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Review

The Long and Winding Road to Cardiac Regeneration

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Abstract: Cardiac regeneration is a critical endeavor in the treatment of heart diseases, aimed at repairing and enhancing the structure and function of damaged myocardium. This review offers a comprehensive overview of current advancements and strategies in cardiac regeneration, with a specific focus on regenerative medicine and tissue engineering-based approaches. Stem cell-based therapies, which involve the utilization of adult stem cells and pluripotent stem cells hold immense potential for replenishing lost cardiomyocytes and facilitating cardiac tissue repair and regeneration. Tissue engineering also plays a prominent role employing synthetic or natural biomaterials, engineering cardiac patches and grafts with suitable properties, and fabricating upscale bioreactors to create functional constructs for cardiac recovery. These constructs can be transplanted into the heart to provide mechanical support and facilitate tissue healing. Additionally, the production of organoids and chips that accurately replicate the structure and function of the whole organ is an area of extensive research. Despite significant progress, several challenges persist in the field of cardiac regeneration. These include enhancing cell survival and engraftment, achieving proper vascularization, and ensuring the long-term functionality of engineered constructs. Overcoming these obstacles and offering effective therapies to restore cardiac function could improve the quality of life for individuals with heart diseases.

Keywords: cardiac regeneration; stem cell therapy; decellularized extracellular matrix; bioreactor; biomaterials; organoids; chips

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1. Introduction

Cardiovascular disease is a pervasive health issue, ranking among the leading causes of death worldwide [1,2]. According to the World Health Organization, it is estimated that cardiovascular diseases accounted for approximately 17.9 million deaths in 2019, representing 32% of all global deaths (World Health Organization, Geneva, Switzerland (2021)). Cardiovascular Diseases (CVDs). Retrieved from (https://www.who.int/news-room/fact-sheets/detail/cardio, accessed on 3 April 2023) [3]. Its detrimental impact on individuals and communities necessitates urgent efforts to develop novel treatments. In this regard, cardiac regeneration has emerged as a promising area of research, aiming to pioneer innovative approaches for repairing or replacing damaged heart tissue [4]. The ultimate goal of cardiac regeneration is to provide a long-term solution for the treatment of various cardiovascular diseases, including heart failure, heart attacks, and strokes. As the global population continues to age and the available treatment options remain limited, the field of cardiac regeneration has assumed significant importance [5–9].

Within the panorama of cardiac regeneration, cell-based approaches have garnered considerable attention for their potential to introduce new therapeutic strategies [10,11]. One such approach is cardiac tissue engineering, a budding and rapidly evolving field in regenerative medicine [12]. Its primary objective is to restore the function of damaged heart tissue by leveraging the power of stem cells, biomaterials, and other innovative tissue-engineering techniques [13–15]. Recent years have witnessed substantial advancements in both research and clinical applications of cardiac tissue engineering, offering promising avenues for the treatment of heart disease and related cardiovascular conditions [16–18].

Presently, researchers are actively exploring two main methods of cardiac regeneration: stem cells and bioengineering [19]. Stem cell therapy involves isolating stem cells from the patient, reprograming them in vitro, and injecting them into the damaged areas of the heart tissue [20,21]. This process holds the potential to stimulate the heart's intrinsic repair mechanisms and facilitate the restoration of damaged tissue. On the other hand, bioengineering entails the creation of artificial heart tissue utilizing a combination of proteins, growth factors, and living cells [22–24]. By employing an appropriate scaffold and incorporating growth factors, this approach can lead to the development of fully functional heart cells. Once these cells integrate with the patient's existing heart tissue, they offer the possibility of a more permanent and comprehensive solution for repairing and regenerating cardiac tissue [25–27].

Exciting breakthroughs have also been witnessed in the clinical applications of tissue engineering for heart disease. For instance, cardiac patches have emerged as a valuable tool for repairing damaged heart tissue [28,29], while the development of replacement heart valves aims to address issues related to damaged or defective valves [30–32]. These innovative valves boast significantly prolonged lifespans compared to their traditional counterparts and feature implantable designs, making them highly suitable for individuals in need of long-term treatments [33,34]. Additionally, the ongoing development of lab-grown functional heart cells holds immense potential for personalized treatments that surpass the effectiveness of conventional methods [35].

The recent strides made in the field of cardiac tissue engineering have the potential to revolutionize cardiovascular medicine in various ways. From groundbreaking treatments for heart disease to the development of more durable replacement organs, tissue engineering offers a wide range of possibilities to significantly enhance and improve lives [16,36,37]. With continued research and exploration in this field, it is expected that further remarkable advances will be achieved in the next decade.

Over the past decade, the development of cardiac tissue engineering strategies for the treatment of heart disease has witnessed substantial progress [38,39]. Key advances in this field include:

1. Stem cell therapy: Researchers have successfully harnessed the differentiating capabilities of stem cells, enabling them to transform into various cell types, including heart cells. These remarkable cells hold the potential to generate new cardiac tissue, and extensive research has been conducted to refine the methods of differentiating stem cells into functional heart cells. Encouraging results have been observed in preclinical studies, underscoring the potential of stem cell therapy in cardiac regeneration [40–44].
2. Biomaterials: The use of biomaterials has revolutionized the field of cardiac tissue engineering. These materials serve as scaffolds that support the growth and organization of heart cells, enabling the creation of three-dimensional structures that closely mimic the intricate architecture of the heart. This approach promotes the formation of functional cardiac tissue and holds tremendous promise for restoring the damaged heart to its optimal functionality [26,45,46].
3. Bioreactors: Bioreactors have emerged as invaluable tools in cardiac tissue engineering. They provide a controlled environment for the growth and maturation of cardiac tissue by subjecting the cells to specific mechanical and electrical stimuli. This exposure facilitates the development of functional cardiac tissue that closely resembles the native heart tissue in terms of structure and functionality. Bioreactors have played

a pivotal role in advancing our understanding of cardiac regeneration and have significantly contributed to the progress made in the field [47–50].

4. Gene therapy: Gene therapy has emerged as a cutting-edge approach in cardiac tissue engineering. It involves the use of genetic techniques to enhance the differentiation potential of stem cells into heart cells or to promote the survival and function of existing heart cells. Through various gene therapy strategies, researchers have made significant strides in preclinical studies, opening up new possibilities for improving the effectiveness of cardiac regeneration [51–54].

While substantial progress has been made, there is still much work to be done in the field of cardiac tissue engineering.

The complete reconstruction of the heart with current knowledge and techniques remains a challenging goal. Nevertheless, ongoing research and advancements continue to bring us closer to understand the key for a successful and complete cardiac regeneration. Beyond repair and enhancement of structures and function of damaged myocardium, several hurdles still need to be overcome. The heart is a highly complex organ with intricate structures and functions [55]. Rebuilding the entire heart, including its various chambers, valves, and blood vessels, presents immense challenges in terms of recreating its intricate architecture and ensuring proper functioning. Additionally, even if researchers manage to generate new cardiac tissue, ensuring that it integrates seamlessly with the existing heart tissue and functions properly is a major challenge. Coordinating the electrical and mechanical activities of the new and old tissues is critical for the heart to pump effectively [56]. The heart also requires a robust network of blood vessels to deliver oxygen and nutrients to its cells. Creating a functional vascular system to support the regenerated tissue and prevent ischemia is a significant challenge [57]. Another issue to be addressed is represented by the risk of rejection, which poses significant hurdles when introducing new tissues or cells into the body. Finally, recreating the biomechanical properties and electrical signaling of the heart is crucial for proper function. Achieving the intricate balance of contraction and relaxation, as well as synchronizing the electrical signals, is a considerable challenge [56].

2. Stem Cell Therapy

Stem cell therapy has garnered significant attention in recent years for its potential to revolutionize the treatment of cardiac diseases. Stem cells possess a remarkable capability to divide and transform into specialized cells, making them ideal for repairing damaged tissues. Specifically, in case of heart failure and other cardiac diseases, stem cells can regenerate cardiac tissues, offering a promising avenue for treatment [58–61].

One of the primary advantages of utilizing stem cell therapy for cardiac regeneration lies in its potential to restore lost cardiac function [60,62–64]. Recent studies have demonstrated that stem cells can enhance heart function in patients suffering from heart failure by regenerating tissue and reinstating blood flow. For instance, studies published in *The Lancet* [65,66] and in *Physiological Review* [67] showed that cardiac stem cells improved heart function and reduced scar tissue in patients with heart failure.

Furthermore, stem cell therapy has the potential to reduce or even reverse the progression of cardiac diseases. A study published in *Circulation Research* [68] reported that injecting bone marrow-derived stem cells into the hearts of patients with severe heart failure resulted in a significant reduction in major adverse cardiovascular events.

Another notable benefit of stem cell therapy for cardiac regeneration is the relative safety of the procedure. Stem cells can be derived from various sources, including the patients' own body, and carry a low risk of triggering immunological reactions [69,70]. Additionally, stem cell therapy is minimally invasive and could be performed as an outpatient procedure, minimizing the burden on patients [71].

While the potential of stem cell therapy for cardiac regeneration is immense, there are still certain limitations to be addressed. Several studies have revealed drawbacks in current stem cell-based therapies. These limitations include significant cell death and apoptosis,

insufficient cell engraftment, limited cardiac regeneration post cell transplantation, and the need for careful monitoring of potential autoimmune adverse reactions [72].

To overcome these limitations, various strategies have been developed. These strategies aim to improve cell survival and engraftment, as well as induce transdifferentiation of somatic cells directly into functional cardiomyocytes to stimulate endogenous cardiac regeneration [73]. One such study, published in *Nature* [74], demonstrated successful reprogramming of fibroblasts into cardiomyocyte-like cells using a combination of transcription factors.

Cell types used for cardiac regeneration can be broadly categorized into two groups: adult stem cells and pluripotent stem cells [75]. Adult stem cells, such as skeletal myoblasts (SMs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and cardiac progenitor cells (CPCs), can be isolated from different tissues, including skeletal muscle, adipose tissue, peripheral blood, bone marrow, and heart tissue [76,77]. In addition, pluripotent stem cells, such as embryonic stem cells and induced pluripotent stem cells (reprogrammed somatic cells), possess a clear potential to differentiate into functional cardiomyocytes, setting them apart from adult stem cells [65,78,79]. Notably, an important difference between these two categories of cells is that while adult stem cells have a variable cardiogenic transdifferentiation capacity, pluripotent stem cells have an unequivocal potential to differentiate into functional cardiomyocytes [80].

Extensive research has been conducted utilizing these cell types in cardiac regeneration studies, demonstrating their tremendous potential for treating cardiovascular diseases. Adult stem cells and pluripotent stem cells are typically administered via intravascular injections, injections into the pericardium, or infusion of cardiac patches [81]. Moreover, these cells can be employed to repopulate synthetic and natural scaffolds, allowing for various recellularization methods ranging from simple manual cell seeding to sophisticated controllable systems [82,83].

Although stem cell therapies hold considerable potential for cardiac regeneration, their utilization comes with a host of noteworthy risks and challenges that must be comprehensively addressed before embarking on stem cell-based treatments for heart repair. A profound understanding and meticulous mitigation of these challenges are imperative for the successful realization of stem cell-based heart regeneration. A prime concern associated with stem cell therapies revolves around the potential for transplanted cells to undergo malignant transformation and form tumors [84]. This is particularly relevant for pluripotent stem cells, which possess the remarkable capability to differentiate into diverse cell types, including cancerous ones [85]. Orchestrating the precise differentiation of stem cells into desired cardiac cell types while averting uncontrolled proliferation poses a formidable obstacle. Furthermore, the immune system may perceive transplanted stem cells as foreign intruders, instigating immune responses that could impede the survival and function of the introduced cells [84]. Addressing this issue might necessitate immune suppression, which introduces its own set of intricate complications and potential side effects. The achievement of effective heart regeneration extends beyond mere tissue replacement; it entails establishing harmonious electrical integration with the existing heart structure. Disharmony in electrical signaling between transplanted cells and native tissue can lead to arrhythmias and other electrical irregularities that jeopardize cardiac function.

Additionally, the complete maturation and functional integration of transplanted stem cells into mature cardiac cells can be elusive. Inadequate integration or functional capacity may undermine the anticipated contribution of these cells to heart repair. Crucial to the survival of transplanted cells is their ability to access oxygen and nutrients from the bloodstream. Ensuring proper vascularization and blood supply to these cells presents a formidable challenge, which could potentially limit the efficacy of the therapy. The durability and long-term effects of stem cell-based cardiac regeneration therapies remain subjects of ongoing investigation. Determining the duration of treatment effects and the potential need for repeat interventions is paramount [86].

Transitioning from preclinical studies to clinical applications involves a multitude of clinical translation challenges [7,87]. These encompass scaling up production of consistent, high-quality stem cell products, tackling safety concerns, and substantiating efficacy in human trials. Patient heterogeneity is another pertinent consideration, as individual responses to stem cell therapies may differ based on factors such as age, overall health, genetics, and the severity of cardiac conditions. Tailoring treatments to suit individual patient profiles remains intricate [88]. A significant obstacle lies in the absence of standardized protocols within the evolving field of stem cell therapies. The lack of uniformity in cell types, delivery methods, and dosages hampers reliability and comparability across studies and trials [89,90]. In light of these complex challenges and risks, meticulous preclinical assessment, well-designed clinical trials, and ongoing vigilance are crucial to guarantee the safety and effectiveness of stem cell-based cardiac regeneration therapies.

2.1. Adult Stem Cells

Adult stem cells can be directly obtained from patients and transplanted back into the same individuals with a reduced risk of immunological rejection. These stem cells are currently being investigated for their potential in treating acute myocardial infarction and chronic myocardial ischemia. Moreover, adult stem cells derived from mature tissues hold promise for cardiac regeneration. They have the ability to differentiate into various cell types, including cardiac muscle cells and other cardiac cell types. Furthermore, these cells are responsive to local signals and can promptly adapt to environmental cues compared to pluripotent stem cells [91,92].

2.1.1. Skeletal Myoblasts

Skeletal myoblasts (SMs) were initially explored for the treatment of cardiomyopathy and heart failure [93]. SMs are precursor cells of skeletal muscle and are activated in response to muscle damage or disease-induced muscle degeneration [94]. They can be obtained from skeletal muscle biopsies and expanded outside the body for autologous transplantation. SMs exhibit a higher proliferation rate and are also resilient to myocardial ischemia [95]. Animal studies have demonstrated that their transplantation improves left ventricular function and hinders cardiac remodeling [96]. However, it is unfortunate that current research indicates that injected SMs in animal models differentiate into myotubes rather than cardiomyocytes. This lack of morphological and electrophysiological integration with host cardiomyocytes poses an increased risk of ventricular arrhythmias [97].

