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# Cardiac Tissue Engineering Therapeutic Products to Enhance Myocardial Contractility

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## Abstract

Researchers continue to develop therapeutic products for the repair and replacement of myocardial tissue that demonstrates contractility equivalent to normal physiologic states. As clinical trials focused on pure adult stem cell populations undergo meta-analysis for preclinical through clinical design, the field of tissue engineering is emerging as a new clinical frontier to repair the myocardium and improve cardiac output. This review will first discuss the three primary tissue engineering product themes that are advancing in preclinical to clinical models: 1) cell-free scaffolds, 2) scaffold-free cellular, and 3) hybrid cell and scaffold products. The review will then focus on the products that have advanced from preclinical models to clinical trials. In advancing the cardiac regenerative medicine field, long-term gains towards discovering an optimal product to generate functional myocardial tissue and eliminate heart failure may be achieved.

### Keywords

tissue engineering; heart failure; therapies; clinical trials

## Introduction

The cardiovascular research community continues to expand in basic science and clinical application to understand the causes of heart disease, maintenance of healthy functional myocardial tissue and approaches to repair and rebuild the heart in response to aging and disease. The challenge of generating functional cardiac tissue continues as results from stem cell trials yielded modest functional improvement. Some of the challenges faced in cardiac regenerative medicine include the general nature of heart failure represented as a geriatric disease(Uchmanowicz et al. 2019), the frequency of diagnosed comorbidities in patients with heart failure(Mentz et al. 2014), and the disconnect in earlier studies involving preclinical animal models compared to the patient population requiring treatment(Grigorian Shamagian et al. 2019). Lessons learned from completed clinical studies for cardiac repair



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and regeneration must be taken into account when developing future potential therapeutics and holds particularly true for researchers that create more complicated products and collaborative research teams.

Cellular therapies for the treatment of heart failure emerged into the clinic in the early 2000's with adult stem cells. Adult stem cells are considered multipotent with the ability to commit to a limited number of cellular lineages and typically cover: mononuclear and bone marrow (stem) cells, mesenchymal stem cells derived from bone marrow or the heart, cardiac stem / progenitor cells, and cardiospheres (Broughton and Sussman 2016; Sanganalmath and Bolli 2013; Telukuntla et al. 2013). Mechanisms of action encompass anti-fibrotic effects, immunomodulation allowing for allografting, neovascularization, stimulation of endogenous repair and blunting of adverse remodeling; functional assessments have typically included free wall thickness, ventricle volume load, ejection fraction and cardiac output (Bagno et al. 2018; Broughton and Sussman 2018; Golpanian et al. 2016b). Current adult stem cell clinical trials for cardiac improvement include: *DREAM-HF* that uses allogeneic mesenchymal precursor cells (clinicaltrials.gov NCT02032004), *ELPIS* that uses allogeneic bone marrow-derived mesenchymal stem cells (clinicaltrials.gov NCT03525418) and *CONCERT-HF* that uses mesenchymal and c-kit+ stem cells in a combinatory fashion. Meta-analysis is ongoing to determine patient population characteristics associated with better functional improvement to improve future clinical design, such as different outcomes in patients with dilated, compared to ischemic, cardiomyopathy. Researchers are beginning to look to pluripotent products as well as more complex products utilizing bioengineering approaches for future directions in the field of cellular therapies for the treatment of heart disease.

Bioengineering, specifically cell and tissue engineering, is the integration of engineering and biological approaches to understand the structure-function relationship of physiologic and pathophysiologic dysfunctional tissue and the development of biological substitutes to maintain, restore or improve tissue function. Tissue engineering continues to expand as a scientific platform to advance cardiac regenerative medicine. Three platforms can define cardiac tissue engineering products: (1) cell-free scaffold approaches, (2) scaffold-free cellular approaches, and (3) cell plus scaffold hybrid approaches(Tomov et al. 2019). Each platform approach encompasses multiple research directions and products and has demonstrated varying levels of success to advance therapeutic products to the clinic, based on the products' strengths and weaknesses (Figure 1). The goal of each research direction is to reestablish a healthy structure and function within the failing myocardium.

