

Stem cell therapy for cardiac regeneration: key points



Kyryk V.

¹Institute of Genetic and Regenerative Medicine, M. D. Strazhesko National Scientific Center of Cardiology, Clinical and Regenerative Medicine, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine

²D. F. Chebotarev State Institute of Gerontology, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine

*Corresponding author's e-mail: labculture@gmail.com

ABSTRACT

Cardiovascular diseases are a leading cause of disability and mortality among the working population, necessitating the development and implementation of new, more effective treatment and rehabilitation methods for such patients, including the use of modern cell and tissue technologies.

In this review, an analysis and summary of research results over the past decades regarding the effectiveness of various types of stem cells in heart pathology were conducted.

Priority directions include the search for more accessible and safe sources of stem cells, the development of new effective methods for their cultivation, and the use of scaffolds for transplantation. Given the pathogenetic mechanisms of cardiovascular pathology and myocardial regeneration, particular interest for clinical application is drawn to tissue-specific progenitors from the myocardium for replacing injured cardiomyocytes, endothelial progenitors for correcting accompanying endothelial dysfunction, and multipotent mesenchymal cells of various origins with low immunogenicity that exhibit trophic, anti-inflammatory, immunomodulatory, and anti-apoptotic effects. Questions regarding the optimal method, dose, and frequency of stem cell administration, as well as the standardization of criteria for their quality and effectiveness, remain open. Additionally, the combined use of different types of stem cells may serve as a new priority strategy in assessing the effectiveness and safety of cell therapy, especially considering the paradigm of repeated transplantation.

The successful translation of obtained preclinical results into further large, well-planned, placebo-controlled clinical trials will enhance the safety and effectiveness of cell therapy for cardiovascular diseases, which is one of the current challenges of modern regenerative medicine.

KEY WORDS: cardiovascular diseases; cardiac regeneration; stem cells; cell therapy; preclinical studies; clinical trials

Prospects of cell therapy for treating main severe socially significant diseases attract the attention of researchers and clinicians worldwide. It is known that cardiovascular diseases occupy leading positions in terms of disability and mortality among the working-age population, and, in recent years, they increasingly affect younger people, leading to even earlier loss of productivity. Specifically, ischemic heart and vascular pathologies account for 17.3 million deaths annually worldwide [3, 54]. Direct and indirect costs for treating such patients in the United States alone exceed 320 billion US dollars annually, with forecasts predicting an increase to over 800 billion US dollars by 2030 [53]. In Ukraine, tens of thousands of patients with ischemic heart disease, cardiomyopathies, and stroke require more effective therapy methods.

Over the past years, several thousand patients worldwide have participated in clinical trials evaluating the effectiveness of cell therapy for various cardiovascular diseases [12, 124]. Accumulated data indicate its safety and efficacy not only in adult patients with ischemic heart disease, cardiomyopathies of various etiologies, and chronic heart failure but also in children with congenital heart defects [46, 47, 74]. Concurrently with

ongoing human studies, experiments on animals modeling myocardial injury continue to be crucial for detailed characterization of stem cells, demonstrating their biological effects, and predicting important clinical outcomes. Among the known pharmacological, instrumental, and surgical experimental approaches for myocardial injury, coronary artery ligation to model myocardial infarction remains the most widely used method [89]. Studies involving cell transplantation from humans to animals are mainly limited to experiments on genetically modified rodents capable of tolerating xenotransplantation. Potential rejection reactions by the recipient necessitate the use of immunosuppressants. Larger experimental animals, such as pigs, can undergo extensive functional and instrumental examinations, contributing to more reliable and clinically significant conclusions regarding the regenerative potential of stem cells [113].

However, despite the extensive research on the impact of cells of different types on the course of heart diseases, researchers and clinicians have not yet definitively determined recommendations regarding the optimal cell source for cell therapy of these diseases [37, 175]. In light of ethical issues related to the use of embryonic and fetal stem cells and the

insufficient efficiency of technologies for obtaining induced pluripotent cells, available sources of adult stem cells for myocardial regeneration include bone marrow, peripheral blood, adipose tissue, skeletal muscles, umbilical cord blood, placenta, and the myocardium itself. In addition to the source, it is important to choose the optimal route of cell delivery, dosage, and frequency of their application, which is a crucial issue in cardiac regenerative medicine.

STEM CELLS SOURCES FOR CARDIAC REGENERATION

Skeletal myoblasts

Research on stem cell transplantation for treating heart failure began with skeletal myoblasts. Skeletal muscles contain immature satellite cells and myoblasts capable of regenerating muscle tissue after damage. These satellite cells can proliferate and contribute to regeneration by differentiating into myotubes and new muscle fibers [11]. The advantages of skeletal myoblasts include their autologous origin and rapid growth in culture. Differentiation of immature myoblasts into cells resembling cardiomyocytes has been demonstrated in studies on dogs [34]. Further pre-clinical trials have shown that transplanting skeletal myoblasts improves heart function after modeled myocardial infarction in rats [148, 168]. Although the ability of transplanted cells to respond to electrical stimuli in damaged myocardium was demonstrated in animal models, they did not express the cardiac-specific marker of heavy myosin chains- α [123]. It was also shown in dogs that the integration of skeletal myoblasts into undamaged areas of the myocardium leads to arrhythmia development [48]. The proarrhythmic effect after skeletal myoblast transplantation may be associated with their loss of connexin-43 expression, leading to inadequate electrical integration with the host myocardium [143]. Other researchers, observing increased levels of troponin-I and interleukin-6 in experiments on pigs after skeletal myoblast transplantation, suggest that their proarrhythmic potential is mediated by local inflammation in response to the transplant [169].

In 2001, the first transplantation of skeletal myoblasts was performed on a 72-year-old patient with myocardial infarction, and subsequent studies on a limited sample of patients demonstrated some improvement in heart function [115]. Later, a multicenter randomized placebo-controlled double-blind clinical trial called MAGIC was conducted, aiming to provide the most comprehensive clinical assessment of skeletal myoblast efficacy. However, its results showed that neither regional nor global left ventricular function parameters, as assessed by echocardiography, significantly improved. Additionally, recipients showed a tendency towards a higher risk of arrhythmias [105, 114]. Overall, these studies indicate that skeletal myoblasts may not be an optimal cell source for cardiac regeneration.

Peripheral blood-derived stem cells

Experimental studies in rats have shown that transplantation of circulating CD34-positive endothelial progenitor cells stimulates neovascularization and remodeling of the damaged myocardium after infarction. Increased capillary density contributes to reducing left ventricular dilatation volume and preserving heart contractility [84]. Following the positive effects observed in animals, 59 patients with acute myocardial infarction were included in a randomized clinical trial TOPCARE-AMI, the results of which demonstrated the feasibility and safety of intracoronary administration of circulating blood progenitor cells. Clinical effects observed from 1 to 5 years of follow-up showed significant improvement in left ventricular function, reduced levels of NT-proBNP, and decreased end-systolic volume, indicating a positive impact of the cells on heart remodeling processes after infarction [5, 94].

In Ukraine, at Odessa National Medical University, in 2012, a phase I study ISIC (NCT01615250) was registered to evaluate the efficacy and safety of intramyocardial implantation of peripheral mononuclear cells including CD34⁺haematopoietic progenitors in patients with ischemic cardiomyopathy after a preparatory course of shock-wave therapy. However, the results of this study are not available in the accessible literature [36].

However, the reduction in the overall number of circulating progenitor cells in elderly individuals, the need for specialized equipment for their isolation, and the requirement for prolonged generation of a sufficient therapeutic dose limit the prospects for wide clinical application of this cell type in patients with cardiovascular diseases.

Bone marrow-derived cells in myocardial regeneration

Bone marrow contains various subpopulations of hematopoietic and mesenchymal stem and progenitor cells, comprising up to 2 % of the total content, capable of differentiating into various specialized phenotypes. The fraction of bone marrow mononuclear cells (BM-MNCs) can be isolated through density gradient centrifugation and does not require expensive cell culture technologies. This has led to wide applications of BM-MNCs in animal experiments.

At the beginning of the 2000s, a group of researchers led by Prof. P. Anversa declared the myogenic differentiation potential of BM-MNCs in mice. BM-MNCs, mobilized by stem cell factor and granulocyte-colony stimulating factor, can home to the infarcted region, replicate, differentiate, and ultimately promote myocardial repair [130]. It was also claimed that Lin⁻c-kit⁺ bone marrow-derived cells injected into the infarct zone promote newly formed myocardium, occupying 68 % of the infarcted portion of the ventricle 9 days after transplantation [131]. However, other groups were unable to replicate similar results, leading to a debate about the contribution of bone marrow cells to myocardial regeneration [6, 122]. Nevertheless, it has been established that BM-MNCs secrete pro-angiogenic cytokines and induce proliferation of endothelial progenitors in pigs with myocardial infarction [49].

In 2002, the first clinical trial evaluating the effectiveness of intracoronary infusion of autologous BM-MNCs in patients with acute myocardial infarction was conducted [159]. Although subsequent studies such as TOPCARE-AMI [5, 93], TOPCARE-CHD (NCT00289822) [4], BOOST (NCT00224536) [186], REPAIR-AMI (NCT00279175) [148], TIME (NCT00684021) [174], and LateTIME (NCT00684060) [173] have demonstrated positive impacts of BM-MNCs transplantation on heart functions, the overall clinical efficacy of this cell fraction in acute myocardial infarction remains controversial [23]. For example, a phase II, randomized, double-blind, placebo-controlled study FOCUS-CCTRN trial (NCT00824005) demonstrated no significant difference in left ventricular ejection fraction (LVEF) or infarct size in patients treated with BM-MNCs [140]. As well as in a multicenter, randomized, double-blind clinical trial MiHeart (NCT00333827) that evaluated intracoronary delivery of BM-MNCs and showed no significant changes in LVEF and left ventricular volumes [111]. However, most of these studies have certain limitations regarding the design, comparison groups, and the number of enrolled patients. Therefore, further research requires a more meticulous and responsible approach to accurately analyze the efficacy of cell therapy.

Multipotent mesenchymal stromal/stem cells (MMSCs)

Stromal-derived stem cells from various sources, capable of differentiating into mesenchymal derivatives such as bone, cartilage, adipose, and other stromal connective tissues, are classified into a distinct group of multipotent mesenchymal stromal/stem cells [68]. According to the recommendations of the International Society for Cellular Therapy, these cells must meet specific minimum criteria *in vitro*: adhesion to plastic, expression of specific intercellular adhesion markers CD105, CD73, and CD90, and lack of expression of haematopoietic CD45, CD34, CD14 or CD11b, CD79 α or CD19, and HLA-DR surface molecules. Additionally, they must have the ability to differentiate into osteogenic, adipogenic, and chondrogenic lineages *in vitro* [42]. The potential for their endothelial, myogenic, cardiomyogenic, and even neurogenic transdifferentiation is also under discussion.

In recent years, the paradigm of MMSCs' regenerative potential being realized solely through direct differentiation into specialized cell types has been somewhat revised. Increasing attention is being paid to the nonspecific paracrine effects of the cell transplant due to the production

of cytokines and growth factors, particularly in the form of exosomes [78]. MMSCs have a tropism for damaged areas and can influence the processes of inflammation and repair. They can suppress excessive inflammatory processes and maintain immune system homeostasis through contact and/or chemical interactions with immune system cells [39]. MMSCs provide immune tolerance to allogeneic cells in the recipient's immune system, which is why they are used in co-transplantation with bone marrow haematopoietic stem cells [203].

The most accessible, safe, and clinically significant sources of MMSCs in the adult body remain bone marrow and subcutaneous adipose tissue. Initially, researchers focused on bone marrow-derived multipotent mesenchymal stromal cells (BM-MMSCs). As early as the 1980s, it was demonstrated that BM-MMSCs could differentiate not only into chondrocytes and osteoblasts but also into skeletal muscle cells and cardiomyocytes [26]. Transplantation of human BM-MMSCs in a rat model of myocardial infarction showed improvement in left ventricular function [132, 201]. Intramyocardial injection in experiments on large animals demonstrated the safety of these cells and the procedure, activation of reverse myocardial remodeling, improvement of regional ventricular contractility, and reduction of post-infarction scars [80, 139, 149].

Several possible mechanisms for the therapeutic effect of MMSCs have been proposed: engraftment and differentiation into functional cardiomyocytes, paracrine signaling through numerous growth factors, stimulation of endogenous cardiac progenitor proliferation, or niche regulation [2, 60, 143]. Moreover, the best effects were anticipated from the application of cultured MMSCs for heart diseases, as indicated by the increasing number of clinical trials involving these types of cells in the early 2000s.

The safety and positive impact of bone marrow-derived MMSCs on left ventricular contractility in patients with myocardial infarction were first demonstrated in 2004 [31]. Subsequent studies confirmed the promise of this type of cell for the comprehensive therapy of acute and chronic ischemic heart disease [77, 112, 158, 182]. Specifically, intramyocardial injection of autologous BM-MMSCs in ischemic heart disease with heart failure, both in the early stages and long-term (12 months), showed an increase in patients' maximum metabolic equivalent, a reduction in the class of heart failure, a decrease in the frequency of angina attacks, and a reduction in the required dose of nitroglycerin. Improvements in quality of life indicators and increased tolerance to physical exercise were also demonstrated [57]. Both autologous and allogeneic MMSCs have shown not only the safety of transplantation but also sufficient therapeutic potential by reducing episodes of ventricular tachycardia, increasing left ventricular ejection fraction, preventing its remodeling, and improving lung function based on forced expiratory volume indicators [59].

One of the first clinical trials to assess the safety and efficacy of cell therapy using autologous BM-MMSCs compared to BM-MNCs in ischemic cardiomyopathy was the phase II randomized, placebo-controlled study TAC-HFT (NCT00768066). The results demonstrated the safety of transcatheter stem cell injection for patients and an improvement in quality of life measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score. However, these clinical effects were not supported by improvements in functional indicators such as LVEF or left ventricular volumes [62].

The POSEIDON-DCM trial (NCT01087996) compared safety and efficiency of allogeneic vs. autologous BM-MMSCs delivered by transcatheter injection in doses 20 million, 100 million, or 200 million cells in patients with ischemic cardiomyopathy. At 1 year, quality of life, functional capacity and LVEF increased significantly only in the allogeneic cell therapy group, but cardiac function improvement were not accompanied with reverse remodeling [58].

Adipose-derived stem cells (ASCs)

Considering the drawbacks of bone marrow aspiration via bone puncture, such as pain, the risk of removing hematopoietic tissue from an active blood-forming site, and the need for colony-stimulating factors

to mobilize stem cells from niches, adipose tissue has become a more prioritized source of MMSCs. The current level of surgery and anesthetic support allows for brief, minimally invasive procedures to obtain the minimal amount of whole adipose tissue or lipoaspirate sufficient for direct application of primary isolated stromal vascular fraction (SVF) or its further cultivation.

In culture, ASCs produce a number of growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), which have cardioprotective effects [8]. Numerous *in vitro* and *in vivo* experiments have demonstrated that multipotent stem cells can be isolated from adipose tissue and are capable of differentiating into cardiomyocytes, prompting active research into their regenerative potential in animal models of cardiovascular pathology [119, 141]. Sca-1⁺ and c-kit⁺ cells from SVF are more prone towards cardiomyogenic differentiation, forming eight times more contractile colonies [134]. ASCs expressing CD133 can also differentiate into cardiomyocyte-like cells when co-cultured with bone marrow or cord blood cells [191]. Enhanced expression of cardio-specific markers, along with increased cell viability and protein synthesis, has been achieved by transfecting IGF-I gene into the ASCs culture [205].

