Biomedicine & Pharmacotherapy 87 (2017) 37–45

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

Recent advances in cardiac regeneration: Stem cell, biomaterial and growth factors

Mostafa Cheraghi[a], Mehrdad Namdari[a,**], Babak Negahdari[b], Ali Eatemadi[b,c,d,*]

[a] Department of Cardiology, Lorestan University of Medical Sciences, Khoramabad, Iran
[b] Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
[c] Razi Herbal Medicine Research Center, Lorestan University of Medical Science, Khorramabad, Iran
[d] Department of Medical Biotechnology, School of Medicine, Lorestan University of Medical Sciences, Lorestan, Iran

ARTICLE INFO

Article history:
Received 16 September 2016
Received in revised form 12 December 2016
Accepted 19 December 2016

Keywords:
Myocardial infarction
Cell therapy
Protein therapy
Biomaterials
Delivery systems

ABSTRACT

Myocardial infarction has been reported to be responsible for about 7.3 million deaths each year globally. Present treatments for myocardial infarction have been more palliative rather than curative. Over the past few years, stem cells have demonstrated its potency in regenerating damaged cardiac tissue, especially after myocardial infarction. However, limited short half-life of the protein and cell therapy and low transplanted cell survival rate as demonstrated via several clinical trials have lead to development of more potent and novel delivery systems like biomaterial delivery system and the use of various growth factors. In this review, we will be enumerating and discussing the recent advances in cardiac regeneration with focus on stem cell, biomaterial and growth factors.

Contents

1. Stem cells and growth factors application in cardiology

Various types of stem/progenitor cells have been commonly used to regenerate cardiac tissues damaged by myocardial infarction Table 1. Human stem cell-derived cardiomyocytes (hSC-DCMs) has been reported to be effective in regenerating cardiac tissue after myocardial infarction. There are four potential mechanisms have been proposed to be involved in stimulating myocardiac repair and functional recovery: Firstly, cardiac regeneration: mesenchymal cells may have the tendency to differentiate into cells that looks like cardiomyocytes; Secondly, the cardiac repair might be through paracrine effect; Thirdly niche contribution: mesenchymal stem cell help to maintain the cardiac niche for cardiac stem cell; and lastly, because of its immunomodulatory tendencies, mesenchymal stem cells helps in the management of immune rejection and its also responsible for inflammatory regulation on cardiac repair and regeneration. It should be noted that all these proposed mechanisms work dependently to regulate stem cell function (Fig. 1) [1–4].

However, stem cell therapy has produced low cell survival and there are still major limitations encountered with consistent derivation of hSC-DCMs populations [6]. Several studies have reported the expression of cell inhibitors like p16 (INK), p21 and p19 (ARF) and cellular stress when mesenchymal stem cell (MSC) are cultured for a very long time, however co-culturing the MSC

* Corresponding author at: Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical sciences, Tehran, Iran.
** Corresponding author at: Department of Cardiology, Lorestan University of Medical Sciences, Khoramabad 6997118544, Iran.
E-mail addresses: hadisdaraee@gmail.com (M. Namdari), a-eatemadi@razi.tums.ac.ir (A. Eatemadi).

http://dx.doi.org/10.1016/j.biopha.2016.12.071
0753-3322/

Table 1
Major stem cell used for Cardiac repair.

Type	Source	Advantages	Disadvantages
Embryonic stem cells	Inner cell mass of pre-implantation blastocyst	Pluripotent, self-renewal capacity	Graft versus host disease, ethical debate, and tumorgenesis
Mesenchymal stem cells	Bone marrow/adipose tissue	Multipotent, easy to isolate and expand, lack of immunogenicity,	Heterogenicity
Endothelial progenitor cells	Bone marrow, peripheral blood	Movement from bone marrow or peripheral blood, important in neovascularization	Need for expansion, Heterogenicity,
Skeletal Myoblasts	Skeletal muscle	High scalability, resistance to ischemia, multipotent, no teratoma formation	Electrophysiologically incompatible, lack of gap junction
Cardiac stem cells	Heart	Resident cells, robust cardiovascular differentiation potential, reduced tumor formation	short survival, and limited supply

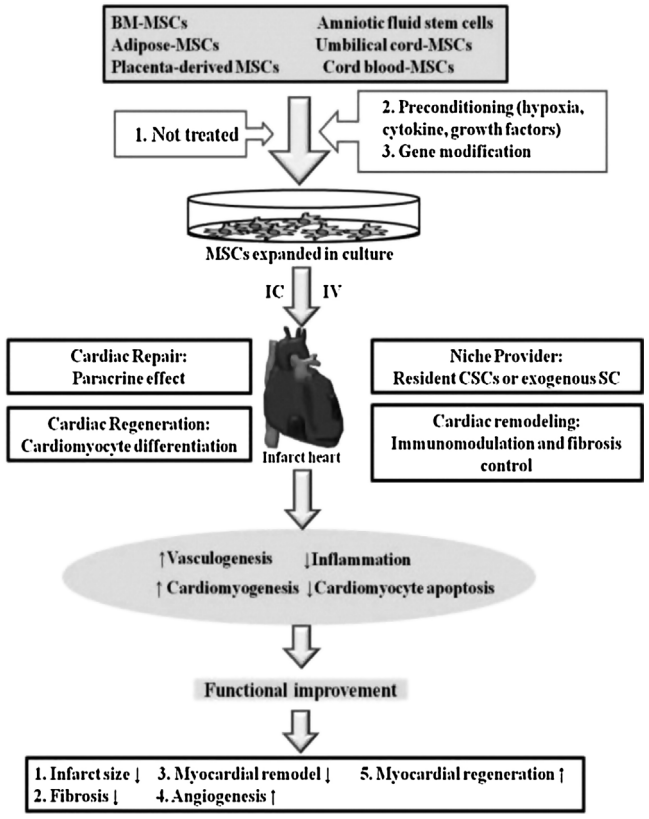

Fig. 1. Mesenchymal mechanisms for cardiac repair. Through cardiac regeneration, paracrine mechanism, niche providing, and inflammatory control, MSCs can reduce infarct size, fibrosis, and myocardial remodeling, then increase angiogenesis and myocardial regeneration. Abbreviations: MSC, mesenchymal stem cells; CSC, cardiac stem cells; SC, stem cells; IV, intravenous; IC, intracoronary [5].

with vascular endothelial growth factor (VEGF) reduces the cellular stress and pro-survival factors like phosphorylated-Akt and Bcl-xL are increased.

Tang and other researchers reported that combined therapy of (MSCs + VEGF) to MI hearts leads to better cell engraftment and cardiac functioning compared to VEGF or MSCs therapy alone [7,8]. It should also be noted that insulin-like growth factor (IGF)-1 co-cultured with MSC is responsible for improving survival rate and also enhances the paracrine release of stromal cell-derived factor (SDF)-1α. Haider and co-worker also reported the role of insulin growth factor-1(IGF-1) in facilitating the migration and differentiation of stem cells to injured heart [9]. As reported by Higashi and colleagues that IGF-1 is responsible for processes like development, cell growth and differentiation [10]. In addition some studies have demonstrated mesenchymal stem cells that overexpressed IGF-1/GF-1R used in an Intramyocardial transplantation procedure lead to enhanced and improved cardiac repair [11]. Furthermore, it has been reported that concurrent overexpression of Ang-1 and Akt in mesenchymal stem cells enhances the survival of these stem cells in the infarcted heart. It should also be noted that insulin growth factor and its receptor are widely distributed in cells like myocytes, cardiac progenitor cells (CPCs), and cardiac fibroblasts in the heart and there activation are responsible for so many biological activities including telomerase activity [12].

In addition to various activities coordinate by IGF-1, its also responsible for the releasing and expression of some growth factor like hepatocyte growth factor (HGF), basic fibroblast growth factor (b-FGF), and importantly, vascular endothelial growth factor which has been demonstrated by so many researchers as an essential regulator of the growth and development of new blood vessels in the heart under hypoxic condition [8]. VEGF has been reported to be indirectly secreted by MSCs and enhances regeneration of cardiac tissue after repairs [13]. At elevated levels, VEGF post-myocardial infarction have been demonstrated to be related with cardiovascular protection and improvements of clinical outcomes [14]. Recent clinical trials have also confirm the potency of VEGF in augmenting perfusion of ischemic myocardium in addition to decrease in defects [15,16]. In another experimental studies, it was reported that when differentiated human umblical cord matrix stem cell combined with VEGF improved left ventricular dysfunction, induces formation of new blood vessels and reduces fibrotic tissue formation in infarcted myocardium in eight weeks post MI when compared to the effect of VEGF alone [17].

