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Editorial Board Member of *World Journal of Stem Cells*, Craig S Atwood, PhD, Associate Professor, Department of Medicine, University of Wisconsin-Madison, Madison, WI 53711, United States

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Moving forward on the pathway of cell-based therapies in ischemic heart disease and heart failure – time for new recommendations?

Miruna Mihaela Micheu

ORCID number: Miruna Mihaela Micheu (0000-0001-7201-3132).

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Miruna Mihaela Micheu, Department of Cardiology, Clinical Emergency Hospital of Bucharest, Bucharest 014461, Romania

Corresponding author: Miruna Mihaela Micheu, MD, PhD, Doctor, Department of Cardiology, Clinical Emergency Hospital of Bucharest, Floreasca Street 8, Bucharest 014452, Romania. mirunamicheu@yahoo.com
Telephone: +40-72-2451755

Abstract

Although substantial advances have been made in treating ischemic heart disease and subsequent heart failure, the overall morbidity and mortality from these conditions remain high. Stem cell-based therapy has emerged as a promising approach for prompting cardiac rejuvenation. Various cell types have been tested in the clinical arena, proving consistent safety results. As for efficiency outcomes, contradictory findings have been reported, partly due to inconsistency in study protocols but also due to poor survival, engraftment and differentiation of transplanted cells in the hostile milieu of the ischemic host tissue. Studies have varied in terms of route of delivery, type and dose of implanted stem cells, patient selection and randomization, and assessment of therapeutic effect. Founded on the main achievements and challenges within almost 20 years of research, a number of official documents have been published by leading experts in the field. Core recommendations have focused on developing and optimizing effective strategies to enrich cell retention and their regenerative potential. Issued consensus and position papers have stemmed from an unmet need to provide a harmonized framework for future research, resulting in improved therapeutic application of cell-based therapies for cardiac regeneration and repair.

Key words: Stem cell therapy; Ischemic heart disease; Heart failure; Cardiac regeneration; Recommendations

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Core tip: Ischemic heart disease and resulting heart failure remain a major public health problem worldwide in spite of therapeutic progresses. Almost two decades ago, stem cell-based therapy appeared as a promising method to stimulate cardiac regeneration. Based on the main findings and challenges faced during clinical trials within this timeframe, a number of consensus and position papers have been issued by key opinion leaders, with the specific aim to empower cell-based cardiac repair and regeneration in patients with the aforesaid maladies.



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INTRODUCTION

In spite of standard-of-care therapies, ischemic heart disease (IHD) remains one of the leading causes of early death and disease burden worldwide, leading to almost 9 million deaths and 170 million disability-adjusted life years globally in 2017^[1]. The poor prognosis is related to the reduced endogenous regenerative ability of the adult human heart. Evidence-based disease management greatly improves patient outcomes, but it does not completely prevent myocyte injury and consequent adverse cardiac remodeling. Ongoing efforts are being made to develop alternative strategies to prompt the restoration of both cardiac structure and function. Advances in understanding stem cell (SC) biology have led to the development of stem cell-based therapy (SCT), which holds high therapeutic promise. The rationale behind SCT is that the supplied cells will facilitate the generation of functional cardiomyocytes and new blood vessels, either by exogenous regenerative responses or by activating endogenous renewal mechanisms^[2].

THE PAST

Since the first in-man SCT for IHD^[3], a substantial number of clinical trials (CTs) have been finalized and comprehensive reviews and meta-analyses have been published, yielding inconsistent results^[4,5]. But when it comes to papers expressing opinion and recommendations from expert authorities, their number is not so impressive. Since current guidelines on SCT in IHD and heart failure (HF) are lacking, experts in the field provided harmonized statements in order to move forward the clinical application of cell-based therapies for cardiac regeneration and repair; three position papers and two consensus documents have been put out in the last 13 years (Figure 1).

The first document of its kind was presented in 2006, when the Task Force of the European Society of Cardiology (ESC) published a consensus document on the use of autologous cell therapy for repair of the heart^[6]. Although the 2006 paper is rather obsolete given the existence of an updated version^[7], it has the merit of establishing a framework for upcoming research.

