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Novel Biological Therapies Targeting Heart Failure: Myocardial Rejuvenation

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Article synopsis

Recovery of ventricular function occurs in a subset of patients with advanced heart failure treated with medical and/or mechanical therapy. Finding strategies that induce ventricular recovery through induction of repair, regeneration of ‘rejuvenation’ is a long sought goal of research programs. Cell-based strategies, use of recombinant growth and survival factors, and gene delivery are under investigation. In this brief review we highlight a few of the biological approaches in development to treat heart failure.

Keywords

Heart failure; rejuvenation; cell therapy; gene therapy

Introduction

‘The great man is he who does not lose his child-like heart’ – Mencius, Confucian Philosopher, ca 300 BC

Cardiovascular disease (CVD) is the leading cause of death across the globe accounting for 17.3 million deaths per year¹. In the United States, >1 in 3 adults suffer from some form of cardiovascular disease (85.6 million people) with 15.5 million experiencing coronary heart disease (CHD)¹. Among the types of CHD, 5.7 million people have heart failure (HF)¹. These statistics highlight the epidemic that is continually growing among the global population. Current therapies for heart failure with reduced ejection fraction (HFrEF) focus on preserving left ventricular function as well as restoring cardiac function through the use of mechanical circulatory support devices or in select patients heart transplant. The enormous growth in our understanding of heart biology as well as pathobiology leading to heart failure over the past several decades promises novel therapeutic approaches that will harness this biology to restore heart function.

Myocardial regeneration to some is the ‘holy grail’ of heart failure translational research. Organ regeneration is an ancient concept. One of the most well-known stories of organ

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regeneration dates back to Greek mythology, where the Titan Prometheus, as punishment for deceiving Zeus, was forever chained to a rock where an eagle came each day to dine on his liver. Each evening his liver regenerated, whereupon the next day the eagle returned to continue its punishment. It is now well known that the adult liver indeed has remarkable regenerative potential, as does the bone marrow. The regenerative potential of the heart has also been recently established, at least in lower vertebrates and young mammals^{2,3}. When the chest of a young zebrafish or mouse is carefully opened, and the apical segment of the ventricular myocardium is clipped away, some organisms will survive through a process of growing new myocardium in its place. This process involved mesenchymal stem cells proliferating and differentiating in an organized way to replace the missing heart muscle in young animals. It is well-known that the adult heart throughout life responds to injury and stress with activated expression of genes involved in cardiac development, the so-called fetal gene program. In addition both mesenchymal and bone marrow derived progenitor cells are activated by cardiac injury. And yet these processes are inadequate to restore heart function. Therapeutic approaches that manipulate these signals and processes are the cornerstone of biologic therapies for heart failure.

Based upon the ancient wisdom of the Confucian scholar, the “Mencius Paradigm” is a term we have coined to characterize the hypothesis that biologic signals and processes critical for cardiac development might be manipulated to improve adult heart function. In this context we propose that the term myocardial ‘rejuvenation’, rather than ‘regeneration’, is a more realistic outcome of these clinically motivated translational research efforts. In this brief review we describe the state of a number of approaches at various stages of development using biologics, many of which fit the Mencius Paradigm.

Cell-based therapies for HFrEF—Developmental biology research has created detailed knowledge over how pluripotent cell lineages differentiate in an organized and highly programmed way to become the functional heart. The recognition that progenitor or stem cells that can differentiate into cardiac cells exist both in the bone marrow as well as the myocardium has led to a number of completed and ongoing experimental efforts asking if these can be used to restore ventricular function. While in general the results are encouraging, it appears we are still some distance away from applying these strategies in the clinic. We will outline a few of the stem cell-based approaches describing how specific cell types are being examined as potential therapy for heart failure.