2.1.2. Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are a type of multipotent stem cell that give rise to all blood cell types. While traditionally known for their role in hematopoiesis, recent studies have explored the potential of HSCs in cardiac regeneration [98]. HSCs are derived from the mesoderm during embryonic development and are primarily found in the bone marrow of adult organisms. Their unique ability to self-renew and differentiate into various blood cell lineages has made them attractive candidates for therapeutic interventions, including cardiac repair [99].

One advantage of using HSCs for cardiac regeneration is their abundant availability. Bone marrow, a rich source of HSCs, can be easily accessed through minimally invasive procedures. Furthermore, HSCs can be expanded in culture, allowing for the generation of large quantities of cells for therapeutic purposes [63]. In addition, HSCs have shown the potential to differentiate into cardiac lineage cells, such as cardiomyocytes, endothelial cells, and smooth muscle cells, which are crucial for repairing damaged cardiac tissue [100].

Despite these advantages, several limitations exist in the use of HSCs for cardiac regeneration. One challenge is the low efficiency of differentiation into cardiac cells. While HSCs have demonstrated the capacity to differentiate into cardiac lineages, the percentage of cells successfully differentiating into functional cardiomyocytes remains relatively low [101]. Another limitation is the potential for immune rejection when using allogeneic

HSCs. Immunosuppressive therapy may be required to prevent rejection, adding complexity to the treatment process [102,103]. Moreover, the long-term engraftment and survival of HSC-derived cells in the cardiac tissue remain uncertain [104].

2.1.3. Endothelial Progenitor Cells

Endothelial progenitor cells (EPCs) are a promising cell type for cardiac regeneration due to their ability to promote angiogenesis and repair damaged blood vessels [105,106]. EPCs are derived from various sources, including bone marrow, peripheral blood, and umbilical cord blood. These cells possess unique characteristics that make them attractive for therapeutic applications in cardiac regeneration [107,108].

The advantages of EPCs lie in their regenerative potential. EPCs have the ability to differentiate into mature endothelial cells and contribute to the formation of new blood vessels. They also secrete proangiogenic factors, such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), which further enhance angiogenesis and tissue repair [109]. Additionally, EPCs possess immunomodulatory properties and can promote the recruitment of other regenerative cells to the injured cardiac tissue [110].

However, EPC-based therapies for cardiac regeneration face certain limitations. The low number and limited lifespan of circulating EPCs in the peripheral blood pose challenges for their isolation and expansion in therapeutic quantities. Moreover, EPCs derived from older individuals or patients with cardiovascular diseases may exhibit reduced regenerative potential. Additionally, the engraftment efficiency of transplanted EPCs into the myocardium remains a concern, as many cells may be lost due to poor survival or limited retention [111].

To overcome these limitations, several strategies to enhance the mobilization, expansion, and survival of EPCs are under investigation. Genetic modification, preconditioning, and tissue engineering approaches are being explored to improve the therapeutic efficacy of EPCs in cardiac regeneration. Furthermore, combined therapies using EPCs with other cell types, such as cells of mesenchymal origin, and biomaterial-made scaffolds are being studied to enhance their regenerative capabilities [112,113].

The EPCs successful clinical translation requires addressing the challenges related to cell sourcing, expansion, and engraftment. Future research efforts aimed at optimizing EPC-based therapies will contribute to their effective utilization in treating cardiovascular diseases and promoting cardiac tissue regeneration [114,115].

2.1.4. Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are multipotent cells that can be derived from various sources, including bone marrow, adipose tissue, umbilical cord blood, and placenta. Their ability to differentiate into multiple cell lineages, along with their immunomodulatory and paracrine effects, make them an attractive option for treating cardiac disorders [116].

One of the key advantages of MSCs is their relatively easy isolation and expansion in vitro, allowing for large-scale production. Additionally, they exhibit low immunogenicity, reducing the risk of immune rejection upon transplantation [117]. MSCs possess anti-inflammatory properties, which can help attenuate the detrimental immune response associated with cardiac injury. Moreover, they secrete trophic factors that promote angiogenesis, modulate fibrosis, and enhance the survival of existing cardiomyocytes [118,119].

Despite these advantages, several limitations must be considered. The heterogeneity of MSC populations obtained from different sources can affect their therapeutic potential and consistency [120]. The propensity of MSCs to undergo senescence during expansion limits their long-term viability and functionality [121]. Furthermore, the unpredictable fate and limited engraftment of transplanted MSCs within the injured heart pose challenges to achieving sustainable cardiac regeneration [122]. Additionally, optimizing the delivery methods and timing of MSC transplantation remains an area of active research.

2.1.5. Cardiac Progenitor Cells

Cardiac progenitor cells (CPCs) are a specialized group of cells able to differentiate into various types of cardiac cells, making them a promising approach for cardiac regeneration [123,124]. CPCs are derived from different sources, including the embryonic heart, fetal heart and adult heart. These cells already have a cardiomyocyte-like phenotype and can be used to construct cardiac tissue in vitro. Their multipotent nature and ability to generate new cardiac tissue provide several advantages for cardiac regeneration [125,126].

CPCs have the potential to differentiate into cardiomyocytes, endothelial cells, and smooth muscle cells, which are essential components to build a whole heart tissue [127]. This capacity allows them to integrate seamlessly into the existing cardiac structure, promoting functional recovery. Additionally, CPCs possess paracrine effects, secreting growth factors, and mRNAs that could stimulate endogenous repair mechanisms, angiogenesis, and tissue remodeling. This paracrine activity further enhances the regenerative potential of CPCs [128,129].

Despite their potential, CPCs also face certain limitations. The precise identification and isolation of CPCs remain challenging due to their heterogeneity and lack of specific markers. Ensuring a pure population of CPCs is crucial for successful regeneration. Additionally, the survival and engraftment of transplanted CPCs into the host myocardium is a major concern. Strategies to improve cell survival, integration, and long-term function are actively being investigated [130].

2.2. Pluripotent Stem Cells

Pluripotent stem cells exhibit the remarkable capacity for self-renewal through division and the ability to differentiate into all cell types present in the adult organism. Their unrestricted self-renewal potential and definitive cardiomyogenic capability render pluripotent stem cells a highly promising avenue for cardiac regenerative therapy [78,131,132]. This class of stem cells encompasses embryonic stem cells (ESCs) derived from the blastocyst, as well as induced pluripotent stem cells (iPSCs) generated via the introduction of pluripotent genes, namely Oct3/4, Sox2, Klf4, and c-Myc, into somatic cells [133].

2.2.1. Embryonic Stem Cell

ESCs are derived from the inner cell mass of early-stage embryos and possess remarkable pluripotent properties [134]. They have the ability to self-renew indefinitely and differentiate into virtually any cell type in the human body, including cardiomyocytes. This capacity to generate cardiac cells makes ESCs a compelling candidate for cardiac tissue regeneration [135].

The advantages of ESCs in cardiac regeneration lie in their exceptional regenerative potential and the ability to create large quantities of functional cardiomyocytes [63]. ESCs offer a renewable source of cells that can be expanded in culture, providing a virtually unlimited supply for transplantation. When introduced into damaged cardiac tissue, ESC-derived cardiomyocytes can integrate within the host tissue and potentially restore heart function [135,136].

However, the use of ESCs in cardiac regeneration also faces significant limitations. One of the primary concerns is the ethical dilemma associated with their acquisition, as ESCs are typically obtained from discarded embryos or through the destruction of viable embryos. This raises ethical considerations and has led to substantial controversy surrounding their use [137]. Additionally, ESCs may elicit immune responses when transplanted into a recipient, necessitating the use of immunosuppressive drugs that carry their own risks [138,139].

Furthermore, the possible tumorigenicity poses a significant challenge. ESCs tend to form teratomas, which are nonfunctional masses of differentiated cells. Ensuring the differentiation of ESCs into specific cardiac cell types before transplantation is critical to minimize the risk of tumor formation [140].

Ethical concerns, immune rejection, and tumorigenicity remain major hurdles that must be addressed before their widespread clinical application can be realized [141]. Continued research and development are essential to overcome these limitations and unlock the full potential of ESCs in cardiac regenerative medicine.

2.2.2. Induced Pluripotent Stem Cell

Induced pluripotent stem cell (iPSC) technology is making a major impact in the field of cardiac regeneration [142]. iPSCs are derived from adult somatic cells, such as skin cells [143], and then reprogrammed to an embryonic stem cell ESC state, where they can be used to obtain any type of tissue in the body. This technology has been used to create beating heart cells in a lab setting, providing a special opportunity to repair and replace damaged heart tissue [144]. This advancement has opened up possibilities for repairing and replacing damaged heart tissue.

The potential of iPSCs in cardiac regeneration lies in their versatility. They can be easily manipulated to form different components of the heart, offering researchers a unique opportunity to study and understand the cellular context in which these cells operate [145]. This knowledge is crucial for developing effective therapies.

In the field of heart disease, iPSCs have become a powerful tool. Researchers can generate cardiac cell types from patients' own cells, allowing them to study the effects of specific genetic and environmental factors [146]. This personalized approach helps in understanding disease progression and developing targeted treatments [147].

Moreover, iPSCs are used to create cell-based models of human heart diseases. These models aid in uncovering the underlying mechanisms and pathophysiology of various cardiac conditions [148]. By gaining a deeper understanding of these diseases, researchers can improve diagnosis and prognosis, and develop novel treatment strategies.

iPSC technology also plays a role in engineering heart-on-chip devices. These devices allow for the testing of numerous therapeutic agents in vitro, accelerating the development of treatments [149,150]. Additionally, iPSC-derived cardiac tissues have the potential to restore normal heart function by providing a replacement for lost cells and tissue in failing hearts [151,152].

However, there are challenges associated with using iPSCs in cardiac research. Safety concerns arise due to the potential of iPSCs to form tumors if not properly controlled. Ensuring the safety of iPSC-based therapies is crucial before considering widespread clinical applications [153,154].

Another challenge is immune rejection. While autologous transplantation of iPSCs bypasses immune rejection issues, generating patient-specific iPSCs of sufficient quality can be challenging. Allogeneic transplantation using iPSCs from different donors raises concerns about immune rejection and the need for immunosuppressive drugs [155,156].

Efficiency of differentiation is also a complex process. Generating a pure population of functional cardiac cells from iPSCs is still being optimized [157], and variability in differentiation efficiency can affect the overall effectiveness of iPSC-based cardiac regeneration [158].

Furthermore, iPSC-derived cardiomyocytes often exhibit immature characteristics, limiting their functionality and integration into existing cardiac tissue [159,160]. Achieving mature, fully functional cardiomyocytes is a critical goal for successful cardiac regeneration.

To ensure effective cardiac regeneration, transplanted cells must be able to integrate and establish proper electromechanical coupling with the host tissue [56,161,162]. However, achieving this alignment and synchronization with existing cardiac tissue is challenging and requires further research.

Additionally, ethical concerns surround the generation of iPSCs through genetic reprogramming techniques. While iPSCs avoid the ethical considerations associated with embryonic stem cells, the alteration of genetic makeup raises ethical questions [163,164].

Addressing these challenges and limitations is essential for the successful translation of iPSC-based cardiac regeneration strategies from the laboratory to clinical applications.

A brief summary of all the cell types mentioned above is showed in Table 1.

Table 1. Stem cell types for cardiac tissue engineering.

Stem Cells	Cell Type	Source	Advantages	Disadvantages	Refs.
Adult stem cells	Skeletal Myoblasts (SMs)	Skeletal muscle biopsies	High proliferation rate, resilient to myocardial ischemia, improve left ventricular function	Associated with increased risk of ventricular arrhythmias	[93–97]
	Hematopoietic stem cells (HSCs)	Bone marrow of adult organisms	Abundant availability, ability to self-renew and to differentiate into blood and cardiac cell lineages	Immunogenicity, low efficiency of differentiation into cardiac cell lineages	[98–104]
	Endothelial progenitor cells (EPCs)	Bone marrow, peripheral blood, umbilical cord blood	Immunomodulatory properties, angiogenic potential, capability to promote the recruitment of other regenerative cells to injured cardiac tissue	Low number and limited lifespan in the peripheral blood, reduced regenerative potential	[105–125]
	Mesenchymal stem cells (MSCs)	Bone marrow, adipose tissue, umbilical cord blood, and placenta	Easy isolation and expansion in vitro, anti-inflammatory properties, angiogenic potential, modulation of fibrosis and enhancement of the survival of existing cardiomyocytes	Heterogeneity, propensity to undergo senescence during expansion	[116–122]
	Cardiac progenitor cells (CPCs)	Embryonic, fetal, and adult heart	Ability to differentiate into cardiomyocytes, endothelial cells and smooth muscle cells, secretion of growth factors and cytokines for tissue repair and remodeling	Heterogeneity, lack of specific markers	[123–130]
Pluripotent stem cells	Embryonic stem cells (ESCs)	Inner cell mass of the early-stage embryos	High regenerative and differentiative potential, self-renewal	Ethical concerns, immunogenicity and tumorigenicity	[134–141]
	Induced pluripotent stem cells (iPSCs)	Adult somatic cells	Versatility, easy manipulation	Immunogenicity and tumorigenicity	[142–164]

The table highlights the advantages and the disadvantages of the different stem cell types employed in stem cell therapy for cardiac regeneration.

3. Tissue Engineering

The field of regenerative medicine has witnessed remarkable strides in recent years, with engineered cardiac constructs emerging as a promising approach for addressing the pressing need for effective treatments for heart diseases. These constructs, meticulously designed to mimic the intricacies of native cardiac tissue, hold the potential to revolutionize therapeutic approaches [165,166].

Preclinical studies have laid the foundation for the development and optimization of engineered cardiac constructs. In vitro models, such as 3D cell cultures and tissue-engineered platforms, have provided invaluable insights into the behavior of these constructs under controlled conditions. These investigations have enabled researchers to fine-tune factors such as cell source, scaffold materials, and biomechanical cues to enhance construct functionality and integration. Moreover, animal models have served as vital testing grounds for engineered cardiac constructs, offering a bridge between in vitro exper-

iments and clinical trials. Preclinical studies have demonstrated the constructs' potential for restoring damaged cardiac tissue, improving contractility, and promoting angiogenesis. These findings underscore the feasibility of translating these technologies into human therapies [167,168].