It took a decade until new papers were issued, a timespan in which important data have been offered by completed CTs. Provided recommendations have been formulated to address the main limitations raised within prior hallmark studies, such as reduced survival and engraftment of delivered cells in ischemic myocardium, lack of effective differentiation of adult SCs into mature and functional cardiomyocytes, insufficient activation of resident cardiac SCs, inadequate electrophysiological integration of the implanted cells with native myocardium, and the use of inappropriate end-points for assessing the outcomes of SCT. Hence, continual development of carrier materials and priming strategies (such as genetic and pharmacological modification) to improve SC retention, survival and differentiation has been recommended. A particularly important aspect is related to the type of SC to be transplanted, which should be carefully chosen. Due to adverse events, the skeletal myoblast is no longer of interest. First-generation cells, such as bone marrow - derived mononuclear cells (commonly referred to as BM-MNCs) or mesenchymal stem cells (MSCs), are considered to prompt endogenous repair mechanisms, while second-generation cells, such as pluripotent SCs and cardiac stem cells/cardiac progenitor cells (CSCs/CPCs), are believed to hold exogenous regenerative potential and actually replace the injured myocardium. Therefore, diverse cell types or a mixture of cell types have been suggested to be tested in randomized CTs. Nevertheless, possible confounders such as gender, age, comorbidities, and daily medications, should permanently be taken into account. Last but not least, the necessity of employing “hard clinically meaningful endpoints” to determine the actual impact on disease burden has been emphasized^[2,7,8].

Notably, disease-specific recommendations have been also envisaged^[7]. On the

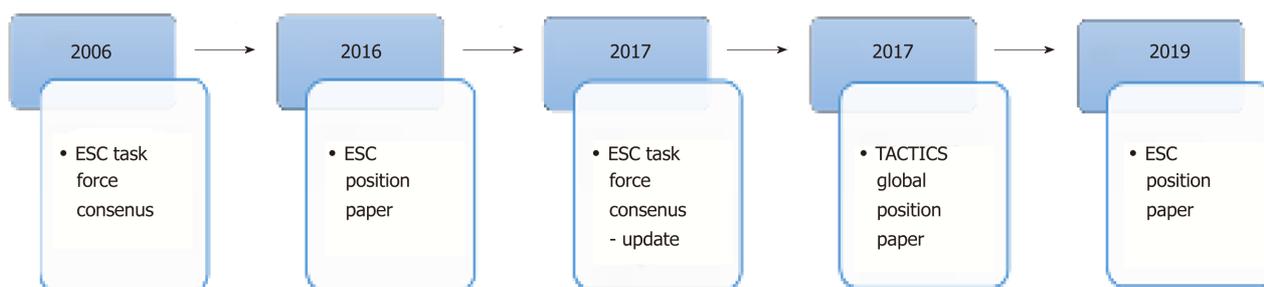


Figure 1 Timeline of expert opinions in cell-based therapies for cardiac regeneration and repair. ESC: European Society of Cardiology; TACTICS: Transnational AllianCe for regenerative Therapies In Cardiovascular Syndromes.

subject of launching additional autologous bone marrow cell CTs in acute myocardial infarction settings, the consensus was to await results from the BAMI trial^[9]. BAMI was designed as the largest phase III randomized CT with the precise goal to provide a conclusive answer whether BM-MNCs plus standard of care therapy can lead to a 25% reduction in mortality when compared to best medical care alone^[10]. It is to emphasize that the study protocol was substantially revised, as the accrual rate was significantly impaired (375 randomized patients instead of the initial target of 3000 patients). Still, the results are eagerly awaited, and the study is being reconsidered as an estimation trial with the aim to assess the treatment effect and event rates in the SCT group. Until now, successful standardization of the bone marrow procurement and cell manufacturing technique has been reported. The full findings will be released after October 2019 (the estimated study completion date). In regard to SCT in chronic HF, the recommendation to use cardiopoietic cells - either primary or engineered - is reiterated. In view of the recognized safety of SCT, repeated administration should be planned in order to achieve improved long-term clinical outcome^[7].

Of note, some of the aforementioned recommendations have already been translated into practice. For example, Bartunek and colleagues used a combination of cardiogenic growth factors to direct patient-derived MSCs toward a cardiopoietic phenotype^[11,12]. Lineage specified MSCs proved to exert beneficial effects on cardiac remodeling, exercise capacity and quality of life^[13,14].

