OPEN ACCESS

GAVIN PUBLISHERS

Cardiology Research and Cardiovascular Medicine

Ishigami S, et al. Cardiolog Res Cardiovasc Med: 165.

DOI: 10.29011/2575-7083.000065

Review Article

The Future of Cell-Based Therapy for Pediatric Heart Disease

Shuta Ishigami[1], Toshikazu Sano[1], Sunaya Krishnapura[1], Shunji Sano[1*], Tatsuo Ito[2]

[1]Department of Pediatric Cardiothoracic Surgery, University of California, San Francisco, USA

[2]Department of Hygiene, Kawasaki Medical University, Japan

[*]**Corresponding author:** Shunji Sano, Department of Pediatric Cardiothoracic Surgery, University of California, San Francisco, Surgical Co-Director of the Pediatric Cardiac Center, UCSF Benioff Children's Hospital, San Francisco, USA

Citation: Ishigami S, Sano T, Krishnapura S, Sano S, Ito T (2020) The Future of Cell-Based Therapy for Pediatric Heart Disease. Cardiolog Res Cardiovasc Med: 165. DOI: 10.29011/2575-7083.000065

Received Date: 13 November, 2020; **Accepted Date:** 19 November, 2020; **Published Date:** 26 November, 2020

Abstract

Advancements in prenatal diagnosis, surgical procedures, interventional cardiology, and pharmaceutical heart failure management have contributed to enhanced rates of survival in children with heart disease. However, long-term morbidity and mortality still present a challenge, especially in children with single ventricle physiology and end stage heart failure. Although heart transplantation is a standard of care for children with end-stage heart failure, the shortage of available organs remains a worldwide problem. For this reason, there is considerable interest in investigating novel therapies for advanced heart failure including mechanical circulatory support devices and regenerative therapy to treat damaged heart tissue and muscle. Accumulated evidence over the years has demonstrated the potential of cell-based therapies to address pediatric heart failure. Since children's hearts appear to have greater regenerative potential compared to adult's, cell-based therapies would be a promising alternative treatment option for pediatric heart failure. In this review, we provide an overview of the current knowledge that exists in the field of cell-based therapy for children with heart disease, and subsequently discuss novel strategies that may be implemented in the near future to enhance the efficacy of these treatments.

Keywords: Clinical trials; Pediatric heart failure; Stem cell therapy

Introduction

Surgical management and interventional cardiology have drastically improved the outcomes for the children with heart disease over the past several decades. Conditions that originally had bleak outcomes, such as Hypoplastic Left Heart Syndrome (HLHS) can now be treated, yielding a 50 -70% survival rate [1]. In spite of these optimistic trends, progressive late-onset heart failure still remains a serious problem, which has been increasingly recognized in children after staged cardiac surgeries. In the United States, congenital heart disease is the predominant cause of around 14,000 childhood heart failure-related hospitalizations (7% mortality rate) annually [2]. Although current therapeutic approaches are directed towards improving heart failure symptoms, they do not address the fundamental problem of the loss of cardiac muscle. Therefore, improvements in anti-heart failure medicine and device therapies are strongly desired.

Myocardial engineering, including stem cell therapy, represents the first realistic strategy for the terminal heart damage. Since the initial report of cell therapy (skeletal myoblasts) in heart failure in 2001 [3], numerous clinical studies have been performed that support the ability of various stem cell populations to improve cardiac function and reduce infarct size in both ischemic and nonischemic cardiomyopathy in adult patients. Evidence of the success of stem cell therapy in children with heart disease seems scarce despite the fact that studies suggests that the regenerative capacity of children's heart muscle may be greater than adult's [4]. To date, no large clinical trials have been attempted to test the viability of cell-based therapies for pediatric heart disease [5]. Despite these limitations, the results from case reports and smaller clinical trials available at present indicate that stem cell therapy may hold great promise for the treatment of pediatric heart disease.

Cell Types Used for Pediatric Heart Failure

Several stem cell populations from people of different ages (neonate to adult) and from different tissues (non-cardiac or cardiac) are under active investigation. Consequently, past studies have investigated the use of various types of stem cells intreating pediatric heart failure. Below, we briefly summarize the different types of stem cells and evaluate the use of these cells in pediatric clinical trials (Table 1). Current studies to date suggest that cardiac

stem cells and mesenchymal stem cells hold the greatest potential for use in cell-based therapies targeting pediatric heart disease [6].