This review will first discuss in detail these three primary cardiac tissue engineering approaches with a focus on preclinical models. Discussions will focus on approaches with products that can advance to the clinic, and will not include approaches or platforms used for basic scientific discovery or disease modeling, such as organ-on-a-chip(Ahadian et al. 2018; An et al. 2015) or BioMEMS devices (Broughton and Russell 2015; Roberts et al. 2019; Serpooshan et al. 2017). The review will then discuss tissue engineering products that have advanced to the clinic. A discussion will compare clinical results involving adult stem cells as compared to clinical trials that utilized tissue engineering approaches for the repair and regeneration of the failing myocardium. By utilizing multi-disciplinary techniques, the field

of cardiac regenerative medicine may continue to advance research strategies forward towards genuine repair of the myocardium and increased functional activity within the heart.

## Cardiac Tissue Engineering Products in Preclinical Models

Tissue engineering may encompass several experimental research topics as applied to basic cardiovascular research such as biological microelectromechanical systems (BioMEMS) to study the mechanical or electrical activity of cardiomyocytes(Akintewe et al. 2017; Tandon et al. 2009), microfluidics for mimicking and studying the vascularization and angiogenesis(Chen and Kaji 2017), or the collective heart-on-a-chip system for predictive modeling of drug screening towards personalized medicine initiatives(Conant et al. 2017). Although ex vivo modeling remains a useful area of cardiac research, this review will focus on devices and drugs that are applicable as cardiac reparative therapeutics with the potential to directly improve cardiac function in patient populations.

The Food and Drug Administration (FDA) classification of cardiac regenerative products is a drug, device, biological product, or combination product in the Federal Food, Drug and Cosmetic Act (FD&C Act). Part 1271 of the Code of Federal Regulations Title 21 provides guidelines specific to regenerative products in the body, with a practical guideline for industry(Administration 2007). Cardiac tissue engineering products are highly complex and require FDA review on a case-by-case basis with many different variables considered in the collective to define the product for FDA regulation and oversight. Three primary platforms are identified as cardiac tissue engineering approaches to repair and regenerate the failing myocardium and discussed from a preclinical standpoint.

## Cell-free scaffold products

Mimicking replacement cardiac extracellular matrix (ECM) is one tissue engineering approach that may rejuvenate the myocardium and improve contractility. Cardiac ECM undergoes a gradual assembly of matrix proteins during the maturation of cardiomyocytes (CMs) during development(Schwach and Passier 2019). As the CMs develop, both electric coupling and mechanical anchorage and elasticity integrate within the ECM in addition to cellular communication, migration, proliferation, maturation, and differentiation of the surrounding cardiac interstitial cells (CICs). In the adult heart, elastin fibers, including collagens I, III, IV and VI, fibrillin, fibronectin, and laminin are expressed in various patterns, ratios, and abundance among the four chambers(Schwach and Passier 2019). For example, collagen fibrils are thick near the heart base near atrioventricular valves, with declines in thickness towards the apex(Jackson et al. 1993). Collagen I and III are more abundant in the atria, compared to the ventricles, and more abundant in the right, compared to left, ventricle, which may result from the pressure differential between the chambers(Oken and Boucek 1957; Smorodinova et al. 2015). Matrix changes are associated with aging(Dworatzek et al. 2016; Horn 2015; Meschiari et al. 2017) and disease(Frangogiannis 2017), particularly an increase of collagen deposition and cross-linking resulting in loss of elasticity and increased stiffness. Scaffold replacement therapeutic approaches target the replacement of inelastic, stiff ECM.

Several natural and synthetic polymers are available for ECM constructs. Natural polymers include gelatin, matrigel, fibrin, vitronectin, hyaluronic acid, and alginate, while FDA-approved synthetic polymers are more numerous and classified under the categories of polyesters, polylactones, elastomers, and polyethers(Schwach and Passier 2019). Natural materials have better biocompatibility and construction capability to mimic endogenous tissue compared to synthetic. Weaknesses of using natural materials include batch variability, limited shelf-life, and higher cost to manufacture compared to synthetic materials. Synthetic polymers have the additional feature of tunable mechanical and degradation properties, which is fundamental when considering the optimum ECM tissue reconstruction requiring durability, conductivity, and elasticity. Tissue engineering approaches to recreate healthy ECM have pursued both natural and synthetic approaches in preclinical studies towards repairing the dysfunctional myocardium.