As a result, transplanted adipose tissue stem cells can improve the heart's contractile function and its vascularization [71]. In a rat infarct model, an increase in left ventricular ejection fraction, wall thickening, and capillary density in the infarct border zone was shown due to the production of cardioprotective factors VEGF, HGF, IGF-I; however, only 0.5 % of the transplanted cells stained positively for myocardium-specific fibrillar proteins [72, 180]. ASCs, when administered intracoronary in pigs, also reduce myocardial damage, increase LVEF, and enhance vessel density [92, 177]. In a rat model of dilated cardiomyopathy, ASC transplantation, in addition to increasing the ejection fraction, also prevented dilatory ventricular remodeling and effectively improved systolic and diastolic heart function [97]. Moreover, the combined administration of ASCs with sildenafil in a dilated cardiomyopathy model is more effective than monotherapy. In this case, angiogenesis, IL-10 expression, anti-apoptotic Bcl-2 expression are enhanced, while the production of apoptotic markers matrix metalloproteinase-9, Bax, and caspase-3 is reduced in the ischemic tissue [101]. ASCs, specifically differentiated into cardiomyocytes, reduce myocardial remodeling in infarction, stabilize the ejection fraction, and promote neovascularization of the ischemic area [95, 192].

In a series of studies by Okura H. et al. and Shudo Y. et al. (Osaka University, Japan), the researchers evaluated the preclinical efficacy of using human adipose-derived multipotent progenitor cells and cardiomyoblast-like cells differentiated from them in the treatment of ischemic heart disease. The efficiency of directed differentiation of human ASCs into cardiomyoblasts *in vitro* was confirmed by quantitative reverse transcription polymerase chain reaction, which showed an increase in the expression of mRNA markers of cardiogenic commitment, such as islet-1, light and heavy myosin chains, as well as transcription factors Nkx2.5 and GATA-4. Echocardiography data indicated that 4 weeks after intracoronary cell transplantation, there was an improvement in myocardial wall motion. In the control group, however, this parameter worsened over the entire study period up to 12 weeks. In the early period after transplantation, there were no significant differences in the diastolic dimensions of the left ventricle, but subsequently, diastolic dysfunction progressed in the control group, whereas this parameter did not change significantly after cell transplantation [129, 153].

The feasibility and safety of clinical application of ASCs have been evaluated in multicenter randomized placebo-controlled trials APOLLO (NCT00442806) and ADVANCE (NCT00426868) in patients with acute myocardial infarction, as well as PRECISE (NCT00426868) and MyStromalCell (NCT01449032) trials – in patients with refractory chronic myocardial ischemia. Overall, increases in left ventricular ejection fraction, improvement in myocardial perfusion, and reduction in infarct size have been demonstrated both pathology in early (6 months) and long-term (up to 3 years) follow-ups after cell transplantation [21, 69, 138]. A prospec-

tive randomized double-blind clinical trial, Athena I/II (NCT01556022/NCT02052427), conducted in 2012-2015 to assess the therapeutic potential of ASCs in ischemic cardiomyopathy, showed increased maximal oxygen uptake and significant improvement in patients' quality of life based on the MLHFQ results at 12 months post intramyocardial ASCs transplantation [64].

Cardiac-derived stem cells (CSCs)

In the pathogenesis of decreased myocardial contractility in ischemic heart disease, dysfunction of resident progenitors plays a significant role, making approaches involving the isolation, expansion, and application of tissue-specific cardiac-derived stem cells the most promising [22, 76, 194].

In the early 2000s, studies by prof. Anversa's group were published regarding the presence of proliferating cells in the myocardium after myocardial infarction [10]. It is assumed that in the adult heart, CSCs are located in niches in close contact with supporting cells that provide conditions for the survival, proliferation, and self-renewal of stem cells [167]. Although their numbers decrease with age (three times more in newborns than in 2-year-old children), functionally active CSCs can still be isolated even from elderly patients [38, 79, 120, 190]. Additionally, Li Z. et al. demonstrated that the structural integrity of the adult human heart's endothelium after myocardial infarction was maintained through clonal proliferation by resident endothelial progenitor cells in the border zone of the infarct, without significant contributions from bone marrow cells or endothelial-to-mesenchymal transition [96, 99, 106].

CSCs can be sourced from myocardial biopsies, interatrial septum, or right atrial appendage ranging from 25 mg to 1 g, obtained during open-heart surgery or through minimally invasive procedures, allowing for the expansion of the necessary therapeutic cell dose over 4-5 weeks [29, 33, 118]. Numerous studies have developed techniques for obtaining resident myocardial progenitor cells in mammals. Following enzymatic processing, tissue fragments are cultured using explant methods, followed by the generation of cardiospheres. Cardiospheres consist of proliferating stem and progenitor cells that undergo spontaneous differentiation towards a cardiac lineage. They have a relatively large size (40–150 μm), making them unsuitable for intracoronary delivery as they may cause embolization. An additional step should involve converting cardiospheres into suspension through enzymatic digestion or culturing on growth substrate-coated surfaces [156, 183, 185].

It has been demonstrated that the formation of cardiospheres from primary culture explants of heart biopsies requires the presence of cardiotrophin as a growth factor and the sequential change of poly-D-lysine and fibronectin as growth substrates. The presence of additional exogenous growth factors and extracellular matrix components is considered a necessary condition for obtaining cardiospheres and a population of cardiac progenitor cells from them [33].

Poly-D-lysine belongs to several types of lysine homopolymers with a molecular weight of 50–150 kDa and serves as a synthetic extracellular matrix. Fibronectin is a high-molecular-weight (~500–600 kDa) glycoprotein of the extracellular matrix that binds to membrane receptor proteins called integrins. Both cell expansion and differentiation depend on the surface properties of the culture substrate. Specifically, the polycationic properties of poly-D-lysine allow it to interact with anionic sites on the membrane, promoting more effective cell attachment to the growth surface. The fibronectin molecule contains an RGD amino acid sequence (Arg-Gly-Asp), which is a binding site for integrins $\alpha 5\beta 1$ and $\alpha v\beta 3$ on the cell membrane surface. Fibronectin also interacts with other extracellular matrix proteins such as collagen, fibrin, and heparan sulfate proteoglycans. The main function of these components is to enhance cell adhesion to the culture surface, promote proliferation, morphogenesis, differentiation, and migration [200].

According to literature data, key markers for CSCs include CD90, CD105, CD117 (c-kit). Additionally, CSCs may moderately express the hematopoietic stem cell marker CD34, the endothelial marker CD31, and

the VEGF receptor (CD309). Flow cytometry phenotyping has shown that by the second passage, CSCs mainly express CD105, and to varying degrees CD90, CD34, CD31, as well as the key marker c-Kit. They are negative for the markers MDR1, CD133, and CD45, distinguishing them significantly from bone marrow and circulating endothelial progenitors that may populate the heart [61, 120]. Clonally proliferating CSCs also express the stem cell antigen Sca-1 and a range of pluripotency-associated genes including NKX2-5, NOTCH1, NUMB [165]. Sca-1⁺ progenitors in the heart have high telomerase activity, the ability to migrate to damaged myocardium, and differentiate into cardiomyocytes [127, 166]. Some transplanted CSCs in animals also form vascular structures and express α -smooth muscle actin. It is suggested that upon terminal differentiation, these cells may express typical cardiomyocyte markers such as troponin I, troponin T, heavy chains of myosin, and connexin-43 [16, 190].

Koninckx et al. identified a population of myocardial cells that actively express aldehyde dehydrogenase, which enhances their survival under ischemic conditions, the marker islet-1, and they had a greater ability to differentiate into cardiomyocytes than previously known CSCs [87]. Bolli et al. confirmed that c-Kit⁺ CSCs are capable of differentiation into all cardiac cell lineages [16].

Immunofluorescence studies with confocal microscopy confirm the high proliferative activity of cardiospheres by Ki-67 expression. Proliferating cells actively express connexin-43 and alpha-sarcomeric actin, indicating a high potential for electrical conduction integration between cells. When co-cultured with cardiomyocytes from newborn rats, human and porcine CSCs exhibit biophysical characteristics of cardiomyocytes, along with calcium transport synchronization between neighboring cells. Importantly, after 3 or more passages (6 population doublings, 60 days in culture), no aberrations were observed in the karyotype [156].

In our study, proliferating cultures of cardiac progenitors were obtained from the myocardium of newborn mice. The appearance of rhythmic contractile activity both in cardiospheres and monolayer cultures during their terminal differentiation indicates a high potential for cell integration *in vitro* and preservation of their excitability. Using flow cytometry and immunocytochemical analysis, our research revealed that the cultured cells from the myocardium express a range of markers corresponding to the CSCs phenotype, suggesting their suitability for further investigations. Early passages of the myocardial cell cultures from explants of newborn mice showed increased expression of markers CD44, CD105, and CD90, as well as CD309 and endothelial marker CD31. We also observed a minor population of CD34⁺117⁺ cells that phenotypically resemble cardiac progenitor cells. In terminally differentiated cultures, spontaneous rhythmic contractile activity *in vitro* was detected, along with confirmed expression of cardiac troponin I [90].

Our research confirms findings by other authors that newborn mice myocardial tissue contains a greater number of cells expressing markers of multipotent progenitors than adult animals. Moreover, the relative content of such cells is higher in the atria than in the ventricles. Therefore, a priority direction for further research is the isolation and cultivation of cells from the myocardium of younger organisms, particularly from the atrial appendages. Our results also support the data presented by Chan H. et al., demonstrating differences in the proliferative potential and marker expression of cells from the atria and ventricles [29]. Due to their relatively large size, cardiospheres cannot be applied intracoronary due to the risk of microvessel embolism. Therefore, an additional step involves dissociation of cardiospheres or their subculture on a fibronectin-coated surface.

In assessing the therapeutic potential in an experiment on immunodeficient mice, Smith et al. demonstrated that human CSCs, when injected at the edge of the myocardial infarction, engrafted and migrated into the damaged area. After 20 days, the percentage of viable cardiomyocytes in the infarct zone was higher in the group receiving CSCs compared to the control group receiving skin fibroblasts. Additionally, an increase in left ventricular ejection fraction was noted [156].

Intramyocardial injection of CSCs from the atrial appendage in pigs with myocardial infarction prevented left ventricular dilation, reduced ejection fraction, and myocardial wall thinning, which are characteristic of the control group. Additionally, there were improvements in regional contractility and cardiomyocyte survival, explained by the successful engraftment of the transplant and its differentiation [44]. Moreover, transplantation of allogeneic CSCs to rats without immunosuppression was found to be safe and only caused a short-lived local immune reaction without signs of systemic immunogenicity. Despite reduced engraftment duration compared to syngeneic cells, allogeneic CSCs showed positive structural and functional effects [108].

The group led by Lauden L. and colleagues demonstrated that human CSCs do not elicit typical immune reactions in rats mediated by Th1 or Th2 lymphocytes. Instead, they suppress effector regulatory T-lymphocytes' proliferation and expansion. The programmed cell death ligand PD-L1 plays an important role in the immune behavior of CSCs, with potential for evaluating its expression as a marker for identifying allogeneic cells with low risk and high regenerative potential. CSCs in an allogeneic context exhibit immunologically tolerant immune behavior, contribute to PD-L1-dependent responses, and modulate immunity [20, 91]. Similar results were obtained in mini pigs with chronic ischemic cardiomyopathy, where transendocardial injection of 150 million allogeneic CSCs not only reduced post-infarction scar size and heart dilation but also improved myocardial viability according to magnetic resonance imaging data. There was no increase in circulating antibody levels or signs of myocardial inflammation in histological examination [197].

From 2008 to 2012, the initial clinical trials SCIPIO (NCT00474461) [13], CADUCEUS (NCT00893360) [109] in the USA, and ALCADIA (NCT00981006) [163] in Japan, involving the transplantation of autologous c-kit⁺ CSCs in patients with ischemic cardiomyopathy and chronic heart failure, demonstrated increased left ventricular ejection fraction, reduced end-systolic and diastolic volumes, decreased size of the post-infarction scar, increased viable myocardial mass, regional contractility, and maximal oxygen consumption. Therapeutic doses of the drug ranged from 1 to 37 million cells, administered via intracoronary infusion or intramyocardial injection. The absence of complications and preservation of positive dynamics were noted in both early (3 months) and long-term (12 months) follow-ups after transplantation [189]. Subsequently, from 2014 to 2020, a randomized placebo-controlled double-blind study called DYNAMIC (NCT02293603) was conducted at Cedars-Sinai Medical Center (USA) involving the transplantation of allogeneic CSCs [28]. A similar multicenter project CAREMI (NCT02439398) was launched in Spain in 2014. Allogeneic cardiac stem cells can be safely administered in ST-segment-elevation myocardial infarction patients with left ventricular dysfunction early after revascularization, although the therapeutic effectiveness was modest [45]. The expected therapeutic effectiveness in reducing scar size was not achieved within 6 months in the II phase of the clinical trial ALLSTAR (NCT01458405), although significant improvement in myocardial segmental contractility, reductions in LV volumes, and NT-proBNP were observed [133].

Additional confirmation of the safety of CSCs, as demonstrated in pilot clinical trials, can be provided by a series of projects TICAP (NCT01273857), PERSEUS (NCT01829750), and APOLLON (NCT02781922) at Okayama University Hospital (Japan), where the efficacy of these cells in children with congenital hypoplastic left heart syndrome and single ventricle is being studied [75, 164].

However, the group led by Molkenkin J. et al. demonstrated that endogenous c-kit⁺ cells did produce new cardiomyocytes within the heart, although at a percentage less than one-tenth of a percent, and therefore may not play a significant role in myocardial regeneration after injury [178]. In contrast, the authors showed that c-kit⁺ cells abundantly generated cardiac endothelial cells, which coincided with our results regarding CD31 expression *in vitro* culture. Thus, a heated scientific debate was reignited regarding the cellular mechanisms involved in heart regeneration. The investigation revealed instances of academic misconduct and

falsification regarding proper evidence of stem cell identification and isolation from the myocardium. As a result, over 30 publications by prof. Anvers's group were retracted from several leading journals, and there is significant caution within the scientific community regarding the theory of cardiac stem cells [81]. The substantial contribution of cardiac stem cells to myocardial regeneration after injury remains a subject of debate and requires further in-depth research.

Perinatal tissue-derived stem cells

Over the past decade, there has been a significant increase in the number of umbilical cord blood, umbilical cord tissue, and placental tissue cryobanks worldwide. This trend is explained by the active interest of researchers and clinicians in these sources of stem cells. These tissues, obtained after childbirth without harm to the health of the newborn or the mother, contain populations of hematopoietic and mesenchymal progenitors with high regenerative potential [43, 135]. Considering the patient's condition-related contraindications to autologous sample collection and the need for early initiation of therapy, there is an objective need for a ready-to-use cellular product that does not require time for expansion. These sources can be particularly relevant in cases where myocardial biopsy for isolating tissue-specific cardiac progenitor cells is not feasible.

Umbilical cord blood stem cells

Umbilical cord blood has long been used in the treatment of immune disorders and oncohematological diseases, thanks to the presence of a significant number of CD34⁺ hematopoietic progenitors. Additionally, autologous cord blood finds application in newborns for replenishing blood loss during heart surgeries for congenital heart defects.

Studies on rats with myocardial infarction have shown that transplantation of cord blood cells significantly improves cardiac contractile function and reduces manifestations of heart failure [63, 65]. Experimentation on pigs has confirmed the safety of the intramyocardial injection technique of cord blood cells into the right ventricle during open-heart surgery [25].

In the short term (1-3 months) after the transplantation of cord blood mononuclear cells, there was a demonstrated partial recovery of left ventricular systolic function by echocardiography and a significant improvement in impaired heart mechanics. No negative effects, complications, or side effects have been detected in the short periods of observation after cord blood-derived cell transplantation [50].

