

# [Heart elicits a domino effect health and social care essay](https://assignbuster.com/heart-elicits-a-domino-effect-health-and-social-care-essay/)

The complexity of the heart as an organ system as exhibited by the electrical, contractile and vascular rolesThe availability of an autologous cardiac progenitor cell population�Various cell therapies yielding positive results have been tried extensively in cardiovascular studies of smaller animals. It is expected that further successful large animal models and clinical trials may translate into approval for clinical utilisation. This essay concentrates on latest research in relation to humans and encompasses induced and endogenous origins of multipotent cells. IntroductionHeart failure is the most common sequela to myocardial impairments and persists as the fastest growing subclass of cardiovascular diseases (CVD) as well as a prominent menace in morbidity and mortality in the western world and a significant public health issue worldwide[1, 2]. Myocardial impairment may be hereditary, environmental, age-related, infection-initiated, trauma-initiated or a complex amalgamation of these factors but it is often accompanied with loss and deficient regeneration of cardiomyocytes. Conventionally, only symptoms of heart failures are managed therapeutically and although beneficial, they cannot revert the loss of cardiac tissue and restore effective functionality[3]. In severe cases, an organ transplant may be the sole therapeutic approach to salvage a patient. Sadly, donor organs are usually not readily obtainable and many a patient succumb to the condition while anticipating donor hearts. This prompted the need for a therapy to regenerate absent cardiomyocytes and potentially increase the quality of life and survival of patients in their millions yearly especially for diseases such as. The remarkable heart regeneration capacities in adult amphibian and fish species such as newts[4] and zebrafish[5] respectively are established as a consensus[6] (See Figure XXY) and studies in these species have greatly expanded the understanding of modern human cardiac developmental biology. In fact, the adult human heart was long held as a post-mitotic, non-regenerating organ until recently proven otherwise[7�10] that postnatal heart regeneration in humans occurs but is markedly narrowed to highly delayed cardiomyocyte replacement with age and in a normal human life span, <50% of cardiomyocytes are replaced[9]. Practically, regeneration at this rate are too low to repair injured myocaradium[11]. Figure XXY. Non-mammalian vertebrates exhibiting extensive cardiac regeneration. At the top is a representative mammalian injury model involving an ischemic myocardial infarct, yielding a focal damage in the left ventricular wall. This damage kills cardiomyocytes, which is supplanted by scar tissue (blue) over 60 days. The heart of the newt (middle) demonstrates a partial regenerative response after apical resection, healing the damage with new muscle (orange) and scar tissue. The heart of the zebrafish (bottom) regenerates a similar apical resection damage with diminutive or no scarring, replacing a significant segment of lost muscle in 60 days. Adapted from Poss 2007[12]. The concept of myocardial regeneration in the context of this essay is straightforward: stem or progenitor cells endogenously sequestered from the patient, expanded in vitro and introduced into the heart with the expectation to not only expand but also incorporate into integral cardiac myocytes and subsequently achieve the critical objective of myocardial regeneration �preventing or treating heart failure. This work examines�This essay�deliberates on�This work summarises up-to-date evidence of myocardial regeneration as a potential mainstream therapy for heart failure in humans based on endogenous cardiac progenitor cells (CPCs), induced pluripotent stem cells (iPSCs) and accompanying techniques as obtainable from clinical trials and other human-related studies. Recent data obtained from phase 1 clinical trials�Clinical trials were also considered�The efficacy and safety�Endogenous Cardiac Progenitor CellsEndogenous CPCs are cells resident in the foetal and adult human heart that were originally formed as intermediates in the course of differentiation of ESCs and can return to the cell cycle after injuries such as myocardial