A natural ECM approach utilizes an endogenous donor tissue. Repopulating decellularized native tissue begins with the removal of cells from intact tissue and using the allogeneic scaffold, with preserved architecture and mechanical properties, for repopulation with autologous cells(Ott et al. 2008; Robinson et al. 2005). The experimental model of a decellularized rat heart with reseeded cardiomyocytes and endothelial cells demonstrated contractile properties, but not nearly sufficient to serve as functionally normal(Ott et al. 2008). The benefit of this approach is the native extracellular matrix composition, which allows for the natural vascular network and exchange of nutrients, paracrine factors, and oxygen throughout the tissue. Additional research regarding pulse synchronization, creation of cardiac patches through native scaffolds, and mimicking native tissue for synthetic tissue creation are all opportunities using this methodology.

Synthetic porous scaffolds that cells can populate are created using a biomimetic approach with scaffolds that allow for oxygen diffusion as well as culture medium and the necessary biochemical reactions found in healthy native tissue(Engelmayr et al. 2008; Radisic et al. 2006). Researchers have been able to mimic the level of oxygen content in culture medium using perfluorocarbon(Radisic et al. 2005), which has enabled for viable scaffolds millimeters-thick with physiologic-like cellular density and response to electrical stimulation(Radisic et al. 2005; Radisic et al. 2006). Biomaterials, including hydrogels and elastomers, can create scaffolds of various porosity and stiffness(Kolewe et al. 2013; Lu et al. 2004; Shin et al. 2013). Research continues with understanding how to better develop and integrate porous scaffolds into healthy, functional myocardium with such research as electrical conduction(Martins et al. 2014), biodegradable scaffolds(Bobe et al. 2013), electro-spun nanofibers(Kai et al. 2013; Qasim et al. 2019), 3D printed scaffolds(Gaetani et al. 2012; Qasim et al. 2019), and the use of adult stem cells(Gaetani et al. 2012; Pagliari et al. 2014; Rajabi-Zeleti et al. 2014).

## Scaffold-free cellular products

One of the most direct methods explored for replacing damaged cardiac tissue with healthy, functional tissue was with the transplantation of cardiomyocytes or muscle cells. In this method using myocytes, cultured allogeneic cardiomyocytes are transplanted into damaged scar tissue region and embed into the endogenous tissue. Researchers have studied the

feasibility of this method using a four-week-old cryoinjury heart model in adult male Sprague-Dawley rats with the transplantation of cardiomyocytes from fetal Sprague-Dawley rat hearts(Li et al. 1996). Results assessed four weeks after transplantation included a smaller scar size (43%) in the treatment group compared to control (55%) and the transplanted cardiomyocytes had successfully embedded and formed cardiac tissue within the scar tissue. A similar study using female adult Sprague-Dawley rats with a left coronary artery occlusion, causing MI and the transplantation of 14–15 day old embryonic rat cardiomyocytes, cultured for three days, was conducted seven days post-MI(Etzion et al. 2001). Cardiac function and cellular engraftment were measured approximately two months after transplantation; findings revealed most embryonic cardiomyocytes did not engraft into the host myocardium, but better left ventricular contractility resulted in the rats with transplanted cardiomyocytes compared to control rats.

Another study using neonatal cardiomyocyte transplantation into adult rats found that nearly half of the cardiomyocytes did not survive the initial transplantation and that, by twelve weeks, only fifteen percent of the cells remained engrafted(Muller-Ehmsen et al. 2002). Findings also revealed that surviving neonate cardiomyocytes transplanted developed visible sarcomeres, which may have aided in ventricular function in the experimental group compared to controls. Although transplantation of neonatal cardiomyocytes was studied in preclinical models using rodents, this method is now expanding to examine the use of human induced pluripotent stem cells derived cardiomyocytes (hIPSC-CMs)(Ishida et al. 2019). Currently, one clinical trial utilizing hIPSC-CM is registered (clinicaltrials.gov, NCT03763136) *Treating Heart Failure with hIPSC-CMs (HEAL-CHF), which is an open-label Phase I trial and is planned to treat five ischemic cardiomyopathy heart failure patients. This trial is estimated to run from May 2019 till December 2020.*