However, the limited volume of cord blood and the lack number of isolated progenitor cells are not always sufficient to achieve an adequate therapeutic effect. Considering the hematopoietic origin of these cells, rejection reactions of the transplant or, conversely, graft-versus-host reactions are not excluded in allogeneic applications.

Umbilical cord Wharton's jelly-derived MMSCs (UC-MMSCs)

The Wharton's jelly of the umbilical cord serves as a convenient and accessible source for isolating MMSCs, which can be used in the treatment of cardiac pathology. Findings from Liu et al. suggest that human umbilical cord-derived MMSCs contribute to cardiac functional recovery and attenuate cardiac remodeling post myocardial infarction. Intramyocardial injection of these cells upregulates CD4⁺FoxP3⁺ Tregs and contributes to the migration of CD4⁺ T cells into the injured heart via the CCL5/CCR5 pathway [103]. Another study indicates that UC-MMSCs, transplanted via intracoronary delivery combined with two intravenous administrations, are safe and significantly improve left ventricular function, perfusion, and remodeling in a large-animal model of chronic myocardial ischemia [102]. Lim et al. have shown that intravenous injection of UC-MMSCs is a feasible and effective way to preserve left ventricular function and ameliorate myocardial remodeling in porcine acute myocardial infarction. The cardioprotective effects of UC-MMSCs are attributed to paracrine factors that appear to augment angiogenesis, limit inflammation, and preserve Cx43 gap junction [100].

The HUC-HEART trial (NCT02323477) was initiated to evaluate the efficacy of human umbilical cord-derived MMSCs for cardiac repair and remodeling in myocardial infarction [24]. In a multicenter trial WJ-MSC-AMI (NCT01291329), which enrolled 116 patients with acute ST-elevation myocardial infarction, intracoronary infusion of UC-MMSCs was found to be safe and effective, providing clinically relevant therapy within a favorable time window during an 18-month follow-up. The absolute increase in myocardial viability by PET and perfusion within the infarcted area by SPECT, as well as the absolute increase in LVEF and decreases in LVESV and LVEDV, were significantly greater in the UC-MMSC treatment group compared to the placebo group [52]. Results from the phase 1/2 randomized controlled trial RIMECARD (NCT01739777) demonstrated improvements in left ventricular function, functional status, and quality of life in patients with stable heart failure and reduced ejection fraction treated with intravenous infusion of UC-MMSCs [9]. Other clinical trials have also shown that using UC-MMSCs in the treatment of congestive heart failure can help improve cardiac remodeling and cardiac function [32, 204]. However, a systematic review and meta-analysis by Abouzid et al. indicate that UC-MMSC transplantation can improve ejection fraction but has no meaningful effect on readmission or mortality rates [1]. Thus, there is a need for expanded clinical trials to further substantiate these findings.

Placenta-derived stem cells

Stem cells from the placenta are becoming promising candidates for regenerative therapy of heart diseases. They can be isolated in significant quantities, easily expanded to the required therapeutic dose, and cryopreserved for long-term storage and future use as needed. Additionally, they exhibit a high potential for multipotent differentiation and low immunogenicity. Considering their additional anti-inflammatory and antifibrotic effects, placental MMSCs are seen as a unique source of cytokines and growth factors capable of reducing the consequences of ischemic tissue injury [18, 187]. It is important to note that the use of placental MMSCs allows us to avoid moral and ethical limitations associated with fetal stem cells. At the same time, they can be safely applied in both autologous and allogeneic settings without triggering harmful host-versus-graft reactions.

The study in rats with modeled myocardial infarction showed that transplantation of human placental stem cells improves the contractile function of the left ventricle, significantly reduces scar size, suppresses inflammation and apoptosis, and stimulates angiogenesis [199]. Additional processing of placental cells with hyaluronan ethers of oleic and retinoic acid, besides the pro-angiogenic effect, promotes their expression of cardiac markers connexin 43 and troponin I [179].

Similar results were obtained in an experiment on mice with a model of chronic heart failure. Four weeks after the introduction of the human placental cell product PDA-001 (Cenplacel-L), intramyocardial injection, unlike their intravenous administration, significantly improved systolic and diastolic function of the left ventricle. Simultaneously, a reduction in fibrosis in the injection areas was noted. Low doses (0.5×10^4 cells per mouse) showed a more pronounced therapeutic effect than high doses (0.5×10^5), which also applied to the levels of proliferative activity of recipient endotheliocytes and cardiomyocytes. However, using *in vivo* visualization, donor cells were detected in the myocardium by luciferase expression only in the first 2 days after administration, indicating the indirect nature of the cells' regenerative potential through paracrine factors [30].

In another study, two months after transplantation of human chorionic plate-derived stem cells into mice with myocardial infarction, a significant increase in the ejection fraction was noted along with a decrease in the end-systolic volume. Despite intramyocardial injection, the localization of the transplant in the myocardium was confirmed only in the first 4 days, and this period decreased for two subsequent repeat injections [136].

The high potential for homing, engraftment, and multipotent differentiation of placental mesenchymal stem cells is supported by experiments showing the migration of fetal origin cells into the myocardium of

pregnant mice with heart injury. In this process, 40 % of these fetal cells expressed the Cdx2 factor associated with trophoblast stem cells of the placenta. Moreover, isolated donor cells from the heart were capable of clonal expansion and differentiation into cardiomyocytes [82].

Vadakke-Madathil et al. demonstrated that intravenous administration of placental Cdx2 cells led to targeted homing, sustained engraftment, and differentiation into cardiomyocytes and vascular cells in injured murine hearts. This significantly improved cardiac function and exhibited the ability to selectively target injury sites [176].

Preclinical analysis of intramyocardial administration of 1×10^7 placental MMSCs in a pig model of myocardial infarction showed, after 4 weeks post-transplantation, no significant changes in ejection fraction, left ventricular volume, or stroke volume, although the size of the infarct scar was significantly reduced by 40 %. Transplantation of cells contributed to improvements in regional wall thickness parameters in the infarct area, maximal circumferential shortening (LVEccmax), and perfusion levels based on positron emission tomography data. Overall mortality rates among animals did not increase after the administration of the cells, indicating the absence of life-threatening complications related to the transplantation procedure or the cells themselves [155].

One of the first cases of clinical application of placental MMSCs in combination with cord blood cells in a patient with dilated cardiomyopathy was described in 2008. Over an 11-month observation period, improvement in the clinical picture was noted without any detected side effects or host-versus-graft reactions [73]. Clinical trials using these cells in patients with critical limb ischemia confirmed that repeated administration of allogeneic placental MMSCs, even in high doses (60×10^6), does not induce graft rejection due to their immunosuppressive and immunomodulatory properties. During the 6-month follow-up period, there was a significant decrease in IL-1 and IFN- γ serum levels following placenta-derived MMSC treatment and cell injection [152].

Currently, there are several dozen clinical trials using placental MMSCs for various diseases, including cardiovascular conditions, where placental MMSCs are administered intravenously or intramuscularly at different doses [36]. One of the world's first safety and primary efficacy evaluation studies of intramyocardial injection of placental MMSCs in patients with ischemic cardiomyopathy and severe heart failure was registered in Ukraine in 2017. The primary results of the clinical trial demonstrated that transepical transplantation of placental MMSCs in combination with myocardial revascularization is safe and significantly improves cardiac contractile function in patients with ischemic cardiomyopathy. This improvement is evidenced by a significant reduction in heart failure symptoms, partial increase in regional myocardial contractility based on speckle-tracking echocardiography data, and improvement in quality of life assessed by MLHFQ and HeartQoL questionnaires [51].

Pluripotent stem cells

Given that type-specific progenitor cells from adult organisms are not always available in sufficient therapeutic quantities, and reprogramming technologies of MMSCs are still far from proven effectiveness, the pluripotent potential of embryonic stem cells (ESCs) from the inner cell mass of the blastocyst is promising for their directed differentiation towards cardiovascular progenitor cells and subsequent clinical application [41, 74].

In a rat model of acute myocardial infarction, Caspi et al. demonstrated that while undifferentiated embryonic stem cells form teratomas, grafted *ex vivo* pre-differentiated ESCs-derived cardiomyocytes survived, proliferated, matured, aligned, and formed gap junctions with host cardiac tissue, attenuating the remodeling process and providing functional benefit [27]. Numerous preclinical studies of pluripotent stem cell-derived cardiomyocyte transplantation have shown improved cardiac functions in laboratory animals with modeled myocardial pathologies, paving the way for clinical trials of these cell types [128].

In the ESCORT trial (NCT02057900), Menasché et al. assessed the safety of ESC-derived Isl-1⁺ SSEA-1⁺ cardiac progenitors embedded into

a fibrin scaffold in patients with severe ischemic left ventricular dysfunction. Although the main limitation of this study is the small sample size of only 6 patients, two of whom died, this trial demonstrates the technical feasibility of producing highly purified clinical-grade human ESC-derived cardiovascular progenitors and supports their short- and medium-term safety in patients with symptomatic improvement due to increased systolic motion of the cell-treated segments [116].

In studies by Yamanaka et al., using viral vectors to introduce transcription factor genes (Oct3/4, Sox2, cMyc, Klf4, Nanog, Lin28) responsible for pluripotency into differentiated cells, a technology was developed to obtain induced pluripotent stem cells – iPS, which, by all characteristics, resemble embryonic stem cells and can be differentiated into cardiomyocytes [193]. In a pig model of myocardial infarction, it was shown that human pluripotent stem cell-derived committed cardiac progenitors remuscularize damaged ischemic hearts and improve their function [196]. Intramyocardial transplantation of iPS cell-derived cardiac spheroids in gelatin hydrogel improves cardiac function by direct engraftment and angiogenesis in small and large animal models [83]. These cells are particularly promising for use in tissue engineering technologies to create cell sheets or patches for regenerative purposes [55, 171].

One of the first official clinical trials involving the application of implant sheets 0.1 mm thick and 4 cm long consisting of 100 million iPSC-derived cardiomyocytes in patients with ischemic cardiomyopathy was initiated in 2020 at Osaka University Graduate School of Medicine, Japan (JRCT2053190081). Positron emission tomography and computed tomography confirmed the potential efficacy and did not detect tumorigenesis in either the heart or other organs under concurrent treatment with immunosuppressive agents. The changes in wall motion at the transplanted site were recovered, and clinical symptoms improved at 6 and 12 months after surgery, with no major adverse events reported, suggesting good tolerance of the patches [85, 121].

In Germany, a study is planned for patients with end-stage heart failure involving the implantation of engineered heart patches constructed from iPSC-derived cardiomyocytes in collagen [117]. In the HEAL-CHF study (NCT03763136) at Nanjing Hospital, China, 100-200 million allogeneic Human Pluripotent Stem Cell-derived Cardiomyocytes in 2.5-5 mL medium suspension were injected into the myocardium during coronary artery bypass grafting surgery [107]. In another study, IDCVTCHF (NCT03759405) at Beijing University of Chinese Medicine, the effectiveness of autologous cardiomyocytes derived from iPS cells will be evaluated through intravenous administration to patients with chronic heart failure [117].

Overall, the transplantation of iPS cell-derived cardiomyocytes represents an alternative to the use of embryonic stem cells, eliminating significant ethical, legal, and even religious constraints associated with experiments involving human embryos.

Cell delivery methods for myocardial regeneration

Stem cell transplantation faces challenges due to limitations such as low cell viability, inadequate homing to damaged sites, poor survival and retention in the disease environment, and insufficient paracrine effects of stem cells. Therefore, alongside choosing the cell source, the safety and effectiveness of cell therapy for both individual patients and the technology as a whole largely depend on selecting the optimal delivery method into the body and the damaged area. The route of administration depends on the diagnosis, disease progression characteristics, severity of the patient's condition, available instrumental and technical means, and the expertise of the personnel. Cell products can be administered to patients through various routes: subcutaneously, systemically intravenously, locally intra-arterial, directly into tissue or an organ, and the use of scaffolds engrafted with cells [86, 157, 188].

Local cell delivery is considered more effective when cells are delivered directly to the site of pathological changes, reducing migration time, increasing the effective therapeutic dose, and reducing graft loss. The efficacy of subcutaneous and intradermal injection delivery has

been demonstrated for dermal fibroblasts and bone marrow or adipose tissue-derived MMSCs in facial and hand plastic surgery, keloid scar correction, wrinkle correction, etc. [126]. Another option for local delivery is transdermal injection of cell suspensions directly into the affected tissue. This method involves injecting cells around trophic ulcers and into leg muscles for treating ischemic complications of diabetes and occlusive vascular diseases; into soft tissues for treating lipodystrophy and body contouring; around fistulas for treating Crohn's disease complications; into the urinary bladder sphincter for stress urinary incontinence; into cavernous bodies for erectile dysfunction; and intra-articular for treating osteoarthritis [35]. The main limitation of this method is the anatomical accessibility of the affected area for direct transdermal injections without the risk of damaging other organs, major vessels, or nerves.

To achieve a local effect, cells can also be delivered through intra-arterial injection into the vascular pool supplying the necessary area. This method is used to deliver cells into the coronary arteries of affected segments in ischemic heart disease, into regional brain vessels in strokes, and in critical limb ischemia in diabetic patients, among others [19, 47]. The main risk in this approach is perforation of large arteries leading to bleeding, as well as embolization of small vessels with cell aggregates, which can result in myocardial infarction, stroke, or tissue necrosis.

When access to affected tissues and organs is limited for transdermal injections, local cell delivery can be performed during surgery as a primary or adjunctive step in comprehensive treatment. The main advantage of this method is the clear visualization of the injection site, allowing for the identification of boundaries of pathologically altered tissues suitable for cell delivery. It helps identify individual anatomical features that may affect treatment outcomes, control the area and depth of cell injection for maximum effectiveness with minimal risks of perforating hollow organs, damaging major vessels or nerves, and use scaffolds for shaping or supporting functions [12].

Choosing the optimal method of cell delivery to the injured myocardium and the necessary frequency of their administration are key factors in the success of cell therapy. Experimental and clinical studies in stem cell therapy for heart diseases employ systemic intravenous, local intracoronary, transendocardial, and transepical cell delivery [151].

Intravenous cell delivery, which is the simplest and least traumatic, aims to maximize the distribution of transplanted cells throughout the body via the bloodstream and is therefore used in practically all types of pathologies where positive systemic effects are expected from cell therapy, such as hematological disorders, diabetes mellitus, cardiovascular diseases, autoimmune pathology, and others. It is known that stem cells can perceive signaling molecules from tissues, migrating specifically to the site of damage (homing) [104]. However, although the ability of intravenously transplanted cells to migrate to the damaged zone and locally differentiate into specialized phenotypes has been demonstrated, the expected colonization of pathological foci by the administered cells in quantities sufficient for a therapeutic effect requires an increase in their transplantation dose or frequency of application, as most of them predominantly reside in the lungs [7, 181, 198].

Compared to previous studies in mice [66, 67], high-precision polymerase chain reaction analysis demonstrated comparable or even better effectiveness of delivering an increased number of myocardial progenitors directly into the left ventricle under 2D ultrasound guidance to prevent their entry into the post-infarction scar or coronary artery. It is worth noting that with this delivery method, only approximately 1 % of the cells remained in the heart after 24 hours. In contrast, intramyocardial delivery resulted in 10 % of cells remaining in the heart after 24 hours, and intracoronary delivery resulted in approximately 5 % of cells remaining after the same period. These findings pave the way for clinical application of a new, technically straightforward, and relatively safe method of delivering an increased number of stem cells into the heart directly into the left ventricle [56].