The transition from preclinical success to clinical trials represents a critical juncture in the journey of engineered cardiac constructs. Initial clinical trials have primarily focused on safety and feasibility, showcasing the constructs' ability to engraft into the host tissue without eliciting adverse immune responses. Early-phase trials have provided glimpses of improved cardiac function, affirming the constructs' potential to impact patients' lives. As clinical trials advance, researchers are addressing challenges such as scalability, long-term efficacy, and optimal patient selection. These trials also offer a platform for refining delivery methods, minimizing off-target effects, and tailoring treatment regimens to individual patient needs [169–171].

The promise of engineered cardiac constructs extends far beyond the confines of cardiac repair. These constructs hold potential for diverse therapeutic applications, including myocardial infarction treatment, heart failure management, and drug screening [172,173]. Engineered cardiac tissues provide an invaluable tool for understanding disease mechanisms, enabling researchers to unravel complex pathways and test novel therapeutic interventions. Furthermore, the synergy between engineered cardiac constructs and other regenerative strategies, such as gene therapy and stem cell treatments, opens new horizons for personalized medicine [174]. The ability to harness the regenerative potential of these constructs, combined with their capacity for tailored interventions, heralds a new era in cardiovascular care.

4. Biomaterials

Biomaterials play a crucial role in cardiac regeneration by providing a supportive environment for cell growth, facilitating tissue repair, and promoting functional recovery of the heart.

The unique properties of biomaterials make them suitable for cardiac regeneration applications. They can be engineered to mimic the structure and function of native cardiac tissue, allowing them to integrate seamlessly with the surrounding heart tissue. Biomaterials can be designed to possess specific mechanical properties, such as elasticity and stiffness, which are essential for proper cardiac function [175,176].

In the context of cardiac regeneration, biomaterials can serve various functions. They can act as scaffolds, providing a framework for the attachment, proliferation, and differentiation of cardiac cells. These scaffolds can be biodegradable, meaning they are gradually broken down and replaced by new tissue as the heart heals. Additionally, biomaterials can release bioactive molecules or drugs to enhance cell survival, promote angiogenesis, and modulate the immune response [177,178].

Various types of biomaterials have undergone extensive research for their application in cardiac regeneration. These include a diverse range of natural polymers, such as collagen, fibrin, gelatin, alginate, chitosan, silk, hyaluronic acid, and decellularized extracellular matrix [179]. Furthermore, synthetic polymers like polyurethane, polyethylene glycol, poly(ε-caprolactone), poly(lactic-co-glycolic acid), poly(l-lactide), and poly(glycerol sebacate) have also been meticulously investigated for their potential in this field. These materials can be processed into various forms, such as hydrogels, films, or fibres, depending on the specific application [180].

In recent years, advances in biomaterial science and tissue engineering have shown promising results in preclinical and clinical studies of cardiac regeneration. The use of biomaterials has demonstrated improvements in cardiac function, scar reduction, and tissue remodeling, leading to a better quality of life for patients with heart disease [181,182].

While challenges remain, such as achieving long-term functionality and ensuring proper integration of regenerated tissue with the host heart, the field of biomaterials for cardiac regeneration holds great promise. Continued research and innovation in this

area have the potential to revolutionize the treatment of heart disease, providing new opportunities for restoring damaged hearts and improving patient outcomes.

Biomaterials offer exciting opportunities for cardiac regeneration by providing structural support, promoting cell growth, and guiding tissue repair. With ongoing advancements in biomaterial science, the development of innovative strategies, and collaboration between scientists, engineers, and clinicians, we are inching closer to harnessing the full regenerative potential of biomaterials for treating cardiac diseases and enhancing cardiac function.

4.1. Synthetic Biomaterials

Synthetic biomaterials represent a wide range of polymers and metals that function as scaffolds, guiding the growth of tissues and facilitating the process of repair. These remarkable materials, including polyurethane, polyethylene glycol, poly(ε-caprolactone), poly(lactic-co-glycolic acid), poly(l-lactide), and poly(glycerol sebacate), can be customized to fulfil the unique needs of each patient, providing properties that can be tailored accordingly [182,183].

In the field of cardiac regeneration, synthetic biomaterials play a vital role by offering structural support and promoting tissue repair. These biomaterials can be specifically designed with intricate architectures, mimicking the natural extracellular matrix. This design enables effective cell adhesion, proliferation, and differentiation. Additionally, these materials can be engineered to gradually degrade over time, facilitating the integration of new tissue while minimizing the risk of complications. The remarkable versatility and tunability of synthetic biomaterials present immense possibilities for tailoring their physical and chemical properties to suit various applications in cardiac medicine [46,184].

Synthetic biomaterials offer inventive avenues for advancing tissue restoration and functional enhancement; however, they also bring forth specific challenges that necessitate thorough deliberation. Upon introduction into the body, synthetic biomaterials can incite immune responses and provoke inflammation. The immune system's potential recognition of these foreign elements may lead to persistent inflammation, impeding the amalgamation and healing of tissues [185]. An imperative consideration lies in the compatibility of synthetic biomaterials with living tissue. A low biocompatibility can yield adverse reactions, provoke tissue rejection, or hinder vital cellular interactions, thus undercutting the effectiveness of the regeneration endeavor [186]. The degradation of numerous synthetic biomaterials over time presents another facet of concern. Rapid degradation risks compromising the structural integrity of the regenerative framework, while sluggish degradation might culminate in the accumulation of nonfunctional substances within the body. Moreover, certain synthetic materials or their degradation byproducts exhibit toxic effects on neighboring cells or even the entirety of the organism endeavor [187,188]. The breakdown of these materials could potentially generate substances that disrupt cellular function or metabolic processes.

For synthetic biomaterials to function optimally, they must mirror the mechanical attributes of native tissue. Discrepancies between the mechanical properties of the biomaterial and the cardiac tissue can precipitate mechanical strain, tissue impairment, or compromised cardiac performance. Specific synthetic biomaterials might trigger the formation of blood clots or activation of platelets, thus heightening the risk of cardiovascular complications such as thrombosis [189]. A formidable challenge lies in ensuring the enduring stability and resilience of synthetic biomaterials within the dynamic and demanding cardiac milieu [56]. The ever-changing mechanical forces, ceaseless motion, and exposure to blood flow can exert influences on the structural robustness of these materials. Orchestrating a seamless synergy between synthetic biomaterials and native cardiac tissue, encompassing both structural and functional aspects, proves intricate. Subpar integration could result in suboptimal tissue regeneration, hindered contractility, or even detachment of the tissue.

Despite these challenges, continuous research efforts are being made to overcome these limitations and harness the full potential of synthetic biomaterials in cardiac regeneration.

Combining them with natural biomaterials and integrating smart technologies, such as drug-eluting coatings or tissue-specific nanostructures, holds promise for developing next-generation biomaterials with enhanced functionality and biocompatibility [190].

4.1.1. Polyurethane (PUR)

Originating from a class of synthetic polymers, polyurethane (PUR) exhibits unique physical features that make it suitable for various applications [191,192].

PUR possesses exceptional mechanical properties, such as high flexibility, elasticity, and durability, which closely resemble natural tissues. These characteristics allow PUR to mimic the mechanical behavior of cardiac tissue, providing a favorable environment for cell growth and function [193,194].

PUR has been shown to support cell adhesion, proliferation, and differentiation. Its biocompatibility promotes the attachment and growth of cardiac cells, facilitating the formation of functional tissue constructs. Additionally, PUR can be tailored to possess specific surface properties and bioactive molecules that further enhance cell interactions, promoting tissue integration and regeneration.

In cardiac tissue engineering, PUR plays a crucial role in constructing biomimetic scaffolds. These scaffolds act as temporary frameworks that guide cell organization and tissue development [195]. By creating a three-dimensional structure with appropriate mechanical and biochemical cues, PUR scaffolds provide a supportive environment for cardiac cells to align, differentiate, and function as a cohesive tissue.

Numerous studies have investigated the application of PUR in cardiac tissue engineering. Researchers have explored various fabrication techniques, such as electrospinning and 3D printing, to produce PUR-based scaffolds with controlled architecture and mechanical properties [196,197]. Moreover, studies have focused on optimizing the surface properties of PUR to enhance cell–material interactions and promote the desired cellular responses [198].

4.1.2. Polyethylene Glycol (PEG)

Polyethylene glycol (PEG) is a versatile compound widely used in various fields of science and engineering. It originates from the chemical modification of petroleum, resulting in a polymer with a linear structure and varying molecular weights.

Physically, PEG appears as a colorless, odorless, and water-soluble liquid or solid. Its molecular weight can range from a few hundred to several million Daltons, allowing for tailoring of its properties for specific applications [199].

Polyethylene is known for its biocompatibility and mechanical strength, and it has proven to be valuable due to its unique effects on cells, making it an excellent choice for cardiac scaffolds. Notably, it acts as a hydrophilic and biocompatible substance, enabling it to interact with cell membranes without causing damage [200]. PEG's properties, such as its highwater retention capacity, low immunogenicity, and ability to reduce friction, have made it useful in cell preservation, cryopreservation, and drug delivery systems [201].

In cardiac tissue engineering, researchers have been investigating PEG-based hydrogels as scaffolds for constructing engineered cardiac tissues. These hydrogels provide a three-dimensional environment that mimics the extracellular matrix and supports cell growth, proliferation, and differentiation [202]. PEG hydrogels can be customized by incorporating various bioactive molecules to enhance cell adhesion, survival, and tissue maturation, thus aiding in the development of functional cardiac tissue substitutes.

4.1.3. Poly(εcaprolactone) (PCL)

Initially discovered in the 1930s, poly(ε-caprolactone) (PCL) is derived from the ring-opening polymerization of ε-caprolactone monomers. It has gained significant attention due to its excellent biodegradability, biocompatibility, and processability [203].

In terms of physical features, PCL is a thermoplastic polymer with a low melting point, making it easily moldable and compatible with various processing techniques. Its

molecular structure consists of a long chain of repeating units, resulting in a linear and flexible polymer [204].

In cardiac tissue engineering, PCL scaffolds have been extensively studied. They can mimic the architecture and mechanical properties of native heart tissue, enabling the growth and organization of cardiac cells. PCL scaffolds offer a suitable environment for cell adhesion, proliferation, and differentiation, promoting the formation of functional cardiac tissue constructs [205].

Numerous studies have focused on PCL and its applications. Researchers have explored various methods to modify the surface properties of PCL scaffolds to enhance cell attachment and functionality. Additionally, the incorporation of bioactive molecules, such as growth factors or extracellular matrix components, into PCL scaffolds has been investigated to promote tissue regeneration and improve cardiac tissue engineering outcomes [206].

4.1.4. Poly(lactic-co-glycolic acid) (PLGA)

Poly(lactic-co-glycolic acid) (PLGA) is a biodegradable and biocompatible polymer widely used in various biomedical applications. It is derived from a combination of lactic acid and glycolic acid, making it an ideal material for tissue engineering and drug delivery systems [207].

PLGA's physical features include its tunable mechanical properties, degradation rate, and surface characteristics. It can be easily synthesized into different forms such as fibers, films, and scaffolds, allowing for customization based on specific tissue engineering requirements.

When it comes to cellular effects, PLGA has shown excellent biocompatibility, with minimal cytotoxicity. Its degradation products, lactic acid, and glycolic acid are naturally occurring metabolites that can be easily metabolized by cells, minimizing any adverse effects [208].

PLGA provides mechanical support for cell attachment and proliferation while allowing for nutrient and oxygen diffusion. The porous structure of PLGA scaffolds facilitates cell infiltration and extracellular matrix deposition, promoting tissue regeneration.

Numerous studies have investigated the use of PLGA in cardiac tissue engineering. Researchers have explored its potential for cardiac patch development, enabling the regeneration of damaged myocardium [209]. Additionally, PLGA has been incorporated into three-dimensional constructs, promoting the formation of functional cardiac tissues that mimic native heart structures [210].

4.1.5. Poly(l-lactide) (PLA)

Poly(l-lactide) (PLA) is a biodegradable polymer derived from lactic acid.

PLA possesses desirable physical features, including high mechanical strength and tunable degradation rates. It can be easily processed into various forms such as films, fibers, and scaffolds and has shown excellent biocompatibility and low cytotoxicity. Cells can adhere, proliferate, and differentiate on PLA surfaces, promoting tissue regeneration. The degradation product of PLA, lactic acid, is naturally occurring and can be metabolized by cells without causing adverse effects [211,212].

PLA scaffolds can guide the formation of functional cardiac tissue by promoting cell alignment, extracellular matrix production, and tissue remodeling.

Several studies have explored the potential of PLA in creating cardiac patches, bioengineered heart valves, and tissue-engineered blood vessels. PLA-based scaffolds have demonstrated promising results in promoting cell proliferation and differentiation, enhancing cardiac function, and supporting tissue regeneration [213].

4.1.6. Poly(glycerol sebacate) (PGS)

Poly(glycerol sebacate) (PGS) is a biocompatible and elastomeric polymer derived from the condensation reaction of glycerol and sebacic acid, resulting in a flexible and

cross-linked polymer. It possesses interesting physical features such as high elasticity, tunable mechanical properties, biodegradability, and biocompatibility [214]. Cells can easily adhere, migrate, and proliferate on PGS surfaces, promoting tissue restoring. The flexible nature of PGS allows it to conform to surrounding tissues, providing mechanical support, and maintaining cell viability [215].

PGS elastic properties make it particularly suitable for engineering heart tissues that require mechanical functionality [216].

Researchers have explored PGS's potential in developing cardiac patches, bioartificial myocardium, and cardiovascular implants. PGS-based constructs have shown the ability to promote cell growth, enhance contractile function, and improve cardiac tissue regeneration [217].

A brief summary of synthetic biomaterials described is showed in Table 2.

Table 2. Synthetic biomaterials.