Furthermore, functional studies have demonstrated that VEGF/MSC transplantation stimulates extensive angiogenesis and myogenesis via the increased expression of cardiac troponin T, CD31, and von Willebrand factor, in an injured heart as such leading to improved functioning of the left ventricle. Hatzistergous and co-worker reported that VEGF/MSC transplantation system enhances the process of angiogenesis through the process of SDF-1α pathway activation that in turn stimulates the differentiation of cardiac stem cells into endothelial cells in infarcted myocardium [18]. As stated before, VEGF is highly expressed by stem cells and MSCs. It should also be noted that MSC-conditioned medium evidently promotes the migration of cardiac stem cell (CSC) through the stromal cell derived factor (SDF) SDF-1α/CXCR4 pathway, which is proposed to be involved by the VEGF/VEGFR-1 and VEGFR-3 (vascular endothelial growth factor receptor-3) systems (Fig. 2).

In the past few years, clinical trials have been carried out using unfractionated adult bone marrow mononuclear cells (BMMNCs) because they are easy to aspirate from bone marrows, contains cardiomyocytes and endothelial precursor cells are present within the mononuclear cell fraction of bone marrow, easily injectable into the heart and lastly, they can be used when there are variable number of cells and different administration routes.

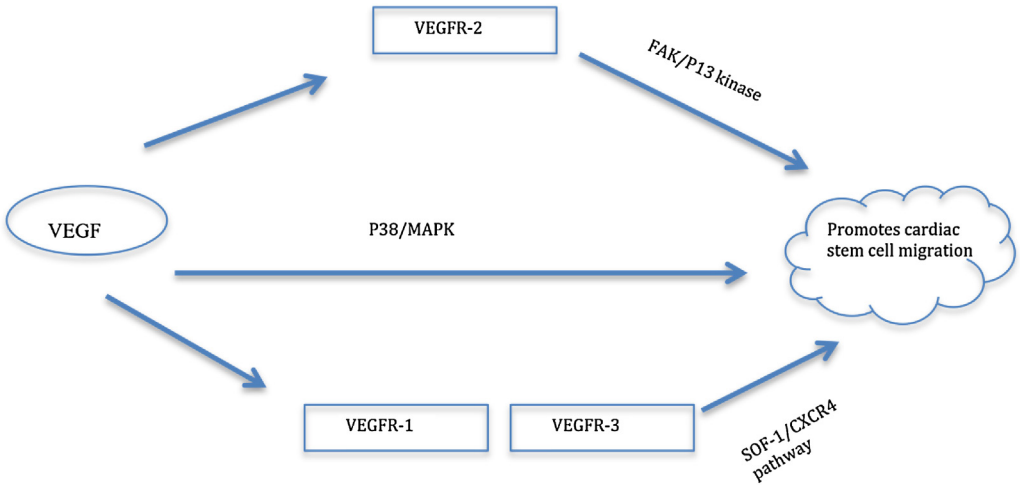

Fig. 2. VEGF/VEGFR system mediates a fast activation of SDF-1α/CXCR4 pathway, which leads to migration of cardiac stem cell (CSC) migration via FAK/PI3-kinase signaling or p38/MAPK pathway. This figure was culled from [19].

Table 2
Bone marrow-mesenchymal stem cell based clinical trial for cardiac repair.

Cell types	Numbers	Route	Delivery day after MI	Outcome	Refs.
BM-MNCs	9–28 × 106	IC	7	Improved contractility and reduced infarct size	[24]
BM-MNCs	2.4 × 108	IC	3–7	Improved LVEF and reduced infarct size	[25]
BM-MNCs	24 × 109	IC	6	Improved EF and increased regional contractility	[26]
BM-MNCs	2.4 × 108	IC	4	Improved EF and reduced infarct size	[27]
BM-MNCs	11–90 × 106	IC	10–15	Significant functional improvement and reduced infarct size	[28]
BM-MNCs	3 × 108	IC	1	Decrease scar size but no improvement in LVEF	[29]
BM-MNCs	8.7 × 107	IC	5–8	No difference	[30]
BM-MNCs	13.4 × 107	IC	6–8	Improved LV function	[31]
BM-MSCs	48–68 × 1010	IC	18	Increased LVEF, regional contractility, and viability of infarct zone	[32]
BM-MSCs	2–4 × 106	IC	Directly	Reduced wall motion score index and improved myocardial viability and contractility	[33]
BM-MSCs	2.1–9.1 × 106	IC/DI	Directly	↓ Perfusion defect and ↑ LVEF	[34]
BM-MSCs	0.5, 1.6, 5 × 106/kg	IV	1,2,3,6 months	Improved LVEF and reverse modeling	[35]
BM-MSCs	5–16 × 107	TESI	Directly	↓ Cardiac remodeling, ↓ ESV and EDV, and ↑ regional contractility	[36]
CP-MSCs	6–12 × 108	EMG	Directly	↑ LVEF and ↓ ESV and EDV	[37]

IC, intracoronary; IV, intravenous; BM-MNCs, unfractionated bone marrow mononuclear cells; MSCs, mesenchymal stem cells; CP MSCs, cardio- poietic mesenchymal stem cells; LVEF, left ventricular ejection fraction; EF, ejection fraction; TESI, transendocardial stem cell injection; EMG, electromechanical guidance; DI, direct intramyocardial injection.

Briefly Table 2 gives a summary of clinical trials involving the use of BMMNCs and MSCs for cardiac repair. So many researchers have investigated the mechanism underlining the mesenchymal-based cell therapy for cardiac repair however more extensive work is still needed as cardiac cells are been replaced by fibrotic tissue [20]. Donor cells transplanted into myocardial infarcted area engrafts into the recipient tissue to finally form into new, developing cardiomyocytes and this is the basis of myocardial cell transplantation. However most researchers do not subscribe to the notion that BMMNCs is the best stem cell source to be used for myocardial transplantation, recent differentiation advancements have identified human pluripotent stem cell(hPSC)- cardiomyocytes as a more potent and promising future of stem cell source, and they have been studied at preclinical level as regards their transplantation into the heart.

Maher and colleagues reported an improvement in the cardiac functions and survival of the animal model when hPSC-cardiomyocytes were engrafted into an infarcted region of several animal models [21]. Fernandes and co-worker further reported that hPSC- cardiomyocytes gives more stability and durable grafts in the infarcted heart when compared to BMMNCs and MSCs [22]. And more recently there has been positive studies proving the stability and the long-term cardiomyocyte engraftment and its functional incorporation in rodents have lead to the incorporation of this approach into a nonhuman primate injury model [23] like Pig- tailed macaques (*Macaca nemestrina*). In an experimental study reported by Chong and colleagues, the pig-tailed macaques received a reperfusion injury by inflating a balloon catheter into the distal left anterior descending coronary artery for 90 min followed by reperfusion (Fig. 3)