Intracoronary cell delivery to the myocardium is relatively safe and convenient, although prolonged retention of the graft in the damaged

zone remains problematic. Moreover, such an approach requires highly qualified personnel and specialized equipment for visualizing vessels and their catheterization. Additionally, in certain types of pathology, the damaged area may be sufficiently isolated to prevent transplanted cells from penetrating it. For example, in chronic ischemic heart disease, blood supply is significantly impaired due to vessel atherosclerosis and myocardial fibrosis. In ischemic strokes, cell migration from vessels is limited due to the presence of the blood-brain barrier and the so-called "penumbra" around the focal neural tissue injury.

It can be assumed that certain positive clinical effects of cell therapy in such cases were primarily associated with nonspecific systemic effects on the body due to the production of numerous cytokines and growth factors by the transplanted cells, which stimulated local regeneration processes indirectly through the activation of endogenous resident progenitors in the recipient's tissues, rather than through the differentiation of the graft [88].

On models of myocardial infarction in animals, it has been shown that long-term persistence of a large number of transplanted cells in the damaged zone is associated with long-term benefits of their influence on heart function. Numerous preclinical studies have demonstrated that intramyocardial cell delivery promotes better cell engraftment in the heart compared to intracoronary delivery and has a more positive impact on their regenerative potential [98, 113, 139]. Intramyocardial transplantation in experiments on large animals and in humans can be accomplished using specialized microinjection catheters inserted into the left ventricular cavity through access in the femoral or brachial artery [80]. However, such transendocardial delivery requires careful instrumental mapping of myocardial contractility to clearly define the post-infarction scar zone and accurately position the injection needle using radiographic visualization methods.

Limitations of transendocardial delivery include access only to the left ventricle, the risk of cardiac wall perforation and arrhythmias, cell loss in a relatively long catheter, significant duration of myocardial mapping and catheter positioning for injection, the need for fluoroscopy for 2D catheters, and overall, the relatively high cost of the necessary equipment. Another option is transcatheter-intramyocardial delivery with access through the femoral vein using intravascular ultrasound guidance, which has less stringent requirements and risks for repeated injections [154, 170]. However, it also carries risks of coronary vein damage and cardiac perforation, limitations related to access to specific heart sections, variability in venous sinus anatomy, the number of injections during the procedure, and residual cell volume in the catheter.

In the case of open-heart surgeries, transeptal cell injections under clear visual control of the required myocardial zone and volume dosing are optimal. The advantages of this approach include wide access to the anterior sections of the heart, visual selection of the injection zone, visual control of injection, and speed of manipulation. However, disadvantages include the need for repeat surgeries and marking of previous injection sites during repeat procedures, as well as limited access to the septum and posterior parts of the heart.

It's understood that in the case of using tissue-engineered cardiomyocyte patches, their implantation directly into the damaged zone into the ventricle epicardium via a minimally invasive surgery is necessary. Overall, local cell delivery has several advantages, but there are also some technical limitations associated with the sizes of experimental animals at the preclinical stage, the need for specialized minimally invasive tools, and the risk of complications. There are substantial grounds to believe that the development of methods for local delivery with better engraftment of the transplant can enhance the effectiveness of cell therapy, especially in chronic ischemic tissue injuries when homing signals for recruiting stem cells from the bloodstream are reduced.

Frequency of cell transplantation

Based on experimental data, cells transplanted systemically are found in the myocardium and other tissues only in the early stages after

injection. To achieve a stable, long-lasting clinical effect, repeated cell transplantations are considered promising [93, 172]. For example, in a myocardial infarction model in rats, even just two administrations of MMSCs compared to a single administration provide better outcomes in terms of ejection fraction growth, associated with increased myocardial mass, arteriolar density, and reduced fibrosis [146]. It is important to note that repeated administrations of allogeneic cardiospheres do not cause local inflammation in the myocardium or systemic rejection reactions [145].

Similarly, experiments on rats with modeled ischemic cardiomyopathy showed the advantage of three-time administration of c-kit⁺ progenitors with a 35-day interval compared to a single administration. It was found that each injection led to regional and overall improvement in left ventricular function. The effect was cumulative, meaning left ventricular function improved threefold compared to a single dose. Triple administration was associated with better myocardial tissue survival, reduced scar size, lower collagen content in the risk zone and non-infarcted zone, and higher myocardial density in the risk zone. Less than 1 % of cells remained in the myocardium and differentiated into myocytes. The authors believe that the action of the injected stem cells is more related to a paracrine effect than to their engraftment and differentiation [172].

In the study by Guo Y. et al. on mice with ischemic cardiomyopathy and triple injections of cardiac-derived mesenchymal progenitors, it was shown that the left ventricular ejection fraction improved after each injection compared to transplantation only once. Multiple injections also led to a reduction in collagen content in the non-infarcted zone. However, engraftment of the injected cells was low in both groups of animals, which may confirm their paracrine effect [56].

It has been demonstrated that improvement in cardiac function with multiple cell injections is characteristic not only for rats with modeled cardiomyopathy but also for other rodents and different cell types [66]. Other authors also consider repeated administration of cell products to be beneficial for achieving a clinical effect, although permanent engraftment of donor cells is not mandatory [17, 110].

It is also important to note that in immunodeficient rats with modeled myocardial infarction, repeated administration of syngeneic and allogeneic cells derived from cardiospheres, compared to placebo and xenogeneic (human) cells did not lead to immune rejection and resulted in a significant and sustained increase in LVEF and a reduction in the size of the post-infarction scar [17].

The above research results support and justify the paradigms of the feasibility and effectiveness of repeated cell injections in treating diseases of many organs, including the heart. In humans, the need for additional thoracotomy for repeated intramyocardial cell injections can be avoided by using echocardiographic visualization of the injection procedure and intracavitary delivery of an increased number of cells [56, 136].

Combined transplantation of cells

Combined application of various types of stem and progenitor cells may contribute to mutual potentiation of their effects, as confirmed by both *in vitro* and *in vivo* studies. Co-culturing human UC-MMSCs with rat embryonic cardiomyocytes led to an increase in the expression levels of the cardiomyocyte transcription factors GATA4, Mef2c, and Cx43 in UC-MMSCs and even the appearance of contractile cardiomyocytes of human origin [162, 195].

In a rat model of ischemic cardiomyopathy, Suss et al. evaluated the efficacy of human umbilical cord-derived stromal cells, umbilical cord blood-derived endothelial cells, or a combination of these cells. The animals in all cell therapy groups, regardless of the cell type transplanted, showed less collagen deposition in their heart tissue and demonstrated a significant improvement in myocardial function by LVEF as well as an increase in the number of blood vessels in the infarcted area, with a greater tendency for the combined cell therapy [160]. After combined transplantation of endothelial progenitor cells and mesenchymal stem cells into a rat model of isoproterenol-induced myocardial injury, the

group of rats that received both types of cells showed an increased level of angiogenic growth factor expression, less collagen deposition, fewer apoptotic cells, and improved regional myocardial blood flow compared to the other groups. These effects resulted in a greater enhancement of cardiac function [202].

Compared to the use of bone marrow-derived MMSCs alone, cell transplantation combined with endothelial progenitor cells after myocardial infarction resulted in better neovascularization and contractility. This suggests that angiogenesis is an important mechanism in attenuating the progression of left ventricular dysfunction after myocardial infarction [161].

Combined application of CSCs and BM-MMSCs also significantly reduces post-infarction scar size and improves cardiac contractile function in various laboratory animals, explaining the ability of bone marrow cells to stimulate proliferation and differentiation of cardiac stem cells and influence their niches in the heart [60, 125, 184]. In experiments on mice, the effectiveness of hybrid progenitors-chimeras, created by merging cardiac and bone marrow stem cells, was demonstrated for myocardial restoration [144]. Moreover, co-transplantation of embryonic stem cells and MMSCs provided better functional preservation in a rat myocardial infarction model compared with single-cell treatment alone. However, there was only modest evidence for an immunosuppressive effect of co-injected MMSCs, and their beneficial effects on patterns of rejection, fibrosis, and angiogenesis seemed to be rather mediated by trophic effects on the host tissue [142].

The CONCERT-HF (NCT02501811) and TAC-HFT II (NCT00768066) trials at the University of Texas and Miami clinics, USA have demonstrated greater effectiveness of combined application of CSCs (1-5 million) together with bone marrow-derived MMSCs in a high dose of 150-200 million compared to each type of cell separately [14, 15, 62]. In a randomized, double-blind, placebo-controlled phase 2B trial, ixCELL-DCM (NCT01670981) intramyocardial delivery of a combined cellular product consisting of CD90⁺ mesenchymal stem cells and CD45⁺CD14⁺ macrophages (Ixmyelocel-T), might improve clinical, functional, symptomatic, and quality-of-life outcomes as well as the safety and efficacy of catheter-based transendocardial injection in patients with heart failure and reduced ejection fractions due to ischemic dilated cardiomyopathy [137].

In summary, on models of heart injury in large and small laboratory animals, using morphological, instrumental, and functional methods, a high regenerative potential of somatic stem cells of different types has been demonstrated, allowing successful translation of results into the clinic. Previous results of clinical studies somewhat tempered high expectations, but they focused researchers' and clinicians' attention on a more responsible approach to designing such studies, taking into account the biology of stem cells.

To avoid potential systematic errors associated with the small number of participants in each study, it is necessary to conduct a meta-analysis of numerous published data. For example, a meta-analysis of 80 preclinical studies on the efficacy of CSCs in a myocardial infarction model (1176 animals) showed a general increase in the left ventricular ejection fraction by 10.7 % (about 5 % for large animals) [206]. It is noted that CSCs show better efficacy compared to bone marrow cells [132].

A meta-analysis of 50 clinical studies involving 2625 patients revealed that bone marrow mononuclear cell transplantation, compared to standard treatment, improves left ventricular function, reduces infarct size, and remodels the hearts of patients with ischemic heart disease [77]. Another meta-analysis of 30 randomized trials (2037 patients) also confirmed an increase in left ventricular ejection fraction, a decrease in end-systolic volume, and infarct size compared to the control group. However, some authors note that these functional changes were not confirmed by magnetic resonance imaging data [40]. The latest results from a meta-analysis of 41 studies (2732 participants) indicate a lack of substantial evidence for a positive effect of bone marrow cell application in patients with acute myocardial infarction. This could be explained by the severe initial condition of the recipients and the limited time for the cells to realize their regenerative potential in conditions of local inflammation and acute ischemia [47]. In contrast, an analysis of 23 other studies (1255 patients) found evidence of a potentially favorable clinical effect of bone marrow cell transplantation on myocardial function and long-term survival prognosis in patients specifically with chronic ischemic heart disease [46].

Therefore, the expected effectiveness of cell therapy directly depends on the design of the clinical trial, which requires careful formation of subgroups, clear definition of timelines, and adequate methods of functional assessment.

CONCLUSION

Given the pathogenetic mechanisms of cardiovascular pathology development and myocardial regeneration, tissue-specific progenitors from the myocardium are of particular interest for replacing lost cardiomyocytes, endothelial progenitors for correcting associated endothelial dysfunction, and multipotent mesenchymal stromal/stem cells of various origins possessing low immunogenicity, trophic, anti-inflammatory, immunomodulatory, and anti-apoptotic effects.

Priority directions include the search for more accessible and safe sources of stem cells, the development of new efficient cultivation methods, and the use of scaffolds for cell transplantation. Questions remain open regarding the optimal route, dose, and frequency of stem cell administration, as well as the standardization of quality and effectiveness criteria. Moreover, the combined use of different types of stem cells may serve as a new priority strategy for assessing the effectiveness and safety of cell therapy, especially considering the paradigm of repeated transplantation. Successful translation of preclinical results into large, well-planned placebo-controlled clinical trials will enhance the safety and effectiveness of cell therapy for cardiovascular diseases, which is one of the current challenges in modern regenerative medicine.

REFERENCES:

