiac function [443]. At the same time, biomaterials can serve as carriers containing functional molecules that boost the regenrative capacity of SCs such as VEGF, bFGF, HGF, IGF-1 and TGF-β [444–448].

In addition to the generation of cell sheets and patches, biomaterials are used for the construction of complex, biomimetic 3-dimensional tissue structures or organoids, a process termed cardiac tissue engineering [449, 450]. For *in vitro* generation of functional heart tissue, various cell types are required. Therefore, pluripotent SCs are the preferred SC type for the generation of multicellular tissue structures [451, 452]. Nakatana et al. have recently engineered a large tissue construct consisting of cardiomyocytes, endothelial cells and vascular cells which were derived from human iPSCs [453]. Likewise, human ESCs and iPSCs have been utilized for the development of 3-dimesional microtissues formed by SC-derived cardiovascular cells [454, 455]. In order to mimick human sized organs, specialized scaffolds are needed that provide characteristics similar to the cardiac ECM, match the strength of native myocardium and allow re-population with cardiac cells. Yet, different scaffolds are under investigation including poly-L-lactic acid (PLLA) and poly(lactic-co-glycolic acid) (PLGA) as well as natural polymers like collagen and alginate [456]. Although designing whole human hearts for transplantation still remains a long way off, there are various immidiate applications for engineered 3-dimensional cardiac tissues. In particular, they can be used for pharmaceutical drug testing and screening or as a model system to better understand the processes regulating cardiac development [451, 457, 458]. Moreover, the possibility to generate individual iPSC lines promotes the establishment of patient-specific disease models to recapitulate the underlying pathophysiological mechanisms.

*Targeting of SCs.* The success of SC therapy correleates with the number of cells retained at the site of injection [459]. Since the heart is a higly perfused organ, 90 – 99% of transplanted cells are typically lost within the first 1 to 2 hours [460–464]. Magnetic cell targeting techniques facilitate guidance of transplanted cells to the site of interest and improve cell retention [465]. For example, magnetic targeting of CDCs led to a 4-fold increase of cell engraftment after injection into ischemic rat hearts [466]. Likewise, labeling of MSCs with superparamagnetic oxide nanoparticles profoundly increased cardiac cell retention by 3-fold using magnetic field and enhanced cardiac performance and capillary density [467]. Further *in vivo* and *in vitro* data confirmed the benefits of magnetic targeting for other SC types [468–471]. At the same time, the application of magnetic nanoparticles offers the possibility to track cells by MRI [472–475]. However, care must be taken when interpreting these MRI data. In long-term tracking studies it was demonstrated that MRI signals originate not only from labelled SCs but also from magnetic particles engulfed by macrophages and from extracellular particles [476, 477].

Recently, ASCs were efficiently directed to the infarct area in the heart by coating cells with microbubbles which were in turn conjugated to an antibody against ICAM-1 [478]. These so called "StemBells" lead to an improved cardiac function compared to untreated ASCs [478].

*Synthetic SCs.* In 2017, Cheng and co-workers published the establishment of synthetic microparticles mimicking the paracrine and biointerfacing activities of cardiosphere-derived CSCs and MSCs [479, 480]. These "synthetic SCs" were generated by encapsulating the secretome of SCs in biodegradable PLGA. To further improve therapeutic interaction with the host tissue, microparticles were coated with membrane fragments derived from SCs. The intramyocardial injection of these synthetic SCs into infarcted mice hearts was shown to reduce infarct size, increase wall thickness and activate endogenous repair mechanisms including recruitment of c-Kit$^+$ cells and induction of angiogenesis. Importantly, the clinical application of synthetic SCs may allow to overcome several limitations linked to SC therapy such as storage stability and tumorigenicity.

## Genetic SC modifications

Genetic modification represents another powerful technique to boost SC efficiency. Compared to non-genetic based pre-conditioning genetic engineering is usually applied to induce prolonged effects on SC activity. In general, three main strategies of genetic modification are utilized, including protein overexpression after deoxyribonucleic acid (DNA) or mRNA delivery, gene editing (transcription activator-like effector nucleases (TALENs), clustered regularly interspaced short palindromic repeats (CRISPR)-Cas nucleases) as well as gene silencing (short interfering RNA (siRNA), miR) [481–484].