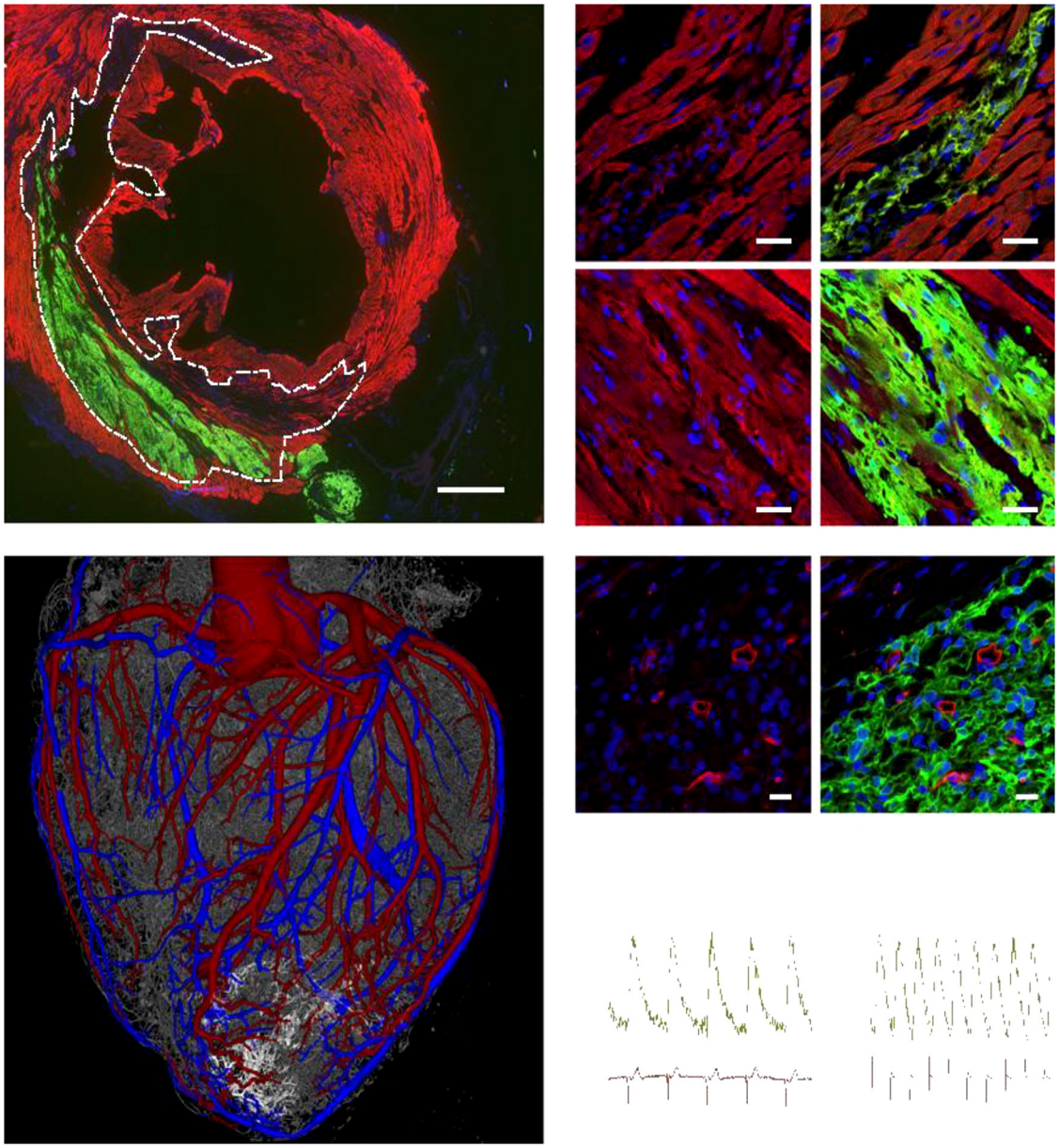

Fig. 3. hPSC-derived cardiomyocytes remuscularize the infarcted macaque heart [23]. Top-left: hESC-cardiomyocytes robustly engraft in the infarcted myocardium, outlined by the dashed line, as indicated by confocal immunofluorescence at day 14 after transplantation. Engrafted cardiomyocytes express GFP (human, green) and both hESC-cardiomyocytes and host cardiomyocytes express the contractile protein alpha-actinin (human and monkey, red) with nuclear DAPI counterstain (blue). Top-right: The in vivo maturation of engrafted hESC-cardiomyocytes is evident from 14 days to 84 days postengraftment by costaining for alpha-actinin (human and monkey, red) and GFP (human, green). Bottom-left: Host vasculature perfuses the hESC-cardiomyocyte graft at 84 days postengraftment, as visualized by 3D rendered microcomputed tomography. Bottom-right: Ex vivo fluorescent GCaMP3 imaging indicates that engrafted human cardiomyocytes are electrically coupled to the infarcted macaque heart at 14 days postengraftment. GCaMP3 fluorescence intensity (green) and host ECG (red) are plotted versus time and demonstrate 1:1 coupling at spontaneous rate as well as during atrial pacing at 3 Hz.

2. Recent studies using biomaterial-based delivery systems in heart regeneration

Biomaterials have been demonstrated in four engineered different ways by which its abilities can be harnessed in the field of cardiology as shown in Fig. 4:

Several studies have demonstrated the potency of biomaterial-based delivery systems integrated with cell and protein therapies in improving the clinical outcomes of cells and proteins [38–44] in cardiac tissue regeneration. Presently several synthetic biomaterials that include caprolactone, polyglycolic and polylactic acids, polyurethane is under careful research investigation [45–53]. Table 3 gives a summary of their merits and demerits.

Leor and co-worker successfully implanted cardiac cell-seeded macroporous alginate scaffolds into an infarcted rat hearts [60]. Dar et al. Further corroborated Leor report and they reported that the seeded fetal rat cardiomyocytes were still viable within the scaffolds, in the space of 24 h [61]. They concluded that the cells successfully differentiated into mature myocardial fibers in the infarcted myocardium by observing the presence of cardiac muscle striation and gap junction formation. It should also be noted that angiogenesis was also observed subsequently leading to attenuation in left ventricular dilatation and improved heart function (Fig. 5) [60]

In pre-clinical animal models of MI, some researcher has reported the combination of cells or protein with biomaterials to

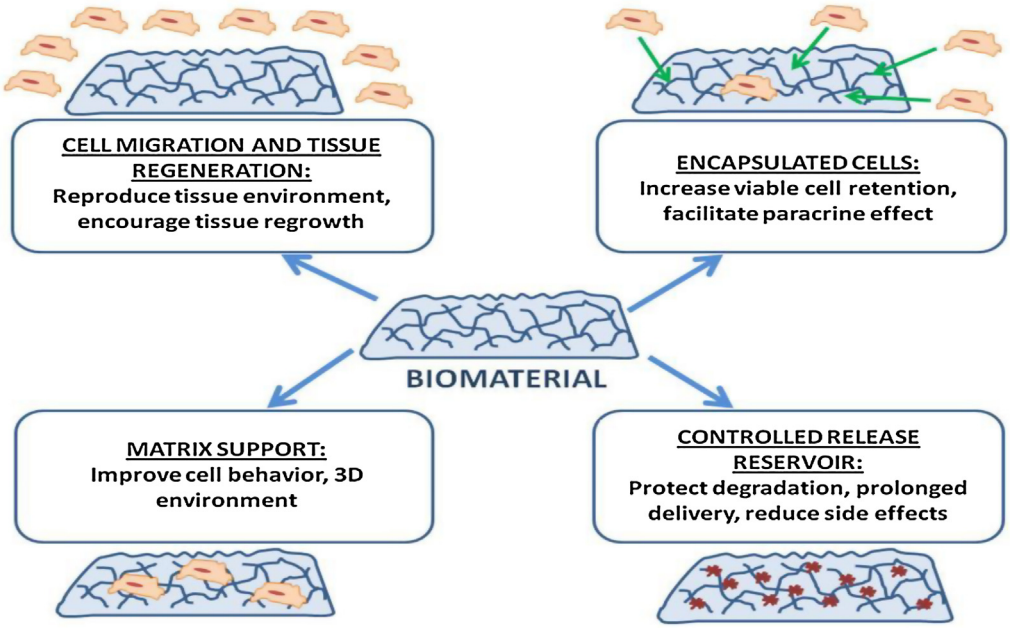

Fig. 4. Showing primary usefulness of biomaterials in cardiology.

Table 3
Synthetic biomaterials employed in cardiac drug delivery system.

Biomaterials	Advantages	Disadvantages
Caprolactone and derivatives	Non-toxic, tissue compatible, mechanical properties, high pH sensitivity	Arduous to synthesize and have a slow biodegradation rate [54,55]
Polyglycolic and polylactic acids and derivatives	Easily biodegradable and high biocompatibility	Acidic environment during degradation, bulk erosion [55]
Polyurethane	Biocompatible, mechanical properties	Biodegradable only when copolymerized with other polymers, Lacks conductivity [55]
Self-assembling peptides RAD	Self-assembly properties, bioreabsorbable, designed 3D microenvironment	Unknown toxicity and side effects [56,57]
Carbon nanotubes	Excellent mechanical and electrical properties	Strong hydrophobicity, physicochemical properties related toxicity, expensive [58]
Polyketals	Biodegradable, non- immunogenic, neutral degradation products, acid sensitivity, low cost	apid macrophage uptake and biodegradation, complex synthesis [59]

effective in improving cardiac functions after MI. Cardiac physiology and anatomy have been restored back to normal biological level by biomaterials together with the use of protein as drug delivery systems that afford protection for growth factors against in vivo degradation. In addition stem cells growth, survival and differentiation depends growth factors. Thus some researchers have researched extensively on the integration of stem cells, growth factors and biomaterial-based delivery systems and this integrated approach is known has tissue engineering triad (Fig. 6).

