Molecular Biology: Open Access
ISSN: 2168-9547

Alam et al., Mol Biol 2016, 5:2
DOI: 10.4172/2168-9547.1000159

Review Article Open Access

Is Cardiac Stem Cell Therapy a New Horizon of Heart Regeneration: Literature Review

Mohammad Afaque Alam[1]*, Muhammad Fawad Ishfaq[1] and Bushra Khanam[2]

[1]University of Tennessee Health Science Center, Memphis, TN, USA
[2]Birla Institute of Technology, Ranchi, India

Abstract

Improvements in the care of patients with cardiovascular disease have led to improved survival but also a burgeoning population of patients with advanced heart disease. Cardiac stem cells (CSC) continue to promise opportunities to repair damaged cardiac tissue. However, precisely how stem cells accomplish cardiac repair, especially after ischemic damage, remains controversial. It has been postulated that the clinical benefit of adult stem cells for cardiovascular disease results from the release of cytokines and growth factors by the transplanted cells, stimulation of new blood vessel growth, enhancing tissue perfusion, and via preservation or even regeneration of myocardial tissue, leading to improvements in cardiac performance after myocardial infarction and in patients with advanced heart failure, reducing inflammation, and scar formation, as well as protecting cardiomyocytes from apoptosis. In addition, reducing fibrosis these factors might also stimulate endogenous repair by activating cardiac stem cells. Interestingly, stem cells discovered to be resident in the heart appear to be functionally superior to extra-cardiac adult stem cells when transplanted for cardiac repair and regeneration. Stem cells are the seeds of tissue repair and regeneration and a promising source for novel therapies. However, apart from hematopoietic stem cell (HSC) transplantation, all other stem cell treatments yet remain experimental. Mounting hopes have encouraged numerous clinical trials, but it has been difficult to obtain unequivocal evidence for robust clinical benefit. This review provides a historic framework and an abridgment of how the theories of CSC origin and potential evolved from early times to the present day. The development of more effective cardiac therapies may thus require targeting this important cell population. Here, we summarize and offer some thoughts on the state of the field of cell therapy for ischemic heart diseases and the therapeutic potential of cardiac stem cells.

Keywords: Cardiovascular disease; Hematopoietic stem cell; Clinical trials; Cardiac therapies

Introduction

Cardiovascular diseases (CVD) is the leading cause of morbidity and mortality world wide and it accounts over 17 million people die per year, a number that is expected to grow to over 23.6 million by 2030 [1]. In the past fifty years, contrary to the advanced therapeutics, better managements, state of the art surgical interventions and organ transplantations, more than half of patients with heart failure die within five years of initial diagnosis [2,3]. Recent reports demonstrated CVD still accounted for 31.3% of all deaths, or ≈1 of every 3 deaths in the USA. It has also been reported that 7.6 million cases of myocardial infarction (MI) and 5.7 million of heart failure patients in USA. Moreover, during 2000 to 2010, the cardiovascular operations and procedures has increased by 28%, which is a huge burden to the healthcare system. For 2011 alone, the direct and indirect estimated costs of CVD and stroke were $320.1 billion verses $216.6 billion for all cancer in the USA [3,4]. Alarmingly, the estimated global expenditure of CVD is $863 billion, and it would rise to $1044 billion by 2030 [5].

The limitation of the current available (drugs, intervention or operation) therapies is unable to compensate the irreversible loss of functional cardiomyocytes [6,7]. On the other hand, it has been reported that the adult heart possesses a stem cell compartment that can regenerate cardiomyocytes and coronary vessels [8-10]. It has immense potential to rejuvenate lost myocardium and to repopulate the hypertrophic decompensated heart with functional cardiomyocytes, which improves vascular contractility, ventricular function and wall thickness [9].