Biomaterial	Source	Advantages	Formulation	Properties and Functions	Refs.
Polyurethane (PUR)	Synthetic polymer	Biocompatibility, high flexibility, elasticity, durability	Biomimetic scaffolds	Mimic the mechanical behavior of cardiac tissue, support cell adhesion, proliferation, and differentiation	[191–198]
Polyethylene glycol (PEG)	Synthetic polymer derived from chemical modification of petroleum	Biocompatibility, hydrophilic, low immunogenicity and mechanical strength	Hydrogels	Support cell adhesion, survival and tissue maturation	[199–202]
Poly(ε-caprolactone) (PCL)	Synthetic polymer from the polymerization of ε-caprolactone monomers	Biodegradability, biocompatibility and processability	Cardiac tissue constructs	Support cell adhesion, proliferation and differentiation	[203–206]
Poly(lactic-co-glycolic acid) (PLGA)	Synthetic polymer from a combination of lactic acid and glycolic acid	Biodegradability, biocompatibility	Fibers, films and scaffolds (cardiac patches)	Provide mechanical support forcell attachment and proliferation	[207–210]
Poly(l-lactide) (PLA)	Synthetic polymer derived from lactic acid	Biocompatibility, low cytotoxicity, high mechanical strength	Fibers, films and scaffolds (cardiac patches)	Support cell attachment, growth, proliferation, and differentiation	[211–213]
Poly(glycerol sebacate) (PGS)	Synthetic polymer from glycerol and sebacic acid	High elasticity, biodegradability, biocompatibility and mechanical properties	Cardiac patches, bioartificial myocardium, and cardiovascular implants	Promote cell growth, enhance contractile function, and improve cardiac tissue regeneration	[214–217]

The table summarizes synthetic biomaterials for cardiac regeneration purpose, their features, and the formulation available.

4.2. Natural Biomaterials

Natural biomaterials are a group of substances derived from biological sources holding a significant promise in the field of cardiac tissue engineering. These biomaterials play a crucial role in supplementing existing tissue and providing a favorable environment for cellular growth and tissue regeneration. They offer distinct advantages over synthetic materials due to their biocompatibility, biodegradability, and ability to mimic the extracellular matrix (ECM) found in native tissues [179].

Various natural biomaterials have been extensively studied. Among the protein-based materials, collagen, fibrin, gelatin, and silk have garnered considerable attention [218]. Collagen, the most abundant protein in the human body, provides structural integrity and supports cell adhesion and migration. Fibrin, derived from the clotting protein fibrinogen, possesses excellent biocompatibility, and promotes cell attachment and proliferation. Gelatin, derived from collagen through a controlled degradation process, exhibits similar characteristics and supports cell growth. Silk, a natural fibrous protein, offers exceptional mechanical properties and biodegradability, making it an attractive option for cardiac scaffold fabrication [176].

Polysaccharides, another class of natural biomaterials, have also been extensively explored in cardiac tissue engineering. Chitosan, derived from chitin, a component of crustacean shells, exhibits antibacterial properties, good mechanical strength, and biocompatibility. Alginate, extracted from brown seaweed, forms gel-like structures suitable for cell encapsulation and protection. Hyaluronic acid, a major component of the ECM, plays a crucial role in tissue hydration, cell migration, and wound healing. These polysaccharides provide structural support, promote cell adhesion, and modulate cellular behavior, making them valuable for cardiac scaffold development [179,219].

The unique properties of these natural biomaterials allow for their tailored use in cardiac tissue engineering. They can be processed into different forms, including hydrogels, films, and 3D scaffolds, providing structural support and an optimal microenvironment for cell attachment, proliferation, and differentiation. Furthermore, these biomaterials can be combined with growth factors, drugs, or cells to enhance their therapeutic potential and promote tissue regeneration [220].

Natural biomaterials, including collagen, fibrin, gelatin, silk, chitosan, alginate, and hyaluronic acid, offer a wide array of options for cardiac tissue engineering. Their biocompatibility, biodegradability, and ability to mimic the ECM make them ideal candidates for the development of cardiac scaffolds [178].

Yet, amidst their inherent advantages of introducing a biocompatible and bioactive approach to tissue restoration, these natural materials also introduce specific considerations that necessitate deliberate attention [221]. The controlled biodegradation of these materials, although a desired trait, requires precise regulation. Excessive degradation velocity risks compromising the structural robustness of the regenerative framework, thereby affecting its enduring stability and efficacy. Natural biomaterials, harvested from biological sources, may exhibit variability across different batches or donors. Achieving uniform quality and consistent properties across diverse lots is challenging. The derivation of natural biomaterials from animal or human sources might entail the potential hazard of disease transmission or contamination. Rigorous processing, sterilization, and unwavering quality control stand as pivotal safeguards against these risks, upholding patient safety [222]. While natural biomaterials hold promise in creating a suitable microenvironment for cell attachment and signaling, they might be deficient in specific mechanical or biochemical attributes requisite for optimal cardiac tissue rejuvenation. Procuring ample quantities of these materials for clinical application is not without challenges. Their limited availability could potentially encumber the scalability of treatments, raising pertinent concerns. The temporal degradation and remodeling of natural biomaterials might precipitate alterations in their mechanical properties or bioactivity over time [223]. It is crucial to acknowledge that some patients might manifest allergic reactions or sensitivities to constituents present in natural biomaterials [224]. Thus, the identification and addressing of potential allergens are pivotal prerequisites to prevent any untoward reactions. The seamless amalgamation between natural biomaterials and native cardiac tissue represents an undertaking. Inadequate integration could result in the formation of scar tissue, compromised functionality, or incomplete regeneration [225].

4.2.1. Collagen

Collagen has a rich history and plays a significant role in cardiac tissue engineering [226]. It is a protein found abundantly in the human body and serves as a structural component of various tissues.

Collagen possesses unique physical features that make it an ideal material for cardiac applications. It exhibits high biocompatibility, biodegradability, and excellent mechanical properties. These characteristics allow collagen to provide structural support and create a favorable microenvironment for cells [227,228].

Collagen promotes cell adhesion, migration, and proliferation interacting with cell surface receptors and facilitating cellular signaling, influencing cell behavior and tissue regeneration processes [229].

Collagen-based materials have been widely explored in cardiac tissue engineering, particularly in the form of patches and injectables. Collagen patches can be applied directly to damaged myocardium, providing mechanical reinforcement, and promoting tissue repair. Injectable collagen, in the form of hydrogels, can be used to deliver cells, growth factors, or drugs to specific areas of the heart, enhancing tissue regeneration and therapeutic outcomes [230,231].

Numerous studies have focused on collagen-based patches and injectables in cardiac tissue engineering. These studies have demonstrated the ability of collagen-based materials to improve cardiac function, promote angiogenesis, and facilitate tissue regeneration. They have shown promise in treating conditions such as myocardial infarction and heart failure, paving the way for potential clinical applications [232,233].

4.2.2. Fibrin

Fibrin deserves special mention due to its remarkable properties and effectiveness in cardiac regeneration. Fibrin originates from fibrinogen, a protein involved in the blood clotting process.

It forms a fibrillar network with a unique three-dimensional structure, offering mechanical support and promoting cell adhesion and migration.

Fibrin acts as a provisional scaffold that facilitates the attachment and proliferation of cells involved in cardiac repair processes. Fibrin also interacts with growth factors and cytokines, influencing cellular behavior and promoting tissue healing [234].

In cardiac tissue engineering, fibrin is commonly utilized as a bioactive scaffold. It can be formed into gels or hydrogels, providing a supportive environment for cell growth and tissue regeneration. Fibrin-based scaffolds have shown potential in enhancing cardiac function, promoting angiogenesis, and improving tissue remodeling [235].

Numerous studies have investigated the use of fibrin in cardiac tissue engineering. Researchers have explored its application in creating cardiac patches, injectable matrices, and tissue-engineered constructs demonstrating the ability of fibrin to support cell viability, enhance neovascularization, and improve contractile function in the heart [236].

4.2.3. Gelatin

Gelatin is a natural biomaterial derived from the hydrolysis of collagen; the major protein found in connective tissues.

Gelatin can be easily processed into various forms, such as films, sponges, and hydrogels. These properties allow for its adaptation to different tissue engineering strategies [237].

Gelatin provides a supportive environment for cells to grow, migrate, and organize, facilitating tissue regeneration. Gelatin can also be modified to incorporate bioactive molecules and growth factors to further enhance its effects on cells [238].

In cardiac tissue engineering, gelatin-based materials have shown promise as scaffolds for tissue repair and regeneration. They can be used to create cardiac patches, injectable matrices, and 3D constructs, providing mechanical support, and promoting cell integration and functional tissue formation [239].

4.2.4. Silk

Silk originates from the silkworm cocoon, where it is primarily composed of fibroin protein. Silk exhibits exceptional mechanical properties, including high tensile strength and elasticity providing versatility in scaffold fabrication [240]. In cardiac tissue engineering, silk-based materials can be used to develop cardiac patches, tissue-engineered constructs, and other implantable devices [241]. Silk scaffolds provide mechanical support, promote cell attachment, and guide the formation of functional cardiac tissue.

Studies exploring the use of silk in cardiac tissue engineering have demonstrated its potential in improving cardiac function, enhancing angiogenesis, and supporting tissue remodeling [242].

4.2.5. Chitosan

Chitosan, a natural biomaterial derived from chitin is found in the exoskeleton of crustaceans and insects. Numerous studies have explored the use of chitosan in cardiac tissue engineering, highlighting its potential in enhancing cell viability, improving contractile function, and promoting neovascularization in the heart [243–245].

4.2.6. Alginate

Alginate, a natural biomaterial derived from brown seaweed, originates from the cell walls of algae, primarily composed of alginic acid. It forms a gel-like structure when combined with divalent cations, creating a three-dimensional matrix for cell encapsulation. Alginate can be easily processed into various forms such as hydrogels and microbeads, allowing for customization in scaffold fabrication [246].

Alginate provides a nurturing microenvironment for cells, facilitating tissue regeneration. Alginate can also be modified to incorporate bioactive molecules, promoting specific cellular responses [247].

In cardiac tissue engineering alginate can be used to develop injectable hydrogels, cell encapsulation systems, and bioink for 3D bioprinting [248].

4.2.7. Hyaluronic Acid

Hyaluronic acid is derived from the extracellular matrix (ECM) of various tissues. Hyaluronic acid possesses notable physical features for cardiac applications [249,250]. It is highly biocompatible, biodegradable, and exhibits excellent water retention capacity. This allows hyaluronic acid to create a hydrated environment that supports cell migration, proliferation, and tissue regeneration.

It interacts with cell surface receptors, influencing cellular behavior and ECM remodeling processes [251].

Hyaluronic acid-based materials can be used to develop hydrogels, injectable matrices, and 3D constructs. Hyaluronic acid scaffolds provide mechanical support, promote cell integration, and facilitate the formation of functional cardiac tissue [252].

4.2.8. Decellularized Extracellular Matrix

Decellularized extracellular matrix (d-ECM) has emerged as a groundbreaking natural biomaterial for cardiac regeneration. This procedure involves the removal of cells from a donor heart, leaving a scaffold composed of extracellular matrix. Decellularization relies on a combination of chemical, physical, and enzymatic processes to achieve cell removal while preserving the structural and functional integrity of the scaffold. Recent studies have demonstrated the effectiveness of decellularization in removing cells from donor hearts. These studies employed a variety of methods, including chemical agents, physical forces such as sonication and pressure, and enzymatic treatments like proteolytic digestion, which proved particularly efficient [253,254].

The choice of a decellularization procedure over other cell removal methods lies in its ability to minimize damage to the heart's ECM [255,256]. This matrix plays a crucial role in providing a supportive environment for the growth and differentiation of new

cells [257]. By obtaining a cell-free matrix, decellularization creates optimal conditions for the proliferation of new cells [258]. Moreover, this technique offers advantages in terms of speed and cost-effectiveness compared to alternative cell removal methods.

What makes d-ECM truly remarkable is its ability to mimic the native cardiac tissue, offering a nurturing environment for cell growth and differentiation.

The preserved three-dimensional architecture of d-ECM plays a pivotal role in promoting the organization of cells and facilitating tissue regeneration within the damaged heart. Moreover, it houses a rich assortment of bioactive molecules, including growth factors and cytokines, which orchestrate cellular activities such as migration, angiogenesis, and tissue repair [259,260].

Customization is a key advantage of d-ECM, as its composition and mechanical properties can be tailored to suit individual patient needs. By serving as a scaffold, it aids in the integration of endogenous or exogenous cells into the damaged tissue, facilitating their regeneration and functional recovery [261].

Studies have demonstrated the remarkable potential of d-ECM in promoting the differentiation of stem cells into cardiomyocytes, thus bolstering the heart contractile capacity. Additionally, its immunomodulatory properties dampen inflammation and reduce the risk of immune rejection, enhancing the acceptance and survival of transplanted cells or tissue grafts [262,263].

Remarkably, d-ECM has already exhibited promising results in clinical settings [264]. Its safety and efficacy in improving cardiac function and reducing scar tissue formation after myocardial infarction have been established, igniting hope for a brighter future in cardiac regeneration [265].

In conclusion, d-ECM stands at the forefront of natural biomaterials for cardiac regeneration. Its ability to closely replicate the native cardiac tissue, facilitate cell integration, and stimulate tissue repair processes has opened new avenues for innovative therapies. With further advancements, this remarkable biomaterial holds the potential to restore heart function and offer renewed hope to patients grappling with heart disease.

The effectiveness of decellularization has been documented through several notable published examples. One standout study conducted by Ott et al. (2008) delved into the regeneration of functional myocardial tissue using decellularization. The researchers achieved success by decellularizing rat hearts through detergent-based methods, resulting in acellular scaffolds. These scaffolds were then repopulated with cardiac cells, which exhibited the remarkable ability to contract and generate electrical signals, indicating the successful regeneration of functional cardiac tissue [266].

Another significant publication by Zhang et al. (2022) shed light on the immense potential of decellularization in human cardiac tissue engineering. Through a combination of physical and chemical methods, the researchers managed to decellularize human myocardial tissue while preserving the extracellular matrix. Repopulating the d-ECM with human iPSC-derived cardiac cells yielded impressive results. The resulting constructs showcased organized tissue structure, contractility, and electrical coupling, effectively demonstrating the successful regeneration of functional human cardiac tissue [267].

Furthermore, a groundbreaking study by Perea-Gil et al. (2018) explored the feasibility of utilizing decellularized porcine cardiac extracellular matrix for cardiac regeneration. By employing a combination of detergents and enzymes, the researchers successfully decellularized porcine hearts, yielding acellular scaffolds. These scaffolds were then seeded and implanted into the infarcted hearts of pigs. The study highlighted that the decellularized scaffolds not only promoted cell survival and tissue integration but also significantly improved cardiac function, offering compelling evidence of the regenerative potential held by d-ECM [268].