Bone marrow-derived mesenchymal stem cells: Mesenchymal stem cells (MSCs) are thought to be one of the most promising cell-based therapies for cardiovascular disease. Bone marrow-derived (BM-) MSCs can differentiate into many mature cardiac cell types including cardiomyocytes, cardiac fibroblasts and smooth muscle cells⁴⁻⁶. This makes BM-MSCs attractive for cell based therapies to treat cardiac injury and heart failure. Under the proper conditions these cells will differentiate into multiple lineages, hence it is hypothesized that by providing these cells to the heart by direct injection they will develop into functional cells that promote cardiac repair and restoration of heart function (for more in-depth review see:^{7,8}). MSCs have been well reported to migrate to an injured site to promote repair by immune modulation through a secretome^{9,10}. The MSC secretome is also

thought to play an important role in MSC repair. The secretome includes cytokines such as interleukins, growth hormones, and exosomes containing factors including microRNAs^{9,10}. Thus these cells may enable rejuvenation at sites of cardiac injury through differentiation into new cardiac cells as well as provision of the necessary factors to aide repair. Bone marrow-derived mesenchymal stem cells are being examined in clinical trials (Table 1) with some evidence of success¹¹⁻¹³.

Cardiac-derived mesenchymal stem cells: In recent years subsets of cells within the heart, rather than the bone marrow, have been characterized as ‘cardiac stem cells’ or ‘cardiac progenitor cells’ due to their unique multipotent properties. Endogenous cardiac progenitor cells, also known as cardiac-derived mesenchymal stem cells, have been characterized by their ability to differentiate to cardiac cell types, including endothelial cells, fibroblasts and myofibroblasts¹⁸⁻²³. Directing differentiation of progenitors toward cardiac myocytes and limiting their conversion into non-myocyte cells, specifically fibroblasts/myofibroblasts is an attractive approach to regenerate cardiac tissue after injury²⁴. Two markers, Adult stem cell antigen-1 (Sca-1) and c-Kit are widely used to identify progenitors within CD45 negative non-hematopoietic cells in adult murine heart. The c-kit⁺CD45⁻ cells, which are also found in the human heart, are undergoing clinical trials to repair cardiac injury^{25,26}. Sca-1 positive cardiac progenitors have been characterized as small interstitial cells located adjacent to the basal lamina and in proximity with CD31 positive endothelial cells (EC)²⁷, indicating a close relationship between EC and progenitor cells. Additional characteristics of this population are strong cell surface expression of CD105 and low or negative expression of CD31/PECAM1 and absence of CD34 and CD45 hematopoietic cell markers. No expression of c-Kit was found on these cells²². Human cardiac CD105+CD31⁻c-Kit⁻ cells have been characterized by ability to differentiate towards cardiac myocytes²².

Cardiac progenitors are thought to be in a quiescent state until they are activated for proliferation and differentiation following injury to the heart. The major issue with these cells being used as therapy for cardiac repair is their limited number within the heart. An alternative strategy would be to find a way to specifically activate these cells to proliferate and differentiate to functional cardiomyocytes in the damaged area. Cardiac progenitors have been shown to promote myocardial regeneration after myocardial injury²¹. Factors that have been shown to alter these cells ability to proliferate and differentiate include paracrine factors such as cytokines and growth hormones, exosomes/microvesicles, and microRNA. For example, miR-133a has been reported to promote protection of cardiac progenitors after myocardial ischemia by inhibiting proapoptotic factors and promoting cell survival²⁸. Inhibition of profibrotic factors promotes cardioprotection of cardiac progenitors by paracrine and autocrine action²⁹. Through paracrine signaling of insulin-like growth factor-1 (IGF-1), one study reports cardioprotection of cardiac progenitors, with improved cardiomyocyte survival and contractility³⁰. A Phase I/II trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01438086) Identifier: NCT01438086) is currently recruiting patients to the RESUS-AMI study titled “Evaluation of the Safety and Efficacy of Using Insulin-like Growth Factor-1 in Patients With a Heart Attack”.

Multi-stem cell therapies: A new area of interest in cell based therapies is treatment with a mixture of multiple cell types. This is thought of as “second generation” cell-based therapy and though similar to BM-MSC therapies, differs as it is a calculated mixture of stem cells instead of a patients isolated BM-MSCs. One cell combination that appears promising for cardiac repair is a mixture of c-kit⁺ cardiac progenitor cells with bone-marrow mesenchymal stem cells³¹. These cells are very similar in that they differentiate to the same types of mature cardiac stem cells but are beneficial for different properties. These mixed cell therapies are referred to as CardioChimeras where these cells are generated *ex vivo* via viral cell fusion³². Mesenchymal stem cells, as previously described, have paracrine effects that limit inflammation, and promote survival and growth of adjacent cells⁹. The cardiac progenitors appear to promote regeneration^{32,33}. To date CardioChimeras have only been tested in preclinical models, where after myocardial infarction their use was associated with reduced infarct size and improved cardiac function³². There is one clinical trial currently recruiting patients to test the effects of mesenchymal stem cell and cardiac stem cell therapies alone or in combination in patients with heart failure (CONCERT-HF, clinicaltrials.gov identifier: NCT02501811).