Fukuhara and co-worker first reported the use of a bioengineered nano-fibers scaffoldmade of polyglycolic acid succeeded in incorporating bone marrow stem cell and fibroblast growth factor. They finally concluded that the overall cardiac function and capillary density were significantly improved in BMSC-FGF-NFs treated animals when compared to BMSC or FGF loaded nanofibers groups [63] and likewise, Díaz-Herráez and colleagues demonstrated the viability of using neuregulin (NRG)-releasing poly(lactic-co-glycolic acid-micro particles PLGA-MPs integrated with adult stem cell as a multiple growth factor delivery-based tissue engineering strategy for engrafting into the infarcted myocardium [64]. They finally concluded that ADSC-NRG-MPs were effective and compatible with intramyocardial injection in a rat MI model and were still present 2 weeks after implantation proving long-term survival (Fig. 7).

Kraehenbuehl reported the delivery of thymosin β4 integrated with embryonic stem cells and smooth-muscle stem cells in ischemic injuries of a rat MI model. It should be noted that the thymosin Tβ4 protein protects cardiac muscle from death after ischemic damage and promotes angiogenesis by activating the survival kinase Akt, thereby announcing its importance as a cardiac regenerative molecule [65]. The use of self-assembling peptide RAD16-II has also be reported to be used to inject a hydrogels incorporating insulin-like growth factor integrated with cardiomyocytes [66] or cardiac progenitor cells [67] for cardiac repair. They finally concluded that in both administrations, the insulin-like growth factor significantly enhanced the recuperation of myocardial structure and function in rats one month after treatment. Furthermore PEGylated fibrin biomatrix has been

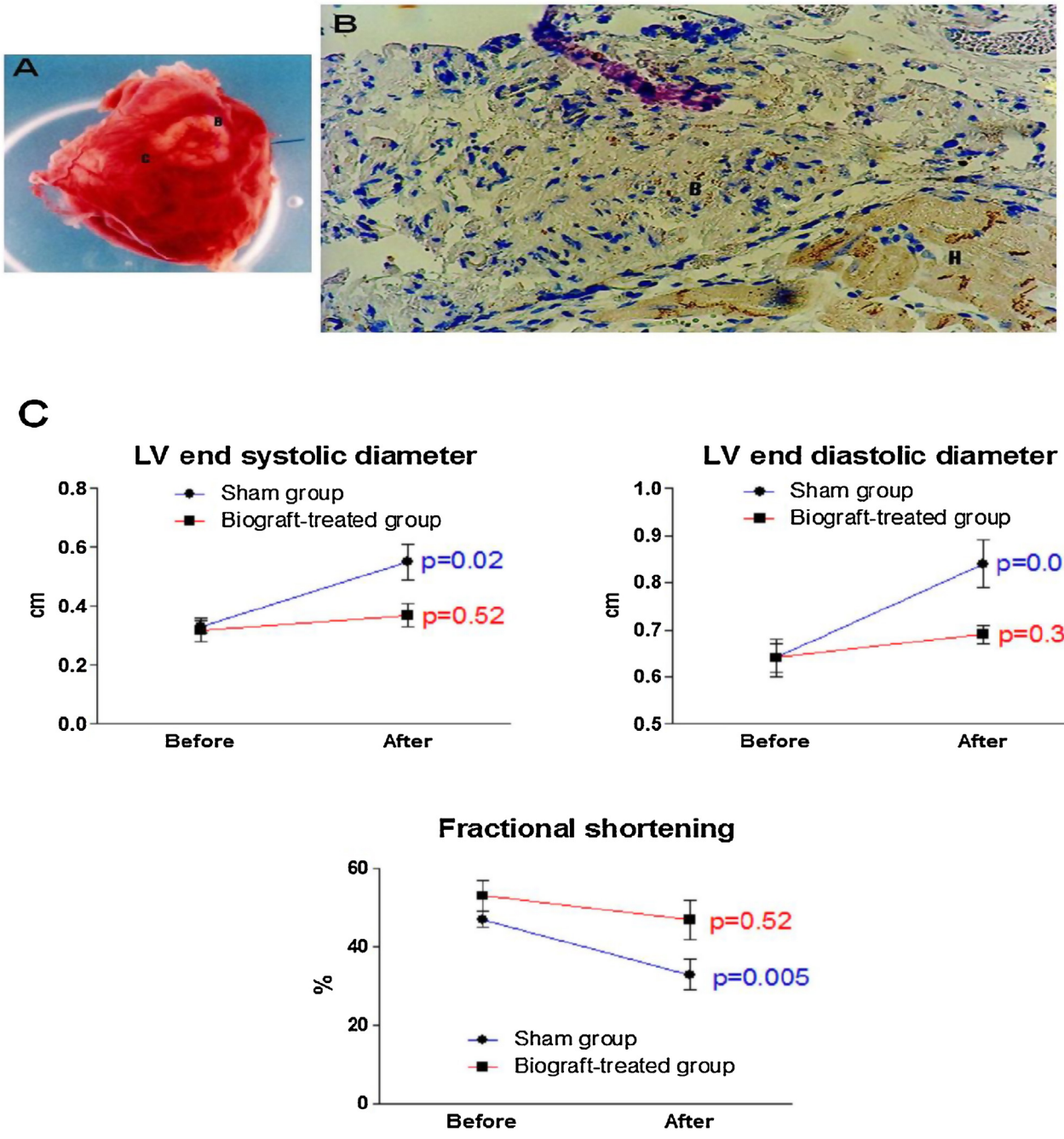

Fig. 5. Bio-engineered cardiac patch implantation on infarct. A. Photograph of heart at week 9 after patch implantation. (b). Note a coronary branch (c) that supplies and covers the patch with extensive network of vessels. B. Microscopic image of integrated patch, immuno-stained for connexin-43 (Cx-43) (brown). C. Results of echocardiography study. Fractional shortening = [(LV end diastolic diameter–LV end systolic diameter)/LV end diastolic diameter] × 100. This figure was reproduced from [62].

reported to competently bind to hepatocyte growth factor and capture bone marrow stem cell that lead to significant increase in cell frequency at myocardial infarction site at least for 4 weeks when compared to free cell administration [68]. In another study by Holladay and colleagues, mesenchymal stem cells were integrated with 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide and N-hydroxysuccinimide together with IL-10(interleukin-10) and dendrimer polyplexes. They finally reported that after four weeks, they found stem cell retention and growth factors were significantly enhanced in animals which received MSC-i10-systems compared to the rest of the groups [69].

3. Conclusion

Over the past few years, cardiac regenerative medicine has made significant advancement [70–82]. Several pre-clinical studies have demonstrated and reported to be successful in the incorporation of cardiac patches to ischemia hearts and its potency to improve the ischemia heart contractile function. However more clinical studies using acellular biomaterials, bone marrow- derived cells and hPSC-derived cardiomyocytes should be carried out and challenges like stability, durability, and cell retention should be addressed using novel biomaterials and novel

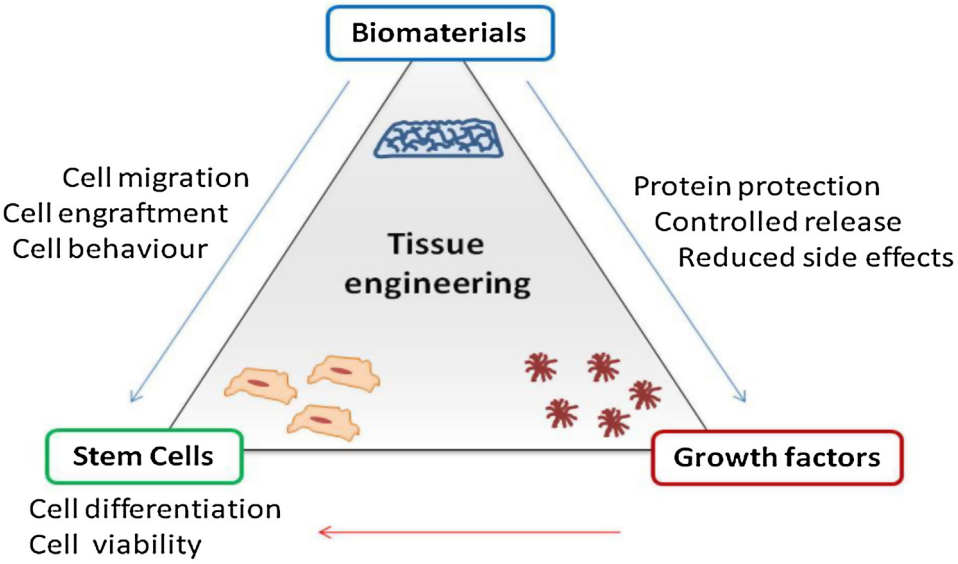

Fig. 6. Tissue engineering triad.