In addition to these studies, an article published by Belviso et al. (2020) further contributes to the understanding of decellularization in cardiac tissue engineering. The researchers focused on the decellularization of human skin to create a scaffold for cardiac cell seeding. By implementing a combination of enzymatic and physical methods, they

successfully decellularized the human skin, preserving the extracellular matrix. Subsequent repopulation of the d-ECM with human CPCs led to the formation of organized tissue structures and the expression of cardiac-specific markers, indicating the potential for functional cardiac tissue regeneration [50,269].

Moreover, a groundbreaking publication by Jiang et al. (2023) investigated the potential of d-ECM materials as a scaffold for cardiac regeneration [270].

Additionally, a noteworthy study by Lee et al. (2017) showcased the regenerative potential of decellularized human skin in a rat model of myocardial infarction. The researchers effectively decellularized human dermal skin using anionic surfactants, resulting in an acellular matrix. By seeding the decellularized matrix with rat cardiac cells and implanting it into the infarcted hearts of rats, the study revealed significant improvements in cardiac function, tissue regeneration, and angiogenesis. These findings underscored the therapeutic potential of decellularized skin for cardiac tissue engineering [271].

Collectively, these published examples provide compelling evidence for the effectiveness of decellularization in cardiac regeneration. They illustrate the successful repopulation of decellularized scaffolds with cardiac cells, ultimately leading to the formation of fully functional cardiac tissue and substantial improvements in cardiac function. These studies highlight the immense potential held by decellularization techniques in advancing the field of cardiac tissue engineering, emphasizing the necessity for further research and development in this promising area of study Inizio modulo.

The application of natural biomaterials for cardiac regeneration has yielded significant achievements across multiple areas. Published studies have demonstrated the creation of new blood vessels using biomaterials-based approaches [272]. Furthermore, innovative heart valves fabricated from biomaterials have shown promise in improving the long-term outcomes of valve replacement surgeries [273,274].

Implantable devices, such as pacemakers, heart valves, and stents, have also witnessed noteworthy advancements due to the integration of biomaterials. These biomaterial-based devices have demonstrated improved biocompatibility and durability, contributing to the restoration of cardiac function and enhanced quality of life for patients with cardiovascular conditions [275,276].

The rapid progress in the field of biomaterials for cardiac regeneration is impressive. These biomaterials hold immense potential for creating new anatomical structures and modifying existing ones to address medical or surgical needs. The potential applications of biomaterials in cardiac regeneration, both direct and indirect, are vast and boundless. It is evident that further advancements and wider implementation of biomaterials in cardiac regeneration will bring considerable benefits to the field of cardiac regenerative medicine.

Indeed, biomaterials have revolutionized the field of cardiac regeneration by providing innovative solutions for repairing and regenerating the damaged heart. With their ability to enhance structural integrity, support tissue engineering, and promote cellular integration, biomaterials offer the possibility to improve patient outcomes and shape the future of cardiovascular medicine.

A brief summary of natural biomaterials described is showed in Table 3.

Table 3. Natural biomaterials.

Biomaterial	Source	Advantages	Formulation	Properties and Functions	Refs.
Collagen	Human/animal	High biocompatibility, biodegradability, excellent mechanical properties	Cardiac patches or injectable hydrogels	Promote cell adhesion, migration, and proliferation	[226–233]
Fibrin	Fibrinogen	Biocompatibility	Gels or hydrogels	Promote cell adhesion, proliferation and migration, influence cell behavior, and promote tissue healing	[234–236]
Gelatin	Collagen	Biocompatibility, biodegradability, low toxicity	Gelatin-based materials used to create cardiac patches, injectable matrices, and 3D constructs	Promote cell adhesion, proliferation, and differentiation	[237–239]
Silk	Silkworm cocoon	Mechanical properties, high tensile strength, and elasticity	Cardiac patches, tissue-engineered constructs	Provide mechanical support, cell attachment and support tissue remodeling	[240–242]
Chitosan	Exoskeleton of crustaceans and insects	Antibacterial properties, mechanical strength, biocompatibility, biodegradability	3D-printed scaffolds for skin and bone and cardiac patches	Enhance cell viability, improving contractile function and promoting neovascularization in the heart	[243–245]
Alginate	Brown seaweed	Bioabsorbability, biocompatibility	Hydrogels, cell encapsulation systems, microbeads	Protect cells and promote the formation of functional cardiac tissue	[246–248]
Hyaluronic Acid	ECM component	Biocompatibility, biodegradability, and water retention capacity	Hydrogels, injectable matrices, and 3D constructs	Support cell migration, proliferation and tissue regeneration Promote cell adhesion and proliferation and modulate cell behavior	[249–252]
Decellularized extracellular matrix	Human or animal tissues	Biocompatibility, safety, and efficacy	Cardiac patches	Preserve tissue native microenvironment, promote cell proliferation, and integration and differentiation	[50,253–276]

The table summarizes natural biomaterials for cardiac regeneration purpose, their features and properties, and the formulation available.

5. Bioreactors

Bioreactors are essential tools for tissue engineering, as they allow to grow cells and tissues in a controlled environment and study their behavior. Bioreactors provide the necessary nutrients and oxygen to the cells, while controlling the temperature and pH levels. Bioreactors come in a variety of shapes and sizes, from small benchtop models to larger, more complex systems. Depending on the type of research being conducted, researchers can choose from a range of technologies, including rotating wall vessels, stirred tanks, rocking platforms, and perfused systems. Bioreactors are not only used in tissue engineering, but also in stem cell research, drug development, and other areas of biomedicine. Their most

important function, though, is to provide a safe and controllable environment for growing tissue and organ in culture.

Bioreactors have been extensively studied in the field of tissue engineering, and numerous published studies have highlighted their critical role in creating optimal environments for cell and tissue growth. For example, a study conducted by Smith et al. demonstrated the importance of nutrient delivery in bioreactors for promoting cell proliferation and maintaining cell viability. The researchers found that by carefully formulating the culture media, they were able to provide cells with optimal nutrition, leading to enhanced growth and maintenance [277,278].

In another study by Jomezadeh Kheibary et al. (2020), the researchers focused on the regulation of oxygen levels within bioreactors. They showed that precise control of oxygenation in the bioreactor environment mimicked physiological conditions and supported cellular metabolism. This study emphasized the significance of maintaining sufficient oxygen levels for promoting proper cellular function and tissue development [279].

Temperature and pH regulation within bioreactors have also been extensively investigated. Research by Chen et al. (2020) demonstrated the impact of temperature control on cell growth and function. The study revealed that maintaining the desired temperature within the bioreactor, matching the physiological conditions of the targeted tissue, contributed to cell growth resembling their natural environment [280]. Similarly, pH levels have been investigated, as highlighted in the study conducted by Lee and colleagues in 2017. They found that carefully monitoring and adjusting the pH to the optimal range within the bioreactor helped cell growth and function [281].

Numerous studies have utilized bioreactor systems to investigate the behavior of cells and tissues in response to different stimuli. For example, a study by Ginai et al. (2013) utilized a bioreactor to study the effects of therapeutic agents on cells. By introducing drugs into the bioreactor system, the researchers were able to observe cellular responses in a controlled environment, providing valuable insights into the efficacy and potential side effects of novel treatments [282].

Various types of bioreactors have been developed to meet specific research needs, as highlighted in the study conducted by Williams et al. (2019). The researchers compared the advantages of different bioreactor designs and demonstrated how these different bioreactor systems offered unique benefits for cell and tissue culture, such as three-dimensional growth, large-scale production, fluid flow simulation, and nutrient exchange [283].

In stem cell research, bioreactors have been extensively used for the maintenance, expansion, and differentiation of stem cells. Several authors showed the utility of bioreactors in generating various cell populations for research, drug screening, and regenerative medicine purposes [284–286]. By providing a controlled environment, bioreactors supported the growth and differentiation of stem cells into specific cell types, enabling the development of a wide range of cell populations [287].

The effectiveness of bioreactors in drug development has also been investigated in several studies. For instance, a study by Scholp et al. (2022) demonstrated how bioreactors can be utilized to evaluate drug response, toxicity, and pharmacokinetics using human-derived cells or tissues. By mimicking physiological conditions, bioreactors offer a more relevant context for assessing the safety and efficacy of potential therapeutics, potentially reducing the reliance on animal models [288–290].

The field of tissue engineering aims to create functional and viable tissues and organs for transplantation, and bioreactors play a crucial role in this effort. Numerous studies have highlighted their significance in achieving this goal. For example, a study by Wang et al. (2020) emphasized how bioreactors provide a suitable environment for growing large-scale tissues with appropriate cellular organization and functionality. By fine-tuning the parameters within the bioreactor, researchers can guide tissue development and maturation, resulting in the creation of tissues that closely resemble their natural counterparts [291–293].

Advancements in bioreactor technology have been the subject of several studies. A number of authors focused on the incorporation of advanced sensors, imaging systems, and

real-time monitoring capabilities in bioreactors. These enhancements provide researchers with more comprehensive data on cellular behavior and tissue development, leading to improved understanding and optimization of tissue engineering processes [294–297].

Furthermore, computational modeling and artificial intelligence algorithms have been integrated with bioreactor systems to improve tissue engineering outcomes. This integration allows for more accurate predictions and optimization of tissue development, further enhancing the capabilities of bioreactors in the field of tissue engineering [298,299].

6. Gene Therapy

Gene therapy has emerged as a cutting-edge and increasingly popular method for treating a wide range of diseases, revolutionizing the field of medicine [300]. Among its vast potential applications, researchers have directed their attention toward exploring the use of gene therapy in cardiac tissue engineering, aiming to overcome the limitations of conventional treatments and provide new options for addressing cardiac diseases [301].

Cardiac tissue engineering involves the intricate process of utilizing gene therapy techniques to create new heart tissue or regenerate damaged tissue, thereby compensating for the effects of various cardiac disorders or injuries. This approach typically involves introducing therapeutic genes into the affected area, either by directly delivering them to the tissue or by using vectors such as viral particles to transport and integrate the genes into the cells [302].

To assess the effectiveness of gene therapy in cardiac tissue engineering, numerous studies have been conducted, spanning both preclinical and clinical settings [303,304].

These investigations have utilized various animal models and in vitro experiments to elucidate the potential of gene therapy interventions in repairing and regenerating cardiac tissue [305–307].

In a notable study focused on the growth and functional improvement of cardiac tissue, researchers employed gene therapy techniques to target specific genes associated with tissue regeneration and angiogenesis, and the formation of new blood vessels. For example, in a study published by Giacca and Zacchigna (2012), researchers introduced genes such as VEGF into damaged cardiac tissue, promoting the growth of new blood vessels and enhancing the contractility and functionality of the tissue. This study demonstrated the ability of gene therapy to generate new heart tissue and highlighted its potential for improving overall heart function [308].

Additional studies have demonstrated the capacity of gene therapy to stimulate the regeneration of cardiac muscle cells, which are vital for proper heart function. For instance, researchers have used gene therapy to deliver genes responsible for cell proliferation, differentiation, and survival to the damaged cardiac tissue. These genes trigger the activation of specific cellular pathways, leading to the replication and maturation of cardiac muscle cells and ultimately improving the contractility and overall performance of the heart [309–312].

Furthermore, gene therapy has shown promise in addressing heart failure, a condition characterized by the loss of cardiac muscle cells and diminished heart function. Studies have investigated the use of gene therapy to stimulate the proliferation and differentiation of CPCs into mature cardiac muscle cells. By delivering genes that enhance the growth and maturation of these progenitor cells, researchers have observed the restoration of cardiac tissue integrity and function, offering hope for individuals suffering from heart failure [312].

Amidst its bright prospects, gene therapy for cardiac regeneration also unveils a spectrum of risks that demand accurate management [313]. This therapeutic modality involves the introduction of foreign genetic material into cells, a process that carries the potential for unintended interactions with the host genome [314]. The repercussions of such off-target effects might manifest as genetic mutations, disruption of normal cellular processes, or, in extreme cases, the initiation of cancerous growth [304,315,316]. The utilization of viral vectors or alternative gene delivery systems in this context can incite immune responses within the body. The immune system's identification of these viral vectors as intruders

might trigger a defensive reaction, potentially neutralizing the intended therapeutic impact and inducing inflammatory reactions [317]. Moreover, the expression of therapeutic genes or proteins could trigger inflammatory responses, culminating in tissue impairment or untoward reactions [318]. Assuring the prolonged safety of gene therapy constitutes a formidable task. The enduring effects of gene therapy might display a transient nature, with the therapeutic benefits diminishing over time as the introduced genetic material becomes diluted or degrades [319]. The utilization of viral vectors to facilitate the delivery of therapeutic genes bears certain risks, including the potential integration of vector DNA into the host genome [317]. This eventuality could disrupt normal gene function or pave the way for oncogenic repercussions. Striking an optimal balance in gene expression assumes pivotal significance. Excessive or deficient expression may precipitate unforeseen consequences, affecting therapeutic efficacy or instigating deleterious effects [51]. In individuals harboring inherited or genetic heart conditions, gene therapy has the potential to interact with existing genetic mutations, thereby complicating therapeutic outcomes or introducing novel risks. Patient responses to gene therapy invariably exhibit variability, influenced by factors spanning genetics, age, and overall health [300,320]. Crafting treatments attuned to the unique exigencies of individual patients while minimizing risks necessitates a personalized approach. The transition from preclinical studies to clinical applications introduces multifaceted complexities. This journey entails refining gene delivery methods, optimizing dosages, and establishing meticulous monitoring protocols [321–323]. The intricate interplay between genes, characterized by complexity and incomplete comprehension, introduces an additional layer of intricacy. Modifying one gene could trigger cascading effects on other genes and pathways, potentially engendering unforeseen outcomes.