Trial	Disease	NCT	Year	Sponsor and Collaborators	Phase	Cell	Status
A Randomized Study of Autologous Bone Marrow Derived Stem Cells in Pediatric Dilated Cardiomyopathy.	DCM	02479776	2008	Great Ormond Street Hospital for Children	I	BM	Reported [14]
Phase I Study of Cardiac Progenitor Cell Therapy in Patients With Single Ventricle Physiology (TICAP).	HLHS	01273857	2011	Okayama University	I	CDCs	Reported [30]
Autologous Cord Blood Cells for Patients With HLHS: Phase I Study of Feasibility and Safety	HLHS	01445041	2011	Duke university	I	UCB	Not Reported
Phase 2 Study of Intracoronary Infusion of Cardiac Progenitor Cells in Patients With Univentricular Heart Disease (PERSEUS).	HLHS, SV	01829750	2013	Okayama University Translational Research Informatics Center, Kobe	II	CDCs	Reported [31]
Safety Study of Autologous Umbilical Cord Blood Cells for Treatment of Hypoplastic Left Heart Syndrome.	HLHS	01883076	2013	University of Oklahoma Children's Hospital of Philadelphia Children's Hospitals and Clinics of Minnesota Children's Hospital Los Angeles Children's Hospital Colorado Mayo Clinic	I	UCB	Reported [24]
Intracoronary Transplantation of Autologous Bone Marrow Derived Mononuclear Cells (MNC) in Idiopathic Dilated Cardiomyopathy in Pediatric Patients.	DCM	02256501	2013	Royan Institute, Tehran, Iran	I	BM	Not reported

Allogeneic Human MEsenchymal Stem Cell (MSC) Injection in Patients With Hypoplastic Left Heart Syndrome: A Phase I/II Study (ELPIS).	HLHS	03525418	2015	Longeveron LLC Emory University/ Childen's Healthcare of Atlanta University of Maryland Medical Center Johns Hopkins University Hospital Cincinnati Children's Hospital Medical Center University of Utah/Heart Center-Primary Children Hospital	I/II	MSCs	Ongoing
Phase I Safety and Feasibility Study of Intracoronary Delivery of Autologous Bone Marrow Derived Mononuclear Cells for Systemic, Single Right Ventricular Failure Due to Congenital Heart Disease.	SV with Fontan circulation	02549625	2015	Mayo Clinic	I	BM	Ongoing
Efficacy and Safety Study of Autologous Cardiac Stem Cells (JRM-001) Treated After Reconstructive Surgery in Pediatric Patients With Congenital Heart Disease: A Multicenter Randomized Single-blind Parallel-group Study (APOLLON).	HLHS, SV	02781922	2016	Japan Regenerative Medicine Co., Ltd. Okayama University Kanagawa Children's Medical Center Shizuoka Children's Hospital	III	CDCs	Ongoing
A Randomized Phase 1 Trial of Cardiac Progenitor Cell Therapy in Children With Dilated Cardiomyopathy (TICAP-DCM).	DCM	03129568	2017	Okayama University	I	CDCs	Ongoing
Mesoblast Stem Cell Therapy for Patients With Single Ventricle and Borderline Left Ventricle.	HLHS, AV-canal	03079401	2017	Boston children's Hospital	I/II	MPCs	Ongoing