Accordingly, thus the current challenges of cardiovascular therapies are to examine extensively for robust and novel concepts of cell based therapy, tissue engineering or reprogramming of adult stem cells (ASCs) [8-11]. Over the decades, researchers have been investigating in order to identify stem cells capable of differentiating into cell lineages different from the organ of origin to be employed for the regeneration of the damaged heart [12-14]. The most studied and characterized stem cells are embryonic stem cells (ESCs) and bone marrow-derived cells (BMCs). However, a remarkable progress has been made in the clinical application of BMCs and many other ASCs in heart failure of ischemic and non-ischemic origin [15-18].

Stem Cells

Stem cells are the mother of all cells. The hallmark of stem cell is the ability to self-renew, proliferate, or differentiate into specialized cell types [19,20]. They retain the potency to divide indefinitely and give rise to new cells to replace cells that die or are lost [18-23]. Importantly, therefore, stem cells are the progenitor cells of the blood, heart, brain, bones, skin, muscles, etc [24,25]. There are different sources of stem cells but all types of stem cells have the same capacity to develop into any types of cells (Figure 1).

In 1997, for the first time researchers were demonstrated that cellular and regenerative therapies hold great promise and showed bone marrow–derived $CD34^+$ cells can give rise to endothelial-like cells and improve neovascularization after ischemia [26]. Latter on multiple experimental and several clinical studies evidenced that a wide variety of cell types such as skeletal myoblasts, cardiac stem cells, and

***Corresponding author:** Mohammad Afaque Alam, 894 Union Avenue, University of Tennessee health science center Memphis, TN38163, USA, Tel: 901-518-6443; Fax: 901-518-6443; E-mail: malam8@uthsc.edu

Received March 15, 2016; **Accepted** March 18, 2016; **Published** March 25, 2016

Citation: Alam MA, Ishfaq MF, Khanam B (2016) Is Cardiac Stem Cell Therapy a New Horizon of Heart Regeneration: Literature Review. Mol Biol 5: 159. doi:10.4172/2168-9547.1000159