infarction. Currently, endogenous CPCs are isolated in the form of tyrosine-protein-kinase kit (c-kit) positive progenitors, cardiospheres-derived cells (CDCs), Islet-1 (Isl1) and a number of other markers depending on the surface marker transcription factors that they express (See table XXY). In vitro and in vivo, endogenous CPCs are multipotent, able to generate cardiomyocytes, vascular endothelial cells and smooth muscle cells as well as being self-renewing and clonogenic[13, 14]. Apart from the ethical issues that is circumvented due to the use of embryos being unnecessary, endogenous CPC and iPSC therapies also bypass the immunological challenges allied with engraftment such as graft-versus-host disease and transplant rejection. There is a conflict of nomenclature with regards to CPCs being accorded the �cardiac stem cell� nomenclature[15, 16], while endogenous CPCs are actually multipotent and can self-renew � qualities of a typical stem cell, their self-renewing capacity is limited. For the sake of distinction, this work considers endogenous CPCs as multipotent adult progenitor cells, being early progenies of pluripotent embryonic stem cells (ESCs). Figure XXY. Sources of cardiac progenitor cells (CPCs). Other sources of pluripotent stem cells can be expanded in vitro and differentiated into CPCs before subsequent differentiation into developed cardiac cell types. Abbreviations: PSC, parthenogenetic stem cell; SGSC, spermatogonial stem cell; iPS cell, induced pluripotent stem cell; ESC, embryonic stem cell. From Wollert and Drexler 2010[17]. Table XXY. Human cardiac progenitor cells (CPCs) and their markers used in isolation. CPCMarkerc-kit+ cardiac stem cells[18]Negative for: CD45, CD34, CD31, and KDRPositive for: c-kit+Vascular c-kit+ stem cells[19]Negative for: CD34, CD45, CD133, aSAPositive for: c-kit, KDR, low levels of CD31 and TGF-�1Myogenic c-kit+ stem cells[19]Negative for: CD34, CD45, CD133, a-SA, CD31, TGF-�1, KDRPositive for: c-kit, low levels of a-SABCRP+ side-population cells[20]Negative for: c-kit, CD31, Sca-1, Oct3/4, SSEA-3, SSEA-4Positive for: Nkx2. 5, aSAIsl1+ cardiac progenitors[21]Positive for: Isl1, c-kit (in foetus)Cardiospheres[22]Negative for: CD34, CD45Positive for: c-kit (core), CD31(periphery), CD90, CD105 (periphery), aMHC (periphery), cTnI (periphery), CD133 (periphery), MDR-1 (periphery), connexin 43, Nkx2. 5 (core), desmin (core)Cardiosphere-derived cells (CDCs)[23]Negative for: CD31, CD34, CD45, CD133Positive for: CD29, CD105, CD90low, c-kitlowMesangioblasts[24]Negative for: CD45, CD133, Isl1Positive for: CD31, CD34, CD44, ckit, CD146, nkx2. 5, GATA-4, MEF2A, Tbx2, Tbx5Abbreviations: c-kit, tyrosine-protein-kinase kit; CD, cluster of differentiation; KDR, kinase insert domain receptor; aSA, sarcomeric alpha actin; TGF-�1, transforming growth factor beta 1; BCRP, breast cancer-resistant protein; SSEA, stage-specific embryonic antigen; Isl1, Islet 1; MDR1, multidrug resistance protein 1; aMHC, alpha myosin heavy chain; cTnI, cardiac troponin I; Nkx2. 5, NK2 homeobox 5; GATA4, GATA-binding protein 4; MEF2A, myocyte enhancer factor 2A; Tbx, T-box. Adapted from Fuentes and Kearns-Jonker 2013[25]. CADUCEUSCADUCEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dySfunction) is a randomised phase 1 study with safety and efficacy end points aimed at testing the possibility of intracoronary injection of endogenous CPCs reducing infarct size and increasing myocardium size significantly[26]. The study involved 25 patients (17 treatment and 8 control) with ventricular dysfunction and was not blinded due to ethical concerns with regard to carrying out right ventricular (RV) biopsies on controls[27]. Introduced endogenous CPCs (CDCs; 25�106 maximum) were derived from the right ventricular (RV) endomyocardial biopsies carried out within the preceding 37days[26] and expanded in vitro. A one year follow-up of this trial presented no mortality, serious arrhythmia or myocardial infection while serious adverse events (SAE) were experienced by 24% of the treatment group and 12% in the control group (p was not statistically significant)[27, 28]. Also, a 12g (-12. 3%) decrease in scar mass, 22. 