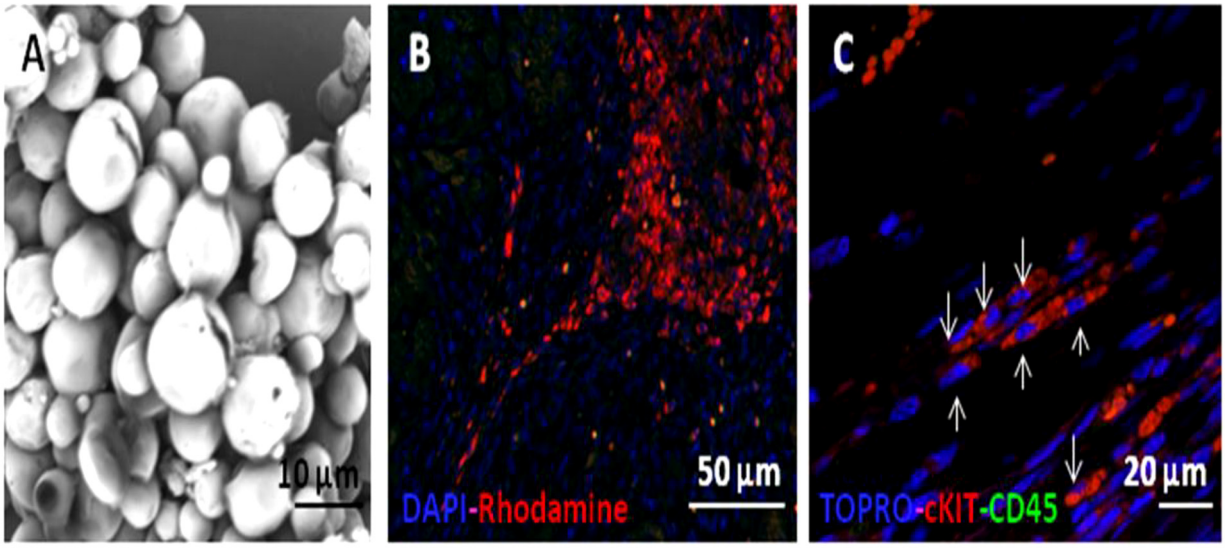

Fig. 7. NRG-PLGA MPs. A) Scanning electron microscopy of NRG-PLGA MPs. B) Tissue retention of fluorescent PLGA MPs 1 month after intramyocardial injection in a rat MI model. C) Cardiac progenitor cell development 1 week after intramyocardial injection of NRG-PLGA MPs [64].

techniques. In conclusion, the technical application of the tissue engineering triad approach on the integration of stem cells, growth factors and biomaterial-based delivery systems should be implemented.

Conflict of interest

None.

Acknowledgments

The authors thanks Department of Medical Biotechnology, School of advance Science in Medicine, Tehran University of Medical Sciences and Department of Cardiology, Lorestan University of Medical Sciences, Khoramabad, Iran.

References

[1] M. Namdari, A. Eatemadi, B. Negahdari, Natriuretic peptides and their therapeutic potential in heart failure treatment: an updated review, Cell. Mol. Biol. (Noisy-Le-Grand) 62 (2016) 1.
[2] M. Ghafarzadeh, M. Namdari, A. Eatemadi, Stem cell therapies for congenital heart disease, Biomed. Pharmacother. 84 (2016) 1163–1171, doi:http://dx.doi.org/10.1016/j.biopha.2016.10.055.
[3] M. Namdari, A. Eatemadi, Nanofibrous bioengineered heart valve—application in paediatric medicine, Biomed. Pharmacother. 84 (2016) 1179–1188, doi:http://dx.doi.org/10.1016/j.biopha.2016.10.058.
[4] M. Ghafarzadeh, A. Eatemadi, Z. Fakhravar, Human amniotic fluid derived mesenchymal stem cells cause an anti-cancer effect on breast cancer cell line in vitro, Cell. Mol. Biol. 2016 (2016) 102–106.
[5] S.H. Chou, S.Z. Lin, W.W. Kuo, P. Pai, J.Y. Lin, C.H. Lai, C.H. Kuo, K.H. Lin, F.J. Tsai, C. Y. Huang, Mesenchymal stem cell insights: prospects in cardiovascular therapy, Cell Transplant. 23 (2014) 513–529, doi:http://dx.doi.org/10.3727/096368914x678436.
[6] J.S. Da Silva, J.M. Hare, Cell-based therapies for myocardial repair: emerging role for bone marrow-derived mesenchymal stem cells (MSCs) in the