Furthermore, a four-arm randomized CT has been designed with the aim to compare the restorative capacity of autologous bone marrow-derived MSCs and c-kit⁺ CPCs, either alone or in combination, in patients with ischemic HF. The estimated study completion date is May 2020^[15].

While the aforesaid studies employed adult SCs, there was a single CT that used human embryonic SC-derived CD15⁺ Isl-1⁺ progenitors to treat patients with severe ischemic HF (the ESCORT study)^[16]. Regardless of study limitations (*i.e.* small sample size, lack of blinded assessment, confounding effect of the concomitant coronary artery bypass grafting), the trial provided proof of concept for further robust studies.

THE PRESENT

In light of today's knowledge, the very recent document published on behalf of ESC has focused on strategies to boost cell delivery and retention within native area by combined administration of cells, biologically active molecules and bio-materials (*e.g.*, hydrogels, cell sheets, prefabricated matrices, microspheres, and injectable matrices)^[17]. Cutting-edge tissue engineering (TE) approaches have been shown to increase the long-term cell retention of more than 80%, and for that reason they have emerged as valuable tools to advance cell therapies for IHD and HF. The use of materials that do not trigger inflammatory or foreign body responses (such as naturally derived polymers with an anti-inflammatory activity, extracellular matrix components, and materials with controlled release of anti-inflammatory/ immunosuppressive molecules) is favored.

Also, the therapeutic potential held by human induced pluripotent stem cells (hiPSCs) is emphasized. Preclinical research revealed that transplanted hiPSC-derived cardiomyocytes (hiPSC-CMs) were able to persist, mature and proliferate within the host myocardium, causing improved cardiac function in recipient animals^[18-20]. For an enhanced regenerative outcome, combinations of cells and bio-materials have been employed. For example, in a porcine ischemic cardiomyopathy model, transplantation of hiPSC-CMs cell sheets together with an omentum flap as a source of blood supply

yielded better results compared with hiPSC-CM administration alone^[21]. Similarly, co-transplantation of multiple hiPSC-derived cardiovascular cell types (*i.e.* cardiomyocytes, endothelial cells and smooth muscle cells) with a 3D fibrin patch impregnated with a pro-survival factor resulted in reduced cardiomyocyte apoptosis, diminished infarct size, and improved cardiac function^[22]. However, the use of iPSC-CMs is not without risks (*i.e.* graft-related arrhythmias). For a safe and effective iPSC-based therapy, targeted cardiomyocyte subtype specification and functional maturation are of the essence. Accordingly, sustained efforts have been made to attain specialized, mature hiPSC-CM phenotypes, which could be further used for human engineered heart muscle constructs^[23-25].

Another topic evoked by the authors of the ESC position paper refers to prompting cardiac regeneration by cell-free *in situ* strategies, such as injection of materials containing instructive signals for cardiac cell reprogramming or SC-derived secretome survival factors. In particular, direct cellular reprogramming of cardiac fibroblasts seems most appealing, given their abundance in infarcted myocardium. Indeed, prior studies have demonstrated that fibroblasts can be driven directly into cardiomyocytes by distinct combinations of lineage-significant transcription factors or microRNAs^[26-30]. Of note, induced *in situ* fibroblast reprogramming improved cardiac function in animal myocardial infarction models, with 30%-40% increase in left ventricle ejection fraction and reduction of fibrotic scar by up to 50%^[31].

At present, with very few exceptions (Table 1^[16,32-34]), the use of tissue-engineered constructs for myocardial regeneration is still in the preclinical phase. To expedite TE and cell-based therapies for cardiac repair, the experts from the ESC Working Group on Cellular Biology of the Heart have issued several key statements. Hence, more effective TE strategies to increase cell retention should be further developed and optimized (including 3D printing to augment the biological ability of TE products). Of note, the whole fabrication of products should be conducted in agreement with regulatory demands, comprising proof of concept in rodent and large animal models^[17].

THE FUTURE

With BAMi's results being expected to be released and pluripotent SC-cardiac derivatives entering the clinical arena, it seems like these are exciting times for mending broken hearts. Hence, one can only ask oneself: What next?