Safety of Autologous Cord Blood Cells in HLHS Patients During Norwood Heart Surgery.	HLHS	03431480	2018	Murdoch Children's Research Institute, Royal Children's Hospital	I	UCB	Ongoing
Phase IIb Study of Intramyocardial Injection of Autologous Umbilical Cord Blood Derived Mononuclear Cells During Stage II Surgical Repair of Right Ventricular Dependent Variants of Hypoplastic Left Heart Syndrome (AutoCell-S2).	HLHS	03779711	2018	University of Oklahoma, Children's Hospital of Philadelphia, Children's Hospital Los Angeles, Children's Hospital Colorado, Children's Hospitals and Clinics of Minnesota, Ochsner Health System, Children's of Alabama	IIb	UCB	Ongoing
Autologous Cardiac Stem Cell Injection in Patients With Hypoplastic Left Heart Syndrome: An Open Label Pilot Study.	HLHS	03406884	2019	Emory University Children's Healthcare of Atlanta University of Maryland	I	C-kit cells	Ongoing
AV-Canal: Atrio-Ventricular Canal; BM: Bone Marrow Derived Stem Cells; Cdcs: Cardiosphere Derived Cells; DCM: Dilated Cardiomyopathy; HLHS; Hypoplastic Left Heart Syndrome; MPC: Mesenchymal Precursor Cells; SV: Single Ventricles; UCB: Umbilical Cord Blood Derived Cells							

Table 1: Reported and ongoing clinical trials for pediatric heart disease.

Bone Marrow Mononuclear Cells (BMMNCs)

Bone Marrow Mononuclear Cells (BMMNCs) can be easily procured by density gradient centrifugation. BMMNCs secrete potent angiogenic cytokines such as Vascular Endothelial Growth Factor (VEGF) and induce proliferation of vascular and endothelial cells in pigs with chronic myocardial infarction [7]. These findings on the cardiac regeneration potential of BMMNCs prompted clinical studies into human cardiac muscle repair. In the pediatric field, there have been several case reports [8-13] and two completed clinical trials (NCT:02479776, 02256501) with only one reported investigating the use of stem cell therapy [14]. Currently, one clinical trial (NCT:02549625) is ongoing for patients with decreased ventricular function with Fontan circulation (Table 1).

Mesenchymal Stem Cells (MSCs)

Mesenchymal Stem/Stromal Cells (MSCs) reside in the bone marrow stroma, adipose tissue [15] and umbilical cord blood [16]. MSCs are relatively easy to grow and can be cultured to produce the appropriate cell numbers required for transplantation [17]. They can differentiate into osteoblasts, chondrocytes, and adipocytes [18,19]. In addition, MSCs can differentiate in vitro into beating Cardiomyocytes (CMs) after exposure to the demethylating agent 5-azacytidine [20]. Because of their demonstrated cardiomyogenic potential, MSCs have been transplanted into animal models of Myocardial Infarction (MI). A previous study demonstrated that transplanted MSCs originally extracted from human bone marrow improved the left ventricular function after myocardial infarction of rat heart models with a myocardial infarction [21]. These findings have spurred interest in using MSCs in clinical trials. In the pediatric field, two clinical trials (NCT:03525418, 03079401) are ongoing to evaluate the safety and efficacy of MSCs (Table 1).

Umbilical Cord Blood (UCB)-derived stem cells

Umbilical Cord Blood (UCB) is a source of both hematopoietic and non-hematopoietic precursors that were initially used in the treatment of hematologic disorders. UCB-derived cells also have been shown to be capable of differentiating in vitro into mesenchymal precursor cells [16]. These cells can be easily

harvested and have been found to self-renew, proliferate, and differentiate into varying lineages. Cardiac regeneration studies in rat MI models have demonstrated that UCB-derived stem cells significantly improved cardiac function and performance [22]. Recently, a study was conducted in which the effects of injecting UCB-derived stem cells into the right ventricle of juvenile pig hearts was observed. The results showed that intramyocardial injection of UCB-derived stem cells could be performed safely when performing open heart surgery [23]. In the pediatric clinical setting, a result from one clinical trial (NCT:01883076) using UCB-derived stem cells was reported [24] and three clinical trials using UCB-derived stem cells (NCT:01445041, 03431480, 03779711) are currently underway (Table 1).