- Abouzid MR, Ali K, Kamel I, Esteghamati S, Saleh A, Ghanim M. The Safety and Efficacy of Human Umbilical Cord-Derived Mesenchymal Stem Cells in Patients With Heart Failure and Myocardial Infarction: A Meta-Analysis of Clinical Trials. *Cureus*. 2023; 15(11):e49645. Available from: <https://doi.org/10.7759/cureus.49645>
- Alam P, Maliken BD, Jones SM, Ivey MJ, Wu Z, Wang Y, et al. Cardiac remodeling and repair: recent approaches, advancements, and future perspective. *Int J Mol Sci*. 2021; 22(23):13104. Available from: <https://doi.org/10.3390/ijms222313104>
- Amini M, Zayeri F, Salehi M. Trend analysis of cardiovascular disease mortality, incidence, and mortality-to-incidence ratio: results from global burden of disease study. *BMC Public Health*. 2017; 21:401(2021). Available from: <https://doi.org/10.1186/s12889-021-10429-0>
- Assmus B, Fischer-Rasokat U, Honold J, Seeger FH, Fichtlscherer S, Tonn T, et al. TOPCARE-CHD Registry. Transcoronary transplantation of functionally competent BMCs is associated with a decrease in natriuretic peptide serum levels and improved survival of patients with chronic postinfarction heart failure: results of the TOPCARE-CHD Registry. *Circ Res*. 2007; 100(8):1234-41. Available from: <https://doi.org/10.1161/01.RES.00000264508.47717.6b>
- Assmus B, Schachinger V, Teupe C, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). *Circulation*. 2002; 106:3009-3017. Available from: <https://doi.org/10.1161/01.cir.0000043246.74879.cd>
- 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(6983):668-73. Available from: <https://doi.org/10.1038/nature02460>
- Barbash IM, Chouraqui P, Baron J, et al. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. *Circulation*. 2003; 108(7):863-868. Available from: <https://doi.org/10.1161/01.CIR.0000084828.50310.6A>
- Barik P, Shibu MA, Hsieh DJ, Day CH, Chen RJ, Kuo WW, et al. Cardioprotective effects of transplanted adipose-derived stem cells under Ang II stress with Danggui administration augments cardiac function through upregulation of insulin-like growth factor 1 receptor in late-stage hypertension rats. *Environ Toxicol*. 2021; 36(7):1466-1475. Available from: <https://doi.org/10.1002/tox.23145>
- Bartolucci J, Verdugo FJ, González PL, Larrea RE, Abarzua E, Goset C, et al. Safety and Efficacy of the Intravenous Infusion of Umbilical Cord Mesenchymal Stem Cells in Patients With Heart Failure: A Phase 1/2 Randomized Controlled Trial (RIMECARD Trial [Randomized Clinical Trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on Cardiopathy]). *Circ Res*. 2017; 121(10):1192-1204. Available from: <https://doi.org/10.1161/CIRCRESAHA.117>
- Beltrami AP, Urbaneck K, Kajstura J, Yan SM, Finato N, Bussani R, et al. Evidence that human cardiac myocytes divide after myocardial infarction. *N Engl J Med*. 2001; 344(23):1750-7. Available from: <https://doi.org/10.1056/NEJM200106073442303>
- Bischoff R. Regeneration of single skeletal muscle fibers *in vitro*. *Anat Rec*. 1975; 182(2):215-35. Available from: <https://doi.org/10.1002/ar.1091820207>
- Blum KM, Mirhaidari GJM, Breuer CK. Tissue engineering: Relevance to neonatal congenital heart disease. *Semin Fetal Neonatal Med*. 2022; 27(1):101225. Available from: <https://doi.org/10.1016/j.siny.2021.101225>
- Bolli R, Chugh AR, D'Amario D, et al. Effect of Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy: Initial Results of the SCIPIO Trial. *Lancet*. 2011; 378(9806):1847-1857. Available from: [https://doi.org/10.1016/s0140-6736\(11\)61590-0](https://doi.org/10.1016/s0140-6736(11)61590-0)
- Bolli R, Hare JM, March KL, Pepine CJ, Willerson JT, Perin EC, et al. Rationale and Design of the CONCERT-HF Trial (Combination of Mesenchymal and c-kit⁺ Cardiac Stem Cells As Regenerative Therapy for Heart Failure). *Circ Res*. 2018; 122(12):1703-1715. Available from: <https://doi.org/10.1161/CIRCRESAHA.118.312978>
- Bolli R, Mitrani RD, Hare JM, Pepine CJ, Perin EC, Willerson JT, et al. A Phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischaemic heart failure: the CCTRN CONCERT-HF trial. *Eur J Heart Fail*. 2021; 23(4):661-674. Available from: <https://doi.org/10.1002/ehf.2178>
- Bolli R, Tang XL, Sanganalmath SK, Rimoldi O, Mosna F, Abdel-Latif A, et al. Intracoronary delivery of autologous cardiac stem cells improves cardiac function in a porcine model of chronic ischemic cardiomyopathy. *Circulation*. 2013; 128(2):122-31. Available from: <https://doi.org/10.1161/circulationaha.112.001075>
- Bolli R. Repeated cell therapy: a paradigm shift whose time has come. *Circ Res*. 2017; 120(7):1072-1074. Available from: <https://doi.org/10.1161/circresaha.117.310710>
- Bollini S, Silini AR, Banerjee A, Wolbank S, Balbi C, Parolini O. Cardiac Restoration Stemming From the Placenta Tree: Insights From Fetal and Perinatal Cell Biology. *Front Physiol*. 2018; 9:385. Available from: <https://doi.org/10.3389/fphys.2018.00385>
- Boncoraglio GB, Ranieri M, Bersano A, Parati EA, Del Giovane C. Stem cell transplantation for ischemic stroke. *Cochrane Database Syst Rev*. 2019; 5(5):CD007231. Available from: <https://doi.org/10.1002/14651858.CD007231>
- Boukouaci W, Lauden L, Siewiera J, et al. Natural killer cell crosstalk with allogeneic human cardiac-derived stem/progenitor cells controls persistence. *Cardiovasc Res*. 2014;104(2):290-302. Available from: <https://doi.org/10.1093/cvr/cvu208>
- Bruun K, Schermer E, Sivendra A, Valaik E, Wise RB, Said R, et al. Therapeutic applications of adipose-derived stem cells in cardiovascular disease. *Am J Stem Cells*. 2018; 7(4):94-103. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6261868>
- Cağavi E, Koz A, Şahoglu Göktaş S. The heart of the matter: cardiac stem cells. *Turk J Biol*. 2016; 40(5):968-980. Available from: <https://doi.org/10.3906/biy-1602-63>
- Cambria E, Pasqualini FS, Wolint P, Günter J Steiger J, Bopp A, et al. Translational cardiac stem cell therapy: advancing from first-generation to next-generation cell types. *npj Regen Med* 2017; 2:17. Available from: <https://doi.org/10.1038/s41536-017-0024-1>
- Can A, Ulus AT, Cinar O, Topal Celikkan F, Simsek E, Akyol M, et al. Human Umbilical Cord Mesenchymal Stromal Cell Transplantation in Myocardial Ischemia (HUC-HEART Trial). A Study Protocol of a Phase 1/2, Controlled and Randomized Trial in Combination with Coronary Artery Bypass Grafting. *Stem Cell Rev Rep*. 2015; 11(5):752-60. Available from: <https://doi.org/10.1007/s12015-015-9601-0>
- Cantero Peral S, Burkhart HM, Oommen S, Yamada S, Nyberg SL, Li X, et al. Safety and feasibility for pediatric cardiac regeneration using epicardial delivery of autologous umbilical cord blood-derived mononuclear cells established in a porcine model system. *Stem Cells Transl Med*. 2015; 4(2):195-206. Available from: <https://doi.org/10.5966/sctm.2014-0195>
- Caplan AI. Molecular and cellular differentiation of muscle, cartilage, and bone in the developing limb. *Prog Clin Biol Res*. 1986; 217(B):307-318.

27. Caspi O, Huber I, Kehat I, Habib M, Arbel G, Gepstein A, et al. Transplantation of human embryonic stem cell-derived cardiomyocytes improves myocardial performance in infarcted rat hearts. *J Am Coll Cardiol*. 2007; 50(19):1884-93. Available from: <https://doi.org/10.1016/j.jacc.2007.07.054>
28. Chakravarty T, Henry TD, Kittleson M, Lima J, Siegel RJ, Slipczuk L, et al. Allogeneic cardiosphere-derived cells for the treatment of heart failure with reduced ejection fraction: the Dilated cardiomyopathy intervention with Allogeneic Myocardially-regenerative Cells (DYNAMIC) trial. *EuroIntervention*. 2020; 16(4):e293-e300. Available from: <https://doi.org/10.4244/EIJ-D-19-00035>
29. Chan HH, Meher Homji Z, Gomes RS, Sweeney D, Thomas GN, Tan JJ, et al. Human cardiosphere-derived cells from patients with chronic ischaemic heart disease can be routinely expanded from atrial but not epicardial ventricular biopsies. *J Cardiovasc Transl Res*. 2012; 5(5):678-87. Available from: <https://doi.org/10.1007/s12265-012-9389-0>
30. Chen HJ, Chen CH, Chang MY, Tsai DC, Baum EZ, Hariri R, et al. Human placenta-derived adherent cells improve cardiac performance in mice with chronic heart failure. *Stem Cells Transl Med*. 2015; 4(3):269-75. Available from: <https://doi.org/10.5966/sctm.2014-0135>
31. Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, et al. 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(1):92-95. Available from: <https://doi.org/10.1016/j.amjcard.2004.03.034>
32. Chen Y, Shen H, Ding Y, Yu Y, Shao L, Shen Z. The application of umbilical cord-derived MSCs in cardiovascular diseases. *J Cell Mol Med*. 2021; 25(17):8103-8114. Available from: <https://doi.org/10.1111/jcmm.16830>
33. Chimenti I, Gaetani R, Forte E, Angelini F, De Falco E, Zoccai GB, et al. Serum and supplement optimization for EU GMP-compliance in cardiospheres cell culture. *J Cell Mol Med*. 2014; 18(4):624-34. Available from: <https://doi.org/10.1111/jcmm.12210>
34. Chiu RC, Zibaitis A, Kao RL. Cellular cardiomyoplasty: myocardial regeneration with satellite cell implantation. *Ann Thorac Surg* 1995; 60(1):12-18.
35. Ciccocioppo R, Klersy C, Leffler DA, Rogers R, Bennett D, Corazza GR. Systematic review with meta-analysis: Safety and efficacy of local injections of mesenchymal stem cells in perianal fistulas. *JGH Open*. 2019; 3(3):249-260. Available from: <https://doi.org/10.1002/jgh3.12141>
36. ClinicalTrials.gov database. Available from: <http://www.clinicaltrials.gov>.
37. Correia CD, Ferreira A, Fernandes MT, Silva BM, Esteves F, Leitão HS, et al. Human Stem Cells for Cardiac Disease Modeling and Preclinical and Clinical Applications-Are We on the Road to Success? *Cells*. 2023 Jun 27; 12(13):1727. Available from: <https://doi.org/10.3390/cells12131727>
38. D'Amario D, Fiorini C, Campbell PM, Goichberg P, Sanada F, Zheng H, et al. Functionally competent cardiac stem cells can be isolated from endomyocardial biopsies of patients with advanced cardiomyopathies. *Circ Res*. 2011; 108(7):857-861. Available from: <https://doi.org/>
39. de Castro LL, Lopes-Pacheco M, Weiss DJ, Cruz FF, Rocco PRM. Current understanding of the immunosuppressive properties of mesenchymal stromal cells. *J Mol Med (Berl)*. 2019;97(5):605-618. Available from: <https://doi.org/10.1007/s00109-019-01776-y>
40. de Jong R, Houtgraaf JH, Samiei S, Boersma E, Duckers HJ. Intracoronary stem cell infusion after acute myocardial infarction: a meta-analysis and update on clinical trials. *Circ Cardiovasc Interv*. 2014; 7(2):156-67. Available from: <https://doi.org/10.1161/CIRCINTERVENTIONS.113.001009>
41. Deinsberger J, Reisinger D, Weber B. Global trends in clinical trials involving pluripotent stem cells: a systematic multi-database analysis. *NPJ Regen Med*. 2020; 5:15. Available from: <https://doi.org/10.1038/s41536-020-00100-4>
42. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006; 8(4):315-7. Available from: <https://doi.org/10.1080/14653240600855905>
43. Erices A, Conget P, Minguell JJ. Mesenchymal progenitor cells in human umbilical cord blood. *Br J Haematol*. 2000; 109(1):235-42.
44. Fanton Y, Robic B, Rummens JL, Daniëls A, Windmolders S, Willems L, et al. Cardiac atrial appendage stem cells engraft and differentiate into cardiomyocytes *in vivo*: A new tool for cardiac repair after MI. *Int J Cardiol*. 2015; 201:10-9. Available from: <https://doi.org/10.1016/j.ijcard.2015.07.066>
45. Fernández-Avilés F, Sanz-Ruiz R, Bogaert J, Casado Plasencia A, Gilaberte I, Belmans A, et al. Safety and Efficacy of Intracoronary Infusion of Allogeneic Human Cardiac Stem Cells in Patients With ST-Segment Elevation Myocardial Infarction and Left Ventricular Dysfunction. *Circ Res*. 2018; 123(5):579-589. Available from: <https://doi.org/10.1161/CIRCRESAHA.118.312823>
46. Fisher SA, Brunskill SJ, Doree C, Mathur A, Taggart DP, Martin-Rendon E. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev*. 2014; 4:CD007888. Available from: <https://doi.org/10.1002/14651858.CD007888.pub2>
47. Fisher SA, Zhang H, Doree C, Mathur A, Martin-Rendon E. Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. 2015; 2015(9):CD006536. Available from: <http://doi.org/10.1002/14651858.CD006536>
48. Fouts K, Fernandes B, Mal N, Liu J, Laurita KR. Electrophysiological consequence of skeletal myoblast transplantation in normal and infarcted canine myocardium. *Heart Rhythm*. 2006; 3(4):452-461.
49. Fuchs S, Baffour R, Zhou YF, Shou M, Pierre A, Tio FO, et al. Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia. *J Am Coll Cardiol*. 2001; 37(6):1726-1732. Available from: https://doi.org/hsrc.himmelfarb.gwu.edu/smhs_pharm_facpubs/715
50. Gabrielyan AV, Yakushev AB, Matyashchuk AS, Domanskiy TM, Kudlay IV, Romanova SV, et al. Changes of intracardiac hemodynamics in patients with decreased myocardial contractility at transplantation of cord blood stem cells. *Cell and Organ Transplantation*. 2015; 3(1):24-27. Available from: <https://doi.org/10.22494/COT.V3I1.26>
51. Gabrielyan AB, Holiuk Ye, Dombrovskiy DB, Kyryk VM, Medvedev VV, Rudenko SA, Shablii VA. The latest methods of using stem cells and bioengineering technologies in regenerative medicine. Ref. work awarded the National Prize of Ukraine named after Boris Paton. Kyiv 2021. Available from: http://www.kdpu-nt.gov.ua/sites/default/files/work_files/4_referat_2.pdf
52. Gao LR, Chen Y, Zhang NK, Yang XL, Liu HL, Wang ZG, et al. Intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells in acute myocardial infarction: double-blind, randomized controlled trial. *BMC Med*. 2015; 13:162. Available from: <https://doi.org/10.1186/s12916-015-0399-z>
53. Giedrimiene D, King R. Burden of cardiovascular disease (CVD) on economic cost. Comparison of outcomes in US and Europe. *Circulation: Cardiovascular Quality and Outcomes*. 2017; 10:A207. Available from: https://doi.org/10.1161/circoutcomes.10.suppl_3.207
54. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation*. 2014; 129(3):e28-e292. Available from: <https://doi.org/10.1161/01.cir.0000441139.02102.80>