Table 1 Ongoing / completed human clinical trials for cardiac tissue engineering

Clinical trial name	Trial identifier	Target sample size	Status
Epicardial Infarct Repair Using CorMatrix [®] -ECM: Clinical Feasibility Study (EIR)	ClinicalTrials.gov Identifier: NCT02887768 ^[52]	8	Completed
Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure (ESCORT)	ClinicalTrials.gov Identifier: NCT02057900 ^[16]	10	Completed
Myocardial Assistance by Grafting a - New Bioartificial Upgraded Myocardium (MAGNUM Trial)		20	Completed
A Study of VentriGel in Post-MI Patients	ClinicalTrials.gov Identifier: NCT02305602 ^[53]	15	Active, not recruiting
Clinical trial of human (allogeneic) induced pluripotent stem cell-derived cardiomyocyte sheet for severe cardiomyopathy	UMIN-CTR Clinical Trial ID: UMIN000032989 ^[54]	3	Not yet recruiting

REFERENCES

- GBD 2017 Disease and Injury Incidence and Prevalence Collaborators.** Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789-1858 [PMID: 30496104 DOI: 10.1016/S0140-6736(18)32279-7]
- Fernández-Avilés F, Sanz-Ruiz R, Climent AM, Badimon L, Bolli R, Charron D, Fuster V, Janssens S, Kastrup J, Kim HS, Lüscher TF, Martin JF, Menasché P, Simari RD, Stone GW, Terzic A, Willerson JT, Wu JC; TACTICS (Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes) Writing Group; Authors/Task Force Members. Chairpersons; Basic Research Subcommittee; Translational Research Subcommittee; Challenges of Cardiovascular Regenerative Medicine Subcommittee; Tissue Engineering Subcommittee; Delivery, Navigation, Tracking and Assessment Subcommittee; Clinical Trials Subcommittee; Regulatory and funding strategies subcommittee; Delivery, Navigation, Tracking and Assessment Subcommittee.** Global position paper on cardiovascular regenerative medicine. *Eur Heart J* 2017; **38**: 2532-2546 [PMID: 28575280 DOI: 10.1093/eurheartj/ehx248]
- Strauer BE, Brehm M, Zeus T, Gattermann N, Hernandez A, Sorg RV, Kögler G, Wernet P.** Intracoronary, human autologous stem cell transplantation for myocardial regeneration following myocardial infarction. *Dtsch Med Wochenschr* 2001; **126**: 932-938 [PMID: 11523014 DOI: 10.1055/s-2001-16579-2]
- Dorobantu M, Popa-Fotea NM, Popa M, Rusu I, Micheu MM.** Pursuing meaningful end-points for stem cell therapy assessment in ischemic cardiac disease. *World J Stem Cells* 2017; **9**: 203-218 [PMID: 29321822 DOI: 10.4252/wjsc.v9.i12.203]
- Micheu MM, Dorobantu M.** Fifteen years of bone marrow mononuclear cell therapy in acute myocardial infarction. *World J Stem Cells* 2017; **9**: 68-76 [PMID: 28491241 DOI: 10.4252/wjsc.v9.i4.68]
- Bartunek J, Dimmeler S, Drexler H, Fernández-Avilés F, Galinanes M, Janssens S, Martin J, Mathur A, Menasche P, Piro S, Strauer B, Tendera M, Wijns W, Zeiher A; task force of the European Society of Cardiology.** The consensus of the task force of the European Society of Cardiology concerning the clinical investigation of the use of autologous adult stem cells for repair of the heart. *Eur Heart J* 2006; **27**: 1338-1340 [PMID: 16543252 DOI: 10.1093/eurheartj/ehi793]
- Mathur A, Fernández-Avilés F, Dimmeler S, Hauskeller C, Janssens S, Menasche P, Wojakowski W, Martin JF, Zeiher A; BAMI Investigators.** The consensus of the Task Force of the European Society of Cardiology concerning the clinical investigation of the use of autologous adult stem cells for the treatment of acute myocardial infarction and heart failure: update 2016. *Eur Heart J* 2017; **38**: 2930-2935 [PMID: 28204458 DOI: 10.1093/eurheartj/ehw640]
- Madonna R, Van Laake LW, Davidson SM, Engel FB, Hausenloy DJ, Lecour S, Leor J, Perrino C, Schulz R, Ytrehus K, Landmesser U, Mummery CL, Janssens S, Willerson J, Eschenhagen T, Ferdinandy P, Sluijter JP.** Position Paper of the European Society of Cardiology Working Group Cellular Biology of the Heart: cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. *Eur Heart J* 2016; **37**: 1789-1798 [PMID: 27055812 DOI: 10.1093/eurheartj/ehw113]
- Mathur A.** The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells (BM-MNC) on All Cause Mortality in Acute Myocardial Infarction. [accessed. 2019; ClinicalTrials.gov [Internet]. United States National Library of Medicine Available from: <http://clinicaltrials.gov/show/NCT01569178> ClinicalTrials.gov Identifier: NCT01569178
- Mathur A, Arnold R, Assmus B, Bartunek J, Belmans A, Böning H, Crea F, Dimmeler S, Dowlut S, Fernández-Avilés F, Galinanes M, Garcia-Dorado D, Hartikainen J, Hill J, Hogardt-Noll A, Homys C, Janssens S, Kala P, Kastrup J, Martin J, Menasche P, Miklik R, Mozd A, San Román JA, Sanz-Ruiz R, Tendera M, Wojakowski W, Ylä-Herttua S, Zeiher A.** The effect of intracoronary infusion of bone marrow-derived mononuclear cells on all-cause mortality in acute myocardial infarction: rationale and design of the BAMI trial. *Eur J Heart Fail* 2017; **19**: 1545-1550 [PMID: 28948706 DOI: 10.1002/ejhf.829]
- Bartunek J, Terzic A.** C-Cure Clinical Trial. [accessed. 2019; ClinicalTrials.gov [Internet]. United States National Library of Medicine Available from: <http://clinicaltrials.gov/show/NCT00810238> ClinicalTrials.gov Identifier: NCT00810238