Cardiac Stem Cells (CSCs)

Previously, it was believed that the fully differentiated heart did not have the capability to self-repair damaged myocardium. However, a study was published in 2002 by Hierlihy et al. found that Cardiac Stem Cells (CSCs) were present within the heart [25]. Although these cells comprised only 1% of the entire population of cardiac cells, they had the potential to differentiate into cardiomyocytes. In 2004, Cardiosphere-Derived Cells (CDCs) were isolated from postnatal atrial or ventricular biopsy specimens of human hearts. CDCs are undifferentiated, heterogeneous, and self-assembling spherical cellular clusters, which arise from myocardial tissue. These cellular structures are composed of a core of undifferentiated cells surrounded by a shell of cardiac-committed cells [26]. In 2007, a clinically applicable method was developed to isolate human cardiac stem cells from endomyocardial biopsies [27]. Human CDCs, which are expressed in infant hearts more than adult hearts, are predominantly present in the right atrium and outflow tract of the heart. These cells have a mesenchymal cell-like phenotype – such as CD105, CD90, CD29, CD73, CD71, and Stro-1– but rarely express c-kit and do not express endothelial and hematopoietic cell surface markers [28].

The discovery of CDCs has led to greater interest in their capacity for proliferation and differentiation. To date, approximately 160 papers have been published regarding the use of CDCs from over 45 independent laboratories worldwide [29]. Results of these studies have revealed that the administration of CDCs improves ventricular function and attenuates ventricular remodeling in animal models of acute and chronic ischemic heart failure. Based on these features, two clinical trials (NCT:01273857, 01829750) for congenital heart disease have been reported [30,31] and two clinical trials (NCT:02781922, 03129568) are currently underway (Table 1).

Stem Cell Therapy for Pediatric Heart Disease

Pediatric stem cell therapy has emerged as a new therapeutic paradigm based on the experiences and the results from the successful cell-based therapy in adult patients. At the moment, current cell-based therapies for children are focused on targeting Dilated Cardiomyopathy (DCM) and single ventricle physiology are targets for cell-based therapy. In this section, we review the reported and published results from case reports and clinical trials of cell-based therapy for pediatric heart disease [32].

Rupp, et al. published a study in 2009 with evidence of the first successful application of cell-based therapy (using BMMNCs) in a child with DCM. No negative complications were observed post-procedure, and at a three-month follow up, the group reported a decreased in serum BNP levels along with an increased in ventricular function. This suggested an improvement in heart function according to NYHA functional classification [33]. In 2017, the first randomized clinical trial exploring the use of autologous BMMNCs as a therapeutic option for pediatric patients with DCM and reduced ejection fraction was published by Pincott et al.(NCT:02479776) [14]. They revealed feasibility and safety of intracoronary BMMNCs infusion for children with DCM. Although there was no change in left ventricular ejection fraction between the groups, they demonstrated left ventricular volumes were significantly reduced at 6 months after stem cell injection compared with placebo, which may reflect reverse remodeling.

In cases of congenital heart disease, Rupp et al. first reported a case of successful cell therapy for an 11-month-old boy with HLHS in 2010. The boy presented with prolonged heart failure, and stem cell infusion prior to heart transplantation was planned. Intracoronary injection of autologous BMMNCs was performed without any complications. Three months after cell therapy his cardiac function improved with marked reduction of end-diastolic and end-systolic volumes [10].

In 2015, we reported the first phase I TICAP trial (NCT:01273857) using stem cells to treat HLHS. In this controlled study, 14 consecutive patients with HLHS were either received intracoronary CDCs one month after cardiac surgery (n=7, CDCs-treated group) or received standard care alone (n=7, Control group). In the CDCs-treated group, no examples of procedural related complications, arrhythmia, acute coronary syndrome, or cardiac death were observed 18 months' post procedure. Overall, right ventricular function in CDCs-treated patients showed a significant improvement compared to the negligible change in the control group. In addition, we found that a significant change in somatic growth was seen patients treated with CDCs-treated group compared to the control group [30]. Over 3-year observational periods of the TICAP trial reaffirmed the sustained improvements in cardiac function in the CDCs-treated group. Interestingly, there were significant correlations between changes in ventricular ejection function and weight for age (z score) as well as ejection fraction at cell infusion and age [34]. Given the promising result of the TICAP trial, we then performed a randomized-controlled,