treatment of the chronically injured heart, Methods Mol. Biol. (2013) 145–163, doi:http://dx.doi.org/10.1007/978-1-62703-505-7-8.
[7] J. Pons, Y. Huang, J. Arakawa-Hoyt, D. Washko, J. Takagawa, J. Ye, W. Grossman, H. Su, VEGF improves survival of mesenchymal stem cells in infarcted hearts, Biochem. Biophys. Res. Commun. 376 (2008) 419–422, doi:http://dx.doi.org/10.1016/j.bbrc.2008.09.003.
[8] J.M. Tang, J.N. Wang, L. Zhang, F. Zheng, J.Y. Yang, X. Kong, L.Y. Guo, L. Chen, Y.Z. Huang, Y. Wan, S.Y. Chen, VEGF/SDF-1 promotes cardiac stem cell mobilization and myocardial repair in the infarcted heart, Cardiovasc. Res. 91 (2011) 402–411, doi:http://dx.doi.org/10.1093/cvr/cvr053.
[9] H.K. Haider, S. Jiang, N.M. Idris, M. Ashraf, IGF-1-overexpressing mesenchymal stem cells accelerate bone marrow stem cell mobilization via paracrine activation of SDF-1α/CXCR4 signaling to promote myocardial repair, Circ. Res. 103 (2008) 1300–1308, doi:http://dx.doi.org/10.1161/CIRCRESAHA.108.186742.
[10] Y. Higashi, S. Sukhanov, A. Anwar, S.Y. Shai, P. Delafontaine, Aging, atherosclerosis, and IGF-1, J. Gerontol. Ser. A Biol. Sci. Med. Sci. 67A (2012) 626–639, doi:http://dx.doi.org/10.1093/gerona/gls102.
[11] M. Grunewald, I. Avraham, Y. Dor, E. Bachar-Lustig, A. Itin, S. Yung, S. Chimenti, L. Landsman, R. Abramovitch, E. Keshet, VEGF-induced adult neovascularization: recruitment, retention, and role of accessory cells, Cell 124 (2006) 175–189, doi:http://dx.doi.org/10.1016/j.cell.2005.10.036.
[12] D. Torella, M. Rota, D. Nurzynska, E. Musso, A. Monsen, I. Shiraishi, E. Zias, K. Walsh, A. Rosenzweig, M.A. Sussman, K. Urbanek, B. Nadal-Ginard, J. Kajstura, P. Anversa, A. Leri, Cardiac stem cell and myocyte aging, heart failure, and insulin-like growth factor-1 overexpression, Circ. Res. 94 (2004) 514–524, doi:http://dx.doi.org/10.1161/01.RES.0000117306.10142.50.
[13] D. Zisa, A. Shabbir, G. Suzuki, T. Lee, Vascular endothelial growth factor (VEGF) as a key therapeutic trophic factor in bone marrow mesenchymal stem cell-mediated cardiac repair, Biochem. Biophys. Res. Commun. 390 (2009) 834–838, doi:http://dx.doi.org/10.1016/j.bbrc.2009.10.058.
[14] K. Matsudaira, K. Maeda, N. Okumura, D. Yoshikawa, Y. Morita, H. Mitsuhashi, H. Ishii, T. Kondo, T. Murohara, Impact of low levels of vascular endothelial growth factor after myocardial infarction on 6-month clinical outcome. Results from the Nagoya acute myocardial infarction study, Circ. J. 76 (2012) 1509–1516.
[15] J. Kastrup, E. Jorgensen, S. Fuchs, S. Nikol, H.E. Botker, M. Gyongyosi, D. Glogar, R. Kornowski, A randomised, double-blind, placebo-controlled, multicentre study of the safety and efficacy of BIOBYPASS (AdGVVEGF121.10NH) gene therapy in patients with refractory advanced coronary artery disease: the NOVA trial, EuroIntervention 6 (2011) 813–818.
[16] R.S. Ripa, Y. Wang, E. Jørgensen, H.E. Johnsen, B. Hesse, J. Kastrup, Intramyocardial injection of vascular endothelial growth factor-A165 plasmid followed by granulocyte-colony stimulating factor to induce angiogenesis in patients with severe chronic ischaemic heart disease, Eur. Heart J. 27 (2006) 1785–1792, doi:http://dx.doi.org/10.1093/eurheartj/ehl117.
[17] K. Moradi, M. Abbasi, F. Aboulhasani, N. Abbasi, K.A. Babatunde, F. Sargolzaeiaval, A.R. Dehpour, Therapeutic angiogenesis promotes efficacy of human umbilical cord matrix stem cell transplantation in cardiac repair, Iran. J. Basic Med. Sci. 18 (2015) 563–570.
[18] K.E. Hatzistergos, H. Quevedo, B.N. Oskouei, Q. Hu, G.S. Feigenbaum, I.S. Margitich, R. Mazhari, A.J. Boyle, J.P. Zambrano, J.E. Rodriguez, R. Dulce, P.M. Pattany, D. Valdes, C. Revilla, A.W. Heldman, I. McNiece, J.M. Hare, Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation, Circ. Res. 107 (2010) 913–922, doi:http://dx.doi.org/10.1161/CIRCRESAHA.110.222703.
[19] F. Pourrajab, M. Babaei Zarch, M. Baghi Yazdi, A. Rahimi Zarchi, A. Vakili Zarch, Application of stem cell/growth factor system, as a multimodal therapy approach in regenerative medicine to improve cell therapy yields, Int. J. Cardiol. 173 (2014) 12–19, doi:http://dx.doi.org/10.1016/j.ijcard.2014.02.006.
[20] P.W.M. Fedak, S. Verma, R.D. Weisel, M. Skrtic, R.K. Li, Cardiac remodeling and failure: from molecules to man (Part III), Cardiovasc. Pathol. 14 (2005) 109–119, doi:http://dx.doi.org/10.1016/j.carpath.2005.03.004.
[21] K.O. Maher, C. Xu, Marching towards regenerative cardiac therapy with human pluripotent stem cells, Discov. Med. 15 (2013) 349–356, doi:http://dx.doi.org/10.1016/j.biotechadv.2011.08.021 (Secreted).
[22] S. Fernandes, A.V. Naumova, W.Z. Zhu, M.A. Laflamme, J. Gold, C.E. Murry, Human embryonic stem cell-derived cardiomyocytes engraft but do not alter cardiac remodeling after chronic infarction in rats, J. Mol. Cell. Cardiol. 49 (2010) 941–949, doi:http://dx.doi.org/10.1016/j.yjmcc.2010.09.008.
[23] J.J.H. Chong, X. Yang, C.W. Don, E. Minami, Y.-W. Liu, J.J. Weyers, W.M. Mahoney, B. Van Biber, S.M. Cook, N.J. Palpant, J.A. Gantz, J.A. Fugate, V. Muskheli, G.M. Gough, K.W. Vogel, C.A. Astley, C.E. Hotchkiss, A. Baldessari, L. Pabon, H. Reinecke, E.A. Gill, V. Nelson, H.-P. Kiem, M.A. Laflamme, C.E. Murry, Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts, Nature 510 (2014) 273–277, doi:http://dx.doi.org/10.1038/nature13233.
[24] B.E. Strauer, M. Brehm, T. Zeus, M. Köstering, A. Hernandez, R.V. Sorg, G. Kögler, P. Wernet, Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans, Circulation 106 (2002) 1913–1918, doi:http://dx.doi.org/10.1161/01.CIR.0000034046.87607.1C.