7. Future Directions

Organoids and organ-on-chip models have emerged as cutting-edge technologies with remarkable potential in the study of human organs, notably the heart, within controlled and physiologically relevant environments. While they offer numerous advantages for drug testing, disease modeling, and mechanistic investigations, they do encounter limitations beyond ethical and regulatory concerns when attempting to translate their findings into effective in vivo treatments [324,325]. While they excel at providing insights into localized organ behavior, they may encounter challenges when replicating the broader systemic effects that manifest within the entire organism during treatment [326,327]. Achieving successful in vivo treatments necessitates a profound comprehension of how therapies impact the entirety of the body-a task that proves intricate to accomplish with isolated organ models. Furthermore, the intricate vascular networks and dynamic microenvironments inherent in vivo are often absent from organoids and organ-on-chip models. Crucial factors such as blood circulation, oxygen delivery, and waste elimination play pivotal roles in organ function and responses to treatment [328]. Emulating these dynamics in vitro poses technical complexities and may influence the metabolism and distribution of drugs or therapies. For treatments requiring extended assessment, especially in the context of chronic diseases, organoids and organ-on-chip models may fall short due to their design being primarily geared towards short-term experiments. Their inability to accurately replicate the long-term effects of treatments, encompassing potential metabolite accumulation and evolving cell behavior over time, presents a notable constraint [329]. It is vital to recognize that in vivo treatments can incite immune reactions and influence multiple organ systems. In this regard, these models frequently lack a functional immune system and fail to fully capture the intricate interplay between immune cells, tissues, and treatments that substantially impact treatment outcomes overall [330].

Even if organoids or organ-on-chip studies yield promising results, their progression to clinical applications mandates thorough validation through animal models and, ultimately, human clinical trials. The inherent variability between species and model systems can introduce complexities when attempting to accurately extrapolate human responses, underscoring the challenges inherent in this translational process.

7.1. Organoids

Organoids are an innovative and highly promising technique in the field of regenerative medicine. They offer a groundbreaking leap forward in tissue engineering, providing a sophisticated and dynamic three-dimensional structure that closely mimics the intricate architecture and functionality of real organs. Organoids are created through a meticulous process involving the cultivation and self-organization of a diverse array of cells within a laboratory environment, resulting in the formation of complex tissue structures that faithfully replicate the complexity of actual organs.

Numerous examples have been published showcasing the successful generation and application of organoids in cardiac regeneration. One notable study published in *Nature Protocols* demonstrated the creation of heart organoids from human pluripotent stem cells. These heart organoids contained different cardiac cell types, including cardiomyocytes, and exhibited spontaneous contractions, representing a crucial step towards generating functional cardiac tissue for transplantation and disease modeling [331].

In another study, Millset al. (2020) developed human heart muscle organoids from iPSCs. These organoids exhibited a high degree of structural and functional similarity to the human heart, including the ability to respond to physiological cues and drug responses. This study highlighted the potential of organoids as a valuable tool for studying cardiac diseases and screening potential therapeutic interventions [332].

Furthermore, in a study published in *Cell*, Hofbauer et al. (2021) demonstrated the use of heart organoids derived from human stem cells to model and study congenital heart disease. The researchers successfully recreated the cellular and molecular features of the disease in the organoids, providing insights into its underlying mechanisms and potential avenues for treatment development [333].

These examples highlight the transformative potential of organoids in cardiac regeneration. By utilizing patient-specific cells, organoids can be tailored to match the unique characteristics of an individual's own heart tissue, minimizing the risk of immune rejection. Moreover, organoids can be engineered to withstand the mechanical forces and dynamic conditions of the cardiac environment, ensuring their long-term viability and functional effectiveness upon transplantation.

One of the key therapeutic potentials of organoids lies in their ability to generate cardiomyocytes. Organoids have been successfully engineered to produce both immature and mature cardiomyocytes, offering a unique opportunity to replace damaged or dysfunctional cells in patients with heart conditions, particularly heart failure. By introducing healthy and functional cardiomyocytes derived from organoids, damaged cardiac tissue can be rejuvenated, leading to improved cardiac function, enhanced quality of life, and potentially even the prevention of adverse cardiac events.

While the field of organoid technology in cardiac regeneration is still in its early stages, ongoing research and advancements continue to unveil new possibilities. Beyond their direct application in transplantation and tissue repair, organoids provide an invaluable platform for studying the genetic and molecular basis of cardiac diseases. Researchers can utilize organoids to investigate the underlying causes, disease mechanisms, and therapeutic targets of various heart conditions in a controlled and representative model system. This deeper understanding of cardiac biology has the potential to drive the development of innovative treatments, personalized medicine approaches, and preventive strategies to treat heart diseases more effectively [334].

Organoids represent a revolutionary breakthrough in the field of cardiac regeneration due to their ability to replicate the intricate structure and functionality of organs, coupled with their resilience and capacity to generate functional cardiomyocytes.

As the field of organoid technology continues to advance, researchers are exploring new strategies to enhance the capabilities and applications of organoids in cardiac regeneration. For instance, efforts are underway to improve the vascularization of organoids by integrating blood vessel networks to better mimic the physiological environment of the heart. This could further enhance the functionality and survival of transplanted organoids.

Additionally, researchers are investigating the use of bioactive molecules, growth factors, and mechanical cues to guide the development and maturation of organoids. By replicating the complex signaling pathways and mechanical forces that influence heart development and function, scientists aim to create organoids that closely resemble adult human hearts in terms of structure and function [335].

Moreover, advancements in tissue engineering and bioprinting technologies hold great promise for the fabrication of larger, more intricate organoids with precise cellular organization. These technologies allow for the creation of multi-layered structures that can better mimic the architecture of the heart, including its different regions and cell types. This level of complexity could lead to more accurate disease modeling and the development of personalized treatments.

It is worth noting that while organoids offer significant potential, there are still challenges to overcome. These include improving the scalability and cost-effectiveness of organoid production, addressing the limitations of current culture methods, and ensuring the safety and long-term functionality of transplanted organoids. Collaborative efforts between researchers, clinicians, and bioengineers are essential to address these challenges and translate organoid technology into clinical practice.

7.2. Organs-on-Chips

Extensive studies have been conducted to explore innovative approaches to regenerate cardiac tissue, and one particularly notable advancement is the use of chips, also known as 'micro-engineered cardiac tissue,' to facilitate the process [336–341]. These chips, which are small in size and comparable to a fingernail, have the remarkable ability to mimic the behavior of real human heart cells. By harnessing this technology, researchers have achieved the creation of 3D scaffolds that closely resemble the natural behavior of a functioning human heart [342–346].

The utilization of chips for cardiac regeneration offers several significant advantages over conventional approaches. Firstly, the cells integrated into the chips can self-renew, which enables them to spontaneously regenerate and repair themselves without external intervention [347].

This means that once the cardiac tissue is repaired using the chip, it can continue to function for extended periods without the need for further adjustments or interventions. This inherent capability of the cells embedded in the chips ensures long-term viability and functionality of the regenerated cardiac tissue.

Moreover, chips have proven to be highly effective in repairing damaged cardiac tissue. By replicating the behavior of damaged cells, the chips can replace them with healthy cells, thus restoring the normal functionality of the tissue. This ability to mimic and replace damaged cells is a significant advantage, as it facilitates the restoration of cardiac function and promotes overall cardiac health [348].

Another notable benefit of chip-based cardiac regeneration is the reduction in the need for extensive human intervention. Traditional regenerative treatments often require long-term hospitalization for patients, which can be burdensome and costly. Additionally, invasive procedures carry a risk of infection and other complications. However, chip-based regeneration minimizes these concerns by eliminating the need for prolonged hospital stays and invasive interventions. This results in improved patient comfort, reduced healthcare costs, and a lower risk of complications.

Furthermore, the use of chips in cardiac regeneration is relatively cost-effective and user-friendly. Chips can be manufactured at a reasonable cost, making them accessible to a wider range of healthcare providers and patients. Additionally, their small size and compatibility with existing medical technologies make them easy to incorporate into clinical practice. This user-friendly aspect allows for widespread adoption and implementation of chip-based cardiac regeneration techniques.

Overall, the utilization of chips for cardiac regeneration presents a multitude of advantages. The self-renewing nature of the cells in the chips ensures long-term repair and

functionality of the cardiac tissue. The ability of chips to replace effectively damaged cells promotes efficient tissue regeneration and restoration of cardiac function. By reducing the need for human intervention, chip-based regeneration mitigates the associated challenges and costs. These factors, coupled with the affordability and user-friendliness of chips, contribute to their increasing popularity as a promising approach in cardiac regeneration. With ongoing advancements and research in this field, it is expected that the use of chips for cardiac regeneration will continue to evolve and gain prominence in the coming years [349].

One of the most extensively studied and published areas of organ-on-chip technology is the development of cardiac or heart-on-chip models. These cardiac organ-on-chip systems aim to replicate the complex structure and function of the human heart, allowing researchers to study cardiac physiology, drug responses, disease mechanisms, and potential therapeutic interventions in a controlled and highly realistic in vitro setting.

Several notable examples of cardiac organ-on-chip models have been published, demonstrating the versatility and effectiveness of this technology. One such example is a study published by Ronaldson-Bouchard et al. (2018). The researchers developed a human-induced pluripotent stem cell (hiPSC)-derived cardiac microtissue on a chip, which recapitulated key features of human heart tissue. The microtissue consisted of hiPSC-derived cardiac cells arranged in a three-dimensional structure that mimicked the native organization of heart tissue. The chip allowed for the monitoring of contractile function, electrical activity, and drug responses, enabling investigations into cardiac diseases, such as hypertrophic cardiomyopathy, and the evaluation of potential therapeutic interventions [350].

Another notable publication by Leung et al. (2022) showed the development of a heart–lung micromodel on a chip. This organ-on-chip platform integrated cardiac and pulmonary functionalities to mimic the physiological interaction between the heart and lungs. The chip contained compartments representing the heart, lung, and vasculature, allowing for the study of cardiopulmonary interactions, oxygen transfer, and drug responses. This model demonstrated the potential to investigate cardiopulmonary diseases, such as pulmonary hypertension, and evaluate the effects of drugs or interventions targeting both the heart and lungs [351].

Furthermore, a study published by Skardal et al. (2017) presented a multi-organ-on-chip platform, where a cardiac microtissue was combined with liver and lung models. This multi-organ chip allowed for the investigation of inter-organ interactions, such as the effects of drug metabolism in the liver on cardiac function. The integrated platform provided a comprehensive in vitro system to study drug toxicity, drug–drug interactions, and the systemic effects of drugs on various organs [352].

These examples highlight the diverse applications and capabilities of cardiac organ-on-chip models. By replicating the structure and function of the human heart, these chips enable researchers to study cardiac physiology and pathophysiology, evaluate drug responses, and investigate disease mechanisms. They also offer the opportunity to test potential therapeutic interventions and evaluate their effectiveness in a highly controlled and realistic environment. Continued research and development in the field of cardiac organ-on-chip technology are expected to yield further advancements and contribute to our understanding and treatment of cardiovascular diseases.

Furthermore, numerous studies have focused on refining and optimizing cardiac organ-on-chip models by incorporating additional features. For instance, researchers have integrated sensors to monitor contractile forces and electrical activity in real-time, enabling precise measurements of cardiac function and drug responses [353]. Other studies have explored the inclusion of vascular networks within the chip to mimic the intricate blood supply to the heart, allowing for investigations into vascular dynamics and the impact of blood flow on cardiac function [354].

7.3. In Vivo Relevance of Organoids and Organ-on-Chip Data

Organoids and organ-on-chip models represent invaluable supplements to conventional research methodologies, yet their successful integration necessitates a comprehensive framework that encompasses animal studies and clinical trials. This integration is imperative to ensure the seamless transition of treatments from theoretical concepts to practical real-world applications. Although organoids and organ-on-chip models strive to mimic specific aspects of organ functionality, they often oversimplify the intricate cellular and physiological interactions inherent in the human body. It is worth noting that these models may not fully encapsulate the intricate tapestry of tissue–tissue interactions, immune responses, and systemic influences that critically shape the safety and effectiveness of in vivo treatments [355,356].

8. Conclusions

In conclusion, cardiovascular disease remains a significant global health issue, and the development of novel treatments is crucial to address this burden. The field of cardiac regeneration holds great promise in providing long-term solutions for treating cardiovascular diseases. Recent advancements in stem cell therapy, biomaterials, bioreactors, and gene therapy have significantly contributed to the progress of cardiac tissue engineering.

Stem cell therapy has shown promising results in differentiating stem cells into heart cells and repairing damaged cardiac tissue. Biomaterials have enabled the creation of scaffolds that support the growth and organization of heart cells, facilitating the formation of functional cardiac tissue. Bioreactors have provided controlled environments to promote the maturation of cardiac tissue, closely resembling native heart tissue. Gene therapy has offered strategies to enhance stem cell differentiation or improve the survival and function of existing heart cells.

Clinical applications of tissue engineering are already being used to repair damaged heart tissue and improve the lifespan of these medical interventions. Furthermore, the development of lab-grown functional heart cells opens the possibility of personalized treatments that surpass traditional methods in effectiveness.

These advancements in cardiac tissue engineering have the potential to revolutionize cardiovascular medicine, offering new treatments and more durable replacement organs. However, further research and clinical trials are necessary to fully evaluate the safety and efficacy of these therapies. Each approach here described has shown potential based on current data, albeit no single technology or strategy has definitively emerged as the most promising. The common assumption among the scientific community is that the right combination of different approaches may hold the most potential for cardiac regeneration. Combining stem cell therapies with tissue engineering, gene therapy, or other techniques could enhance the overall regenerative effect, as the complexity of the regeneration process needs a multipronged approach focused on diverse and fundamental aspects related to cardiac regeneration, such as cells, biological signaling and microenvironment. Future perspectives in the field of cardiac tissue engineering are highly promising and hold great potential, and some key focus and potential advancements can be expected:

1. Advanced cell-based therapies: Stem cell therapy is a rapidly evolving area, and ongoing research aims to optimize the use of different stem cell types to enhance their regenerative potential. Strategies to improve stem cell survival, engraftment, and differentiation into functional heart cells will be explored further. Additionally, the development of off-the-shelf cell products and strategies for immune modulation to overcome rejection issues will be crucial for widespread clinical implementation.
2. Bioengineered heart tissue: The field of bioengineering will continue to advance, focusing on the development of artificial heart tissue with improved functionality and durability. Integration of advanced biomaterials, such as bioactive scaffolds and hydrogels, with growth factors and living cells will allow for the creation of more sophisticated and functional cardiac tissue constructs. Techniques like 3D bioprinting

will play a pivotal role in fabricating complex structures that closely resemble native heart tissue.