55. Guo R, Morimatsu M, Feng T, Lan F, Chang D, Wan F, et al. Stem cell-derived cell sheet transplantation for heart tissue repair in myocardial infarction. *Stem Cell Res Ther.* 2020; 11(1):19. Available from: <https://doi.org/10.1186/s13287-019-1536-y>
56. Guo Y, Wysoczynski M, Nong Y, Tomlin A, Zhu X, Gumpert AM, et al. Repeated doses of cardiac mesenchymal cells are therapeutically superior to a single dose in mice with old myocardial infarction. *Basic Res Cardiol.* 2017; 112(2):18. Available from: <https://doi.org/10.1007/s00395-017-0606-5>
57. Haack-Sørensen M, Friis T, Mathiasen AB, Jørgensen E, Hansen L, Dickmeiss E, et al. Direct intramyocardial mesenchymal stromal cell injections in patients with severe refractory angina: one-year follow-up. *Cell Transplant.* 2013; 22(3):521-8. Available from: <https://doi.org/10.3727/096368912X636830>
58. Hare JM, DiFede DL, Rieger AC, Florea V, Landin AM, El-Khorazaty J, et al. Randomized comparison of allogeneic versus autologous mesenchymal stem cells for nonischemic dilated cardiomyopathy: POSEIDON-DCM Trial. *J Am Coll Cardiol.* 2017; 69:526–37. Available from: <https://doi.org/10.1016/j.jacc.2016.11.009>
59. Hare JM, Traverse JH, Henry TD, Dib N, Strumpf RK, Schulman SP, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (Prochymal) after acute myocardial infarction. *J Am Coll Cardiol.* 2009; 54(24):2277–86. Available from: <https://doi.org/10.1016/j.jacc.2009.06.055>
60. Hatzistergos KE, Quevedo H, Oskoueï BN, Hu Q, Feigenbaum GS, Margitich IS, et al. Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. *Circ Res.* 2010; 107(7):913–922.
61. He JQ, Vu DM, Hunt G, et al. Human cardiac stem cells isolated from atrial appendages stably express c-kit. *PLoS One.* 2011; 6(11):e27719.
62. Heldman AW, DiFede DL, Fishman JE, Zambrano JP, Trachtenberg BH, Karantalis V, et al. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. *JAMA.* 2014; 311(1):62–73. Available from: <https://doi.org/10.1001/jama.2013.282909>
63. Henning RJ, Abu-Ali H, Balis JU, Morgan MB, Willing AE, Sanberg PR. Human umbilical cord blood mononuclear cells for the treatment of acute myocardial infarction. *Cell Transplant.* 2004; 13(7–8):729–739.
64. Henry TD, Pepine CJ, Lambert CR, Traverse JH, Schatz R, Costa M, et al. The Athena trials: Autologous adipose-derived regenerative cells for refractory chronic myocardial ischemia with left ventricular dysfunction. *Catheter Cardiovasc Interv.* 2017; 89(2):169–177. Available from: <https://doi.org/10.1002/ccd.26601>
65. Hirata Y, Sata M, Motomura N, Takanashi M, Suematsu Y, Ono M, Takamoto S. Human umbilical cord blood cells improve cardiac function after myocardial infarction. *Biochem Biophys Res Commun.* 2005; 327(2):609–614.
66. Hong KU, Guo Y, Li QH, Cao P, Al-Maqtari T, Vajravelu BN, et al. c-kit⁺ Cardiac stem cells alleviate post-myocardial infarction left ventricular dysfunction despite poor engraftment and negligible retention in the recipient heart. *PLoS One.* 2014; 9:e96725. Available from: <https://doi.org/10.1371/journal.pone.0096725>
67. Hong KU, Li QH, Guo Y, Patton NS, Moktar A, Bhatnagar A, Bolli R. A highly sensitive and accurate method to quantify absolute numbers of c-kit⁺ cardiac stem cells following transplantation in mice. *Basic Res Cardiol.* 2013; 108:346. Available from: <https://doi.org/10.1007/s00395-013-0346-0>
68. Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, et al. Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. *Cytotherapy.* 2005; 7(5):393–395. Available from: <https://doi.org/10.1080/14653240500319234>
69. Houtgraaf JH, den Dekker WK, van Dalen BM, Springeling T, de Jong R, van Geuns RJ, et al. First experience in humans using adipose tissue-derived regenerative cells in the treatment of patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol.* 2012;59(5):539–40. Available from: <http://doi.org/10.1016/j.jacc.2011.09.065>
70. Huang H, Huang W. Regulation of endothelial progenitor cell functions in ischemic heart disease: new therapeutic targets for cardiac remodeling and repair. *Front Cardiovasc Med.* 2022; 9:896782. Available from: <https://doi.org/10.3389/fcvm.2022.896782>
71. Hutchings G, Janowicz K, Moncrieff L, Dompe C, Strauss E, Kocherova I, et al. The proliferation and differentiation of adipose-derived stem cells in neovascularization and angiogenesis. *Int J Mol Sci.* 2020; 21(11):3790. Available from: <https://doi.org/10.3390/ijms21113790>
72. Hwangbo S, Kim J, Her S, Cho H, Lee J. Therapeutic potential of human adipose stem cells in a rat myocardial infarction model. *Yonsei Med J.* 2010; 51(1):69–76. Available from: <https://doi.org/10.3349/ymj.2010.51.1.69>
73. Ichim TE, Solano F, Brenes R, Glenn E, Chang J, Chan K, et al. Placental mesenchymal and cord blood stem cell therapy for dilated cardiomyopathy. *Reprod Biomed Online.* 2008;16(6):898–905. Available from: [https://doi.org/10.1016/s1472-6483\(10\)60159-9](https://doi.org/10.1016/s1472-6483(10)60159-9)
74. Ilic D, Ogilvie C. Concise review: Human embryonic stem cells—what have we done? What are we doing? Where are we going? *Stem Cells.* 2017; 35(1):17–25. Available from: <https://doi.org/10.1002/stem.2450>
75. Ishigami S, Sano T, Krishnapura S, Ito T, Sano S. An overview of stem cell therapy for paediatric heart failure. *Eur J Cardiothorac Surg.* 2020; 58(5):881–887. Available from: <https://doi.org/10.1093/ejcts/ezaa155>
76. Itzhaki-Alfia A, Leor J. Resident Cardiac Progenitor Cells. 2014. Available from: https://doi.org/10.1007/978-94-017-8657-7_2
77. Jeevanantham V, Butler M, Saad A, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. *Circulation.* 2012; 126(5):551–68. Available from: <https://doi.org/10.1161/CIRCULATIONAHA.111.086074>
78. Joo HS, Suh JH, Lee HJ, Bang ES, Lee JM. Current knowledge and future perspectives on mesenchymal stem cell-derived exosomes as a new therapeutic agent. *Int J Mol Sci.* 2020; 21(3):727. Available from: <https://doi.org/10.3390/ijms21030727>
79. Kajstura J, Rota M, Cappelletta D, Ogórek B, Arranto C, Bai Y, et al. Cardiomyogenesis in the aging and failing human heart. *Circulation.* 2012; 126(15):1869–81. Available from: <https://doi.org/10.1161/CIRCULATIONAHA.112.118380>
80. Kanazawa H, Malliaras K, Yee K, Tseliou E, Marbán L, Makkar R, et al. Comparison of cardiac engraftment with two catheter-based delivery methods: catheter-mediated intramyocardial delivery outperforms intracoronary delivery of cardiosphere-derived cells in porcine ischemic cardiomyopathy. *Circulation.* 2011; Abstract 124:A16466. https://doi.org/10.1161/circ.124.suppl_21.A16466
81. Kanisicak O, Vagnozzi RJ, Molkentin JD. Identity crisis for regenerative cardiac cKit⁺ cells. *Circ Res.* 2017; 121(10):1130–2. Available from: <https://doi.org/10.1161/CIRCRESAHA.117.311921>

82. Kara RJ, Bolli P, Karakikes I, Matsunaga I, Tripodi J, Tanweer O, et al. Fetal cells traffic to injured maternal myocardium and undergo cardiac differentiation. *Circ Res*. 2012;110(1):82-93. Available from: <https://doi.org/10.1161/CIRCRESAHA.111.249037>
83. Kawaguchi S, Soma Y, Nakajima K, Kanazawa H, Tohyama S, Tabei R, et al. Intramyocardial Transplantation of Human iPS Cell-Derived Cardiac Spheroids Improves Cardiac Function in Heart Failure Animals. *JACC Basic Transl Sci*. 2021; 6(3):239-254. Available from: <https://doi.org/10.1016/j.jacbts.2020.11.01>
84. Kawamoto A, Gwon HC, Iwaguro H, et al. Therapeutic potential of *ex vivo* expanded endothelial progenitor cells for myocardial ischemia. *Circulation*. 2001; 103(5):634-637.
85. Kawamura T, Ito Y, Ito E, Takeda M, Mikami T, Taguchi T, et al. Safety confirmation of induced pluripotent stem cell-derived cardiomyocyte patch transplantation for ischemic cardiomyopathy: first three case reports. *Front Cardiovasc Med*. 2023; 10:1182209. Available from: <https://doi.org/10.3389/fcvm.2023.1182209>
86. Kitsuka T, Takahashi F, Reinhardt J, Watanabe T, Ulziibayar A, Yimit A, et al. Advances in Cardiac Tissue Engineering. *Bioengineering (Basel)*. 2022; 9(11):696. Available from: <https://doi.org/10.3390/bioengineering9110696>
87. Koninckx R, Dani Is A, Windmolders S, Mees U, Macianskiene R, Mubagwa K, et al. The cardiac atrial appendage stem cell: a new and promising candidate for myocardial repair. *Cardiovasc Res*. 2013; 97(3):413-23. Available from: <https://doi.org/10.1093/cvr/cvs427>
88. Krause M, Phan TG, Ma H, Sobey CG, Lim R. Cell-based therapies for stroke: are we there yet? *Front Neurol*. 2019;10:656. Available from: <https://doi.org/10.3389/fneur.2019.00656>
89. Kumar M, Kasala ER, Bodduluru LN, Dahiya V, Sharma D, Kumar V, et al. Animal models of myocardial infarction: Mainstay in clinical translation. *Regul Toxicol Pharmacol*. 2016; 76:221-30. Available from: <http://doi.org/10.1016/j.yrtph.2016.03.005>
90. Kyryk V, Ustymenko A. Isolation and phenotyping of cardiac-derived progenitor cells from neonatal mice. *Cell Organ Transpl*. 2021; 9(2):126-133. Available from: <https://doi.org/10.22494/cot.v9i2.125>
91. Lauden L, Boukouaci W, Borlodo LR, Lopez IP, Sep lveda P, Tamouza R, et al. Allogenicity of human cardiac stem/progenitor cells orchestrated by programmed death ligand 1. *Circ Res*. 2013;112(3):451-64. Available from: <https://doi.org/10.1161/CIRCRESAHA.112.276501>
92. Lee HW, Lee HC, Park JH, Kim BW, Ahn J, Kim JH, et al. Effects of intracoronary administration of autologous adipose tissue-derived stem cells on acute myocardial infarction in a porcine model. *Yonsei Med J*. 2015; 56(6):1522-9. Available from: <https://doi.org/10.3349/ymj.2015.56.6.1522>
93. Lee SR, Lee SH, Moon JY, Park JY, Lee D, Lim SJ, et al. Repeated administration of bone marrow-derived mesenchymal stem cells improved the protective effects on a remnant kidney model. *Ren Fail*. 2010; 32(7):840-848.
94. Leistner DM, Fischer-Rasokat U, Honold J, Seeger FH, Sch chinger V, Lehmann R, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI): final 5-year results suggest long-term safety and efficacy. *Clin Res Cardiol*. 2011; 100(10):925-34. Available from: <http://doi.org/10.1007/s00392-011-0327-y>
95. L obon B, Roncalli J, Joffre C, Mazo M, Boisson M, Barreau C, et al. Adipose-derived cardiomyogenic cells: *in vitro* expansion and functional improvement in a mouse model of myocardial infarction. *Cardiovasc Res*. 2009; 83(4):757-67. Available from: <http://doi.org/10.1093/cvr/cvp167>
96. 9Leong YY, Ng WH, Ellison-Hughes GM, Tan JJ. Cardiac stem cells for myocardial regeneration: they are not alone. *Front Cardiovasc Med*. 2017; 4:47. Available from: <http://doi.org/10.3389/fcvm.2017.00047>
97. Li L, Xia Y. Study of adipose tissue-derived mesenchymal stem cells transplantation for rats with dilated cardiomyopathy. *Ann Thorac Cardiovasc Surg*. 2014; 20(5):398-406. Available from: <http://doi.org/10.5761/atcs.0a.13-00104>
98. Li Q, Guo Y, Ou Q, Chen N, Wu WJ, Yuan F, et al. Intracoronary administration of cardiac stem cells in mice: a new, improved technique for cell therapy in murine models. *Basic Res Cardiol*. 2011; 106(5):849-864.
99. Li Z, Solomonidis EG, Meloni M, Taylor RS, Duffin R, Dobie R, et al. Single-cell transcriptome analyses reveal novel targets modulating cardiac neovascularization by resident endothelial cells following myocardial infarction. *Eur Heart J*. 2019; 40:2507-2520. Available from: <https://doi.org/10.1093/eurheartj/ehz305>
100. Lim M, Wang W, Liang L, Han ZB, Li Z, Geng J, et al. Intravenous injection of allogeneic umbilical cord-derived multipotent mesenchymal stromal cells reduces the infarct area and ameliorates cardiac function in a porcine model of acute myocardial infarction. *Stem Cell Res Ther*. 2018; 9(1):129. Available from: <https://doi.org/10.1186/s13287-018-0888-z>
101. Lin YC, Leu S, Sun CK, Yen CH, Kao YH, Chang LT, et al. Early combined treatment with sildenafil and adipose-derived mesenchymal stem cells preserves heart function in rat dilated cardiomyopathy. *J Transl Med*. 2010; 8:88. Available from: <https://doi.org/10.1186/1479-5876-8-88>
102. Liu CB, Huang H, Sun P, Ma SZ, Liu AH, Xue J, et al. Human Umbilical Cord-Derived Mesenchymal Stromal Cells Improve Left Ventricular Function, Perfusion, and Remodeling in a Porcine Model of Chronic Myocardial Ischemia. *Stem Cells Transl Med*. 2016; 5(8):1004-13. Available from: <https://doi.org/10.5966/sctm.2015-0298>
103. Liu J, Liang X, Li M, Lin F, Ma X, Xin Y, et al. Intramyocardial injected human umbilical cord-derived mesenchymal stem cells (HucMSCs) contribute to the recovery of cardiac function and the migration of CD4+ T cells into the infarcted heart via CCL5/CCR5 signaling. *Stem Cell Res Ther*. 2022; 13(1):247. Available from: <https://doi.org/10.1186/s13287-022-02914-z>
104. Liu M, Lei H, Dong P, Fu X, Yang Z, Yang Y, et al. Adipose-derived mesenchymal stem cells from the elderly exhibit decreased migration and differentiation abilities with senescent properties. *Cell Transplantation*. 2017; 26(9):1505-1519. Available from: <https://doi.org/10.1177/0963689717721221>
105. Liu YW, Su CT, Yen CY, Lin LJ, Hsieh PC. Arrhythmogenesis: a roadblock to cardiac stem cell therapy. *Curr Treat Options Cardiovasc Med*. 2016; 18(10):61. Available from: <http://doi.org/10.1007/s11936-016-0481-7>
106. Makino S, Fukuda K, Miyoshi S, et al. Cardiomyocytes can be generated from marrow stromal cells *in vitro*. *J Clin Invest*. 1999; 103(5):697-705.
107. Mallapaty S. Revealed: two men in China were first to receive pioneering stem-cell treatment for heart disease. *Nature*. 2020; 581:249-250. Available from: <https://doi.org/10.1038/d41586-020-01285-w>
108. Malliaras K, Li TS, Luthringer D, Terrovitis J, Cheng K, Chakravarty T, et al. Safety and efficacy of allogeneic cell therapy in infarcted rats transplanted with mismatched cardiosphere-derived cells. *Circulation*. 2012; 125(1):100-12. Available from: <https://doi.org/10.1161/CIRCULATIONAHA.111.042598>
109. Malliaras K, Makkar RR, Smith RR, Cheng K, Wu E, Bonow RO, et al. Intracoronary cardiosphere-derived cells after myocardial infarction: evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS trial (CARDiosphere-Derived aUTologous stem CELls to reverse ventricUlar dySfunction). *J Am Coll Cardiol*. 2014; 63(2):110-122.