Using DNA-based modifications, overexpression of therapeutic factors can be induced, which promotes the regeneration process of MI-damaged tissue by paracrine signaling, including VEGF, SDF-1, FGF and IGF [485]. Explant-derived human CSCs were transduced with a lentivirus construct leading to overexpression and increased secretion of SDF-1α [486]. Mice treated with these modified SCs demonstrated a significant higher EF and reduced scar burden compared to unmodified control cells [486]. Interestingly, these cells were further shown to induce a 2-fold increase of proliferating cardiomyocytes and promote the recruitment of BM-derived cells which were frequently found embedded in vascular structures [486]. In another *in vivo* study, IGF-1 overexpression was utilized to beneficially influence the paracrine signature of human CSCs [487]. Cardiac function was slightly improved when IGF-1 modified SCs were applied [487]. Moreover, apoptotic events in the infarcted myocardium were less frequent, while myocardial regeneration was significantly enhanced [487]. Likewise, IGF-1 overexpression in ASCs improved the EF 6 weeks after cell transplantation into rats suffering from MI [488]. Zhao and colleagues induced overexpression of HGF in MSCs following administration into a mouse model of MI [489]. In addition to increased survival of modified MSCs probably induced by increased B cell lymphoma (Bcl)-2 and reduced Bax and caspase-3 levels [490], the authors detected an enhancement of angiogenesis, LVEF and proliferation capacity of resident cardiomyocytes upon SC treatment [489]. Moreover, overexpression of anti-apoptotic factors like Bcl-xL and Bcl-2 was found to positively influence the viability and therapeutic efficiency of applied SCs [491, 492]. Likewise, overexpression of Akt and integrin-linked kinase (ILK) promoted SC survival in the ischemic myocardium and increased regenerative SC properties [493–497]. Enhanced survival of MSCs was found after co-overexpression of Akt and Ang-1 [498]. As a result the number of blood vessels in the peri-infarct and infarct areas increased and global cardiac function was improved [498]. The therapeutic outcome of SC therapy was also improved via modifications of SC attachment to the ECM via lentiviral mediated overexpression of integrin β1 [499]. Moreover, genetic modifications have been extensively used for (re)programming of pluripotent ESCs and iPSCs and multipotent adult SCs into cardiovascular cell types, suitable for cell therapeutic application (summarized in: [404]).

The stable integration of DNA into the genome of modified SCs can provoke undesired activation of oncogenic genes, which may limit their use in regenerative medicine. To reduce the risk of mutagenesis and tumorigenesis gene editing technologies, such as TALENs and CRISPR-Cas nucleases, can be utilized, which allows precise insertion of therapeutic genes into the SC genome without causing dysfunctions of neighboring genes [481]. At the same time, small regulatory RNAs offer a safe possibility to optimize SC potency without altering the genome of the target cell [482, 500]. As already mentioned for DNA, the introduction of miRs was reported to modulate the paracrine activity of SCs. For instance, MSCs exhibited a 3-fold enhanced release of VEGF when transfected with miR-146, which in turn led to improved pro-angiogenic effects and cardiac performance after transplantation into rats [501]. A similar high level of VEGF expression was induced by application of miR-126 and miR-377 mimics [502–504]. Furthermore, miRs are involved in the regulation of apoptosis and thus have been used to increase the viability of SCs after transplantation [505]. CPCs treated with a miR cocktail containing miR-21, miR-24 and miR-221 survived significantly longer after intramyocardial injection which in turn boost therapeutic efficacy of cells [506]. MiRs have also been proven to be important translational determinants of the SC fate [507]. A combination of 5-azacytine and miR-1 overexpression induces the expression of cardiac specific genes like Nkx2.5 and troponin I via activation of the Wnt/β-catenin signaling pathway in MSCs [508, 509]. In addition, miR-133a and miR-499 were shown to promote the commitment of MSCs and CSCs/CPCs towards a cardiomyogenic lineage [510–513]. Likewise, miR overexpression has been reported to influence the differentiation and maturation of pluripotent SC-derived cardiac cell types [514–516].