3. Maturation of engineered tissues: Achieving functional maturity in bioengineered heart tissue remains a challenge. Future research will focus on refining bioreactor systems that mimic the mechanical and electrical cues experienced by the heart during development. By exposing cardiac cells to appropriate stimuli, researchers aim to promote the formation of fully matured tissue that can seamlessly integrate with the host tissue and exhibit proper contractile function.
4. Gene therapy advancements: Gene therapy approaches will continue to evolve, with a focus on enhancing the regenerative potential of stem cells and improving the survival and function of existing heart cells. Techniques such as gene editing and genetic reprogramming hold promise for precisely manipulating cell behavior and enhancing therapeutic outcomes.
5. Personalized medicine: The development of patient-specific therapies will be a major focus in the future. Advances in stem cell technology, tissue engineering, and genetic profiling will enable the generation of personalized cardiac tissue constructs that closely match an individual's specific needs. This tailored approach has the potential to improve significantly treatment outcomes and reduce the risk of rejection or adverse reactions.
6. Translation to clinical practice: Clinical trials evaluating the safety and efficacy of cardiac tissue engineering approaches are currently underway. As research progresses, these therapies are expected to advance from experimental stages to become viable treatment options for patients with heart disease. The optimization of manufacturing processes, scalability of production, and regulatory approval will be critical for the successful translation of these therapies into routine clinical practice.

In conclusion, the future of cardiac tissue engineering holds immense potential for revolutionizing the treatment of cardiovascular diseases. Continued research, technological advancements, and clinical trials will pave the way for the development of effective and personalized regenerative therapies. These innovations have the potential to improve significantly the quality of life for patients with heart disease and reduce the global burden of cardiovascular mortality.

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References

1. Mc Namara, K.; Alzubaidi, H.; Jackson, J.K. Cardiovascular disease as a leading cause of death: How are pharmacists getting involved? *Integr. Pharm. Res. Pract.* **2019**, *8*, 1–11. [CrossRef] [PubMed]
2. Kreatsoulas, C.; Anand, S.S. The impact of social determinants on cardiovascular disease. *Can. J. Cardiol.* **2010**, *26*, 8C–13C. [CrossRef] [PubMed]
3. World Health Organization. *Global Action Plan for the Prevention and Control of NCDs 2013–2020*; World Health Organization: Geneva, Switzerland, 2021.
4. Garbern, J.C.; Lee, R.T. Heart regeneration: 20 years of progress and renewed optimism. *Dev. Cell* **2022**, *57*, 424–439. [CrossRef]
5. Sadek, H.; Olson, E.N. Toward the Goal of Human Heart Regeneration. *Cell Stem Cell* **2020**, *26*, 7–16. [CrossRef]

6. Wang, J.; An, M.; Haubner, B.J.; Penninger, J.M. Cardiac regeneration: Options for repairing the injured heart. *Front. Cardiovasc. Med.* **2023**, *9*, 981982. [CrossRef]
7. Hashimoto, H.; Olson, E.N.; Bassel-Duby, R. Therapeutic approaches for cardiac regeneration and repair. *Nat. Rev. Cardiol.* **2018**, *15*, 585–600. [CrossRef]
8. Choi, W.Y.; Poss, K.D. Cardiac regeneration. *Curr. Top. Dev. Biol.* **2012**, *100*, 319–344. [CrossRef] [PubMed]
9. Bouten, C.V.C.; Cheng, C.; Vermue, I.M.; Gawlitta, D.; Passier, R. Cardiovascular Tissue Engineering and Regeneration: A Plead for Further Knowledge Convergence. *Tissue Eng. Part A* **2022**, *28*, 525–541. [CrossRef]
10. Ghiroldi, A.; Piccoli, M.; Cirillo, F.; Monasky, M.M.; Ciconte, G.; Pappone, C.; Anastasia, L. Cell-Based Therapies for Cardiac Regeneration: A Comprehensive Review of Past and Ongoing Strategies. *Int. J. Mol. Sci.* **2018**, *19*, 3194. [CrossRef]
11. Luo, L.; Li, T.S. Mini Review: Recent Advances in the Cell-Based Therapies for Cardiac Regeneration. *Curr. Stem Cell Res. Ther.* **2020**, *15*, 649–660. [CrossRef]
12. Curtis, M.W.; Russell, B. Cardiac tissue engineering. *J. Cardiovasc. Nurs.* **2009**, *24*, 87–92. [CrossRef]
13. Leor, J.; Amsalem, Y.; Cohen, S. Cells, scaffolds, and molecules for myocardial tissue engineering. *Pharmacol. Ther.* **2005**, *105*, 151–163. [CrossRef] [PubMed]
14. Yu, D.; Wang, X.; Ye, L. Cardiac Tissue Engineering for the Treatment of Myocardial Infarction. *J. Cardiovasc. Dev. Dis.* **2021**, *8*, 153. [CrossRef]
15. Salgado, A.J.; Oliveira, J.M.; Martins, A.; Teixeira, F.G.; Silva, N.A.; Neves, N.M.; Sousa, N.; Reis, R.L. Tissue engineering and regenerative medicine: Past, present, and future. *Int. Rev. Neurobiol.* **2013**, *108*, 1–33. [CrossRef]
16. Kitsuka, T.; Takahashi, F.; Reinhardt, J.; Watanabe, T.; Ulziibayar, A.; Yimit, A.; Kelly, J.; Shinoka, T. Advances in Cardiac Tissue Engineering. *Bioengineering* **2022**, *9*, 696. [CrossRef]
17. Sharma, V.; Dash, S.K.; Govarthanan, K.; Gahtori, R.; Negi, N.; Barani, M.; Tomar, R.; Chakraborty, S.; Mathapati, S.; Bishi, D.K.; et al. Recent Advances in Cardiac Tissue Engineering for the Management of Myocardium Infarction. *Cells* **2021**, *10*, 2538. [CrossRef] [PubMed]
18. Nguyen, A.H.; Marsh, P.; Schmiess-Heine, L.; Burke, P.J.; Lee, A.; Lee, J.; Cao, H. Cardiac tissue engineering: State-of-the-art methods and outlook. *J. Biol. Eng.* **2019**, *13*, 57. [CrossRef] [PubMed]
19. Chingale, M.; Zhu, D.; Cheng, K.; Huang, K. Bioengineering Technologies for Cardiac Regenerative Medicine. *Front. Bioeng. Biotechnol.* **2021**, *9*, 681705. [CrossRef] [PubMed]
20. Hoang, D.M.; Pham, P.T.; Bach, T.Q.; Ngo, A.T.L.; Nguyen, Q.T.; Phan, T.T.K.; Nguyen, G.H.; Le, P.T.T.; Hoang, V.T.; Forsyth, N.R.; et al. Stem cell-based therapy for human diseases. *Signal Transduct. Target. Ther.* **2022**, *7*, 272. [CrossRef] [PubMed]
21. Augustine, R.; Dan, P.; Hasan, A.; Khalaf, I.M.; Prasad, P.; Ghosal, K.; Gentile, C.; McClements, L.; Maureira, P. Stem cell-based approaches in cardiac tissue engineering: Controlling the microenvironment for autologous cells. *Biomed. Pharmacother.* **2021**, *138*, 111425. [CrossRef]
22. Vunjak-Novakovic, G.; Lui, K.O.; Tandon, N.; Chien, K.R. Bioengineering heart muscle: A paradigm for regenerative medicine. *Annu. Rev. Biomed. Eng.* **2011**, *13*, 245–267. [CrossRef]
23. Smagul, S.; Kim, Y.; Smagulova, A.; Raziyeva, K.; Nurkesh, A.; Saparov, A. Biomaterials Loaded with Growth Factors/Cytokines and Stem Cells for Cardiac Tissue Regeneration. *Int. J. Mol. Sci.* **2020**, *21*, 5952. [CrossRef]
24. Rebouças, J.S.; Santos-Magalhães, N.S.; Formiga, F.R. Cardiac Regeneration using Growth Factors: Advances and Challenges. *Arq. Bras. Cardiol.* **2016**, *107*, 271–275. [CrossRef]
25. Dai, Y.; Foley, A. Tissue engineering approaches to heart repair. *Crit. Rev. Biomed. Eng.* **2014**, *42*, 213–227. [CrossRef]
26. Roacho-Pérez, J.A.; Garza-Treviño, E.N.; Moncada-Saucedo, N.K.; Carriquiry-Chequer, P.A.; Valencia-Gómez, L.E.; Matthews, E.R.; Gómez-Flores, V.; Simental-Mendía, M.; Delgado-Gonzalez, P.; Delgado-Gallegos, J.L.; et al. Artificial Scaffolds in Cardiac Tissue Engineering. *Life* **2022**, *12*, 1117. [CrossRef]
27. O'Brien, T.; Barry, F.P. Stem cell therapy and regenerative medicine. *Mayo Clin. Proc.* **2009**, *84*, 859–861. [CrossRef]
28. Akbarzadeh, A.; Sobhani, S.; Soltani Khaboushan, A.; Kajbafzadeh, A.M. Whole-Heart Tissue Engineering and Cardiac Patches: Challenges and Promises. *Bioengineering* **2023**, *10*, 106. [CrossRef] [PubMed]
29. Li, M.; Wu, H.; Yuan, Y.; Hu, B.; Gu, N. Recent fabrications and applications of cardiac patch in myocardial infarction treatment. *View* **2022**, *3*, 20200153. [CrossRef]
30. Mendelson, K.; Schoen, F.J. Heart valve tissue engineering: Concepts, approaches, progress, and challenges. *Ann. Biomed. Eng.* **2006**, *34*, 1799–1819. [CrossRef] [PubMed]
31. Stassen, O.M.J.A.; Muylaert, D.E.P.; Bouten, C.V.C.; Hjortnaes, J. Current Challenges in Translating Tissue-Engineered Heart Valves. *Curr. Treat. Options Cardiovasc. Med.* **2017**, *19*, 71. [CrossRef]
32. Combs, M.D.; Yutzey, K.E. Heart valve development: Regulatory networks in development and disease. *Circ. Res.* **2009**, *105*, 408–421. [CrossRef] [PubMed]
33. Goubergrits, L.; Affeld, K.; Kertzscher, U. Innovative developments of the heart valves designed for use in ventricular assist devices. *Expert Rev. Med. Devices* **2005**, *2*, 61–71. [CrossRef] [PubMed]
34. Albert, B.J.; Butcher, J.T. Future prospects in the tissue engineering of heart valves: A focus on the role of stem cells. *Expert Opin. Biol. Ther.* **2023**, *23*, 553–564. [CrossRef]
35. Nasser, M.I.; Qi, X.; Zhu, S.; He, Y.; Zhao, M.; Guo, H.; Zhu, P. Current situation and future of stem cells in cardiovascular medicine. *Biomed. Pharmacother.* **2020**, *132*, 110813. [CrossRef]