110. Mann I, Rodrigo SF, van Ramshorst J, Beeres SL, Dibbets-Schneider P, de Roos A, et al. Repeated intramyocardial bone marrow cell injection in previously responding patients with refractory angina again improves myocardial perfusion, anginal complaints, and quality of life. *Circ Cardiovasc Interv.* 2015; 8:e002740. Available from: <https://doi.org/10.1161/circinterventions.115.002740>
111. Martino H, Brofman P, Greco O, Bueno R, Bodanese L, Clausell N, et al. Multicentre, randomized, double-blind trial of intracoronary autologous mononuclear bone marrow cell injection in non-ischaemic dilated cardiomyopathy (the dilated cardiomyopathy arm of the MiHeart study) *Eur Heart J.* 2015; 36:2898–904. Available from: <https://doi.org/10.1093/eurheartj/ehv477>
112. Mathiasen AB, Jørgensen E, Qayyum AA, Haack-Sørensen M, Ekblond A, Kastrup J. Rationale and design of the first randomized, double-blind, placebo-controlled trial of intramyocardial injection of autologous bone-marrow derived Mesenchymal Stromal Cells in chronic ischemic Heart Failure (MSC-HF Trial). *Am Heart J.* 2012; 164(3):285-91. Available from: <https://doi.org/10.1016/j.ahj.2012.05.026>
113. McCall FC, Telukuntla KS, Karantalis V, Suncion VY, Heldman AW, Mushtaq M, et al. Myocardial infarction and intramyocardial injection models in swine. *Nat Protoc.* 2012; 7(8):1479-96. Available from: <http://doi.org/10.1038/nprot.2012.075>
114. Menasché P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Trinquart L, et al. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. *Circulation.* 2008; 117(9):1189-200. Available from: <http://doi.org/10.1161/circulationaha.107.734103>
115. Menasché P, Hagege AA, Scorsin M, Pouzet B, Desnos M, Duboc D, et al. Myoblast transplantation for heart failure. *Lancet.* 2001; 357(9252):279-280. Available from: [http://doi.org/10.1016/S0140-6736\(00\)03617-5](http://doi.org/10.1016/S0140-6736(00)03617-5). PMID: 11214133
116. Menasché P, Vanneaux V, Hagege A, Bel A, Cholley B, Parouchev A, et al. Transplantation of Human Embryonic Stem Cell-Derived Cardiovascular Progenitors for Severe Ischemic Left Ventricular Dysfunction. *J Am Coll Cardiol.* 2018; 71(4):429-438. Available from: <https://doi.org/10.1016/j.jacc.2017.11.047>
117. Menasché P. Cell Therapy With Human ESC-Derived Cardiac Cells: Clinical Perspectives. *Front Bioeng Biotechnol.* 2020; 8:601560. Available from: <https://doi.org/10.3389/fbioe.2020.601560>
118. Messina E, De Angelis L, Frati G, Morrone S, Chimenti S, Fiordaliso F, et al. Isolation and expansion of adult cardiac stem cells from human and murine heart. *Circ Res.* 2004; 95(9):911-921. Available from: <https://doi.org/10.1161/01.res.0000147315.71699.51>
119. Miranville A, Heesch C, Sengenès C, Curat CA, Busse R, Bouloumié A. Improvement of postnatal neovascularization by human adipose tissue-derived stem cells. *Circulation.* 2004; 110(3):349-355. Available from: <https://doi.org/10.1161/01.cir.0000135466.16823.d0>
120. Mishra R, Vijayan K, Colletti EJ, Harrington DA, Matthiesen TS, Simpson D, et al. Characterization and functionality of cardiac progenitor cells in congenital heart patients. *Circulation.* 2011; 123(4):364-373. Available from: <https://doi.org/10.1161/circulationaha.110.971622>
121. Miyagawa S, Kainuma S, Kawamura T, Suzuki K, Ito Y, Iseoka H, et al. Case report: Transplantation of human induced pluripotent stem cell-derived cardiomyocyte patches for ischemic cardiomyopathy. *Front Cardiovasc Med.* 2022; 9:950829. Available from: <https://doi.org/10.3389/fcvm.2022.950829>
122. Murry CE, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M, et al. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature.* 2004; 428(6983):664-8. Available from: <https://doi.org/10.1038/nature02446>
123. Murry CE, Wiseman RW, Schwartz SM, Hauschka SD. Skeletal myoblast transplantation for repair of myocardial necrosis. *J Clin Invest.* 1996; 98(11):2512-2523. Available from: <https://doi.org/10.1172/jci119070>
124. Nakamura K, Murry CE. Function follows form - a review of cardiac cell therapy. *Circ J.* 2019; 83(12):2399-2412. Available from: <https://doi.org/10.1253/circj.CJ-19-0567>
125. Natsumeda M, Florea V, Rieger AC, Tompkins BA, Banerjee MN, Golpanian S, et al. A Combination of Allogeneic Stem Cells Promotes Cardiac Regeneration. *J Am Coll Cardiol.* 2017; 70(20):2504-2515. Available from: <https://doi.org/10.1016/j.jacc.2017.09.036>
126. Nowacki M, Kloskowski T, Pietkun K, Zegarski M, Pokrywczyńska M, Habib SL, et al. The use of stem cells in aesthetic dermatology and plastic surgery procedures. A compact review of experimental and clinical applications. *Postepy Dermatol Alergol.* 2017; 34(6):526-534. Available from: <https://doi.org/10.5114/ada.2017.72456>
127. Oh H, Bradfute SB, Gallardo TD, Nakamura T, Gausson V, Mishina Y, et al. Cardiac progenitor cells from adult myocardium: homing, differentiation, and fusion after infarction. *Proc Natl Acad Sci U S A.* 2003; 100(21):12313-12318. Available from: <https://doi.org/10.1073/pnas.2132126100>
128. Okano S, Shiba Y. Therapeutic Potential of Pluripotent Stem Cells for Cardiac Repair after Myocardial Infarction. *Biol Pharm Bull.* 2019; 42(4):524-530. Available from: <https://doi.org/10.1248/bpb.b18-00257>
129. Okura H, Saga A, Soeda M, Miyagawa S, Sawa Y, Daimon T, et al. Intracoronary artery transplantation of cardiomyoblast-like cells from human adipose tissue-derived multi-lineage progenitor cells improve left ventricular dysfunction and survival in a swine model of chronic myocardial infarction. *Biochem Biophys Res Commun.* 2012; 425(4):859-65. Available from: <https://doi.org/10.1016/j.bbrc.2012.08.004>
130. Orlic D, Kajstura J, Chimenti S, Limana F, Jakoniuk I, Quaini F, et al. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. *Proc Natl Acad Sci U S A.* 2001; 98(18):10344-10349. Available from: <https://doi.org/10.1073/pnas.181177898>
131. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, et al. Bone marrow cells regenerate infarcted myocardium. *Nature.* 2001; 410(6829):701-5. Available from: <https://doi.org/10.1038/35070587>
132. Oskoueï BN, Lamirault G, Joseph C, Treuer AV, Landa S, Da Silva J, et al. Increased potency of cardiac stem cells compared with bone marrow mesenchymal stem cells in cardiac repair. *Stem Cells Transl Med.* 2012; 1(2):116-24. Available from: <https://doi.org/10.5966/sctm.2011-0015>
133. Ostovaneh MR, Makkar RR, Ambale-Venkatesh B, Ascheim D, Chakravarty T, Henry TD, et al. Effect of cardiosphere-derived cells on segmental myocardial function after myocardial infarction: ALLSTAR randomised clinical trial. *Open Heart.* 2021; 8(2):e001614. Available from: <https://doi.org/10.1136/openhrt-2021-001614>
134. Palpant NJ, Yasuda S, MacDougald O, Metzger JM. Non-canonical Wnt signaling enhances differentiation of Sca1⁺/c-kit⁺ adipose-derived murine stromal vascular cells into spontaneously beating cardiac myocytes. *J Mol Cell Cardiol.* 2007; 43(3):362-70. Available from: <https://doi.org/10.1016/j.yjmcc.2007.06.012>
135. Parolini O, Alviano F, Bagnara GP, Bilic G, Bühring HJ, Evangelista M, et al. Concise review: isolation and characterization of cells from human term placenta: outcome of the first international Workshop on Placenta Derived Stem Cells. *Stem Cells.* 2008; 26:300-311. Available from: <https://doi.org/10.1634/stemcells.2007-0594>

136. Passipieri JA, Kasai-Brunswick TH, Suhett G, Martins AB, Brasil GV, Campos DB, et al. Improvement of cardiac function by placenta-derived mesenchymal stem cells does not require permanent engraftment and is independent of the insulin signaling pathway. *Stem Cell Res Ther.* 2014 Aug 21;5(4):102. Available from: <https://doi.org/10.1186/scri490>
137. Patel AN, Henry TD, Quyyumi AA, Schaer GL, Anderson RD, Toma C, et al. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. *Lancet.* 2016; 387(10036):2412-21. Available from: [https://doi.org/10.1016/S0140-6736\(16\)30137-4](https://doi.org/10.1016/S0140-6736(16)30137-4)
138. Perin EC, Sanz-Ruiz R, Sánchez PL, Lasso J, Pérez-Cano R, Alonso-Farto JC, et al. Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PRECISE Trial. *Am Heart J.* 2014; 168(1):88-95.e2. Available from: <http://doi.org/10.1016/j.ahj.2014.03.022>
139. Perin EC, Silva GV, Assad JA, Vela D, Buja LM, Sousa AL, et al. Comparison of intracoronary and transendocardial delivery of allogeneic mesenchymal cells in a canine model of acute myocardial infarction. *J Mol Cell Cardiol.* 2008; 44(3):486-495. Available from: <https://doi.org/10.1016/j.yjmcc.2007.09.012>
140. Perin EC, Willerson JT, Pepine CJ, Henry TD, Ellis SG, Zhao DX, et al. Cardiovascular Cell Therapy Research Network (CCTRN). Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. *JAMA.* 2012; 307(16):1717-26. Available from: <https://doi.org/10.1001/jama.2012.418>
141. Planat-Bénard V, Menard C, André M, Puceat M, Perez A, Garcia-Verdugo JM, et al. Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. *Circ Res.* 2004; 94(2):223-229. Available from: <https://doi.org/10.1161/01.res.0000109792.43271.47>
142. Puymirat E, Geha R, Tomescot A, Bellamy V, Larghero J, Trinquart L, et al. Can mesenchymal stem cells induce tolerance to cotransplanted human embryonic stem cells? *Mol Ther.* 2009; 17(1):176-82. Available from: <https://doi.org/10.1038/mt.2008.208>
143. Quevedo HC, Hatzistergos KE, Oskouei BN, Feigenbaum GS, Rodriguez JE, Valdes D, et al. Allogeneic mesenchymal stem cells restore cardiac function in chronic ischemic cardiomyopathy via trilineage differentiating capacity. *Proc Natl Acad Sci U S A.* 2009; 106(33):14022-14027. Available from: <https://doi.org/10.1073/pnas.0903201106>
144. Quijada P, Salunga HT, Hariharan N, Cubillo JD, El-Sayed FG, Moshref M, et al. Cardiac stem cell hybrids enhance myocardial repair. *Circ Res.* 2015; 117(8):695-706.
145. Reich H, Tseliou E, de Couto G, Angert D, Valle J, Kubota Y, et al. Repeated transplantation of allogeneic cardiosphere-derived cells boosts therapeutic benefits without immune sensitization in a rat model of myocardial infarction. *J Heart Lung Transplant.* 2016; 35(11):1348-1357. Available from: <https://doi.org/10.1016/j.healun.2016.05.008>
146. Richardson JD, Psaltis PJ, Frost L, Paton S, Carbone A, Bertaso AG, et al. Incremental benefits of repeated mesenchymal stromal cell administration compared with solitary intervention after myocardial infarction. *Cytotherapy.* 2014; 16(4):460-70. Available from: <https://doi.org/10.1016/j.jcyt.2013.07.016>
147. Rubart M, Soonpaa MH, Nakajima H, Field LJ. Spontaneous and evoked intracellular calcium transients in donor-derived myocytes following intracardiac myoblast transplantation. *J Clin Invest.* 2004; 114(6):775-783. Available from: <https://doi.org/10.1172/jci21589>
148. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Hölschermann H, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med.* 2006; 355(12):1210-1021. Available from: <https://doi.org/10.1056/nejmoa060186>
149. Schuleri KH, Feigenbaum GS, Centola M, Weiss ES, Zimmet JM, Turney J, et al. Autologous mesenchymal stem cells produce reverse remodelling in chronic ischaemic cardiomyopathy. *Eur Heart J.* 2009; 30(22):2722-2732. Available from: <https://doi.org/10.1093/eurheartj/ehp265>
150. Scorsin M, Hagège A, Vilquin JT, Fiszman M, Marotte F, Samuel JL, et al. Comparison of the effects of fetal cardiomyocyte and skeletal myoblast transplantation on postinfarction left ventricular function. *J Thorac Cardiovasc Surg.* 2000; 119(6):1169-1175. Available from: <https://doi.org/10.1067/mtc.2000.104865>
151. Sheng CG, Zhou L, Hao J. Current stem cell delivery methods for myocardial repair. *Biomed Res Int.* 2013; 2013:547902. Available from: <https://doi.org/10.1155/2013/547902>
152. Shirbaghaee Z, Heidari Keshel S, Rasouli M, Valizadeh M, Hashemi Nazari SS, et al. Report of a phase 1 clinical trial for safety assessment of human placental mesenchymal stem cells therapy in patients with critical limb ischemia (CLI). *Stem Cell Res Ther.* 2023; 14(1):174. Available from: <https://doi.org/10.1186/s13287-023-03390-9>
153. Shudo Y, Miyagawa S, Ohkura H, Fukushima S, Saito A, Kawaguchi N, et al. Adipose tissue-derived multi-lineage progenitor cells improve left ventricular dysfunction in porcine ischemic cardiomyopathy model. *J Heart Lung Transplant.* 2017; 36(2):237-239. Available from: <https://doi.org/10.1016/j.healun.2016.11.012>
154. Siminiak T, Fiszler D, Jerzykowska O, Grygielska B, Rozwadowska N, Kałmucki P, et al. Percutaneous trans-coronary-venous transplantation of autologous skeletal myoblasts in the treatment of post-infarction myocardial contractility impairment: the POZNAN trial. *Eur Heart J.* 2005; 26(12):1188-95. Available from: <https://doi.org/10.1093/eurheartj/ehi159>
155. Simioniuc A, Campan M, Lionetti V, Marinelli M, Aquaro GD, Cavallini C, et al. Placental stem cells pre-treated with a hyaluronan mixed ester of butyric and retinoic acid to cure infarcted pig hearts: a multimodal study. *Cardiovasc Res.* 2011; 90(3):546-56. Available from: <https://doi.org/10.1093/cvr/cvr018>
156. Smith RR, Barile L, Cho HC, Leppo MK, Hare JM, Messina E, et al. Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens. *Circulation.* 2007; 115(7):896-908. Available from: <https://doi.org/10.1161/circulationaha.106.655209>
157. Sokol A, Grekov D, Yemets G, Galkin A, Shchotkina N, Dovghaliuk A, et al. The Efficiency of Decellularization of Bovine Pericardium by Different Concentrations of Sodium Dodecyl Sulfate. *Innov Biosyst Bioeng.* 2020; 4(4):189-98.
158. Squillaro T, Peluso G, Galderisi U. Clinical trials with mesenchymal stem cells: an update. *Cell Transplant.* 2016; 25(5):829-48. Available from: <https://doi.org/10.3727/096368915X689622>
159. Strauer BE, Brehm M, Zeus T, Köstering M, Hernandez A, Sorg RV, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation.* 2002; 106(15):1913-1918. Available from: <https://doi.org/10.1161/01.cir.0000034046.87607.1c>
160. Suss PH, Capriglione LG, Barchiki F, Miyague L, Jackowski D, Fracaro L, et al. Direct intracardiac injection of umbilical cord-derived stromal cells and umbilical cord blood-derived endothelial cells for the treatment of ischemic cardiomyopathy. *Exp Biol Med (Maywood).* 2015; 240(7):969-78. Available from: <https://doi.org/10.1177/1535370214565077>
161. Suuronen EJ, Price J, Veinot JP, Ascah K, Kapila V, Guo XW, et al. Comparative effects of mesenchymal progenitor cells, endothelial progenitor cells, or their combination on myocardial infarct regeneration and cardiac function. *J Thorac Cardiovasc Surg.* 2007; 134(5):1249-58. Available from: <https://doi.org/10.1016/j.jtcvs.2007.07.028>

