Narrative Review Article

Induced Pluripotent Stem Cells and 3D Bioprinting Strategies for Cardiac Regeneration After Myocardial Infarction

Nandita Shenoy

Las Lomas High School, 1460 South Main St., Walnut Creek, California, 94596, United States

ABSTRACT

Cardiovascular disease is the leading cause of death worldwide, often resulting in a myocardial infarction (MI), which can lead to irreversible cell death and heart failure (HF). While advances in bioengineering and regenerative medicine offer promising solutions for patients, traditional heart transplantations are limited due to a shortage of organ donors. To address this issue, differentiating induced pluripotent stem cells (iPSCs) into cardiomyocytes via signaling pathways can provide a patient-specific source of functional cardiomyocytes, and as a long-term goal it may be capable of replacing damaged myocardial tissue. This study evaluates the role of iPSCs and different biofabrication methods, such as bioprinting, used to create ventricular constructs and cardiac patches that support injured regions of the heart post-MI. However, for patients with HF, bioprinting a whole-heart construct is being explored as a future objective and is necessary to restore cardiac function when cardiac patches or ventricular constructs are not sufficient. Despite the progress made in the field, few studies have addressed the need to improve bioprinting vascular networks, adopt appropriate bioinks, and reduce costs for iPSC differentiation and bioprinting technologies. If successful, this work can eventually mitigate symptoms post-MI or contribute to addressing HF solutions, offering patients a new quality of life.

Keywords: Heart disease; myocardial infarction; bioprinting; stem cells, ventricles; cardiac patches; bioink

INTRODUCTION

Heart disease is the leading cause of mortality globally (1). In 2021, approximately 20.5 million deaths were attributed to cardiovascular diseases (CVDs), and roughly 930,000 of those deaths occurred in the United States (2). Because of the high mortality rate, CVDs are a major public health concern. Broadly defined, CVDs are chronic diseases affecting the heart and its vascular network, composed of arteries, veins, and capillaries. Some common cardiovascular diseases include coronary artery disease, myocardial infarction (MI), arrhythmia, heart failure, congenital heart defects, and vascular stenosis. The effects of CVDs may be seen from a cellular level to an organ level. The leading cause of death from CVDs is myocardial infarction (MI), commonly known as a heart attack. MI refers to the death of myocardial cells, which can lead to heart failure (3). On a cellular level, limited access to oxygen to the myocardium leads to irreversible cell death. On an organ level, the death of myocardium can lead to heart failure and cardiac arrest (4). Fortunately, the field of cardiovascular medicine has been continuously advancing to improve patients'

Corresponding author: Nandita Shenoy, E-mail: nanditashenoy8@gmail.com.

Accepted August 6, 2026
https://doi.org/10.70251/HYJR2348.44867875

quality of life and health outcomes. Current therapies for heart disease prevention and treatment range from pharmaceutical options like cardiac medications (cholesterol, anti-platelet, or nonsteroidal anti-inflammatory medications) (5), to surgical interventions like coronary artery bypass grafting (CABG) or angioplasty. While CABG can be used to treat some CVDs, there are also many downsides to the procedure like the risk of internal bleeding, arrhythmias, or heart attacks (6). While these options are great for patients to alleviate symptoms, they still are not sufficient because they do not restore cardiac function and are associated with many potential risks. Following MI, the death of myocardial cells cannot be reversed with pharmaceutical or medical technology approaches, leaving patients at an increased risk of heart failure (7).

Emerging advancements in regenerative medicine offer a promising approach for treating and preventing CVDs. For example, stem cells can be differentiated into various cell types (8). One type of stem cell, an induced pluripotent stem cell (iPSC), is obtained from patient-derived somatic cells that are reprogrammed to pluripotent cells, allowing them to be differentiated into specific cell types, such as cardiomyocytes and endothelial cells (9). Stem cell-derived cells can be assembled into implantable, functional tissues using different bioprinting methods, including: inkjet-based bioprinting, microextrusion, and laser-assisted bioprinting, which are being developed into experimental interventions such as cardiac patches, bioprinted heart valves, and eventually as a research goal, a new functional 3D bioprinted heart (10). Stem cell-based therapies coupled with biofabrication techniques serve not only as a way to diminish patient symptoms but also create a path towards personalized treatment plans to prevent further heart disease for the patient, ideally leading to improved patient outcomes and a higher life expectancy (Figure 1).