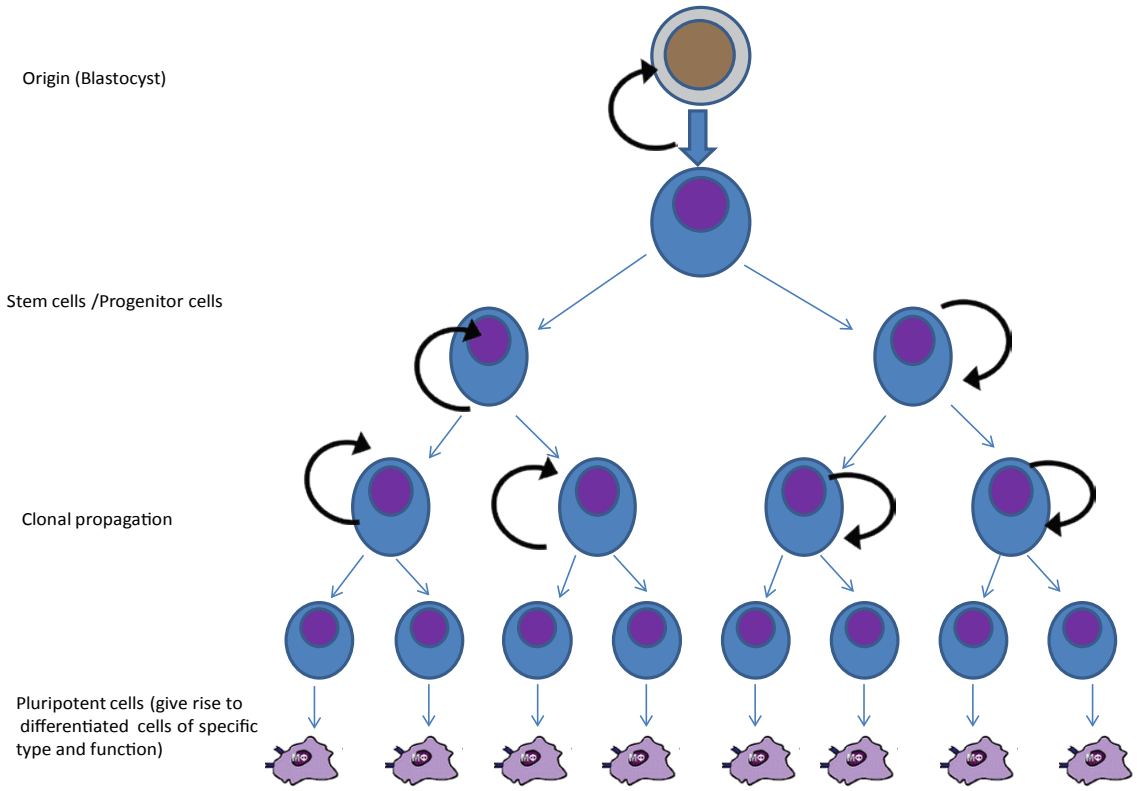

Figure 1: Schematic representation of stem cell differentiation. Embryonic stem cells (ESCs) undergo clonal propagation to produce high number of same cells without differentiating. It remains undifferentiated, until it receives a signal to develop into a specialized cell, where it goes through multilineage differentiation to become specialized cells such as bone, skin, heart, brain and blood cells and perform specific function.

mesenchymal stem cells showed their ability to mend the heart [27-30]. Subsequent clinical trials showed some benefit but also raised safety concerns with respect to arrhythmic events induced by non-integrated skeletal muscle cells [22]. However, cultured bone marrow-derived, cardiac stem cells, embryonic stem cells, or induced pluripotent stem cells are the important sources for producing cardiomyocytes.

Types of stem cells

There are two most common sources of stem cells based on their origin:

1. Embryos (embryonic stem cells) and
2. Adult tissue (adult stem cells).

Embryos (embryonic stem cells): The origin of embryonic stem cells (ESCs) is embryo of blastocyst stage. In humans, mice and other primates, the embryo, at this stage is a ball of approximately 100 cells. Human embryonic stem cells (hESCs) are obtained from supernumerary human IVF (in vitro fertilization) embryos by submiting ethical norms that cannot be used for the couple's infertility treatment. The derivation of mouse ES cells was first reported in 1981 [31,32]. Their regenerative property distinguishes them from all other organ-specific stem cells identified so far.

1. It can be maintained and propagated indefinitely as homogeneous population of undifferentiated cells in culture, and they can retain normal karyotypes following extensive passages in culture.
2. They are pluripotent cells, with high potential to produce every cell type in the body. The pluripotent property of mouse ESCs was demonstrated by their ability to contribute to all tissues of adult mice including the cardiac progenitor cells [31,33,34].

The unique property of the ESCs paves the way for in vitro model of embryonic development for studying the fundamental mechanisms of the early development of cell lineage induction and specification. Additionally, the ESCs differentiation system is viewed by many as a novel and unlimited source of cells and tissues for transplantation for the treatment of all sorts of diseases. Subsequently, in 1998 human embryonic stem cells (hESCs) was isolated which significantly elevated the interest in the embryonic stem cell therapy and also put forth the concept of regenerative medicine remarkably closer to reality [35,36]. Because of their pluripotent nature and potency to differentiate to all cell types in the body, they have been considered as a paramount source for regenerative medicine [37,38]. In view of the fact that ground breaking discovery of hESCs, extensive studies have been performed regarding factors regulating pluripotency and differentiation to specialized functional cell types [39-41]. In particular, these properties made ESCs interesting for cardiac regeneration [42], but still long road to go for perfection.

Adult (somatic) stem cells: Adult stem cells (ASCs) are undifferentiated cells found throughout the body that divide to replace dying cells and regenerate injured tissues. ASCs can be isolated from several sources for example from body amniotic fluid, and other ASCs (Table 1).