prospective phase II PERSEUS trial (NCT01829750). Thirty-four patients were randomly assigned 1:1 to the CDCs-treated or control group. Patients were then observed at a three-month follow up appointment to determine the efficacy of the CDCs therapy. At this appointment, an overall 6.4% increase in global ventricular ejection fraction was observed in patients treated with CDCs compared to the control group, in which only a 1.3% rise was seen. Following this appointment, the control group was then received the CDCs treatment. At a follow up appointment 12 months later after CDCs therapy, thirty-four patients were then assessed to determine change in cardiac function, heart failure status, somatic growth, Quality of Life (QOL), and parenting stress. Cardiac function increased (by 6.4%) and positive changes in somatic growth, relief of heart failure status, and parenting stress index values were also improved [31]. Additionally, in comparing the 41 patients treated with CDCs in the TICAP and PERSEUS trials to 60 control patients with single ventricle physiology control patients, overall mortality rates were lower in those patients who received CDCs treatment [35].

In 2019, Burkhart, et al. reported a phase I clinical trial to treat children with HLHS using direct intramyocardial injection of autologous umbilical cord blood-derived mononuclear cells (NCT:01883076). They delivered the cells at the time of stage II palliative surgery. This phase I clinical trial showed that delivering autologous umbilical cord blood-derived mononuclear cells directly into the right ventricular myocardium during planned stage II surgical palliation for HLHS was safe and feasible. They also reported preservation of baseline right ventricular function throughout follow-up and normalized growth [24].

Future Perspective

Initially, it was believed that stem cells contribute to tissue and muscle regeneration in the heart as they possess the intrinsic capability to differentiate into cardiomyocytes, endothelial and smooth muscle cells. However, large amounts of in vitro and in vivo data have identified paracrine pathways (via exosomes or soluble factors) as the main mechanisms that create the positive regenerative results observed in cell-based therapies [36]. Paracrine factors secreted by stem cells stimulate the growth and division of somatic cells and formation of new blood vessels. Numerous pre-clinical studies are still underway to fully clarify these mechanisms of stem cell therapy and to boost up the efficacy of this strategy. Here, we discuss new trends in the field to enhance the application of cardiac stem cell therapy.

Application of Biomaterial to Increase Cell Engraftment

Stem cell "wash out" in the heart has proven to be a consistent challenge over the years due to repeated muscle contraction and blood circulation. The challenge in maintaining stem cells post injection in the damaged area subsequently limits the expected regenerative effects. A study published by Terrovitis et al. demonstrated that over the course of 24 hours, 90% of cells injected into the heart of animal models were subject to "wash out" [37]. To overcome these problems, biomaterials represent promising group of technology that may reduce stem cell "wash out". They are 3-dimensional polymeric scaffolds that have been engineered to protect cells against harsh environments and to prevent substantial cell loss after transplantation. The usage of injectable scaffolds such as fibrin and synthetic hydrogels improve engraftment and survival and increase the efficacy of cell therapy. Recently, Ichihara, et al. reported that epicardial coated MSCs incorporated in PuraMatrix® (PM; 3-D Matrix, Ltd) significantly enhanced global cardiac function and decreased ventricular dilatation compared to intramyocardially injected MSCs in rat models of AMI and ischemic cardiomyopathy. Furthermore, they indicated a significantly greater survival rates of donor cells and detected an upregulation of repair- related genes in the myocardium [38].

Genetic Modification

Genetic modification is highly desirable as another powerful technique to boost stem cell efficiency. Recent advances in gene editing using techniques CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9) may allow us to enhance the efficacy of cell-based therapy. In 2020, our group reported on the use the CRISPR/dCas9 system to regulate Tnnt2 gene activation in CDCs, allowing us to potentially modulate and promote stem cell differentiation into CDCs [39].

Conclusion

Given the limited supply of donor organs, the need to develop alternative therapeutic options to address pediatric heart failure is greater than ever. Over the years, several stem cell populations, ranging from BMMNCs to CSCs, have been investigated to assess their regenerative capacity to heal damaged heart muscle and tissue. Although fewer clinical trials have been conducted in children compared to adults, those that have been conducted to date suggest that call-based therapies represent the next frontier in the treatment of pediatric heat failure.

References

1. Feinstein JA, Benson DW, Dubin AM, Cohen MS, Maxey DM, et al. (2012) Hypoplastic left heart syndrome: current considerations and expectations. J Am Coll Cardiol 59: S1-S42.