THE DIFFERENTIATION OF STEM CELLS INTO FUNCTIONAL CARDIOMYOCYTES

Stem cells are cells capable of self-renewal and multipotency. Their ability to differentiate into other cell types varies among stem-cell classes. Pluripotent stem cells such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) can differentiate into all cell types from all three germ layers. Multipotent stem cells (adult stem cells) are typically restricted to lineages within their tissue of origin. Totipotent stem cells are the only stem cells that aren't limited in any way and can differentiate into extraembryonic cells. They are derived from fertilized oocytes during early stages of development (11).

Historically, stem cell research has faced criticism and drawn ethical debate due to the use of embryonic stem cells (ESCs). However, in 2006, Shinya Yamanaka and his group produced iPSCs derived from dermal fibroblasts. Their experiments concluded that terminally differentiated adult somatic (skin) cells could be reprogrammed into a pluripotent stem cell state through the upregulation of four specific transcription factors: Oct3/4, Sox2, c-Myc, and Klf4 (now known as Yamanaka's factors) (12). These iPSCs exhibit the same properties as ESCs, but are patient-derived and their procurement is relatively non-controversial. Their differentiation can be directed into virtually any human cell type, including neurons, adipocytes, endothelial cells, and cardiomyocytes (heart cells).

Cardiomyocytes, the most prominent cell type in the heart, are responsible for driving the heart's rhythmic beating. Their differentiation from pluripotent stem cells can be distinguished into four different stages: mesoderm formation, cardiogenic mesoderm differentiation, cardiac progenitors, and mature cardiomyocytes (Figure 2) (13). Each stage requires

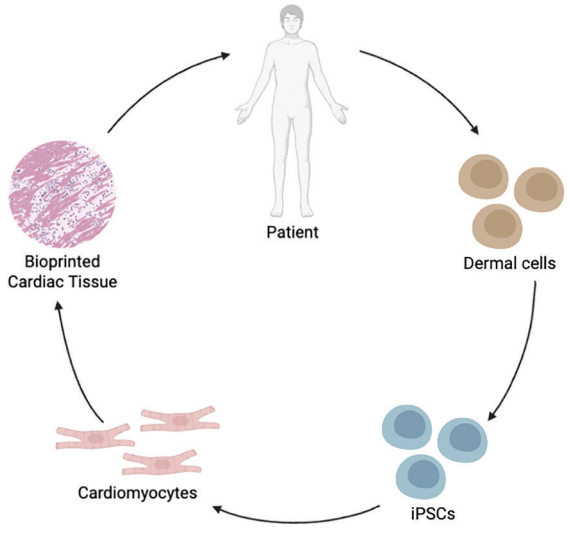

Figure 1. *Overview of patient-specific bioprinted cardiac tissue using induced pluripotent stem cells (iPSCs). Dermal cells are reprogrammed into iPSCs using Yamanaka factors, then differentiated into cardiomyocytes, and incorporated in bioprinting techniques to develop bioprinted cardiac tissues for regenerative therapies.*

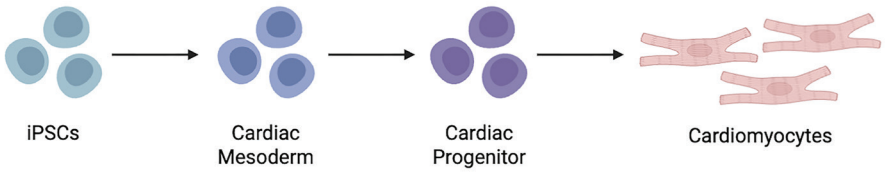

Figure 2. *Steps for differentiating induced pluripotent stem cells (iPSCs) into cardiomyocytes. Pluripotent stem cells (iPSCs) are first induced towards cardiac mesodermal cells via WNT signaling pathway. Mesodermal cells are then directed into cardiac progenitor cells by initiating growth factors VEGF/MESP1. Mature cardiomyocytes are formed through Notch or Hedgehog pathways. Mature cardiomyocytes can be seen after 14 days of differentiation.*