Reprogramming scarring—Scar formation and fibrosis represents a major problem for cardiac regeneration and rejuvenation efforts after cardiac injury. Recent work has explored strategies to reverse scarring via reprogramming. Using genetic manipulation strategies, investigators have identified key factors that can be targeted to undifferentiated myofibroblasts in order to reprogram cells to form functional heart muscle and limit fibrosis. One strategy under investigation is reprogramming cardiac fibroblasts into functional cardiomyocyte-like cells. By locally delivering developmentally critical transcription factors (Gata4, Mef2c, and Tbx5) to the infarcted area, cardiac fibroblasts were reprogrammed into binucleated cardiomyocyte-like cells with mechanical and electrical coupling to existing cardiac myocytes³⁴. This approach also decreased the size of the infarct zone and modestly attenuated cardiac dysfunction in the months following injury³⁴. Addition of thymosin b4 to the transcription factor mix further improved cardiac function and scarring³⁴. While this approach remains at the preclinical-phase of development, the demonstration that fibroblasts can be reprogrammed represents a promising therapeutic avenue.

Stimulating myocyte cell cycle reentry—Cardiac myocytes build the myocardium during development and complete growth of the heart during adolescence as the cardiomyocytes reach mature size and structure. Cardiac myocytes within the heart have very little turnover throughout life. Since cardiac myocytes are fundamental to heart function, a method to promote these cells to reenter cell cycle through dedifferentiation followed by proliferation and formation of new functional cardiac myocytes following cardiac damage is an area of therapeutic interest (for more information on this topic³⁵). In one example, studies with *in vivo* and *in vitro* treatment of oncostatin M, an inflammatory cytokine of the IL-6 family, dedifferentiates cardiac myocytes and promotes cardiac protection of the myocardium^{36,37}. Cardiac myocytes reenter cell cycle and proliferate after periostin treatment which activates integrins and the PI3K pathway³⁸. When provided as treatment in an *in vivo* model of myocardial infarction, long-term delivery of periostin through an epicardial patch improved cardiac function, reduced fibrosis, and reduced

hypertrophy³⁸. Interestingly, stimulation with neuregulin-1 (NRG-1, described in more detail below) promotes cardiac myocyte dedifferentiation and proliferation both *in vitro* and *in vivo*³⁹. Additionally, *in vivo* treatment of NRG-1 in mice following cardiac injury resulted in myocardial regeneration and repair³⁹. Targeting cardiac myocyte proliferation through factors such as these or in conjunction with factors discussed in the two sections below on promoting myocardial rejuvenation could protect the myocardium upon injury or promote myocardial repair following injury.

Manipulating cell signaling to promote myocardial rejuvenation—A number of recombinant proteins have been explored as potential treatments for heart failure. Growth factors with roles in heart development or cardiomyocyte differentiation top the list and are discussed below (Table 2). Other factors not listed in the table but worthy of mentioning include insulin growth factor 1 (IGF-1), fibroblast growth factors, and vascular endothelial growth factor (VEGF). IGF-1 promotes cardiac stem cell repair and activates pro-survival pathways⁴⁰. Fibroblast growth factors (FGFs) such as FGF9 improve contractile function following myocardial infarction and promote myocardial vascularization⁴¹.

Neuregulin 1 beta: Neuregulin (NRG) is a developmentally critical growth factor that works through inducing ErbB-receptor tyrosine kinase activation and subsequent downstream signaling pathways. The NRG-1 β isoform of NRG has effects on cardiomyocyte survival as well as structure and function *in vitro*, in addition to endothelial cell and fibroblast responses^{42,43}. In addition, NRG-1 β activates differentiation of progenitor cell populations toward cardiac cell lineages, at least *in vitro*^{44,45}. Some or all of these effects may explain how recombinant NRG-1 β given to both animals and humans with systolic dysfunction is associated with improvements in heart function. There are two distinct recombinant NRG-1 β proteins in clinical development. The EGF-domain only fragment of NRG-1 β has progressed to late stage clinical trials^{46,47} (for more detail:⁴⁸). When given as a parenteral infusion over many days, a sustained improvement in cardiac function has been reported⁴⁷. The larger recombinant glial growth factor 2 (GGF2), which is a naturally expressed type II NRG-1 β isoform, is effective in improving cardiac function in small and large animals^{49,50}. Early results in humans have been presented^{51,52} (for more detail⁵³).