- 12 **Terzic A**, Bartunek J. Safety and Efficacy of Autologous Cardiopoietic Cells for Treatment of Ischemic Heart Failure. [accessed. 2019; ClinicalTrials.gov [Internet]. United States National Library of Medicine Available from: <http://clinicaltrials.gov/show/NCT01768702> ClinicalTrials.gov Identifier: NCT01768702
- 13 **Bartunek J**, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, El Nakadi B, Banovic M, Beleslin B, Vrolix M, Legrand V, Vrints C, Vanoverschelde JL, Crespo-Diaz R, Homsy C, Tendera M, Waldman S, Wijns W, Terzic A. 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* 2013; **61**: 2329-2338 [PMID: 23583246 DOI: 10.1016/j.jacc.2013.02.071]
- 14 **Bartunek J**, Terzic A, Davison BA, Filippatos GS, Radovanovic S, Beleslin B, Merkely B, Musialek P, Wojakowski W, Andrecka P, Horvath IG, Katz A, Dolatabadi D, El Nakadi B, Arandjelovic A, Edes I, Seferovic PM, Obradovic S, Vanderheyden M, Jagic N, Petrov I, Atar S, Halabi M, Gelev VL, Shochat MK, Kasprzak JD, Sanz-Ruiz R, Heyndrickx GR, Nyolczas N, Legrand V, Guédès A, Heyse A, Moccetti T, Fernandez-Aviles F, Jimenez-Quevedo P, Bayes-Genis A, Hernandez-Garcia JM, Ribichini F, Gruchala M, Waldman SA, Teerlink JR, Gersh BJ, Povsic TJ, Henry TD, Metra M, Hajjar RJ, Tendera M, Behfar A, Alexandre B, Seron A, Stough WG, Sherman W, Cotter G, Wijns W; CHART Program. Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial. *Eur Heart J* 2017; **38**: 648-660 [PMID: 28025189 DOI: 10.1093/eurheartj/ehw543]
- 15 **Bolli R**, Hare JM, March KL, Pepine CJ, Willerson JT, Perin EC, Yang PC, Henry TD, Traverse JH, Mitrani RD, Khan A, Hernandez-Schulman I, Taylor DA, DiFede DL, Lima JAC, Chugh A, Loughran J, Vojvodic RW, Sayre SL, Bettencourt J, Cohen M, Moyé L, Ebert RF, Simari RD; Cardiovascular Cell Therapy Research Network (CCTRN). 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**: 1703-1715 [PMID: 29703749 DOI: 10.1161/CIRCRESAHA.118.312978]
- 16 **Menasché P**. *Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure*. [accessed 2019; ClinicalTrials.gov [Internet]. United States National Library of Medicine Available from: <http://clinicaltrials.gov/show/NCT02057900> ClinicalTrials.gov Identifier: NCT02057900
- 17 **Madonna R**, Van Laake LW, Botker HE, Davidson SM, De Caterina R, Engel FB, Eschenhagen T, Fernandez-Aviles F, Hausenloy DJ, Hulot JS, Lecour S, Leor J, Menasché P, Pesce M, Perrino C, Prunier F, Van Linthout S, Ytrehus K, Zimmermann WH, Ferdinandy P, Sluijter JPG. ESC Working Group on Cellular Biology of the Heart: position paper for Cardiovascular Research: tissue engineering strategies combined with cell therapies for cardiac repair in ischaemic heart disease and heart failure. *Cardiovasc Res* 2019; **115**: 488-500 [PMID: 30657875 DOI: 10.1093/cvr/cvz010]
- 18 **Funakoshi S**, Miki K, Takaki T, Okubo C, Hatani T, Chonabayashi K, Nishikawa M, Takei I, Oishi A, Narita M, Hoshijima M, Kimura T, Yamanaka S, Yoshida Y. Enhanced engraftment, proliferation, and therapeutic potential in heart using optimized human iPSC-derived cardiomyocytes. *Sci Rep* 2016; **6**: 19111 [PMID: 26743035 DOI: 10.1038/srep19111]
- 19 **Shiba Y**, Gomibuchi T, Seto T, Wada Y, Ichimura H, Tanaka Y, Ogasawara T, Okada K, Shiba N, Sakamoto K, Ido D, Shiina T, Ohkura M, Nakai J, Uno N, Kazuki Y, Oshimura M, Minami I, Ikeda U. Allogeneic transplantation of iPSC cell-derived cardiomyocytes regenerates primate hearts. *Nature* 2016; **538**: 388-391 [PMID: 27723741 DOI: 10.1038/nature19815]