[25] B. Assmus, V. Schächinger, C. Teupe, M. Britten, R. Lehmann, N. Döbert, F. Grünwald, A. Aicher, C. Urbich, H. Martin, D. Hoelzer, S. Dimmeler, A.M. Zeiher, Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI), Circulation 106 (2002) 3009–3017, doi:http://dx.doi.org/10.1161/01.CIR.0000043246.74879.CD.
[26] G.P. Meyer, K.C. Wollert, J. Lotz, J. Steffens, P. Lippolt, S. Fichtner, H. Hecker, A. Schaefer, L. Arseniev, B. Hertenstein, A. Ganser, H. Drexler, Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (Bone marrow transfer to enhance ST-elevation infarct regeneration) trial, Circulation 113 (2006) 1287–1294, doi:http://dx.doi.org/10.1161/circulationaha.105.575118.
[27] G.V. Silva, S. Litovsky, J.A.R. Assad, A.L.S. Sousa, B.J. Martin, D. Vela, S.C. Coulter, J. Lin, J. Ober, W.K. Vaughn, R.V.C. Branco, E.M. Oliveira, R. He, Y.J. Geng, J.T. Willerson, E.C. Perin, Mesenchymal stem cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a canine chronic ischemia model, Circulation 111 (2005) 150–156, doi:http://dx.doi.org/10.1161/01.CIR.0000151812.86142.45.
[28] F. Fernández-Avilés, J.A. San Román, J. García-Frade, M.E. Fernández, M.J. Peñarrubia, L. de la Fuente, M. Gómez-Bueno, A. Cantalapiedra, J. Fernández, O. Gutierrez, P.L. Sánchez, C. Hernández, R. Sanz, J. García-Sancho, A. Sánchez, Experimental and clinical regenerative capability of human bone marrow cells after myocardial infarction, Circ. Res. 95 (2004) 742–748, doi:http://dx.doi.org/10.1161/01.RES.0000144798.54040.ed.
[29] S. Janssens, C. Dubois, J. Bogaert, K. Theunissen, C. Deroose, W. Desmet, M. Kalantzi, L. Herbots, P. Sinnaeve, J. Dens, J. Maertens, F. Rademakers, S. Dymarkowski, O. Gheysens, J. Van Cleemput, G. Bormans, J. Nuyts, A. Belmans, L. Mortelmans, M. Boogaerts, F. Van De Werf, Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial, Lancet 367 (2006) 113–121, doi:http://dx.doi.org/10.1016/S0140-6736(05)67861-0.
[30] K. Lunde, S. Solheim, S. Aakhus, H. Arnesen, M. Abdelnoor, T. Egeland, K. Endresen, A. Ilebekk, A. Mangschau, J.G. Fjeld, H.J. Smith, E. Taraldsrud, H.K. Grøgaard, R. Bjørnerheim, M. Brekke, C. Müller, E. Hopp, A. Ragnarsson, J.E. Brinchmann, K. Forfang, Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction, N. Engl. J. Med. 355 (2006) 1199–1209, doi:http://dx.doi.org/10.1056/NEJMoa055706.
[31] V.K. Shah, A.J. Desai, J.B. Vasvani, M.M. Desai, B.P. Shah, T.K. Lall, M.R. Mashru, K.K. Shalia, V. Tanavde, S.S. Desai, B.J. Jankharia, Bone marrow cells for myocardial repair–a new therapeutic concept, Indian Heart J. 59 (2007) 482–490.
[32] S.L. Chen, W.W. Fang, F. Ye, Y.H. Liu, J. Qian, S.J. Shan, J.J. Zhang, R.Z. Chunhua, L. M. Liao, S. Lin, J.P. Sun, Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction, Am. J. Cardiol. 94 (2004) 92–95, doi:http://dx.doi.org/10.1016/j.amjcard.2004.03.034.
[33] D.G. Katritsis, P.A. Sotiropoulou, E. Karvouni, I. Karabinos, S. Korovesis, S.A. Perez, E.M. Voridis, M. Papamichail, Transcoronary transplantation of autologous mesenchymal stem cells and endothelial progenitors into infarcted human myocardium, Catheter. Cardiovasc. Interv. 65 (2005) 321–329, doi:http://dx.doi.org/10.1002/ccd.20406.
[34] M. Mohyeddin-Bonab, M.R. Mohamad-Hassani, K. Alimoghaddam, M. Sanatkar, M. Gasemi, H. Mirkhani, H. Radmehr, M. Salehi, M. Eslami, A. Farhig-Parsa, H. Emami-Razavi, M. Ghasemi al-Mohamad, A.A. Solimani, A. Ghavamzadeh, B. Nikbin, Autologous in Vitro expanded mesenchymal stem cell therapy for human old myocardial infarction, Arch. Iran. Med. 10 (2007) 467–473 (009 [pii]\r07104/AIM.009).
[35] J.M. Hare, J.H. Traverse, T.D. Henry, N. Dib, R.K. Strumpf, S.P. Schulman, G. Gerstenblith, A.N. DeMaria, A.E. Denktas, R.S. Gammon, J.B. Hermiller, M.A. Reisman, G.L. Schaer, W. Sherman, A randomized, double-blind, placebo-controlled,v dose-escalation study of intravenous adult human mesenchymal stem cells (Prochymal) after acute myocardial infarction, J. Am. Coll. Cardiol. 54 (2009) 2277–2286, doi:http://dx.doi.org/10.1016/j.jacc.2009.06.055.
[36] A.R. Williams, B. Trachtenberg, D.L. Velazquez, I. McNiece, P. Altman, D. Rouy, A.M. Mendizabal, P.M. Pattany, G.A. Lopera, J. Fishman, J.P. Zambrano, A.W. Heldman, J.M. Hare, Intramyocardial stem cell injection in patients with ischemic cardiomyopathy: functional recovery and reverse remodeling, Circ. Res. 108 (2011) 792–796, doi:http://dx.doi.org/10.1161/CIRCRESAHA.111.242610.
[37] J. Bartunek, A. Behfar, D. Dolatabadi, M. Vanderheyden, M. Ostojic, J. Dens, B. El Nakadi, M. Banovic, B. Beleslin, M. Vrolix, V. Legrand, C. Vrints, J.L. Vanoverschelde, R. Crespo-Diaz, C. Homsy, M. Tendera, S. Waldman, W. Wijns, A. Terzic, Cardiopoietic stem cell therapy in heart failure: the C-CURE (cardiopoietic stem cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics, J. Am. Coll. Cardiol. 61 (2013) 2329–2338, doi:http://dx.doi.org/10.1016/j.jacc.2013.02.071.
[38] S. Vahabi, A. Eatemadi, Nanoliposome encapsulated anesthetics for local anesthesia application, Biomed. Pharmacother. 86 (2017) 1–7, doi:http://dx.doi.org/10.1016/j.biopha.2016.11.137.
[39] A. Eatemadi, H. Daraee, H.T. Aiyelabegan, B. Negahdari, B. Rajeian, N. Zarghami, Synthesis and characterization of chrysin-loaded PCL-PEG-PCL nanoparticle and its effect on breast cancer cell line, Biomed. Pharmacother. (2016).
[40] S. Vahabi, A. Eatemadi, Phyto-anesthetics: a mini-review on herb–anesthesia drug interactions, Biomed. Pharmacother. (2016).
[41] S. Jaferian, B. Negahdari, A. Eatemadi, Colon cancer targeting using conjugates biomaterial 5-flurouracil, Biomed. Pharmacother. 84 (2016) 780–788.
[42] S. Nadri, H. Mahmoudvand, A. Eatemadi, Magnetic nanogel polymer of bupivacaine for ankle block in rats, J. Microencapsul. (2016) 1–23.