Among them bone marrow is the rich source of stem cells that can be used to treat several chronic diseases including heart diseases. For years, scientists are working to uncover the potential use of stem cells to treat ischemic heart diseases and repair injured tissues of the

From body	Almost all tissues and organs contain a tiny number of ASCs that helps in maintaining them, live dormant for years. They divide and produce new cells only when they are activated by tissue injury, disease or anything else that makes the body need more cells. Examples are bone marrow, blood vessels, heart, skeletal muscle, skin, brain, gut, liver, etc.
From amniotic fluid	Amniotic fluid contains fetal cells including mesenchymal stem cells, which are able to make a variety of cells and tissues.
From pluripotent stem cells	Any types of ASCs can be isolated from pluripotent stem cells. These ASCs are the *in-vitro* model for testing different compounds and mechanical factors. Since, these cells match genetically so it eliminates the problem of tissue rejection and toxic therapies to suppress the immune system.
From other adult stem cells	ASCs can trans differentiate into apparently unrelated cell types (such as brain stem cells that differentiate into blood cells or blood-forming cells that differentiate into cardiac muscle cells). Indeed, it is unclear whether trans differentiation may occur in human cells, or whether it could be made to happen reliably in the lab.

Table 1: Sources of adult stem cells.

infarcted organ [8,15]. Notably, accumulative data on clinical cardiac regeneration proposes that stem cell therapy can be done, but it also stresses the necessity for consistent results for their successful use [16,43]. The most important challenges are the identification and selection of the best suited stem cells for regeneration therapy [44]. Of note, a number of adult stem cells derived from BMCs, myocardium or adipose tissue were already in use for clinical trials. Lately, Aratyn-Schaus et al [43] demonstrated that the coupling of primary and stem cell derived cardiomoycytes effectively generate contractile force at the junction between newly formed and spared myocytes.

Remarkably, methodologies and protocols have been developed to transform adult stem cells directly into parenchymal cells, cardiomyocytes, induced pluripotent stem cells (iPSCs) evidently going through the multipotent stage by introducing microRNAs, epigenetic factors or tissue-specific transcriptional factors [45-50]. This novel discovery led to the Nobel Prize in Physiology or Medicine to Sir John B. Gurdon and Shinya Yamanaka in 2012 [51,52]. Takahashi et al. [51] generated so called induced pluripotent stem cells (iPSCs) by retroviral delivery and subsequent overexpression of a four-gene-set (Klf4, c-Myc, Oct4 and Sox2) from murine and human dermal fibroblasts.

Stem cell potency

Stem cells further classified in different types based on their potency (Table 2).

Cardioreparative functions of transplanted cardiac stem cells

Induction of neovascularization: Pro-angiogenic factors play a vital role in promoting the most important part of cardioreparative function, neovasculiraztion. Several pro-angiogenic and anti-apoptotic factors factors interlink with each other to carryout repair mechanism which include transcription factor Gata-4, neovascular endothelial growth factor (VEGF), angiogenin, angiopoietin, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF-1), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) [53].

Cell survival: Several cytoprotective factors along with anti-apoptic factors also play an integral role to protect cardiomyocytes. Cytoprotective factors, VEGF, HGF, IGF, SDF-1, act alone or in the combination with several other factors to execute their actions. Anti-apoptic factors work by decreasing the expression of transcripts specific to cell death such as Bax, caspase-3 and Fas are pParacrine factors produced by CSCs are known to exert potent cytoprotective effects in cardiovascular cell types (53,18) microRNAs in CSC derived exosome have also shown promising cytoprotective effect by improving tube formation of endothelial cells and decreased pro-fibrotic gene expression of fibroblasts [54].

Remodeling of extracellular matrix: Remodelling of extracellular matrix (ECM) by CSC is carried out by various promoters such as metalloproteinases (MMPs), adrenomedulin and thymosin-β. assist CSC migration into the scarred tissue, an effect that was potentiated when CSCs were treated with HGF and IGF-1. These molecules suppress MMP-2 and MMP-9 protein expression, an also assist migration of CSC into scarred tissue [53].