- 20 **Rojas SV**, Kensah G, Rotaermel A, Baraki H, Kutschka I, Zweigerdt R, Martin U, Haverich A, Gruh I, Martens A. Transplantation of purified iPSC-derived cardiomyocytes in myocardial infarction. *PLoS One* 2017; **12**: e0173222 [PMID: 28493867 DOI: 10.1371/journal.pone.0173222]
- 21 **Kawamura M**, Miyagawa S, Fukushima S, Saito A, Miki K, Funakoshi S, Yoshida Y, Yamanaka S, Shimizu T, Okano T, Daimon T, Toda K, Sawa Y. Enhanced Therapeutic Effects of Human iPSC Cell Derived-Cardiomyocyte by Combined Cell-Sheets with Omental Flap Technique in Porcine Ischemic Cardiomyopathy Model. *Sci Rep* 2017; **7**: 8824 [PMID: 28821761 DOI: 10.1038/s41598-017-08869-z]
- 22 **Ye L**, Chang YH, Xiong Q, Zhang P, Zhang L, Somasundaram P, Lepley M, Swingen C, Su L, Wendel JS, Guo J, Jang A, Rosenbush D, Greder L, Dutton JR, Zhang J, Kamp TJ, Kaufman DS, Ge Y, Zhang J. Cardiac repair in a porcine model of acute myocardial infarction with human induced pluripotent stem cell-derived cardiovascular cells. *Cell Stem Cell* 2014; **15**: 750-761 [PMID: 25479750 DOI: 10.1016/j.stem.2014.11.009]
- 23 **Lee JH**, Protze SI, Laksman Z, Backx PH, Keller GM. Human Pluripotent Stem Cell-Derived Atrial and Ventricular Cardiomyocytes Develop from Distinct Mesoderm Populations. *Cell Stem Cell* 2017; **21**: 179-194.e4 [PMID: 28777944 DOI: 10.1016/j.stem.2017.07.003]
- 24 **Lemme M**, Ulmer BM, Lemoine MD, Zech ATL, Flenner F, Ravens U, Reichenspurner H, Rol-Garcia M, Smith G, Hansen A, Christ T, Eschenhagen T. Atrial-like Engineered Heart Tissue: An In Vitro Model of the Human Atrium. *Stem Cell Reports* 2018; **11**: 1378-1390 [PMID: 30416051 DOI: 10.1016/j.stemcr.2018.10.008]
- 25 **Zhao Y**, Rafatian N, Feric NT, Cox BJ, Aschar-Sobbi R, Wang EY, Aggarwal P, Zhang B, Conant G, Ronaldson-Bouchard K, Pahnke A, Protze S, Lee JH, Davenport Huyer L, Jekic D, Wickeler A, Naguib HE, Keller GM, Vunjak-Novakovic G, Broeckel U, Backx PH, Radisic M. A Platform for Generation of Chamber-Specific Cardiac Tissues and Disease Modeling. *Cell* 2019; **176**: 913-927.e18 [PMID: 30686581 DOI: 10.1016/j.cell.2018.11.042]
- 26 **Qian L**, Huang Y, Spencer CI, Foley A, Vedantham V, Liu L, Conway SJ, Fu JD, Srivastava D. In vivo reprogramming of murine cardiac fibroblasts into induced cardiomyocytes. *Nature* 2012; **485**: 593-598 [PMID: 22522929 DOI: 10.1038/nature11044]
- 27 **Song K**, Nam YJ, Luo X, Qi X, Tan W, Huang GN, Acharya A, Smith CL, Tallquist MD, Neilson EG, Hill JA, Bassel-Duby R, Olson EN. Heart repair by reprogramming non-myocytes with cardiac transcription factors. *Nature* 2012; **485**: 599-604 [PMID: 22660318 DOI: 10.1038/nature11139]
- 28 **Addis RC**, Epstein JA. Induced regeneration--the progress and promise of direct reprogramming for heart repair. *Nat Med* 2013; **19**: 829-836 [PMID: 23836233 DOI: 10.1038/nm.3225]
- 29 **Jayawardena TM**, Egemnazarov B, Finch EA, Zhang L, Payne JA, Pandya K, Zhang Z, Rosenberg P, Mirotsov M, Dzau VJ. MicroRNA-mediated in vitro and in vivo direct reprogramming of cardiac fibroblasts to cardiomyocytes. *Circ Res* 2012; **110**: 1465-1473 [PMID: 22539765 DOI: 10.1161/CIRCRESAHA.112.269035]
- 30 **Jayawardena TM**, Finch EA, Zhang L, Zhang H, Hodgkinson CP, Pratt RE, Rosenberg PB, Mirotsov M, Dzau VJ. MicroRNA induced cardiac reprogramming in vivo: evidence for mature cardiac myocytes and improved cardiac function. *Circ Res* 2015; **116**: 418-424 [PMID: 25351576 DOI: 10.1161/CIRCRESAHA.116.304510]