Scaffold-free cellular sheets is another cellular engineering approach to improve cardiac function, which begins with monolayers of cells cultured on temperature-sensitive polymer surfaces that detach from the surface without enzymes(Shimizu et al. 2002; Shimizu et al. 2003). The monolayers are then stacked, and the cells form junctions, establish signal propagation, and develop contractile properties. Research has also shown the development of microvascular networks through the use of endothelial cellular sheets(Sekiya et al. 2006). The cell type employed in developing scaffold-free cellular sheets for cardiac regeneration has spanned from cardiomyocytes to endothelial cell(Sekiya et al. 2006; Shimizu et al. 2002; Shimizu et al. 2003) to myoblast (Memon et al. 2005), adult stem cells(Miyahara et al. 2006; Wang et al. 2008), pluripotent(Masumoto et al. 2012), and embryonic stem cells(Matsuura et al. 2011; Stevens et al. 2009). Scaffold-free cellular sheets remain under investigation for electrical synchronization, survival, and integration into natural tissue.

Self-assembling cellular clusters is a more recent approach, which expands the concept of scaffold-free cellular sheets. In this combinatory cell approach, cell combinations can be selectively chosen and optimized for the number of cells, type of cells, and self-assembly method to control the size and architecture of the cluster. The benefit of using a self-assembled cellular structure is enhanced engraftment and persistence after injection. One reason these cells may perform superior to single-cell injection is the biological properties returning to a more endogenous state after self-assembly rather than modified profile cells

experience upon typical culture conditions(Kim et al. 2018). The second benefit of cellular clusters is the potential to use an autologous cellular approach(Monsanto et al. 2017) and minimize an autoimmune response.

Scaffold-free cellular approach and cellular-free scaffold approach both demonstrate strengths and weaknesses (Figure 1). As it remains challenging for measurable cardiac repair and regeneration in mammalian models, the hybrid approach of using cells plus scaffolds remains a reasonable direction to enhance tissue engineering therapeutics.

## Hybrid cell plus scaffold products

Products utilizing the benefits from both cellular and scaffold platforms can advance a more complex but delicately tuned product. Natural scaffold products combined with autologous cells may experience the least immune response.

The product design of cells with scaffold may provide a needed balance to improve vascularization, preserve myocardial muscle tissue, and reduce fibrous tissue inhibiting contractility and cardiac output. 3D multiphoton-excited (3D-MPE) advances the use of conventional 3D printing technique printing to better mimic natural tissue with ECM architecture at more natural sizes(Gao et al. 2017). In this design, the 3D-MPE ECM was created using gelatin methacrylate and crosslinked to mimic fibronectin. Human cardiac fibroblasts were reprogrammed into pluripotent stem cells then differentiated into cardiomyocytes, smooth muscle cells, and endothelial cells before seeding onto the 3D-MPE ECM. These human cardiac muscle patches (hCMPs) were then tested on adult mice with surgically induced myocardial infarction and measured for cardiac function, vascularization, and scar size, among other parameters at one and four weeks after treatment. Results demonstrated an engraftment rate of 24% at one week and 11% by four weeks and a slightly improved ejection fraction and fractional shortening between one- and four-weeks post-MI in the hCMP group compared to sham or scaffold-alone. An alternative to 3D printing, polymer cast constructions can also be used to create ECM and a cardiac patch.

Hydrogel rings are designed with cells, such as neonate cardiomyocytes, liquid type I collagen, matrigel, and growth supplements, which collectively set in a circular mold(Zimmermann et al. 2006; Zimmermann et al. 2002). After the hydrogel sets, the rings are then mechanically stimulated to develop the neonate cardiomyocytes into more matured cardiac cells with increased force contractility and mitochondrial density. The rings can be adhered to each other in a layered approach and engrafted into host tissue, as shown with neonate rat ventricular myocytes onto a rat heart, post-myocardial infarction(Zimmermann et al. 2006). Results indicated no electrical signal delay on the engrafted rings without arrhythmia as well as improved ventricular wall thickening in the infarct region of the heart. Cardiac patches have incorporated human dermal fibroblast sheets with co-cultured MSCs and endothelial cells(Qian et al. 2019), collagen/alginate-chitosan scaffolds with human umbilical vein endothelial cells(Zhang et al. 2017), microgroove collagen scaffolds with myoblasts(Chen et al. 2015) and porous polyglycerol sebacate (PGS) with endothelial cells(Maidhof et al. 2010). Further understandings of the engraftment, use of alternative

cells, and comparison of cast patches to other hybrid tissue engineering products or cardiac cellular therapeutics will assist in determining substantive benefit.