Activation of endogenous stem cells and re-entry of cardiomyocyte cell cycle: Transplanted CSC also activate endogenous original stem cells. Several secreted proteins are interlinked to carry out this function. The proteins which contribute to the activation of endogenous CSCs for cardiac repair are adrenomedulin, connective tissue growth factor, atrial natriuretic factor and interleukin-1 receptor-like-1, IL-1 receptor-like-1 [53]. Factors released by CSC which help in activation of endogenous stem cells and migration of CSC are c-Kit+, Nkx2.5+, GRO-α/CXCL-1, ENA-78/CXCL-5, MIF and HGF. Follistatin like-1 (FSTL-1) protein has also been studied in mice and pigs as a key factor responsible for the activation of endogenous stem cells [55].

Conclusions

Stem cell therapy for various kind of heart diseases has recently been emerged as a promising therapy which can lead to improvement in the care of patients and better survival benefit. However, precisely how stem cells act to repair the damaged cardiomyocytes, especially

Totipotent stem cells	Ability to develop into any cell type present in an organism. Example the zygote (blastocyst) is the first totipotent stem cell.
Pluripotent or Embryonic stem cells	Potential to differentiate into almost all cell types in the body. Examples are embryo, bone marrow, hematopoietic stem cells
Induced pluripotent stem cells (iPSCs)	A terminally differentiated or adult somatic cells can be made pluripotent stem cells by manipulating their genetic makeup in the lab. The first iPSCs were generated by using a cocktail of four transcription factors in mice and human somatic cells.
Multipotent or Somatic/adult stem cells	Ability to differentiate into a closely related family of cells. They exist in mature tissues such as haematopoietic, neural, gastrointestinal and mesenchymal tissues. For example, haematopoietic (adult) stem cells give rise to blood cells and bulge stem cells can produce new skin).
Oligopotent stem cells	potential to give rise to only a few different cell types within a certain lineage. Examples include the common lymphoid or myeloid progenitors that give rise to NK, T, and B lymphocytes and granulocytes in the haematopoietic system and cornea stem cell can produce epithelial and goblet cells.
Unipotent stem cells	It arises from multipotent cells, but they can only produce cells of their own type. For example, hepatoblasts into hepatocytes, myoblast into cardiac skeletal and smooth muscle cells.

Table 2: Potency of the stem cells.

after ischemic damage, are still not very well studied. Large clinical trials are still needed to bring the clarity to this dynamic field of cardiac stem cell therapy.