162. Szaraz P, Gratch YS, Iqbal F, Librach CL. In Vitro Differentiation of Human Mesenchymal Stem Cells into Functional Cardiomyocyte-like Cells. *J Vis Exp*. 2017; (126):55757. Available from: <https://doi.org/10.3791/55757>
163. Takehara N, Nagata M, Ogata T, Kami D, Nakamura T, Matoba S, et al. The ALCADIA (Autologous Human Cardiac-derived Stem Cell To Treat Ischemic Cardiomyopathy) trial. 2012; *Circulation*. 126:2776-2799. Available from: <https://doi.org/10.1161/CIR.0b013e318278c90d>
164. Tarui S, Ishigami S, Ousaka D, Kasahara S, Ohtsuki S, Sano S, et al. Transcoronary infusion of cardiac progenitor cells in hypoplastic left heart syndrome: Three-year follow-up of the transcoronary infusion of cardiac progenitor cells in patients with single-ventricle physiology (TICAP) trial. *J Thorac Cardiovasc Surg*. 2015; 150(5):1198-1207, 1208.e1-2. Available from: <https://doi.org/10.1016/j.jtcvs.2015.06.076>
165. Tateishi K, Ashihara E, Honsho S, Takehara N, Nomura T, Takahashi T, et al. Human cardiac stem cells exhibit mesenchymal features and are maintained through Akt/GSK-3beta signaling. *Biochem Biophys Res Commun*. 2007; 352(3):635-641. Available from: <https://doi.org/10.1016/j.bbrc.2006.11.096>
166. Tateishi K, Ashihara E, Takehara N, Nomura T, Honsho S, Nakagami T, et al. Clonally amplified cardiac stem cells are regulated by Sca-1 signaling for efficient cardiovascular regeneration. *J Cell Sci*. 2007; 120(Pt 10):1791-1800. Available from: <https://doi.org/10.1242/jcs.006122>
167. Tateishi K, Takehara N, Matsubara H, Oh H. Stemming heart failure with cardiac- or reprogrammed-stem cells. *J Cell Mol Med*. 2008; 12(6A):2217-2232. Available from: <https://doi.org/10.1111/j.1582-4934.2008.00487.x>
168. Taylor DA, Atkins BZ, Hungspreugs P, Jones TR, Reedy MC, Hutcheson KA, et al. Regenerating functional myocardium: improved performance after skeletal myoblast transplantation. *Nat Med*. 1998; 4(8):929-933. Available from: <https://doi.org/10.1038/nm0898-929>
169. Terajima Y, Shimizu T, Tsuruyama S, Sekine H, Ishii H, Yamazaki K, et al. Autologous skeletal myoblast sheet therapy for porcine myocardial infarction without increasing risk of arrhythmia. *Cell Med*. 2013; 6(3):99-109. Available from: <http://doi.org/10.3727/215517913X672254>
170. Thompson CA, Nasser BA, Makower J, Houser S, McGarry M, Lamson T, et al. Percutaneous transvenous cellular cardiomyoplasty. A novel nonsurgical approach for myocardial cell transplantation. *J Am Coll Cardiol*. 2003; 41(11):1964-71. Available from: [https://doi.org/10.1016/s0735-1097\(03\)00397-8](https://doi.org/10.1016/s0735-1097(03)00397-8)
171. Tiburcy M, Hudson JE, Balfanz P, Schlick S, Meyer T, Chang Liao ML, et al. Defined Engineered Human Myocardium With Advanced Maturation for Applications in Heart Failure Modeling and Repair. *Circulation*. 2017; 135(19):1832-1847. Available from: <https://doi.org/10.1161/CIRCULATIONAHA.116.024145>
172. Tokita Y, Tang XL, Li Q, Wysoczynski M, Hong KU, Nakamura S, et al. Repeated administrations of cardiac progenitor cells are markedly more effective than a single administration: a new paradigm in cell therapy. *Circ Res*. 2016; 119(5):635-51. Available from: <https://doi.org/10.1161/CIRCRESAHA.116.308937>
173. Traverse JH, Henry TD, Ellis SG, Pepine CJ, Willerson JT, Zhao DX, et al. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. *JAMA*. 2011; 306(19):2110-2119. Available from: <https://doi.org/10.1001/jama.2011.1670>
174. Traverse JH, Henry TD, Pepine CJ, Willerson JT, Zhao DX, Ellis SG, et al. Effect of the use and timing of bone marrow mononuclear cell delivery on left ventricular function after acute myocardial infarction: the TIME randomized trial. *JAMA*. 2012; 308(22):2380-2389. Available from: <https://doi.org/10.1001/jama.2012.28726>
175. Turner D, Rieger AC, Balkan W, Hare JM. Clinical-based Cell Therapies for Heart Disease-Current and Future State. *Rambam Maimonides Med J*. 2020; 11(2):e0015. Available from: <https://doi.org/10.5041/RMMJ.10401>
176. Vadakke-Madathil S, LaRocca G, Raedschelders K, Yoon J, Parker SJ, Tripodi J, et al. Multipotent fetal-derived Cdx2 cells from placenta regenerate the heart. *Proc Natl Acad Sci U S A*. 2019; 116(24):11786-11795. Available from: <https://doi.org/10.1073/pnas.1811827116>
177. Valina C, Pinkernell K, Song YH, Bai X, Sadat S, Campeau RJ, et al. Intracoronary administration of autologous adipose tissue-derived stem cells improves left ventricular function, perfusion, and remodelling after acute myocardial infarction. *Eur Heart J*. 2007; 28(21):2667-77. Available from: <https://doi.org/10.1093/eurheartj/ehm426>
178. van Berlo JH, Kanisicak O, Maillet M, Vagnozzi RJ, Karch J, Lin SC, et al. c-kit+ cells minimally contribute cardiomyocytes to the heart. *Nature*. 2014; 509:337-341 Available from: <https://doi.org/10.1038/nature13309>
179. Ventura C, Cantoni S, Bianchi F, Lionetti V, Cavallini C, Scarlata I, et al. Hyaluronan mixed esters of butyric and retinoic acid drive cardiac and endothelial fate in term placenta human mesenchymal stem cells and enhance cardiac repair in infarcted rat hearts. *J Biol Chem*. 2007; 282:14243-14252. Available from: <https://doi.org/10.1074/jbc.m609350200>
180. Wang L, Deng J, Tian W, Xiang B, Yang T, Li G, et al. Adipose-derived stem cells are an effective cell candidate for treatment of heart failure: an MR imaging study of rat hearts. *Am J Physiol Heart Circ Physiol*. 2009; 297(3):H1020-31. Available from: <http://doi.org/10.1152/ajpheart.01082.2008>
181. Wang T, Tang W, Sun S, Ristagno G, Huang Z, Weil MH. Intravenous infusion of bone marrow mesenchymal stem cells improves myocardial function in a rat model of myocardial ischemia. *Crit Care Med*. 2007; 35(11):2587-2593. Available from: <https://doi.org/10.1097/01.ccm.0000285992.99391.7e>
182. Ward MR, Abadeh A, Connelly KA. Concise Review: Rational Use of Mesenchymal Stem Cells in the Treatment of Ischemic Heart Disease. *Stem Cells Transl Med*. 2018 Jul;7(7):543-550. Available from: <https://doi.org/10.1002/sctm.17-0210>
183. White AJ, Smith RR, Matsushita S, Chakravarty T, Czer LS, Burton K, et al. Intrinsic cardiac origin of human cardiosphere-derived cells. *European Heart Journal*. 2013; 34:68-75. Available from: <https://doi.org/10.1093/eurheartj/ehr172>
184. Williams AR, Hatzistergos KE, Addicott B, McCall F, Carvalho D, Suncion V, et al. Enhanced effect of combining human cardiac stem cells and bone marrow mesenchymal stem cells to reduce infarct size and to restore cardiac function after myocardial infarction. *Circulation*. 2013; 127(2):213-23. Available from: <https://doi.org/10.1161/CIRCULATIONAHA.112.131110>
185. Windmolders S, Willems L, Daniëls A, Linsen L, Fanton Y, Hendrikx M, et al. Clinical-scale *in vitro* expansion preserves biological characteristics of cardiac atrial appendage stem cells. *Cell Prolif*. 2015; 48(2):175-86. Available from: <https://doi.org/10.1111/cpr.12166>
186. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet*. 2004; 364(9429):141-148. Available from: [https://doi.org/10.1016/s0140-6736\(04\)16626-9](https://doi.org/10.1016/s0140-6736(04)16626-9)
187. Wu M, Zhang R, Zou Q, Chen Y, Zhou M, Li X, et al. Comparison of the biological characteristics of mesenchymal stem cells derived from the human placenta and umbilical cord. *Sci Rep*. 2018; 8(1):5014. Available from: <https://doi.org/10.1038/s41598-018-23396-1>
188. Wu S, Duan B, Qin X, Butcher JT. Living nano-micro fibrous woven fabric/hydrogel composite scaffolds for heart valve engineering. *Acta Biomater*. 2017; 51:89-100. Available from: <http://doi.org/10.1016/j.actbio.2017.01.051>

189. Yacoub MH, Terrovitis J. CADUCEUS, SCPIO, ALCADIA: Cell therapy trials using cardiac-derived cells for patients with post myocardial infarction LV dysfunction, still evolving. *Glob Cardiol Sci Pract*. 2013; 2013(1):5-8. Available from: <https://doi.org/10.5339/gcsp.2013.3>
190. Yadav SK, Mishra PK. Isolation, characterization, and differentiation of cardiac stem cells from the adult mouse heart. *J Vis Exp*. 2019; 143:10.3791/58448. Available from: <https://doi.org/10.3791/58448>
191. Yamada Y, Yokoyama S, Fukuda N, Kidoya H, Huang XY, Naitoh H, et al. A novel approach for myocardial regeneration with educated cord blood cells cocultured with cells from brown adipose tissue. *Biochem Biophys Res Commun*. 2007; 353(1):182-8. Available from: <https://doi.org/10.1016/j.bbrc.2006.12.017>
192. Yamaguchi S, Shimizu Y, Murohara T, Shibata R. Adipose-derived regenerative cells as a promising therapy for cardiovascular diseases: an overview. *Nagoya J Med Sci*. 2022; 84(2):208-215. Available from: <https://doi.org/10.18999/nagjms.84.2.208>
193. Yamanaka S. Strategies and new developments in the generation of patient-specific pluripotent stem cells. *Cell Stem Cell*. 2007; 1(1):39-49. Available from: <https://doi.org/10.1016/j.stem.2007.05.012>
194. Yang CJ, Yang J, Yang J, Fan ZX. Cardiac atrial appendage stem cells therapy: a novel and promising approach for myocardial reparation after MI. *Int J Cardiol*. 2016; 203:1153-4. Available from: <https://doi.org/10.1016/j.ijcard.2015.10.039>
195. Yannarelli G, Dayan V, Pacienza N, Lee CJ, Medin J, Keating A. Human umbilical cord perivascular cells exhibit enhanced cardiomyocyte reprogramming and cardiac function after experimental acute myocardial infarction. *Cell Transplant*. 2013;22(9):1651-66. Available from: <https://doi.org/10.3727/096368912X657675>
196. Yap L, Chong LY, Tan C, Adusumalli S, Seow M, Guo J, et al. Pluripotent stem cell-derived committed cardiac progenitors remuscularize damaged ischemic hearts and improve their function in pigs. *NPJ Regen Med*. 2023; 8(1):26. Available from: <https://doi.org/10.1038/s41536-023-00302-6>
197. Yee K, Malliaras K, Kanazawa H, Tseliou E, Cheng K, Luthringer DJ, et al. Allogeneic cardiospheres delivered via percutaneous transendocardial injection increase viable myocardium, decrease scar size, and attenuate cardiac dilatation in porcine ischemic cardiomyopathy. *PLoS One*. 2014; 9(12):e113805. Available from: <https://doi.org/10.1371/journal.pone.0113805>
198. Yu Q, Li Q, Na R, Li X, Liu B, Meng L, et al. Impact of repeated intravenous bone marrow mesenchymal stem cells infusion on myocardial collagen network remodeling in a rat model of doxorubicin-induced dilated cardiomyopathy. *Mol Cell Biochem*. 2014; 387(1-2):279-285. Available from: <https://doi.org/10.1007/s11010-013-1894-1>
199. Yu S, You X, Liang H, Li Y, Fu Y, Zhang X, et al. First trimester placental mesenchymal stem cells improve cardiac function of rat after myocardial infarction via enhanced neovascularization. *Heliyon*. 2021; 7(1):e06120. Available from: <https://doi.org/10.1016/j.heliyon.2021.e06120>
200. Zhang J, Tao R, Lalit P, Carvalho J, Markandeya Y, Palecek S, et al. Cardiac differentiation of human pluripotent stem cells using defined extracellular matrix proteins reveals essential role of fibronectin. *bioRxiv*. 2021. Available from: <https://doi.org/10.1101/2021.04.09.439173>
201. Zhang S, Jia Z, Ge J, Gong L, Ma Y, Li T, et al. Purified human bone marrow multipotent mesenchymal stem cells regenerate infarcted myocardium in experimental rats. *Cell Transplant*. 2005; 14(10):787-798. Available from: <https://doi.org/10.3727/000000005783982558>
202. Zhang X, Wei M, Zhu W, Han B. Combined transplantation of endothelial progenitor cells and mesenchymal stem cells into a rat model of isoproterenol-induced myocardial injury. *Arch Cardiovasc Dis*. 2008; 101(5):333-42. Available from: <https://doi.org/10.1016/j.acvd.2008.05.002>
203. Zhao L, Chen S, Yang P, Cao H, Li L. The role of mesenchymal stem cells in hematopoietic stem cell transplantation: prevention and treatment of graft-versus-host disease. *Stem Cell Res Ther*. 2019; 10(1):182. Available from: <https://doi.org/10.1186/s13287-019-1287-9>
204. Zhao XF, Xu Y, Zhu ZY, Gao CY, Shi YN. Clinical observation of umbilical cord mesenchymal stem cell treatment of severe systolic heart failure. *Genet Mol Res*. 2015; 14(2):3010-7. Available from: <https://doi.org/10.4238/2015.April.10.11>
205. Zhu Y, Liu T, Ye H, Song K, Ma X, Cui Z. Enhancement of adipose-derived stem cell differentiation in scaffolds with IGF-I gene impregnation under dynamic microenvironment. *Stem Cells Dev*. 2010; 19(10):1547-56. Available from: <https://doi.org/10.1089/scd.2010.0054>
206. Zwetsloot PP, Végh AM, Jansen of Lorkeers SJ, van Hout GP, Currie GL, Sena ES, et al. Cardiac stem cell treatment in myocardial infarction: a systematic review and meta-analysis of preclinical studies. *Circ Res*. 2016; 118(8):1223-32. Available from: <https://doi.org/10.1161/CIRCRESAHA.115.307676>



ARTICLE ON THE SITE
TRANSPLANTOLOGY.ORG

The author declares that there is no potential conflict of interest regarding the research, authorship and/or publication of this article

УДК 611.12:616.12-008+612.683

Терапія стовбуровими клітинами для регенерації серця: основні аспекти



Кирик В. М.

¹Інститут генетичної та регенеративної медицини ДУ "Національний науковий центр "Інститут кардіології, клінічної та регенеративної медицини імені академіка М. Д. Стражеска Національної академії медичних наук України", Київ, Україна

²ДУ "Інститут геронтології імені Д. Ф. Чеботарьова Національної академії медичних наук України", Київ, Україна

РЕЗЮМЕ

Серцево-судинні захворювання є однією з провідних причин інвалідизації та смертності серед працездатного населення, а тому потребують розробки та впровадження нових більш ефективних методів лікування та реабілітації таких пацієнтів, зокрема із застосуванням сучасних клітинних та тканинних технологій.

В огляді проведено аналіз та узагальнення результатів досліджень за останні десятиріччя щодо оцінки ефективності застосування різних типів стовбурових клітин при патології серця.

Пріоритетними напрямками є пошук більш доступних та безпечних джерел стовбурових клітин, розробка нових ефективних варіантів їх культивування, використання матриксів-носіїв для трансплантації. Враховуючи патогенетичні механізми розвитку серцево-судинної патології та регенерації міокарда, на особливий інтерес щодо перспектив клінічного застосування заслуговують тканинспецифічні прогенітори з міокарда з метою заміщення втрачених кардіоміоцитів, ендотеліальні прогенітори для корекції супутньої ендотеліальної дисфункції та мультипотентні мезенхімальні клітини різного походження, які мають низьку імуногенність та реалізують трофічні, протизапальні, імуномодулюючі та антиапоптотичні ефекти. Відкритими залишаються і питання щодо вибору оптимального способу, дози та кратності введення стовбурових клітин, а також стандартизації критеріїв їх якості та ефективності. При цьому комбіноване застосування різних типів стовбурових клітин може виступати новою пріоритетною стратегією при оцінці ефективності та безпеки клітинної терапії, особливо з огляду на парадигму багаторазового проведення трансплантації.

Успішна трансляція отриманих доклінічних результатів у подальших масштабних, належним чином спланованих плацебо-контрольованих клінічних дослідженнях підвищить безпеку та ефективність клітинної терапії захворювань серцево-судинної системи, що є одним з актуальних завдань сучасної регенеративної медицини.

КЛЮЧОВІ СЛОВА: серцево-судинні захворювання; регенерація серця; стовбурові клітини; клітинна терапія; доклінічні дослідження; клінічні випробування