a defined expression of genes and signaling. The first phase in differentiating cardiomyocytes is directing the differentiation of iPSCs into mesodermal cells, the third germ layer of pluripotent stem cells that give rise to bone, tissues, blood cells, and heart cells. Numerous signaling proteins are required for cardiomyocyte differentiation. The cell signaling molecule CHIR99021, a GSK-3 inhibitor, activates the WNT signaling pathway by stabilizing B-catenin mimicking earlier stages of mesoderm differentiation (14, 15). The β-catenin then enters the nucleus and drives differentiation. Growth factor signaling then directs the differentiated mesoderm cells towards a cardiogenic mesoderm fate. Among these signals, vascular endothelial growth factor (VEGF) acts on endothelial cells to promote angiogenesis, supporting formation of the vascular network that will later supply the myocardium with oxygen and nutrients (16). Since the mesoderm germ layer can differentiate into skeletal muscle, smooth muscle, etc., expression of transcription factor MESP1 along with other specialized lineage genes are required to direct mesoderm cells into cardiomyocytes (17). To generate cardiac progenitors, the continuous WNT signaling pathway must terminate.

Secreted WNT inhibitors (i.e iWR-1, sFRP, Dkk1) suppress the pathway, allowing developmental transcription factors (i.e NKX2.5, MEF2C, etc.) to be upregulated and specify the cardiac progenitors. Cardiac progenitors differentiate into cardiomyocytes as WNT signaling is further modulated alongside Notch and Hedgehog signaling, pathways that regulate cardiomyocyte proliferation and maturation (18). In early stages of maturation, cells slowly reveal signs of sarcomeres, allowing the cells to contract (13). In the early stages of differentiation, sarcomeres are sparse. However as the iPSC-derived cardiomyocytes continue to mature, sarcomeres become more abundant.

During this differentiation process, scientists observe the expression of transcription factors, NKX2.5 and ISL1 on day 4, which are crucial factors in cardiac development (19). By day eight, tropomyosin binding subunit troponin T (cTnT), a cardiomyocyte-identity marker, becomes apparent in cells. cTnT regulates muscle contraction and relaxation, essential for blood flow (20). Between days 8-10, clusters of cardiomyocytes work together to create spontaneous contractions (19). After 14 days of differentiation, scientists assessed cardiomyocyte maturation using WNT pathway inhibitors, sfrp2and XAV939. Results show that Srfp2 lengthened the cardiomyocytes' sarcomeres the most, creating long cells with uniform sarcomeres (21).

The final stage of cardiomyocyte differentiation results in the formation of mature cardiomyocytes that express the cardiomyocyte-identity marker cTnT and maturation marker a-actinin. Their proper differentiation into mature cardiomyocytes can be confirmed using microscopic techniques such as immunofluorescence (IF) imaging, which also confirms the presence of sarcomere structures in the mature cardiomyocytes. IF imaging relies on the use of immunolabeling and antibodies which bind to proteins, such as myofibers present in the sarcomeres of iPSC-derived cardiomyocytes. Differentiated mature cardiomyocytes also express α-actinin, which is found in the Z line and defines boundaries, and MLC2a, which is found in the A band and mimics the patterns of myosin filaments found in human cardiac tissues (22, 23).

BIOPRINTING CARDIAC PATCHES AND VENTRICLES TO TREAT POST-MYOCARDIAL INFARCTION INJURY

Myocardial infarction (MI) is defined as the decreased or obstructed blood flow to the myocardium. The lack of oxygen to the myocardium leads to sarcolemmal disruption and eventually to the irreversible death of cardiomyocytes (3). MI most commonly involves the left ventricle, causing it to dilate and thin over time.

Damage disrupts blood flow and can progress to adverse left ventricular (LV) remodeling (24, 25). Because MI preferentially affects specific regions of the heart, therapeutic strategies that target those regions may be more beneficial. While it is difficult to achieve transplants for the growing number of heart failure cases caused by MIs, bioprinting implantable cardiac patches and small subsets of the heart may become a realistic option for patients in the future.

One method bioengineers are researching to address this is to bioprint small-scale cardiac patches to treat the necrotic region of the heart following MIs. There are numerous types of bioprinted patches, and each method offers promising strategies. The most common varieties include hydrogel-based, elastomer-based, and nanofiber-based patches (26). Hydrogel patches are the most prominent MI patches because of their ability to mimic the mechanical properties of the heart. They are composed of decellularized extracellular matrix (ECM), referred to as dECM, synthetic, and natural biomaterials. Hydrogel materials must be biocompatible and mimic the ECM to ensure proper cellular maturation and function and to avoid stimulating an unwanted immune system response (26, 27). Elastomer patches are known for their superior elasticity, biodegradability, and sustainability, with low toxicity and high strength when integrated with the body (28). Specifically for bioprinting heart subsets, bioinks- the biodegradable mixtures of biomaterials in a hydrogel form mixed with cardiomyocytes, endothelial cells, and stromal cells- are used to create myocardium (Figure 3) (29).