References

1. Global Status Report on Noncommunicable Diseases (2010) Geneva, Switzerland: World Health Organization.
2. Kahan BD (2011) Fifty years in the vineyard of transplantation: looking back. Transplant Proc 43: 2853-2859.
3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. (2015) Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 131: e29-322.
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, et al. (2013) Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 127: e6-e245.
5. Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, et al. (2011) The Global Economic Burden of Non-communicable Diseases. Geneva, Switzerland: World Economic Forum.
6. Engel FB (2005) Cardiomyocyte proliferation: a platform for mammalian cardiac repair. Cell Cycle 4: 1360-1363.
7. Yi BA, Mummery CL, Chien KR (2013) Direct cardiomyocyte reprogramming: a new direction for cardiovascular regenerative medicine. Cold Spring Harb Perspect Med 3: a014050.
8. Assmus B, Zeiher AM (2013) Early cardiac retention of administered stem cells determines clinical efficacy of cell therapy in patients with dilated cardiomyopathy. Circ Res 112: 6-8.
9. Laflamme MA, Murry CE (2011) Heart regeneration. Nature 473: 326-335.
10. Nadal-Ginard B, Ellison GM, Torella D (2014) The cardiac stem cell compartment is indispensable for myocardial cell homeostasis, repair and regeneration in the adult. Stem Cell Res 13: 615-630.
11. Nam YJ, Song K, Luo X, Daniel E, Lambeth K, et al. (2013) Reprogramming of human fibroblasts toward a cardiac fate. Proc Natl Acad Sci U S A 110: 5588-5593.
12. Pavo N, Charwat S, Nyolczas N, Jakab A, Murlasits Z, et al. (2014) Cell therapy for human ischemic heart diseases: critical review and summary of the clinical experiences. J Mol Cell Cardiol 75: 12-24.
13. Ni NC, Li RK, Weisel RD (2014) The promise and challenges of cardiac stem cell therapy. Semin Thorac Cardiovasc Surg 26: 44-52.
14. Garbern JC, Lee RT (2013) Cardiac stem cell therapy and the promise of heart regeneration. Cell Stem Cell 12: 689-698.
15. Strauer BE, Brehm M, Zeus T, Bartsch T, Schannwell C, et al. (2005) Regeneration of human infarcted heart muscle by intracoronary autologous bone marrow cell transplantation in chronic coronary artery disease: the IACT Study. J Am Coll Cardiol 46: 1651-1658.
16. Stamm C, Kleine HD, Westphal B, Petzsch M, Kittner C, et al. (2004) CABG and bone marrow stem cell transplantation after myocardial infarction. Thorac Cardiovasc Surg 52: 152-158.
17. Leri A, Kajstura J, Anversa P (2005) Cardiac stem cells and mechanisms of myocardial regeneration. Physiol Rev 85: 1373-1416.
18. Hasan A, Waters R (2016) Engineered Biomaterials to Enhance Stem Cell-Based Cardiac Tissue Engineering and Therapy. Macromol Biosci .
19. Yamanaka S (2012) Induced pluripotent stem cells: past, present, and future. Cell Stem Cell 10: 678-684.
20. Nadig RR (2009) Stem cell therapy - Hype or hope? A review. J Conserv Dent 12: 131-138.
21. Leri A, Kajstura J, Anversa P (2011) Role of cardiac stem cells in cardiac pathophysiology: a paradigm shift in human myocardial biology. Circ Res 109: 941-961.
22. Menasché P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, et al. (2008) The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation 117: 1189-1200.
23. Li M, Izpisua Belmonte JC (2016) Mending a Faltering Heart. Circ Res118 : 344-351
24. Khanabdali R, Rosdah AA, Dusting GJ, Lim SY (2016) Harnessing the secretome of cardiac stem cells as therapy for ischemic heart disease. Biochem Pharmacol .
25. Fox IJ, Daley GQ, Goldman SA, Huard J, Kamp TJ, et al. (2014) Stem cell therapy. Use of differentiated pluripotent stem cells as replacement therapy for treating disease. Science 345: 1247391.
26. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, et al. (1997) Isolation of putative progenitor endothelial cells for angiogenesis. Science 275: 964-967.
27. Sanganalmath SK, Bolli R (2013) Cell therapy for heart failure: a comprehensive overview of experimental and clinical studies, current challenges, and future directions. Circ Res 113: 810-834.
28. Leobon B, Garcin I, Menasche P, Vilquin JT, Audinat E, et al. (2003) Myoblasts transplanted into rat infarcted myocardium are functionally isolated from their host. Proc Natl Acad Sci USA 100: 7808-7811.
29. Kawamura M, Miyagawa S, Fukushima S, Saito A, Miki K, et al. (2013) Enhanced survival of transplanted human induced pluripotent stem cell-derived cardiomyocytes by the combination of cell sheets with the pedicled omental flap technique in a porcine heart. Circulation 128: S87-94.
30. Khan M, Nickoloff E, Abramova T, Johnson J, Verma SK, et al. (2015) Embryonic stem cell-derived exosomes promote endogenous repair mechanisms and enhance cardiac function following myocardial infarction. Circ Res 117: 52-64
31. Evans MJ, Kaufman MH (1981) Establishment in culture of pluripotential cells from mouse embryos. Nature 292:154-156.
32. Martin GR (1981) Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells. Proc Natl Acad Sci USA 78: 7634-7638.
33. Dierickx P, Doevendans PA, Geijsen N, van Laake LW (2012) Embryonic template-based generation and purification of pluripotent stem cell-derived cardiomyocytes for heart repair. J Cardiovasc Transl Res 5:566-5680.
34. Smith A.G (2001) Embryo-derived stem cells: Of mice and men. Annu. Rev. Cell Dev. Biol. 17: 435–462.
35. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz J J, Swiergiel V S, et al. (1998) Embryonic stem cell lines derived from human blastocysts. Science 282: 1145–1147.
36. Damdimopoulou P, Rodin S, Stenfelt S, Antonsson L, Tryggvason K, et al. (2016) Human embryonic stem cells. Best Pract Res Clin Obstet Gynaecol 31: 2-12.
37. Rathjen PD, Lake J, Whyatt LM, Bettess MD, Rathjen J (1998) Properties and uses of embryonic stem cells: prospects for application to human biology and gene therapy. Reprod Fertil Dev. 10: 31-47.
38. Nelson TJ, Ge ZD, Van Orman J, Barron M, Rudy-Reil D, et al. (2006) Improved cardiac function in infarcted mice after treatment with pluripotent embryonic stem cells. Anat Rec A Discov Mol Cell Evol Biol 288: 1216-1224.
39. Hovatta O, Rodin S, Antonsson L, Tryggvason K (2014) Concise review: animal substance-free human embryonic stem cells aiming at clinical applications. Stem Cells Transl Med 3: 1269-1274.
40. Cohen DE, Melton D (2011) Turning straw into gold: directing cell fate for regenerative medicine. Nat Rev Genet 12: 243-252.
41. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T et al. (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131: 861-872
42. Templin C, Luscher TF, Landmesser U (2011) Cell-based cardiovascular repair and regeneration in acute myocardial infarction and chronic ischemic cardiomyopathy-current status and future developments. Int J Dev Biol 55: 407-417.
43. Aratyn-Schaus Y, Pasqualini FS, Yuan H, McCain ML, Ye GJ, et al. (2016) Coupling primary and stem cell-derived cardiomyocytes in an in vitro model of cardiac cell therapy. J Cell Biol 212: 389-397.
44. Strauer BE, Steinhoff G (2011) 10 years of intracoronary and intramyocardial bone marrow stem cell therapy of the heart: from the methodological origin to clinical practice. J Am Coll Cardiol 58: 1095-1104.
45. Yamanaka S (2007) Strategies and new developments in the generation of patient-specific pluripotent stem cells. Cell Stem Cell 1: 39-49.
46. Robinton DA, Daley GQ (2012) The promise of induced pluripotent stem cells in research and therapy. Nature 481: 295-305.