Injectable, biodegradable hydrogels with cells is another approach in cardiovascular regeneration approaches. This method is closely related to biological approaches discussed below, which also focuses on the injection of suspended cells. The unique tissue engineering approach, however, is suspending the cells in a matrix, which may improve the engraftment, survival, and persistence of the injected cells. Researchers are currently investigating how to match hydrogel to patient profiles in an autologous fashion to improve immune compatibility(Edri et al. 2019). Hydrogels are utilized to suspend cells in a position that increases engraftment and survival while contributing to improving functional activity in the myocardium post-injection(Christman et al. 2004; Li et al. 2015; Malafaya et al. 2007; Martens et al. 2009; Nicodemus and Bryant 2008; Zhang et al. 2019). Research on how to improve products to increase cellular engraftment, survival, and contractility of damaged myocardium continues to be a challenge for the bioengineering research community.

## Cardiac Tissue Engineering Products Advancing to the Clinic

Clinical trials using cellular therapies for cardiac repair have advanced over the past twenty years, as discussed in many reviews(Broughton and Sussman 2016; Sanganalmath and Bolli 2013; Telukuntla et al. 2013). Functional outcomes have demonstrated modest improvements, however, and researchers are reflecting upon the preclinical model design(Grigorian Shamagian et al. 2019), the elaborate medical complications of the human patient population with heart failure(Broughton 2019), and future strategies to improve cardiac cellular therapies in the clinic(Golpanian et al. 2016a; Vrtovec and Bolli 2019). One strategy which may improve functional outcomes is the use of tissue engineering strategies and products. Preclinical models using tissue engineering-based products have demonstrated varying levels of advancement and success. Most of the products that have advanced into the clinic are hybrid cells plus scaffold products and are Phase I clinical trials.

One of the earliest tissue engineering-based cardiac clinical trials focused on pediatric patients with univentricular physiology. In this USA-based trial (clinicaltrials.gov NCT01034007), patients underwent implantation of tissue-engineered vascular grafts (TEVGs) seeded with autologous bone marrow mononuclear cells(Hibino et al. 2010; Sugiura et al. 2018). The TEVGs were composed of fabric poly-l-lactide acid or polyglycolic acid and a 50:50 poly (l-lactic-co-ɛ-caprolactone copolymer. The average patient age was 5.5 years old, and the average follow-up period was 11.1 years in 25 patients(Sugiura et al. 2018). Results demonstrated that seven patients (28%) had graft stenosis requiring balloon angioplasty and one patient (4%) having graft thrombosis requiring anticoagulation therapy after implantation and no graft-related deaths. This trial was the first TEVG study in humans and demonstrated feasibility, safety, and the potential for long-term implantation success. The challenge with many heart failure patients is older age and lack of sufficient ventricular contractile function.

Another early tissue engineering-based cardiac clinical trial was aimed to determine if a bioabsorbable cardiac matrix (BCM) would attenuate left ventricular remodeling after a

large myocardial infarction. This study, *A Placebo Controlled, Multicenter, Randomized Double Blind Trial to Evaluate the Safety and Effectiveness of IK-5001 for the Prevention of Remodeling of the Ventricle and Congestive Heart Failure After Acute Myocardial Infarction* (clinicaltrials.gov NCT01226563; PRESERVATION I), focused on a device that replaces the damaged ECM and halt the remodeling process following acute MI(Frey et al. 2014; Rao et al. 2016). The product was an injectable bioabsorbable alginate, which was to provide temporary structural support in the infarction region by cross-linking to reduce myocyte death and reduce remodeling. The BCM product degrades and is naturally excreted in three to six months post-injection. Results demonstrated no significant difference in left ventricular end diastolic volume between baseline and six months after treatment. These results demonstrated the challenge in a successful small study(Frey et al. 2014) followed by less successful outcomes when upscaling the patient population, surgical intervention team and follow-up care (Rao et al. 2016).