Stromal cell-derived factor 1 (SDF-1): SDF-1 is a chemokine involved in cell recruitment. Within the heart, CXCR4 is the primary receptor that SDF-1 acts through and promotes cell homing, remodeling, and cardiomyocyte survival^{54,55}. After myocardial ischemia, SDF-1 treatment increases migration and recruits progenitor cells to sites of cardiac damage^{56–58}. A multifunctional fusion protein of SDF-1 and glycoprotein VI given after myocardial infarction induced recruitment of bone marrow cells to the damaged myocardium and reduced infarct size⁵⁹. Thus SDF-1 treatment may complement stem cell-based therapies through enhancing cell homing and promoting remodeling. Clinical trials using gene therapy for overexpression of SDF-1 are continuing to be investigated to therapeutic potential⁵⁴.

Follistatin-related protein 1 (FSTL1): FSTL1 is a glycoprotein expressed within the epicardium that inhibits TGF β signaling. Upon myocardial ischemia, BMP4 and

phosphorylated SMADs 1/5/8 are elevated in the heart but with FSTL1 treatment phosphorylated SMAD1/5/8 levels are attenuated⁶⁰. Recombinant human FSTL1 delivered via epicardial patch after myocardial infarction activated cardiomyocyte cell cycle reentry and subsequent division of preexisting cardiomyocytes, in association with improved cardiac function and survival^{61,62}. Interestingly, transgenic overexpression of FSTL1 in this model did not lead to improved cardiac function or survival^{61,62}. This phenomenon is thought to be dependent on the location or origin of FSTL1 which may affect the glycosylation of the protein and provide a different response. Preclinical investigations are ongoing to determine the proper delivery strategy of FSTL1 for clinical trial studies.

Biologic vasodilators: Natriuretic peptides are also considered part of the ‘fetal gene program’, with strong activation of expression upon cardiac injury or stress. Physiologically these peptides induce vasodilation and sodium excretion, while antagonizing the effects of angiotensin II and aldosterone through activation of guanylate cyclase (GC) receptors A and B. Recombinant natriuretic peptides that have been developed to treat heart failure such as nesiritide (recombinant B-type natriuretic peptide [BNP]) have lost traction in clinical practice⁶³. New natriuretic peptides and other vasodilators with additional biological properties are being developed to improve heart failure outcomes. Atrial natriuretic peptide (aka A-type NP, ANP) remains under investigation⁶⁴. Cenderitide (CD- NP) is a recombinant engineered natriuretic peptide that combines elements of naturally occurring C- and D-type NP which optimizes its agonist action on both GC-A and B⁶⁵, and may have unique anti-fibrotic activity. Combined with bio-engineered scaffolds and other drug delivery methods this novel peptide holds particular promise for vascular as well as myocardial disease^{66,67}.

One promising non-natriuretic peptide vasodilator is the placenta-derived factor relaxin, which mediates cardiovascular adaptation to pregnancy. In addition to its potent action as a vasodilator, relaxin regulates extracellular matrix and remodeling, increases angiogenesis and improves function following ischemic injury^{68,69}. Serelaxin, a recombinant human relaxin-2, has been studied in humans with acute heart failure where it is tolerated⁷⁰ and in a larger international trial has been associated with symptomatic relief⁷¹. Serelaxin remains under investigation primarily for the treatment of acute heart failure. For more information on this topic we suggest a few detailed reviews^{68,72}.

Manipulating gene expression to promote myocardial rejuvenation

Sarcoplasmic reticulum Ca^{2+} ATPase (SERCA): The expression of sarcoplasmic reticulum Ca^{2+} ATPase (SERCA), essential to electrical-mechanical coupling in cardiac myocytes, is sensitive to cardiac injury. Reduction of SERCA2a activity is correlated with a variety of cardiac disease states including heart failure. In a variety of animal models of heart failure, increasing expression of SERCA restores Ca^{2+} handling, improves contractility and reduces cardiac injury^{73,74}. This has led to an ongoing effort using an adeno-associated viral vector to restore myocardial expression of SERCA2a. While a small phase 2 trial demonstrated improvement in clinical parameters as well as cardiac function⁷⁵, these were not reproduced in a larger phase 2 trial⁷⁶. Further clinical trials will be necessary to determine whether this approach can be of benefit to heart failure patients. However the

advances in viral vectors for use in gene therapy is an important advance made during this program's development.