47. Qian L, Berry EC, Fu JD, Ieda M, Srivastava D (2013) Reprogramming of mouse fibroblasts into cardiomyocyte-like cells in vitro. Nat Protoc 8: 1204-1215.

48. Jayawardena TM, Egemnazarov B, Finch EA, Zhang L, Payne JA, et al. (2012) MicroRNA-mediated in vitro and in vivo direct reprogramming of cardiac fibroblasts to cardiomyocytes. Circ. Res 110:1465-1473.

49. Song K, Nam YJ, Luo X, Qi X, Tan W, et al. (2012) Heart repair by reprogramming non-myocytes with cardiac transcription factors. Nature 485: 599-604.

50. Andrée B, Zweigerdt R (2016) Directing Cardiomyogenic Differentiation and Transdifferentiation By Ectopic Gene Expression - Direct Transition Or Reprogramming Detour?. Curr Gene Ther 16: 14-20.

51. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell126: 663-676.

52. Gurdon JB (1962) The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. J Embryol Exp Morphol 10: 622-640.

53. Cashman TJ, Josowitz R, Gelb BD, Li RA, Dubois NC, et al. (2016) Construction of Defined Human Engineered Cardiac Tissues to Study Mechanisms of Cardiac Cell Therapy. J Vis Exp. 109.

54. Gupta SK, Itagaki R, Zheng X, Batkai S, Thum S, et al. (2016) miR-21 promotes fibrosis in an acute cardiac allograft transplantation model. Cardiovasc Res pii: cvw030.

55. Teng L, Bennett E, Cai C (2016) Preconditioning c-Kit Positive Human Cardiac Stem Cells with a Nitric Oxide Donor Enhances Cell Survival through Activation of Survival Signaling Pathways. J Biol Chem M115.687806.