The Phase I clinical trial *Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure (ESCORT)* (clinicaltrials.gov NCT02057900), focused on the treatment of ischemic cardiomyopathy heart failure and utilized a fibrin patch seeded with human embryonic stem cell-derived stage-specific embryonic antigen (SSEA)-1 positive, Insulin gene enhancer protein ISL-1 positive cardiac progenitors (Menasche et al. 2018). In this study, six patients with median age 66.5 and left ventricular ejection fraction(LVEF) of 26% received a median dose of 8.2 million hESC-derived cardiac progenitors embedded in a fibrin patch and epicardially delivered during a coronary artery bypass procedure. On average 1.5 years after surgery, no tumors were detected, and no patients presented arrhythmias. One patient died from unrelated comorbidities early postoperatively, and one patient died of heart failure twenty-two months after treatment (81 years old at the time of surgery). The remaining four patients demonstrated a decrease in New York Heart Association function class from a baseline value of III to I/II and an increase in LVEF from 26% to 38.5% by the 1-year follow-up. Although this trial had a relatively small patient population, the trial demonstrated the technical feasibility and short- and medium-term safety points after transplant. As this is the first clinical study involving a fibrin patch with seeded cells, it is yet to be determined if the patch, cell-choice or the hybrid combination contributed to the reported 12.5% LVEF functional improvement.

Multiple tissue-engineering based clinical Phase I or Phase I/II trials are reported on clinicaltrials.gov, all of which utilize hybrid products (Table 1). A study based in China, *Human Umbilical Cord-derived Mesenchymal Stem Cells With Injectable Collagen Scaffold Transplantation for Chronic Ischemic Cardiomyopathy* (clinicaltrials.gov NCT02635464), is scheduled from October 2015 – December 2019 with an enrollment estimate of 45 patients diagnosed with ischemic cardiomyopathy. Another study, *Pericardial Matrix With Mesenchymal Stem Cells for the Treatment of Patients With Infarcted Myocardial Tissue (PERISCOPE)* (clinicaltrials.gov NCT03798353), is a Phase I trial, based in Spain, with an estimated enrollment of 12 patients with a history of myocardial infarction. Another planned trial is based out of Columbia and expected to run from July 2019 to June 2023. This trial, *Randomized Study of Coronary Revascularization Surgery With Injection of WJ-MSCs and Placement of an Epicardial Extracellular Matrix (scorem-cells)* (clinicaltrials.gov NCT04011059), is a Phase I/II trial with an estimated enrollment of 40 patients, all with

history of myocardial infarction. Each trial utilizes a hybrid tissue engineering product, composed of a natural scaffold material combined with stem cell treatment. Parallel to completed stem cell cardiac clinical trials, the complex medical conditions of the patients may hinder functional improvements. However, a fundamental difference in the use of a scaffold plus cellular therapeutic may demonstrate an increased performance of myocardial repair, decreased scar tissue, and improved cardiac output. It is in the outcomes of these trials that researchers will have a better understanding of specific scaffold materials or cellular therapeutics yield superior results, compared to prior trials, and give hope to future studies.

## Discussion

The development of a robust cellular therapeutic for the repair of cardiac muscle remains a challenge in the cardiovascular community. Researchers have demonstrated the potential of cellular therapeutics to improve vascularization in the myocardium, reduce scar tissue, and increase the free wall thickness. These changes are essential to reduce environmental stress upon the heart and increase endogenous repair. However, the fundamental aspect of the generation of new cardiomyocytes remains a primary hurdle to increase contractility and return cardiac output to a normal physiologic state.

Researchers have repeatedly demonstrated cardiomyocyte turnover, and new myocyte generation in adult mammalian hearts occurs at a painstakingly low frequency(Ali et al. 2014; Bergmann et al. 2015; Senyo et al. 2013), and is not sufficient to endogenously repair the functionally failing myocardium with new cardiac muscle. Evidence also supports the point that using cell cycle factors to encourage reentry into cell-cycle does not lead to generation of new myocytes(Liu et al. 2010; Ponnusamy et al. 2017). As shown in mouse models, environmental stress leads to an increase in cell-cycle activity in myocytes(Alvarez et al. 2019; Patterson et al. 2017; Ponnusamy et al. 2017). Adult mouse myocytes complete karyokinesis but fail to symmetrically divide with incomplete cytokinesis(Hesse et al. 2018; Leone et al. 2018), resulting in an increased frequency of binucleation. Human myocytes are even more challenged, compared to the mouse model, as adult myocytes from the failing myocardium are frequently mononuclear with higher levels of chromosomal content(Herget et al. 1997), demonstrating human myocytes undergo DNA synthesis, fail karyokinesis and do not attempt cytokinesis. These challenges in endogenous cardiomyocyte division, therefore, require researchers to design products that enhance the replacement of scar tissue with functional muscle.