### Personalized SC therapy

As discussed above, genetic and non-genetic modifications of cellular properties represent a crucial strategy for the improvement of SC efficiency. At the same time, a system of patient´s response predictors need to be developed to identify patients who will benefit most from cardiac SC therapy – a concept which contributes to the field of personalized medicine. Personalized medicine is based on targeted therapeutic treatment, focusing on patient specific characteristics in order to provide the highest quality of therapy, whereas the risk of side effects and costs of ineffective interventions are reduced [517, 518].

In 2008, Dimmeler *et al.* postulated that aging, disease and cardiovascular risk factors, like hypercholesterolemia, hypertension and smoking, not only affect the therapeutic potential of endogenous SCs, but also influence the tissue environment in which cells are transplanted [519]. A collaborative meta-analysis of randomized clinical trials revealed that younger patients and patients with a lower LVEF at baseline derived superior therapeutic benefit from intracoronary BM-derievd cell therapy [385]. These results were confirmed in a post hoc analysis of the REPAIR-AMI trial (NCT00279175) suggesting that higher age is associated with lower treatment benefit, while higher weight and massive initial functional loss are associated with enhanced response to BM-derived MNC therapy [520]. To further discriminate patients beneficially responding to SC application from non-responding patients, a specific responder score is required based on patients' characteristics that enables the classification and selection of patient cohorts. Molecular diagnostics like plasma and blood profiling could help to identify novel biomarkers in order to predict the outcome of SC therapy prior possible intervention. Jokerst and co-workers performed a comprehensive analysis of circulating proteins and cytokines in baseline plasma samples of MI patients that had undergone BM-MNC therapy [521]. They showed that certain biomarkers, like IL-15, IL-5 and stem cell factor (SCF), correlate with an improved cardiac function upon SC treatment indicating that elevated levels of specific circulating cytokines are suitable as selection criteria for personalized cell-based therapies [521]. Likewise, higher serum levels of high-sensitive troponin T have been attributed to improve the response of patients receiving BM-derived MNC [522]. Recently, in the phase III clinical trial PERFECT our group

provided evidence that only patients showing an improved cardiac function (ΔLVEF >5%) 6 months after CABG are responsive to intramyocardial $CD133^+$ SC application (~60% of patients) [99]. In contrast, patients showing no improved LVEF after CABG also failed to respond to SC treatment (~40% of patients). Interestingly, using machine learning we identified 20 parameters, including pre-operative clinical data and biomarker laboratory parameters, such as circulating EPCs, thrombocytes, VEGF, EPO, IP-10, which allow pre-operative discrimination between responders and non-responders with an accuracy of ~80% [99].

In addition, the recent advances in high throughput sequencing technologies bear enormous potential to generate patient specific profiles for their classification as responders vs. non-responders. Data acquired from RNA sequencing provide valuable information about the complex biological networks regulating pathological and physiological processes [523]. Subsequent analysis of these comprehensive data can be used to conclude about gene expression, splice variants, promotor activity, predicted miRNA/long non-coding RNA (lncRNA)-target interactions etc., and thus will allow identification of novel biomarkers for personalized SC-based therapy of CVDs.

## Conclusion

The groundbreaking discoveries of ongoing cardiomyocyte turnover [170, 171] and of stem and progenitor cells located in the myocardium [172] identified the human adult heart as an organ bearing potential for self-renewal. However, the limited endogenous degree of cardiac regeneration is insufficient to compensate for the massive loss of cardiomyocytes occurring after acute injury and the consecutive adverse remodeling.

The transplantation of SCs emerged as a new approach to restore damaged myocardial tissue. Encouraging pre-clinical studies reporting significant SC-mediated cardiac regeneration rapidly paved the way for clinical translation. Unfortunately, data from human studies are contradictory, overall showing modest to no therapeutic SC effects [81, 382, 392].