6g increase in viable hear mass, improved regional systolic wall thickening and regional contractility were also observed after one year follow-up[25, 28]. On the other hand, functional quantifications of end-systolic volume, end-diastolic volume and left ventricular ejection fraction (LVEF) were not significantly different between groups on follow-up[25, 28] (See Table XXY). This trial is an unprecedented study on the safety and efficacy of injection of CDCs as a class of CPC in humans. Result assessment by magnetic resonance imaging (MRI) also improved the significance of the study (See Figure XXX). Figure XXY. MRI indicating changes in scar size in randomly chosen participants in the treatment and control groups. A. Short-axis MRI of heart at baseline (82 days after myocardial infarction); B. 6 months after CDC infusion; C. Short-axis MRI of heart at baseline (77 days after myocardial infarction); D. After 6 months. Hyperintensity areas (white) represent infarct scar tissue (green arrows) while viable myocardium are dark. Abbreviations: MRI, magnetic resonance imaging; CDC, cardiosphere-derived cell. Adapted from Makkar et al. 2012[29]. SCIPIOSCIPIO (cardiac Stem Cell In Patients with Ischemic cardiomyopathy) is an open label, randomised phase 1 clinical trial with safety plus efficacy end points targeted at patients with level ventricular (LV) dysfunction and 33 patients (20 treatment and 13 control) were involved[16, 30]. Endogenous CPCs (c-kit+) were isolated from the right atrial appendage, expanded in vitro, extracted using magnetic beads, meticulously tested for capability to proliferate and absence of senility[16, 25]. Cells (106 = patients with large anterior infarcts and 0. 5�106 for patients with smaller posterior infarcts) were delivered into the heart during CABG surgery by intracoronary injections[16, 25]. (See table XXX for details). A two year follow-up reported no mortality or major SAE, LVEF increased (12% and 12. 1% by 3-D echo and MRI respectively) with an associated 12. 2% increase in left ventricular viable mass and infarct size decreased by 15. 7%[25, 27, 31]. In contrast, controls experienced no improvements[25, 27, 31]. Induced Pluripotent Stem CellsIPSCs ReprogrammingHybrid cell therapyALCADIAALCADIA (AutoLogous Human CArdiac-Derived Stem Cell to Treat Ischemic cArdiomyopathy) was a small, open label, non-randomised phase 1 clinical trial with safety and efficacy end points and the most preliminary among the clinical trials discussed[27, 32, 33]. ALCADIA involved six patients without controls and was directed at patients with ischemic cardiomyopathy as well as heart failure and utilised hybrid cell therapy by combining endogenous CPCs with controlled release of basic Fibroblast Growth Factor (bFGF)[27, 32, 33]. Endogenous CPCs (CDCs) were isolated by endomyocardial biopsies and expanded in vitro for about a month and delivered into the heart during coronary artery bypass graft (CABG) surgery by 20 intramyocardial injections (0. 5�106/kg). 200�g of bFGF contained in biodegradable gelatin hydrogel was then implanted on the epicardium over the injection sites regions[27]. Acute occlusion of a graft was encountered by one patient 3 weeks after CABG surgery and was excepted from subsequent assessment. Of the continuing five patients, one suffered a deteriorating heart failure event during the follow-up. No other serious adverse events (SAE) were experienced over a one year follow-up. Reports from a six-month follow-up showed that Left Ventricular Ejection Fraction (LVEF) had improved (9% and 12% by 3-D echo and MRI respectively), infarct volume had decreased (14. 4%), an associated wall motion score had decreased from 17. 2 to 6. 6 and remarkably, exercise ability was also enhanced as observed by an increase in maximum consumption of O2 (12. 2 to 16. 7)[27, 32, 33] (See table XXY for other details). While no serious safety concerns were raised and hybrid cell therapy can be said to be safe at this stage, due to the absence of a control group, inferences about the efficacy of this hybrid approach utilised in this trial can�t be deduced until further comparisons are established. Phase 1 clinical trials Safety and efficacy of�were established�Delivery strategiesIntracoronary infusionHost responseSelf-renewal potentialLimitationsBefore this therapies go mainstream, some limitations need to be surmounted. Currently, a major challenge is how to obtain endogenous CPCs without yielding morbidity or mortality in patients. Future outlooksConclusionSummarise your points, state main conclusions. Don�t include any new information.