To bioprint the different cardiac patches, biomedical engineers can use different biofabrication methods. Electrospinning is a technique that produces nanofibers similar to ECMs, offering excellent support and the ability to incorporate different drugs into the patch (30). The reliable technique can create vascular grafts from various synthetic or biological materials. It promotes endothelial cell growth and controls proliferation (31). Electrospinning is also used to fabricate nanofiber and elastomer patches, which use polyester and gelatinous materials. While electrospinning is simple to operate, it can only work with a limited range of materials and equipment, limiting customization. 3D bioprinting, another biofabrication technique, combines bioinks and computer-assisted software (CAD), to create hydrogel patches and elastomer patches. Bioinks are printed onto scaffolds via different bioprinting methods; for example, inkjet-based bioprinting, extrusion-based bioprinting, and laser-assisted bioprinting show high precision in bioprinting vascular networks (10). While 3D bioprinting can fabricate larger, more complex structures, it requires more advanced, expensive materials and equipment.

To focus on developing cardiac patches that minimize myocardial cell death following an MI, scientists initially focused on delivering therapeutics. During the initial stages following an MI, cardiac patches can be printed to sense and adapt to post-MI stages. The patches are composed of stacked scaffolds that express therapeutic substances in response to changes in reactive oxygen species (26). Cardiac patches are prefabricated in vitro and can remain stable for subsequent in vivo implantation. Patches can be made of different materials and methods, making them a personalized option for different patients. The overall goal of creating post-MI cardiac patches is to surgically implant them to protect the cardiac tissue from further oxidative damage, improve mitochondrial performance, and prevent further cardiovascular cell death (Figure 4).

While the approaches mentioned above focus on preventing cardiomyocyte death after MI, they cannot fully restore contractility and function. Consequently, bioengineers are researching the development of bioprinted cardiac constructs to replace the function of lost cardiomyocytes. These approaches, including bioprinting specialized anatomical divisions, aim to restore normal cardiac function (32). To bioprint subsets of the heart, specific biocompatible materials are mixed with cells to create functional tissues.

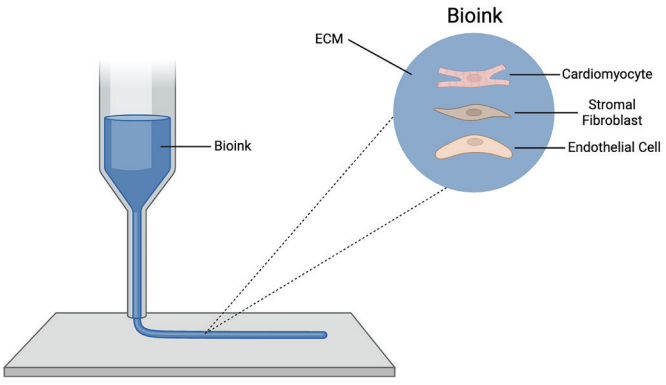

Figure 3. *Components of cardiac bioinks. Cardiac bioinks consist of biomaterials such as cardiomyocytes, stromal fibroblasts, and endothelial cells. Incorporated with biomaterials like hydrogels and extracellular matrix components to create functional cardiac tissue.*