To overcome this discrepancy, a deeper understanding of disease and endogenous reparative mechanisms as well as their interactions with SCs is urgently needed [524]. Indeed, there is growing evidence that patient characteristics, such as disease state, co-morbidities, co-medications and cardiovascular risk factors, critically influence the therapeutic outcome of SC application [99, 385, 520]. This finding clearly demands the implementation of personalized cardiac SC therapies in which the selection of SC source, modification and application is subjected to these individual characteristics [525]. Thus, prospective research should focus on the development of specific responder scores and the identification of prognostic biomarkers to identify patient cohorts who benefit most from distinct SC treatments [526, 527]. Thereby, a higher standardization of study designs and the establishment of a global open-access database for the registration and publication of pre-clinical and clinical trials would greatly improve the comparability and access of obtained data [526, 528, 529].

## Abbreviations

AMI (Acute myocardial infarction); Ang (Angiopoietin); ASC (Adipose-derived stromal/stem cell); Bcl (B cell lymphoma); bFGF (Basic fibroblast growth factor); BM (Bone marrow); BMP (Bone morphogenetic protein); CABG (Coronary artery bypass grafting); CCR5 (C-C chemokine receptor type 5); CDC (Cardiosphere-derived cell); CPC (Cardiac progenitor cell); CRISPR (Clustered regularly interspaced short palindromic repeat); CSC (Cardiac stem cell); CVDs (Cardiovascular diseases); CXCR (CXC chemokine receptor); DNA (Deoxyribonucleic acid); ECM (Extracellular matrix); EF (Ejection fraction); EGF (Epidermal growth factor); EPC (Endothelial progenitor cell); EPO (Erythropoietin); ERK (Extracellular

signal-regulated kinase); ESC (Embryonic stem cell); FGF (Fibroblast growth factor); G-CSF (Granulocyte colony-stimulating factor); HF (Heart failure); HGF (Hepatocyte growth factor); HIF (Hypoxia-inducible factor); HLA-G5 (Human leukocyte antigen class I molecule G5); HSC (Hematopoietic stem cell); HSF (Heat shock factor); HSP (Heat shock protein); ICAM-1 (Intercellular adhesion molecule 1); ICM (Chronic ischemic cardiomyopathy); IDO (Indoleamine 2, 3-dioxygenase); IFN (Interferon); IGF (Insulin-like growth factor); IL (Interleukin); ILK (Integrin-linked kinase); iPSC (Induced pluripotent stem cell); Isl (Insulin gene enhancer protein); Klf (Kruppel-like factor); lncRNA (long non-coding RNA); LV (Left ventricular); LVEF (Left ventricular ejection fraction); Ly6C (Lymphocyte antigen 6 complex, locus C); MI (Myocardial infarction); miR (MicroRNA); MMP (Matrix metalloproteinase); MNC (Mononuclear cell); MRI (Magnetic resonance imaging); mRNA (Messenger RNA); MSC (Mesenchymal stromal/stem cell); NK (cell, Natural killer cell); NO (Nitric oxide); NYHA (New York Heart Association); Oct (Octamer-binding transcription factor 4); PB (Peripheral blood); PD-1 (Programmed cell death protein 1); PDE-5 (Phosphodiesterase-5); PLGA (poly(lactic-co-glycolic acid)); PLLA (Poly-L-lactic acid); RNA (Ribonucleic acid); SC (Stem cell); Sca (Stem cell antigen); SCF (Stem cell factor); SDF (Stromal cell-derived factor); siRNA (Short interfering RNA); SSEA (Stage-specific embryonic antigen); SVF (Stroma vascular fraction); TALEN (Transcription activator-like effector nuclease); TGF (Transforming growth factor); TNF (Tumor necrosis factor); Treg (Regulatory T cell); VCAM (Vascular cell adhesion molecule); VEGF (Vascular endothelial growth factor).

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## Disclosure Statement

The authors declare no conflict of interests.

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