Since the discovery of induced pluripotent stem cells and derivation to cardiomyocytes, the potential of these cells has brought new hope as a therapeutic option. Researchers have continued to improve the efficiency of inducing committed cells to stem cells as well as enhanced the maturation and functional characteristics of the iPSC-CM(Pianezzi et al. 2019; Ronaldson-Bouchard et al. 2018; Waas et al. 2019). The use of iPSC-CMs as a therapeutic product for the treatment of heart failure may demonstrate improved contractility beyond enhancement found in clinical trials using adult stem cells.

Enhancing adult stem cell products, such as self-assembling cellular clusters, may demonstrate better effectiveness for engraftment and survival(Broughton and Sussman 2018) to enrich the paracrine activity identified as a crucial element to the effectiveness of the intervention. Likewise, stackable cellular sheets may provide structural integrity for the myocardium to increase contractility(Kaynak Bayrak and Gumusderelioglu 2019; Roberts et al. 2019). Alternatively, cell-free scaffolds may provide the necessary structure for cellular integration(Becker et al. 2018; Jang et al. 2017), with ongoing studies to determine improvement in functional myocardium. The combinatorial approach of a scaffold plus cellular component may demonstrate the benefits of both elements (Figure 1) as these hybrid products are more frequently advancing to the clinic (Table 1). Results from the ESCORT trial, for example, have demonstrated enhanced functional activity of the myocardium by a year after transplant(Menasche et al. 2018). Mechanisms of improvement may be from structural integrity of the patch or paracrine and secretome from the hESC-derived cardiac progenitors triggering cell-cell communication and activation. This study, although promising, requires expansion to a broader patient population as five patients is too small of a patient sample size to demonstrate myocardial functional enhancement beyond studies previously conducted using single cell or combinatory cell approaches.

As cardiac regenerative medicine studies continue onward, a primary goal should remain focused upon the generation of products that will enhance functional myocardial muscle. The methodology of tissue engineering incorporates structural, mechanical and electrical in scaffolds, biological and chemical in cellular and a blend in hybrid products. Future experiments may also incorporate the combinatorial approach of pluripotent-derived cells with cells or exosome product that promote paracrine effects, such as iPSC-CMs with MSCs or cardiac stem cells. The upcoming shift in cardiac clinical trials focused on the use of tissue engineering products should be viewed as the ongoing quest of the research community to discover and unbiasedly evaluate ways in which heart failure may become a curable disease of the past.

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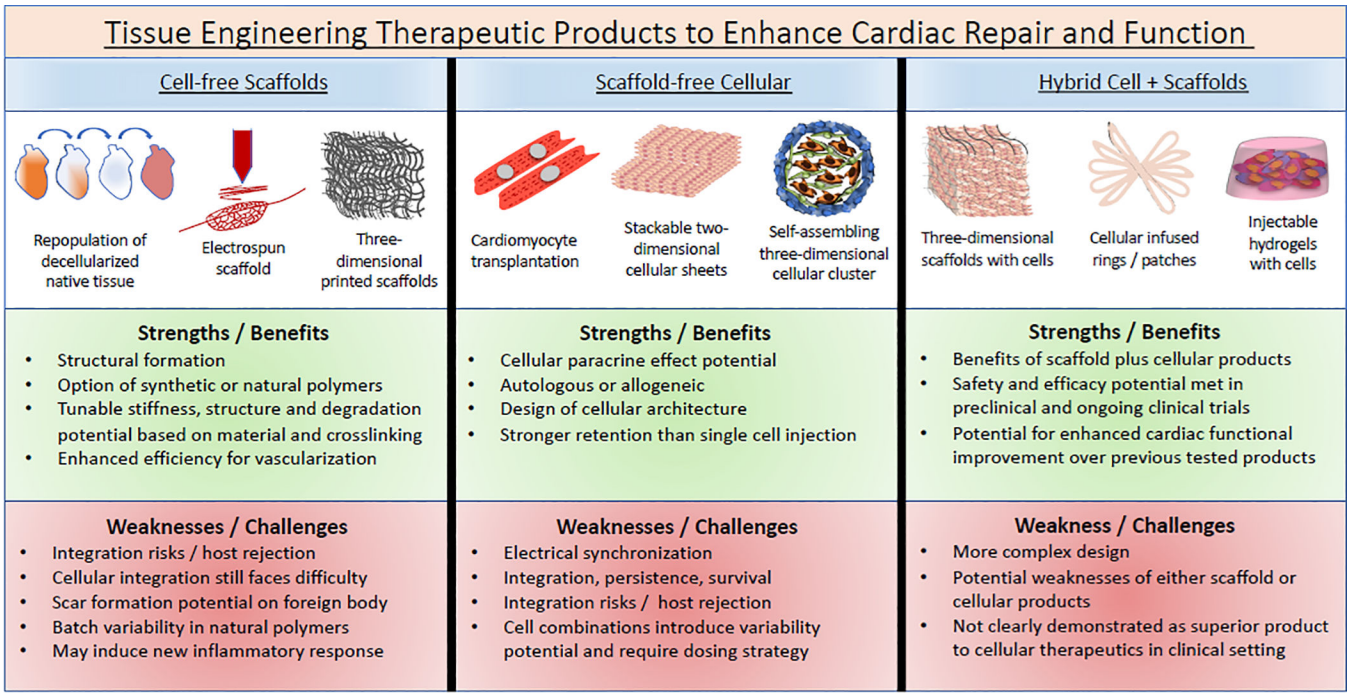