Proto-oncogene serine/threonine-protein kinase (Pim1): Pim1 is an enzyme involved in cell cycle, transcriptional activation, and apoptosis. Within the heart, Pim1 overexpression has been shown to protect the heart from myocardial infarction through increasing SERCA2a expression, thereby improving calcium dynamics and promoting cardiomyocyte survival⁷⁷. Using a mouse model of myocardial infarction, injection of human cardiac progenitors into the heart that overexpressed Pim1 resulted in improved cardiac function with reduced myocardial damage and elevated homing of treatment progenitor cells⁷⁸. Studies of Pim1 have also shown beneficial effects on the myocardium through promoting contractility of myocytes and enhancing the proliferative effects of cardiac progenitors⁷⁹ thus providing evidence that Pim1 could be utilized as heart failure therapy.

miR-15: microRNAs are small non-coding nucleotides that regulate transcript and protein of their target genes through mRNA inhibition or degradation. The specific microRNA miR-15 increases in expression in the heart after injury and inhibits the TGF β signaling pathway resulting in increased fibrosis⁸⁰. Functionally, inhibition of miR-15 *in vivo* in a myocardial infarction model increases the viability of cardiomyocytes and increases differentiation^{81,82}. Thus miR-15 has been proposed as a target following cardiac injury to promote cardiomyocyte vitality and growth⁸³. While this strategy remains in preclinical development, microRNAs in general represent an exciting area of investigation as potential targets for heart failure therapies.

Conclusions

Biological therapeutics are an exciting area of development with potential to change the dynamics of heart failure therapy. While there has been much written about myocardial regeneration, we believe that 'rejuvenation' is perhaps a better term to describe the desired state of reverse remodeling and ventricular recovery for heart failure patients. Despite decades of research, this field is still in its 'infancy', pun intended. A promising direction is the continued investigation of signals and events in cardiac development and the progressive study of interesting leads that might promote myocardial rejuvenation after injury in the adult heart. Thus further investigation is needed by both developmental biologists as well as translational scientists to fully explore the Mencius paradigm and bring biological therapies for advanced heart failure to fruition.

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Key Points

- Therapies targeting myocardial rejuvenation represent a promising area of investigation for advanced heart failure.
- Bone marrow-derived and cardiac-derived mesenchymal stem cells have exhibited some promising results, though further investigation is needed.
- Scarring and fibrosis which occur in some forms of heart failure require a search for ways to reprogram fibroblasts, or find strategies to rebuild cardiac tissue.
- Developmentally critical cell signaling factors such as NRG1 β , SDF-1, or FSTL1 offer possible strategies to manipulate cardiac repair and rejuvenation.
- Gene delivery strategies are improving, allowing for induction of cardiac specific expression of proteins involved in improving mechanical function such as SERCA or Pim1.