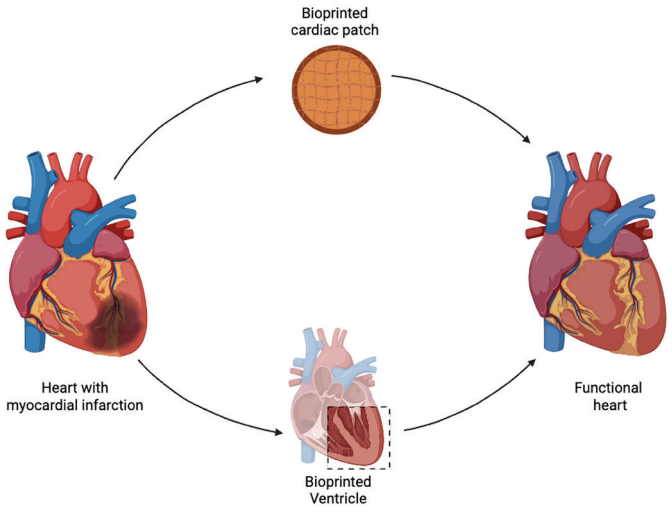

Figure 4. *Therapeutic application of bioprinted cardiac tissue following myocardial infarction (MI). Bioprinted cardiac patches are placed on damaged myocardial regions, and bioprinted ventricles replace damaged ventricles post MI. Both medical interventions improve tissue repair and restore cardiac function.*

The left ventricle (LV) pumps blood at higher pressure, handling greater mechanical stress due to its thicker wall compared to the right ventricle (33). Freeform Reversible Embedding of Suspended Hydrogels (FRESH) is an experimental method for creating 3D bioprinted subsets of the heart. FRESH is currently undergoing further investigation as a potential future bioprinting strategy for severe patient cases that require more treatment than a cardiac patch. FRESH can produce patient-specific anatomical structures by bioprinting collagen, the primary constituent of the cardiovascular ECM in the human body (32). It works by bioprinting collagen and cardiomyocyte-laden bioinks in a gelatin thermoreversible bath. After printing, the bath is melted, leaving behind the detailed 3D ventricular construct (34, 35). Left ventricular replacement might be necessary if the whole left ventricle is affected post-MI.

To 3D bioprint the LV with FRESH techniques, collagen bioinks (for structure) and high-density cell bioinks (with incorporated iPSCs) are used. The shape was designed with an ellipsoidal shell, and the inner and outer walls were lined with collagen, human embryonic stem cell-derived cardiomyocytes (rather than the iPSC-derived cardiomyocytes discussed elsewhere in this review), and cardiac fibroblasts (34). The sample was printed and cultured for 28 days to test the stability and hold geometry of the collagen walls. On day four, the first signs of function appeared. The ventricles started to contract, and reprogrammed heart cells were alive. On day seven, cells beat synchronously as a unit. This was confirmed by IF staining for a-actin, demonstrating myofibrils, and by calcium imaging (14, 27).

BIOPRINTING THE WHOLE HUMAN HEART FOR HEART FAILURE PATIENTS

For every million patients in the United States who were hospitalized for heart failure (HF), one-third of them had a history of MI (36). Causes of HF include irreversible death of cardiomyocytes, diminished contractility of the heart, and fibrosis. To date, heart transplants remain the gold standard, life-extending, and definitive option to improve cardiac function in patients with end-stage heart failure, offering a new quality of life that cardiac patches or valve replacements cannot. Unfortunately, due to the shortage of donor organs, surgical complications, and immune system rejections, heart transplantations aren't possible for many patients.

Bioprinting a functional whole-heart organ using stem cell-derived cardiomyocytes is being investigated as a future bioprinting method, yet the approach is currently in preclinical stages. Unlike other tissue engineering approaches, 3D bioprinting can create vascular networks that enable the development of cellularly dense tissues in larger forms (37). One bioprinting strategy for creating a whole-heart construct is Sacrificial Writing Into Functional Tissue (SWIFT), a new technique that can bioprint dense 3D figures of the heart with living tissue by embedding vascular channels into a living matrix made of stem cell organ building blocks (OBBs) (38, 39). SWIFT is a two-step process. First, a slurry of cardiac spheroid OBBs are aggregated into a dense, granular matrix capable of supporting embedded bioprinting. Second, the vascular network is printed into the tissue matrix, embedding a sacrificial vascular network (39). Vascularized tissue allows nutrient flow throughout the heart letting it function properly. SWIFT eliminates the need to print each cell individually by embedding cellular OBBs within a support matrix. The process takes less time and blood vessels are built on thicker tissues, keeping the 3D figure in larger heart constructs (40). It enables the creation of thick, perfusable tissue, which is difficult to achieve in other bioprinting applications.