- 31 **Rosengart TK**, Patel V, Sellke FW. Cardiac stem cell trials and the new world of cellular reprogramming: Time to move on. *J Thorac Cardiovasc Surg* 2018; **155**: 1642-1646 [PMID: 29397153 DOI: 10.1016/j.jtcvs.2017.11.104]
- 32 **Fedak PW**. Epicardial Infarct Repair Using CorMatrix[®]-ECM: Clinical Feasibility Study. [accessed 2019 May 30]. In: ClinicalTrials.gov [Internet]. United States National Library of Medicine. Available from: URL: <http://clinicaltrials.gov/show/NCT02887768> ClinicalTrials.gov Identifier: NCT02887768
- 33 **Ventrix Inc**. A Study of VentiGel in Post-MI Patients. [accessed 2019 May 30]. In: ClinicalTrials.gov [Internet]. United States National Library of Medicine. Available from: URL: <http://clinicaltrials.gov/show/NCT02305602> ClinicalTrials.gov Identifier: NCT02305602
- 34 **Sawa Y**. Clinical trial of human (allogeneic) induced pluripotent stem cell-derived cardiomyocyte sheet for severe cardiomyopathy. [accessed 2019 May 30]. In: upload.umin.ac.jp [Internet]. Available from: URL: <https://upload.umin.ac.jp/R000037108> UMIN-CTR Clinical Trial ID: UMIN000032989



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