Table 1**Clinical Trials for Mesenchymal Stem Cell Therapy for Heart Failure**

Study	ClinicalTrials.gov Identifier	Phase	Status	Outcomes
Autologous Mesenchymal Stromal Cell Therapy in Heart Failure	NCT00644410	Phase I/II	Completed	Therapy by intra-myocardial injection of MSCs was safe and improved ejection fraction by >6% compared to placebo ¹⁴ .
Efficacy and Safety of Allogeneic Mesenchymal Precursor Cells for the Treatment of Chronic Heart Failure	NCT02032004	Phase III	Recruiting	N/A – estimated study completion is August 2018
Transendocardial Delivery of Allogeneic Mesenchymal Precursor Cells (MPCs) in Heart Failure	NCT00721045	Phase II	Completed	No publication or results currently reported.
Safety and Efficacy of Intracoronary Adult Human Mesenchymal Stem Cells After Acute Myocardial Infarction (SEED-MS-C)	NCT01392105	Phase II/III	Completed	One month after myocardial infarction patients received MSC treatment; at 6 months post-MI there was a slight improvement in LVEF; treatment was safe and there were no significant complications ¹⁵ .
Intravenous Dose of (aBMC) to Subjects With Non-ischemic Heart Failure	NCT02467387	Phase II	Recruiting	N/A – estimated study completion is April 2017
Transendocardial Autologous Cells (hMSC or hBMC) in Ischemic Heart Failure Trial (TAC-HFT)	NCT00768066	Phase I/II	Completed	Transendocardial injection of MSCs appeared safe, but due to sample size distinct conclusions were difficult to elucidate; results provided evidence for larger cohort investigations ¹⁶ .
Transendocardial Autologous Cells (hMSC or hMSC and hCSC) in Ischemic Heart Failure Trial (TAC-HFT II)	NCT02503280	Phase I/II	Not open yet to recruiting	N/A
Safety Study of Adult Mesenchymal Stem Cells (MSC) to Treat Acute Myocardial Infarction	NCT00114452	Phase I	Completed	No publication or results currently reported but an associated preclinical study in a swine myocardial infarction model showed attenuation of contractile dysfunction in pigs treated with MSCs ¹⁷ .
Mesenchymal Stem Cells and Myocardial Ischemia (MESAMI)	NCT01076920	Phase I/II	Completed	No publication or results currently reported.

Table 2

Gene targets for heart failure therapy

Biological Factor	Mechanism of Action	In Vivo Support	
NRG-1 β (EGF-domain only and GGF2 isoforms)	Multiple including cardiac myocyte structure, function and survival, suppression of fibrosis and inflammation	<ul style="list-style-type: none"> • Swine with myocardial infarction treated with GGF2 have reduced fibrosis in association with improved left ventricular remodeling and contractile function⁴⁹. • Rats with myocardial infarction treated with GGF2 exhibit improved left ventricular function⁵⁰. • Clinical trials with EGF-domain recombinant human NRG-1 have shown improvement in left ventricular ejection fraction in patients with chronic heart failure⁴⁷. • Early clinical trials of the GGF2 isoform of NRG-1 indicate the safety of this therapy and demonstrate similar success as to the EGF-domain recombinant human NRG-1 therapy^{51,52}. 	
SERCA	Improves calcium dynamics	<ul style="list-style-type: none"> • Transgenic SERCA1a hearts following myocardial ischemia have improved contractility and reduced infarct size compared to non-transgenic hearts⁷³. • SERCA2a gene therapy in a chronic heart failure rat model exhibited stabilized sarcoplasmic reticulum calcium load and reduced spontaneous and catecholamine-induced ventricular arrhythmias⁷⁴. • Despite promising results from proof-of-concept studies, intracoronary infusion of AAV1/SERCA2a did not improve the clinical course of patients with heart failure and reduced ejection fraction^{75,76}. 	
Pim1	Inhibition of cardiomyocyte cell death and enhanced calcium dynamics.	<ul style="list-style-type: none"> • Transgenic Pim1 mice exhibited cardiac protection from myocardial infarction through inhibition of cardiomyocyte apoptosis as well as improved calcium dynamics through elevated SERCA2a expression⁷⁷. • Injection of Human cardiac progenitor cells overexpressing Pim1 kinase into mice after myocardial infarction improved cardiac function and structure with reduced infarct⁷⁸. 	
SDF-1	Promotes migration of progenitor cells to sites of injury.	<ul style="list-style-type: none"> • SDF-1 promotes recruitment of progenitor cells to sites of cardiac damage following myocardial ischemia^{56,57}. • A bifunctional protein of SDF-1 and glycoprotein VI tested in a mouse model of myocardial infarction increased recruitment of bone marrow cells to the infarct area which reduced infarct size and preserved cardiac function⁵⁹. 	
miR-15	Suppresses myocyte proliferation and viability.	<ul style="list-style-type: none"> • Inhibition of miR-15 increases systolic function and myocyte proliferation following myocardial infarction in mice⁸². • miR-15 inhibition increases viability of cardiomyocytes, decreases fibrosis, improves ejection fraction and reduces infarct size following ischemia-reperfusion injury⁸¹. 	
FSTL1	Stimulates myocyte proliferation.	<ul style="list-style-type: none"> • Human FSTL1 epicardial patch improves cardiac function and survival in swine and mouse myocardial injury models^{61,62}. 	