Microextrusion-based bioprinting is another approach to biofabricate cardiac tissue. The computer controlled process uses pneumatic or mechanical

systems to transfer continuous lines of bioink, layer by layer, onto defined surfaces (10). Some advantages of microextrusion-based bioprinting include high cell density and higher resolution. The final construct enables strong tissue that can withstand physical stress similar to SWIFT (10). Although microextrusion-based constructs have lower cell densities, the scaffolds provide a strong framework to support cell survival and maturation. Although whole-heart constructs are currently in early-stages of development, it is a promising future outlook for patients with HF post-MI. Bioprinting approaches like SWIFT and microextrusion combine stem cells (via bioinks or OBBs) to create larger, thicker, perfusable, and vascularized cardiac tissues.

These technologies have the potential to alleviate patients' symptoms and combat irreversible myocardial cell death. As research continues, advancements in bioprinting approaches promise regenerative solutions to patients with HF after MI.

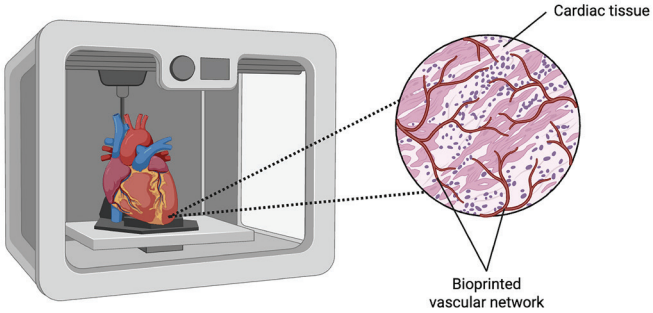

Figure 5. *Bioprinting strategies for generating 3D bioprinted and vascularized organs.*

LIMITATIONS AND FUTURE DIRECTIONS

The future of bioengineering solutions for post-MI patients using stem cells and bioprinting presents promise, but the fields still face several limitations and challenges that must first be addressed. Bioinks play a critical role in determining the success or failure of biofabricated vascularized tissues, yet scientists often struggle to recapitulate the physiologic function and structure of the heart's ECM. While natural bioinks can encourage improved cell maturation and communication, they typically provide poor mechanical support. Synthetic bioinks offer mechanical support but lack effective binding sites (10). Perfusable engineered cardiac tissue should incorporate a mix of materials from synthetic and natural bioinks, but this remains challenging with current biofabrication techniques. To improve bioinks, researchers are developing new bioinks that mimic the durability and characteristics of human heart tissue. Beyond biomaterials, iPSC reprogramming, differentiation, and bioprinting technologies are typically associated with high costs. To overcome this challenge, current efforts are focused on developing more cost-effective solutions. Bioreactors are systems that provide a simulated environment that mimics conditions in the human body to support cell growth and encourage organoid development. Some bioreactors are developed to preserve viability and achieve high-yield iPSC populations- reducing overall costs for clinical implementations (41). One considerable challenge when bioprinting cardiac tissue is establishing a micro-vascular network. A well-developed vascular network, including capillaries, is essential for removing waste products, facilitating nutrient movement, and supporting oxygen flow throughout the body (42). Bioengineers are researching growth factors, which promote vessel formation (43). Angiogenic factor VEGF promotes vascularization by stimulating endothelial cell proliferation to form new blood vessels (43). As progress in bioengineering research continues, whole-heart constructs can offer reduced reliance on organ donors and provide more options to patients with organ failure in the future.

CONCLUSION

Patient heart transplants remain the gold standard for HF patients. However, the increasing shortage of donors makes this close to impossible for most patients with HF. Stem cell-derived cardiomyocytes, coupled with biomaterials and advanced bioprinting techniques, represent a promising approach toward the development of personalized-heart tissues. Research demonstrates that reprogramming iPSCs into cardiomyocytes is a successful approach to provide patient-specific, functional, and ethically obtained cell sources. Reprogrammed cells combined with biomaterials can mitigate damaged regions by bioprinting ventricular constructs and cardiac patches. For cases of HF, emerging biofabrication techniques aim to offer whole-heart constructs with vascular networks, possibly alleviating symptoms and possibly restoring function. While this still remains a long-term research goal, bioprinted constructs focus on restoring cardiac function. In the future, as the field overcomes limitations in cost, bioink availability, and

vascularization, these bioengineering strategies will reduce dependence on organ donors and offer patients a new quality of life.

ACKNOWLEDGEMENTS

This narrative review was completed under the guidance of a PhD student mentor, Jeffrey Aceves.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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