**Figure 1:**

Tissue Engineering Therapeutic Products to Enhance Cardiac Repair and Function. Tissue engineering based products can be categorized in three primary categories, each category of products demonstrating strengths and weaknesses towards cardiac repair and improving physiologic function in the failing myocardium.

**Table 1**

Cardiac Tissue Engineering-Based Products in the Clinic

| Trial Number | Trial Name | Clinical Trial Phase | Patient Enrollment | Disease | Therapeutic Strategy | Country | Reference |
|---|---|---|---|---|---|---|---|
| NCT01034007 | A Pilot Study Investigating the Clinical Use of Tissue Engineered Vascular Grafts in Congenital Heart Surgery | Phase I; start / completion: Dec 2009 - Dec 2017 | 4 patients | Single Ventricle Cardiac Anomaly | Tissue engineered vascular grafts seeded with autologous bone-marrow mononuclear cells | USA | Hibino et al. 2010; Sugiura et al. 2018 |
| NCT01226563 | IK-5001 for the Prevention of Remodeling of the Ventricle and Congestive Heart Failure After Acute Myocardial Infarction (PRESERVATION-1) | Multi-center; start / completion: Apr 2012 - Dec 2015 | 303 patients; 201 treated | Myocardial Infarction before onset of adverse remodeling | Bioabsorbable cardiac matrix for reducing adverse LV remodeling | USA / multi-country | Frey et al. 2014; Rao et al. 2016 |
| NCT02057900 | Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure (ESCORT) | Phase I; start / completion: May 2013 - Mar 2018 | 10 enrolled | Ischemic Cardiomyopathy HF | ESCs in fibrin patch | France | Menasche et al. 2018 |
| NCT02635464 | Human Umbilical Cord-derived Mesenchymal Stem Cells With Injectable Collagen Scaffold Transplantation for Chronic Ischemic Cardiomyopathy | Phase I/II; start / completion: Oct 2015 - Dec 2019 | 45 (estimate) | Ischemic Cardiomyopathy | human umbilical cord-derived MSCs with collagen scaffold injection | China | |
| NCT03798353 | Pericardial Matrix With Mesenchymal Stem Cells for the Treatment of Patients With Infarcted Myocardial Tissue (PERISCOPE) | Phase I; expected start / completion: May 2019 - May 2021 | 12 (estimated) | Myocardial Infarction | PeriCord: Expanded and cryopreserved allogeneic umbilical cord Wharton's jelly-derived adult mesenchymal stem cells colonized on human pericardial matrix. | Spain | |
| NCT04011059 | Randomized Study of Coronary Revascularization Surgery With Injection of WJ-MSCs and Placement of an Epicardial Extracellular Matrix (scorem-cells) | Phase I/II; start / completion: July 2019 - Jun 2023 | 40 (estimated) | Previous myocardial infarction | ECM patch seeded with Wharton's jelly-derived MSCs (WJ-MSCs) isolated from human umbillical cord plus injection of WJ-MSCs | Columbia | |