2. Rossano JW, Shaddy RE (2014) Heart failure in children: etiology and treatment. J Pediatr 165: 228-233.

3. Menasché P, Hagège AA, Scorsin M, Pouzet B, Desnos M, et al. (2001) Myoblast transplantation for heart failure. Lancet 357: 279-280.

4. Sadek HA, Porrello ER (2020) Neonatal heart regeneration: Moving from phenomenology to regenerative medicine. J Thorac Cardiovasc Surg 159: 2451-2455.

5. Tsilimigras DI, Oikonomou EK, Moris D, Schizas D, Economopoulos KP, et al. (2017) Stem Cell Therapy for Congenital Heart Disease: A Systematic Review. Circulation 136: 2373-2385.

6. Selem SM, Kaushal S, Hare JM (2013) Stem cell therapy for pediatric dilated cardiomyopathy. Curr Cardiol Rep 15: 369.

7. Fuchs S BR, Zhou YF, Shou M, Pierre A, Tio FO, et al. (2001) Transendocardial Delivery of Autologous Bone Marrow Enhances Collateral Perfusion and Regional Function in Pigs with Chronic Experimental Myocardial Ischemia. J Am Coll Cardiol 37: 1726-1732.

8. de Lezo JS, Pan M, Herrera C (2009) Combined percutaneous revascularization and cell therapy after failed repair of anomalous origin of left coronary artery from pulmonary artery. Catheter Cardiovasc Interv 73: 833-837.

9. Limsuwan A, Pienvichit P, Limpijankit T, Khowsathit P, Hongeng S, et al. (2010) Transcoronary bone marrow-derived progenitor cells in a child with myocardial infarction: first pediatric experience. Clin Cardiol 33: E7-E12.

10. Rupp S, Zeiher AM, Dimmeler S, Tonn T, Bauer J, et al. (2010) A regenerative strategy for heart failure in hypoplastic left heart syndrome: intracoronary administration of autologous bone marrow-derived progenitor cells. J Heart Lung Transplant 29: 574-577.

11. Lacis A, Erglis A (2011) Intramyocardial administration of autologous bone marrow mononuclear cells in a critically ill child with dilated cardiomyopathy. Cardiol Young 21: 110-112.

12. Rupp S, Jux C, Bönig H, Bauer J, Tonn T, et al. (2012) Intracoronary bone marrow cell application for terminal heart failure in children. Cardiol Young 22: 558-563.

13. Bergmane I, Lacis A, Lubaua I, Jakobsons E, Erglis A (2013) Follow-up of the patients after stem cell transplantation for pediatric dilated cardiomyopathy. Pediatr Transplant 17: 266-270.

14. Pincott ES, Ridout D, Brocklesby M, McEwan A, Muthurangu V, et al. (2017) A randomized study of autologous bone marrow-derived stem cells in pediatric cardiomyopathy. J Heart Lung Transplant 36: 837-844.

15. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, et al. (2001) Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng 7: 211-228.

16. Erices A, Conget P, Minguell JJ (2000) Mesenchymal progenitor cells in human umbilical cord blood. Br J Haematol 109: 235-242.

17. Alhadlaq A, Mao JJ (2004) Mesenchymal stem cells: isolation and therapeutics. Stem Cells Dev 13: 436-448.

18. Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, et al. (2002) Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 418: 41-49.

19. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, et al. (1999) Multilineage potential of adult human mesenchymal stem cells. Science 284: 143-147.

20. Makino S, Fukuda K, Miyoshi S, Konishi F, Kodama H, et al. (1999) Cardiomyocytes can be generated from marrow stromal cells in vitro. J Clin Invest 103: 697-705.

21. Zhang S, Jia Z, Ge J, Gong L, Ma Y, et al. (2005) Purified Human Bone Marrow Multipotent Mesenchymal Stem Cells Regenerate Infarcted Myocardium in Experimental Rats. Cell transplantation 14: 787-798.

22. Henning RJ A-AH, Balis JU, Morgan MB, Willing AE, Sanberg PR (2004) Human umbilical cord blood mononuclear cells for the treatment of acute myocardial infarction. Cell Transplant 13: 729-39.