[43] P. Namdari, H. Daraee, A. Eatemadi, Recent advances in silicon nanowire biosensors: synthesis methods properties, and applications, Nanoscale Res. Lett. 11 (2016) 406.
[44] A. Eatemadi, H. Daraee, N. Zarghami, H. Melat Yar, A. Akbarzadeh, Nanofiber: synthesis and biomedical applications, Artif. Cells Nanomed. Biotechnol. 44 (2016) 111–121.
[45] S. Beiranvand, A. Eatemadi, A. Karimi, New updates pertaining to drug delivery of local anesthetics in particular bupivacaine using lipid nanoparticles, Nanoscale Res. Lett. 11 (2016) 1–10.
[46] H. Daraee, A. Eatemadi, E. Abbasi, S. Fekri Aval, M. Kouhi, A. Akbarzadeh, Application of gold nanoparticles in biomedical and drug delivery, Artif. Cells Nanomed. Biotechnol. 44 (2016) 410–422.
[47] H.T. Aiyelabegan, S.S.Z. Zaidi, S. Fanuel, A. Eatemadi, M.T.K. Ebadi, E. Sadroddiny, Albumin-based biomaterial for lungs tissue engineering applications, Int. J. Polym. Mater. Polym. Biomater. (2016).
[48] H. Daraee, A. Etemadi, M. Kouhi, S. Alimirzalu, A. Akbarzadeh, Application of liposomes in medicine and drug delivery, Artif. Cells Nanomed. Biotechnol. 44 (2016) 381–391.
[49] A. Eatemadi, M. Darabi, L. Afraidooni, N. Zarghami, H. Daraee, L. Eskandari, H. Mellatyar, A. Akbarzadeh, Comparison, synthesis and evaluation of anticancer drug-loaded polymeric nanoparticles on breast cancer cell lines, Artif. Cells Nanomed. Biotechnol. 44 (2016) 1008–1017.
[50] F. Mohammadian, A. Eatemadi, Drug loading and delivery using nanofibers scaffolds, Artif. Cells Nanomed. Biotechnol. (2016) 1–8.
[51] H. Mellatyar, A. Akbarzadeh, M. Rahmati, M.G. Ghalhar, A. Etemadi, K. Nejati-Koshki, N. Zarghami, A. Barkhordari, Comparison of inhibitory effect of 17-DMAG nanoparticles and free 17-DMAG in HSP90 gene expression in lung cancer, Asian Pac. J. Cancer Prev. 15 (2014) 8693–8698.
[52] K. Seidi, A. Eatemadi, B. Mansoori, R. Jahanban-Esfahlan, D. Farajzadeh, Nanomagnet-based detoxifying machine: an alternative/complementary approach in HIV therapy, J. AIDS Clin. Res. 2014 (2014).
[53] A. Eatemadi, H. Daraee, H. Karimkhanloo, M. Kouhi, N. Zarghami, A. Akbarzadeh, M. Abasi, Y. Hanifehpour, S.W. Joo, Carbon nanotubes: properties, synthesis, purification, and medical applications, Nanoscale Res. Lett. 9 (2014) 1–13.
[54] T.K. Dash, V.B. Konkimalla, Poly--caprolactone based formulations for drug delivery and tissue engineering: a review, J. Control. Release 158 (2012) 15–33, doi:http://dx.doi.org/10.1016/j.jconrel.2011.09.064.
[55] R. Lakshmanan, U.M. Krishnan, S. Sethuraman, Polymeric scaffold aided stem cell therapeutics for cardiac muscle repair and regeneration, Macromol. Biosci. 13 (2013) 1119–1134, doi:http://dx.doi.org/10.1002/mabi.201300223.
[56] K. Mi, G. Wang, Z. Liu, Z. Feng, B. Huang, X. Zhao, Influence of a self-assembling peptide, RADA16, compared with collagen I and matrigel on the malignant phenotype of human breast-cancer cells in 3D cultures and in vivo, Macromol. Biosci. 9 (2009) 437–443, doi:http://dx.doi.org/10.1002/mabi.200800262.
[57] S. Zhang, F. Gelain, X. Zhao, Designer self-assembling peptide nanofiber scaffolds for 3D tissue cell cultures, Semin. Cancer Biol. 15 (2005) 413–420, doi:http://dx.doi.org/10.1016/j.semcancer.2005.05.007.
[58] X.Z.J. Du, S. Wang, H. You, Understanding the toxicity of carbon nanotubes in the environment is crucial to the control of nanomaterials in producing and processing and the assessment of health risk for human, Environ. Toxicol. Pharmacol. 36 (2013) 451–462.
[59] B.D. Ulery, L.S. Nair, C.T. Laurencin, Biomedical applications of biodegradable polymers, J. Polym. Sci. Part B Polym. Phys. 49 (2011) 832–864, doi:http://dx.doi.org/10.1002/polb.22259.
[60] J. Leor, S. Aboulafia-Etzion, A. Dar, L. Shapiro, I.M. Barbash, A. Battler, Y. Granot, S. Cohen, Bioengineered cardiac grafts: a new approach to repair the infarcted myocardium? Circulation 102 (2000) III56–I61, doi:http://dx.doi.org/10.1161/01.CIR.102. suppl_3.III-56.
[61] A. Dar, M. Shachar, J. Leor, S. Cohen, Optimization of cardiac cell seeding and distribution in 3D porous alginate scaffolds, Biotechnol. Bioeng. 80 (2002) 305–312, doi:http://dx.doi.org/10.1002/bit.10372.
[62] E. Ruvinov, Y. Sapir, S. Cohen, Cardiac tissue engineering: principles, materials, and applications, Synth. Lect. Tissue Eng. 4 (2012) 1–200, doi:http://dx.doi.org/10.2200/S00437ED1V01Y201207TIS009.
[63] S. Fukuhara, S. Tomita, T. Nakatani, T. Fujisato, Y. Ohtsu, M. Ishida, C. Yutani, S. Kitamura, Bone marrow cell-seeded biodegradable polymeric scaffold enhances angiogenesis and improves function of the infarcted heart, Circ. J. 69 (2005) 850–857 (JST.JSTAGE/circj/69.850[pii]).
[64] P. Díaz-Herráez, E. Garbayo, T. Simón-Yarza, F.R. Formiga, F. Prosper, M.J. Blanco-Prieto, Adipose-derived stem cells combined with neuregulin-1 delivery systems for heart tissue engineering, Eur. J. Pharm. Biopharm. 85 (2013) 143–150, doi:http://dx.doi.org/10.1016/j.ejpb.2013.03.022.
[65] D. Srivastava, M. Ieda, J. Fu, L. Qian, Cardiac repair with thymosin??4 and cardiac reprogramming factors, Ann. N. Y. Acad. Sci. 1270 (2012) 66–72, doi:http://dx.doi.org/10.1111/j.1749-6632.2012.06696.x.
[66] M.E. Davis, P.C.H. Hsieh, T. Takahashi, Q. Song, S. Zhang, R.D. Kamm, A.J. Grodzinsky, P. Anversa, R.T. Lee, Local myocardial insulin-like growth factor 1 (IGF-1) delivery with biotinylated peptide nanofibers improves cell therapy for myocardial infarction, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 8155–8160, doi:http://dx.doi.org/10.1073/pnas.0602877103.
[67] M.E. Padin-Iruega, Y. Misao, M.E. Davis, V.F.M. Segers, G. Esposito, T. Tokunou, K. Urbanek, T. Hosoda, M. Rota, P. Anversa, A. Leri, R.T. Lee, J. Kajstura, Cardiac progenitor cells and biotinylated insulin-like growth factor-1 nanofibers improve endogenous and exogenous myocardial regeneration after infarction, Circulation 120 (2009) 876–887, doi:http://dx.doi.org/10.1161/CIRCULATIONAHA.109.852285.
[68] G. Zhang, Q. Hu, E. a, L.J. Braunlin, J. Suggs, Enhancing efficacy of stem cell transplantation to the heart with a PEGylated fibrin biomatrix, Tissue Eng. Part A 14 (2008) 1025–1036, doi:http://dx.doi.org/10.1089/ten.tea.2007.0289.
[69] C.A. Holladay, A.M. Duffy, X. Chen, M.V. Sefton, T.D. O'Brien, A.S. Pandit, Recovery of cardiac function mediated by MSC and interleukin-10 plasmid functionalised scaffold, Biomaterials 33 (2012) 1303–1314, doi:http://dx.doi.org/10.1016/j.biomaterials.2011.10.019.
[70] H. Ahmadvand, S. Bagheri, A. Tamjidi-Poor, M. Cheraghi, M. Azadpour, B. Ezatpour, S. Moghadam, Effects of oleuropein on lipid peroxidation, lipid profile, atherogenic indices, and paraoxonase 1 status in gentamicin-induced nephrotoxicity in rats, ARYA 11 (2015) 153.
[71] H. Ahmadvand, S. Bagheri, A. Tamjidi-Poor, M. Cheraghi, M. Azadpour, B. Ezatpour, S. Moghadam, G. Shahsavari, M. Jalalvand, Biochemical effects of oleuropein in gentamicin-induced nephrotoxicity in rats, ARYA Atheroscler. 12 (2016) 87–93.
[72] A. Maleki, M. Cheraghi, S.R.J. Kerman, M. Montazeri, N. Rashidi, R. Ghanavati, S. Foroughi, F. Alyari, H. Ahmadvand, Aspirin resistance in different doses by bleeding time and urinary 11-dehydro-thromboxane B2, Indian J. Physiol. Pharmacol. 60 (2016) 30–37.
[73] M. Cheraghi, M. Sadeghi, A. Tavassoli, N. Sarrafzadegan, A. Pourmoghadas, M.A. Ramezani, Prognostic factors for survival at 6-Month follow-up of hospitalized patients with decompensated congestive heart failure, ARYA Atheroscler. 6 (2010) 111–116.
[74] A. Mohamadi, M. Namdari, B. Rasoulian, A. Raoufi, A. Nazari, Pre-exposure to normobaric hyperoxia has no effect on myocardial injury biomarkers after percutaneous transluminal coronary angioplasty, Cardiology (2015) 281.
[75] M. Ghafarzadeh, S. Moeininasab, M. Namdari, Effect of early amniotomy on dystocia risk and cesarean delivery in nulliparous women: a randomized clinical trial, Arch. Gynecol. Obstet. 292 (2015) 321–325, doi:http://dx.doi.org/10.1007/s00404-015-3645-x.
[76] B.B. Ahmadi, M. Namdari, H. Mobarakeh, Erectile dysfunction as a predictor of early stage of Coronary artery disease, J. Tehran Univ. Heart Cent. 9 (2014) 70.
[77] T. Tolabi, Z. Vanaki, R. Memarian, M. Namdari, Quality of nursing documentations in CCU by hospital information system (HIS), J. Crit. Care Nurs. 5 (2012) 53–62.
[78] M. Namdari, M. Ghafarzadeh, M.A. Nikoo, Efficacy of intramuscular methyl prednisolone in preventing restenosis after coronary artery stenting with bare-metal stainless steel stent: a double-blind, randomised, controlled clinical trial, Cardiovasc. J. Afr. 22 (2011) 67.
[79] A.R. Khosravi, M. Pourmoghadas, M. Ostovan, G.K. Mehr, M. Gharipour, H. Zakeri, B. Soleimani, M. Namdari, M. Hassanzadeh, A.A. Tavassoli, The impact of generic form of Clopidogrel on cardiovascular events in patients with coronary artery stent: results of the OPCES study, J. Res. Med. Sci. Off. J. Isfahan Univ. Med. Sci. 16 (2011) 640.
[80] M. Ghafarzadeh, M. Namdari, H. Ashraf, Vaginal birth after cesarean section: a retrospective study, Pak. J. Med. Sci. Oct. December 26 (2010) 987–989.
[81] M. Ghafarzadeh, M. Namdari, Effect of soybean diet on serum lipids an lipoproteins of postmenopausal women, Pak. J. Med. Sci. April. 26 (2010) 407–410.
[82] B. Baharvand, M.E. Dehaj, B. Rasoulian, M. Namdari, Y. Shikhani, A.A. Kiani, Delayed anti-arrhythmic effect of nitroglycerin in anesthetized rats: involvement of CGRP, PKC and mK ATP channels, Int. J. Cardiol. 135 (2009) 187–192.