23. Cantero Peral S, Burkhart HM, Oommen S, Yamada S, Nyberg SL, et al. (2015) Safety and feasibility for pediatric cardiac regeneration using epicardial delivery of autologous umbilical cord blood-derived mononuclear cells established in a porcine model system. Stem cells translational medicine 4: 195-206.

24. Burkhart HM, Qureshi MY, Rossano JW, Cantero Peral S, O'Leary PW, et al. (2019) Autologous stem cell therapy for hypoplastic left heart syndrome: Safety and feasibility of intraoperative intramyocardial injections. J Thorac Cardiovasc Surg 158: 1614-1623.

25. Hierlihy AM, Seale P, Lobe CG, Rudnicki MA, Megeney LA (2002) The post-natal heart contains a myocardial stem cell population. FEBS letters 530: 239-243.

26. Messina E, De Angelis L, Frati G, Morrone S, Chimenti S, et al. (2004) Isolation and expansion of adult cardiac stem cells from human and murine heart. Circulation research 95: 911-921.

27. Smith RR, Barile L, Cho HC, Leppo MK, Hare JM, et al. (2007) Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens. Circulation 115: 896-908.

28. Tateishi K, Ashihara E, Honsho S, Takehara N, Nomura T, et al. (2007) Human cardiac stem cells exhibit mesenchymal features and are maintained through Akt/GSK-3beta signaling. Biochem Biophys Res Commun 352: 635-641.

29. Sanz-Ruiz R, Fernández-Avilés F (2018) Autologous and allogeneic cardiac stem cell therapy for cardiovascular diseases. Pharmacol Res 127: 92-100.

30. Ishigami S, Ohtsuki S, Tarui S, Ousaka D, Eitoku T, et al. (2015) Intracoronary autologous cardiac progenitor cell transfer in patients with hypoplastic left heart syndrome: the TICAP prospective phase 1 controlled trial. Circ Res 116: 653-664.

31. Ishigami S, Ohtsuki S, Eitoku T, Ousaka D, Kondo M, et al. (2017) Intracoronary Cardiac Progenitor Cells in Single Ventricle Physiology: The PERSEUS (Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease) Randomized Phase 2 Trial. Circ Res 120: 1162-1173.

32. Ishigami S, Sano T, Krishnapura S, Ito T, Sano S (2020) An overview of stem cell therapy for paediatric heart failure. Eur J Cardiothorac Surg 58: 881-887.

33. Rupp S, Bauer J, Tonn T, Schachinger V, Dimmeler S, et al. (2009) Intracoronary administration of autologous bone marrow-derived progenitor cells in a critically ill two-yr-old child with dilated cardiomyopathy. Pediatr Transplant 13: 620-623.

34. Tarui S, Ishigami S, Ousaka D, Kasahara S, Ohtsuki S, et al. (2015) Transcoronary infusion of cardiac progenitor cells in hypoplastic left heart syndrome: Three-year follow-up of the Transcoronary Infusion of Cardiac Progenitor Cells in Patients With Single-Ventricle Physiology (TICAP) trial. J Thorac Cardiovasc Surg 150: 1198-1207.

35. Sano T, Ousaka D, Goto T, Ishigami S, Hirai K, et al. (2018) Impact of Cardiac Progenitor Cells on Heart Failure and Survival in Single Ventricle Congenital Heart Disease. Circ Res 122: 994-1005.

36. Marban E (2018) A mechanistic roadmap for the clinical application of cardiac cell therapies. Nat Biomed Eng 2: 353-361.

37. Terrovitis JV, Smith RR, Marban E (2010) Assessment and optimization of cell engraftment after transplantation into the heart. Circ Res 106: 479-494.

38. Ichihara Y, Kaneko M, Yamahara K, Koulouroudias M, Sato N, et al. (2018) Self-assembling peptide hydrogel enables instant epicardial coating of the heart with mesenchymal stromal cells for the treatment of heart failure. Biomaterials 154: 12-23.

39. Sano T, Ito T, Ishigami S, Bandaru S, Sano S (2020) Intrinsic activation of cardiosphere-derived cells enhances myocardial repair. J Thorac Cardiovasc Surg.