36. Rodrigues, I.C.P.; Kaasi, A.; Maciel Filho, R.; Jardini, A.; Gabriel, L.P. Cardiac tissue engineering: Current state-of-the-art materials, cells and tissue formation. *Einstein* **2018**, *1*, eRB4538. [CrossRef] [PubMed]
37. Olson, J.L.; Atala, A.; Yoo, J.J. Tissue engineering: Current strategies and future directions. *Chonnam Med. J.* **2011**, *47*, 1–13. [CrossRef]
38. Häneke, T.; Sahara, M. Progress in Bioengineering Strategies for Heart Regenerative Medicine. *Int. J. Mol. Sci.* **2022**, *23*, 3482. [CrossRef]
39. Fujita, B.; Zimmermann, W.H. Myocardial tissue engineering strategies for heart repair: Current state of the art. *Interact. CardioVasc. Thorac. Surg.* **2018**, *27*, 916–920. [CrossRef]
40. Terashvili, M.; Bosnjak, Z.J. Stem Cell Therapies in Cardiovascular Disease. *J. Cardiothorac. Vasc. Anesth.* **2019**, *33*, 209–222. [CrossRef]
41. Banovic, M.; Poglajen, G.; Vrtovec, B.; Ristic, A. Contemporary Challenges of Regenerative Therapy in Patients with Ischemic and Non-Ischemic Heart Failure. *J. Cardiovasc. Dev. Dis.* **2022**, *9*, 429. [CrossRef]
42. Vaka, R.; Davis, D.R. State-of-play for cellular therapies in cardiac repair and regeneration. *Stem Cells* **2021**, *39*, 1579–1588. [CrossRef] [PubMed]
43. Madonna, R.; Van Laake, L.W.; Botker, H.E.; Davidson, S.M.; De Caterina, R.; Engel, F.B.; Eschenhagen, T.; Fernandez-Aviles, F.; Hausenloy, D.J.; Hulot, J.S.; et al. ESC Working Group on Cellular Biology of the Heart: Position paper for Cardiovascular Research: Tissue engineering strategies combined with cell therapies for cardiac repair in ischaemic heart disease and heart failure. *Cardiovasc. Res.* **2019**, *115*, 488–500. [CrossRef] [PubMed]
44. Boyle, A.J.; Schulman, S.P.; Hare, J.M.; Oettgen, P. Is stem cell therapy ready for patients? Stem Cell Therapy for Cardiac Repair. Ready for the Next Step. *Circulation* **2006**, *114*, 339–352. [CrossRef] [PubMed]
45. Huyer, L.D.; Montgomery, M.; Zhao, Y.; Xiao, Y.; Conant, G.; Korolj, A.; Radisic, M. Biomaterial based cardiac tissue engineering and its applications. *Biomed. Mater.* **2015**, *10*, 034004. [CrossRef]
46. Reis, L.A.; Chiu, L.L.; Feric, N.; Fu, L.; Radisic, M. Biomaterials in myocardial tissue engineering. *J. Tissue Eng. Regen. Med.* **2016**, *10*, 11–28. [CrossRef]
47. Paez-Mayorga, J.; Hernández-Vargas, G.; Ruiz-Esparza, G.U.; Iqbal, H.M.N.; Wang, X.; Zhang, Y.S.; Parra-Saldivar, R.; Khademhosseini, A. Bioreactors for Cardiac Tissue Engineering. *Adv. Healthc. Mater.* **2019**, *8*, e1701504. [CrossRef]
48. Massai, D.; Cerino, G.; Gallo, D.; Pennella, F.; Deriu, M.A.; Rodriguez, A.; Montevecchi, F.M.; Bignardi, C.; Audenino, A.; Morbiducci, U. Bioreactors as engineering support to treat cardiac muscle and vascular disease. *J. Healthc. Eng.* **2013**, *4*, 329–370. [CrossRef]
49. Massai, D.; Pisani, G.; Isu, G.; Rodriguez Ruiz, A.; Cerino, G.; Galluzzi, R.; Pisanu, A.; Tonoli, A.; Bignardi, C.; Audenino, A.L.; et al. Bioreactor Platform for Biomimetic Culture and in situ Monitoring of the Mechanical Response of in vitro Engineered Models of Cardiac Tissue. *Front. Bioeng. Biotechnol.* **2020**, *8*, 733. [CrossRef]
50. Belviso, I.; Romano, V.; Sacco, A.M.; Ricci, G.; Massai, D.; Cammarota, M.; Catizone, A.; Schiraldi, C.; Nurzynska, D.; Terzini, M.; et al. Decellularized Human Dermal Matrix as a Biological Scaffold for Cardiac Repair and Regeneration. *Front. Bioeng. Biotechnol.* **2020**, *8*, 229. [CrossRef]
51. Kim, Y.; Zharkinbekov, Z.; Sarsenova, M.; Yeltay, G.; Saparov, A. Recent Advances in Gene Therapy for Cardiac Tissue Regeneration. *Int. J. Mol. Sci.* **2021**, *22*, 9206. [CrossRef]
52. Mason, D.; Chen, Y.Z.; Krishnan, H.V.; Sant, S. Cardiac gene therapy: Recent advances and future directions. *J. Control. Release* **2015**, *215*, 101–111. [CrossRef]
53. Barbato, J.E.; Kibbe, M.R.; Tzeng, E. The emerging role of gene therapy in the treatment of cardiovascular diseases. *Crit. Rev. Clin. Lab. Sci.* **2003**, *40*, 499–545. [CrossRef] [PubMed]
54. Kozarsky, K.F. Gene therapy for cardiovascular disease. *Curr. Opin. Pharmacol.* **2001**, *1*, 197–202. [CrossRef] [PubMed]
55. Tran, D.B.; Weber, C.; Lopez, R.A. Anatomy, Thorax, Heart Muscles. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
56. Vunjak-Novakovic, G.; Tandon, N.; Godier, A.; Maidhof, R.; Marsano, A.; Martens, T.P.; Radisic, M. Challenges in cardiac tissue engineering. *Tissue Eng. Part B Rev.* **2010**, *16*, 169–187. [CrossRef] [PubMed]
57. Masson-Meyers, D.S.; Tayebi, L. Vascularization strategies in tissue engineering approaches for soft tissue repair. *J. Tissue Eng. Regen. Med.* **2021**, *15*, 747–762. [CrossRef] [PubMed]
58. Mahmud, S.; Alam, S.; Emon, N.U.; Boby, U.H.; Kamruzzaman Ahmed, F.; Monjur-Al-Hossain, A.S.M.; Tahamina, A.; Rudra, S.; Ajrin, M. Opportunities and challenges in stem cell therapy in cardiovascular diseases: Position standing in 2022. *Saudi Pharm. J.* **2022**, *30*, 1360–1371. [CrossRef]
59. Rheault-Henry, M.; White, I.; Atoui, R. Therapeutic Uses of Stem Cells for Heart Failure: Hype or Hope. In *Handbook of Stem Cell Therapy*; Haider, K.H., Ed.; Springer: Singapore, 2022; pp. 1–34. [CrossRef]
60. du Pré, B.C.; Doevendans, P.A.; van Laake, L.W. Stem cells for cardiac repair: An introduction. *J. Geriatr. Cardiol.* **2013**, *10*, 186–197. [CrossRef]
61. Smits, A.M.; van Vliet, P.; Hassink, R.J.; Goumans, M.J.; Doevendans, P.A. The role of stem cells in cardiac regeneration. *J. Cell. Mol. Med.* **2005**, *9*, 25–36. [CrossRef] [PubMed]
62. Garbern, J.C.; Lee, R.T. Cardiac stem cell therapy and the promise of heart regeneration. *Cell Stem Cell* **2013**, *12*, 689–698. [CrossRef]

63. Sun, Q.; Zhang, Z.; Sun, Z. The potential and challenges of using stem cells for cardiovascular repair and regeneration. *Genes Dis.* **2014**, *1*, 113–119. [CrossRef]
64. Isomi, M.; Sadahiro, T.; Ieda, M. Progress and Challenge of Cardiac Regeneration to Treat Heart Failure. *J. Cardiol.* **2019**, *73*, 97–101. [CrossRef] [PubMed]
65. Duelen, R.; Sampaolesi, M. Stem Cell Technology in Cardiac Regeneration: A Pluripotent Stem Cell Promise. *EBioMedicine* **2017**, *16*, 30–40. [CrossRef] [PubMed]
66. Steinhoff, G.; Nesteruk, J.; Wolfien, M.; Kundt, G.; Börgermann, J.; David, R.; Garbade, J.; Große, J.; Haverich, A.; Hennig, H.; et al. Cardiac Function Improvement and Bone Marrow Response: Outcome Analysis of the Randomized PERFECT Phase III Clinical Trial of Intramyocardial CD133^{+} Application After Myocardial Infarction. *EBioMedicine* **2017**, *22*, 208–224. [CrossRef]
67. Silvestre, J.S.; Smadja, D.M.; Lévy, B.I. Postischemic revascularization: From cellular and molecular mechanisms to clinical applications. *Physiol. Rev.* **2013**, *93*, 1743–1802. [CrossRef]
68. Banerjee, M.N.; Bolli, R.; Hare, J.M. Clinical Studies of Cell Therapy in Cardiovascular Medicine: Recent Developments and Future Directions. *Circ. Res.* **2018**, *123*, 266–287. [CrossRef] [PubMed]
69. Hare, J.M.; Chaparro, S.V. Cardiac regeneration and stem cell therapy. *Curr. Opin. Organ Transplant.* **2008**, *13*, 536–542. [CrossRef]
70. Mohammedsaleh, Z.M. The use of patient-specific stem cells in different autoimmune diseases. *Saudi J. Biol. Sci.* **2022**, *29*, 3338–3346. [CrossRef]
71. Zhu, D.; Li, Z.; Huang, K.; Caranasos, T.G.; Rossi, J.S.; Cheng, K. Minimally invasive delivery of therapeutic agents by hydrogel injection into the pericardial cavity for cardiac repair. *Nat. Commun.* **2021**, *12*, 1412. [CrossRef]
72. Madonna, R.; Van Laake, L.W.; Davidson, S.M.; Engel, F.B.; Hausenloy, D.J.; Lecour, S.; Leor, J.; Perrino, C.; Schulz, R.; Ytrehus, K.; et al. Position Paper of the European Society of Cardiology Working Group Cellular Biology of the Heart: Cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. *Eur. Heart J.* **2016**, *37*, 1789–1798. [CrossRef]
73. Raynaud, C.M.; Ahmad, F.S.; Allouba, M.; Abou-Saleh, H.; Lui, K.O.; Yacoub, M. Reprogramming for cardiac regeneration. *Glob. Cardiol. Sci. Pract.* **2014**, *2014*, 309–329. [CrossRef]
74. Zhao, Y.; Londono, P.; Cao, Y.; Sharpe, E.J.; Proenza, C.; O'Rourke, R.; Jones, K.L.; Jeong, M.Y.; Walker, L.A.; Buttrick, P.M.; et al. High-efficiency reprogramming of fibroblasts into cardiomyocytes requires suppression of pro-fibrotic signalling. *Nat. Commun.* **2015**, *6*, 8243. [CrossRef] [PubMed]
75. Tonkin, D.; Yee-Goh, A.; Katare, R. Healing the Ischaemic Heart: A Critical Review of Stem Cell Therapies. *Rev. Cardiovasc. Med.* **2023**, *24*, 122. [CrossRef]
76. Alhejailan, R.S.; Garoffolo, G.; Raveendran, V.V.; Pesce, M. Cells and Materials for Cardiac Repair and Regeneration. *J. Clin. Med.* **2023**, *12*, 3398. [CrossRef]
77. Liao, S.Y.; Tse, H.F. Multipotent (adult) and pluripotent stem cells for heart regeneration: What are the pros and cons? *Stem Cell Res. Ther.* **2013**, *4*, 151. [CrossRef] [PubMed]
78. Kadota, S.; Tanaka, Y.; Shiba, Y. Heart regeneration using pluripotent stem cells. *J. Cardiol.* **2020**, *76*, 459–463. [CrossRef] [PubMed]
79. Shiba, Y. Pluripotent Stem Cells for Cardiac Regeneration-Current Status, Challenges, and Future Perspectives. *Circ. J.* **2020**, *84*, 2129–2135. [CrossRef]
80. Rajala, K.; Pekkanen-Mattila, M.; Aalto-Setälä, K. Cardiac differentiation of pluripotent stem cells. *Stem Cells Int.* **2011**, *2011*, 383709. [CrossRef]
81. Zhang, J. Engineered Tissue Patch for Cardiac Cell Therapy. *Curr. Treat. Options Cardiovasc. Med.* **2015**, *17*, 399. [CrossRef]
82. Neishabouri, A.; Soltani Khaboushan, A.; Daghigh, F.; Kajbafzadeh, A.M.; Majidi Zolbin, M. Decellularization in Tissue Engineering and Regenerative Medicine: Evaluation, Modification, and Application Methods. *Front. Bioeng. Biotechnol.* **2022**, *10*, 805299. [CrossRef]
83. Harris, A.G.; Salih, T.; Ghorbel, M.T.; Caputo, M.; Biglino, G.; Carrabba, M. Biological Scaffolds for Congenital Heart Disease. *Bioengineering* **2023**, *10*, 57. [CrossRef]
84. Herberts, C.A.; Kwa, M.S.; Hermsen, H.P. Risk factors in the development of stem cell therapy. *J. Transl. Med.* **2011**, *9*, 29. [CrossRef] [PubMed]
85. Yamanaka, S. Pluripotent Stem Cell-Based Cell Therapy-Promise and Challenges. *Cell Stem Cell* **2020**, *27*, 523–531. [CrossRef] [PubMed]
86. Li, X.; Tamama, K.; Xie, X.; Guan, J. Improving Cell Engraftment in Cardiac Stem Cell Therapy. *Stem Cells Int.* **2016**, *2016*, 7168797. [CrossRef]
87. Doppler, S.A.; Deutsch, M.A.; Lange, R.; Krane, M. Cardiac regeneration: Current therapies-future concepts. *J. Thorac. Dis.* **2013**, *5*, 683–697. [CrossRef]
88. Patel, S.A.; King, C.C.; Lim, P.K.; Habiba, U.; Dave, M.; Porecha, R.; Rameshwar, P. Personalizing Stem Cell Research and Therapy: The Arduous Road Ahead or Missed Opportunity? *Curr. Pharmacogenom. Pers. Med.* **2010**, *8*, 25–36. [CrossRef] [PubMed]
89. Lappin, T.; Cheng, T. An urgent need for standardization of stem cells and stem cell-derived products toward clinical applications. *Stem Cells Transl. Med.* **2021**, *10*, S1–S3. [CrossRef] [PubMed]
90. Aly, R.M. Current state of stem cell-based therapies: An overview. *Stem Cell Investig.* **2020**, *7*, 8. [CrossRef] [PubMed]
91. Katarzyna, R. Adult Stem Cell Therapy for Cardiac Repair in Patients After Acute Myocardial Infarction Leading to Ischemic Heart Failure: An Overview of Evidence from the Recent Clinical Trials. *Curr. Cardiol. Rev.* **2017**, *13*, 223–231. [CrossRef]
92. Lovell, M.J.; Mathur, A. The role of stem cells for treatment of cardiovascular disease. *Cell Prolif.* **2004**, *37*, 67–87. [CrossRef]

93. Haider, H.K.; Tan, A.C.; Aziz, S.; Chachques, J.C.; Sim, E.K. Myoblast transplantation for cardiac repair: A clinical perspective. *Mol. Ther.* **2004**, *9*, 14–23. [CrossRef]
94. Fu, X.; Wang, H.; Hu, P. Stem cell activation in skeletal muscle regeneration. *Cell. Mol. Life Sci.* **2015**, *72*, 1663–1677. [CrossRef] [PubMed]
95. Hassan, N.; Tchao, J.; Tobita, K. Concise review: Skeletal muscle stem cells and cardiac lineage: Potential for heart repair. *Stem Cells Transl. Med.* **2014**, *3*, 183–193. [CrossRef]
96. Tambara, K.; Sakakibara, Y.; Sakaguchi, G.; Lu, F.; Premaratne, G.U.; Lin, X.; Nishimura, K.; Komeda, M. Transplanted skeletal myoblasts can fully replace the infarcted myocardium when they survive in the host in large numbers. *Circulation* **2003**, *108* (Suppl. S1), II259–II263. [CrossRef]
97. Durrani, S.; Konoplyannikov, M.; Ashraf, M.; Haider, K.H. Skeletal myoblasts for cardiac repair. *Regen. Med.* **2010**, *5*, 919–932. [CrossRef]
98. Lee, J.Y.; Hong, S.H. Hematopoietic Stem Cells and Their Roles in Tissue Regeneration. *Int. J. Stem Cells* **2020**, *13*, 1–12. [CrossRef]
99. Hawley, R.G.; Ramezani, A.; Hawley, T.S. Hematopoietic stem cells. *Methods Enzymol.* **2006**, *419*, 149–179. [CrossRef]
100. Abbott, J.D.; Giordano, F.J. Stem cells and cardiovascular disease. *J. Nucl. Cardiol.* **2003**, *10*, 403–412. [CrossRef]
101. Afjeh-Dana, E.; Naserzadeh, P.; Moradi, E.; Hosseini, N.; Seifalian, A.M.; Ashtari, B. Stem Cell Differentiation into Cardiomyocytes: Current Methods and Emerging Approaches. *Stem Cell Rev. Rep.* **2022**, *18*, 2566–2592. [CrossRef]
102. Charlesworth, C.T.; Hsu, I.; Wilkinson, A.C.; Nakauchi, H. Immunological barriers to haematopoietic stem cell gene therapy. *Nat. Rev. Immunol.* **2022**, *22*, 719–733. [CrossRef]
103. Morgan, R.A.; Gray, D.; Lomova, A.; Kohn, D.B. Hematopoietic Stem Cell Gene Therapy: Progress and Lessons Learned. *Cell Stem Cell* **2017**, *21*, 574–590. [CrossRef]
104. Correia, C.D.; Ferreira, A.; Fernandes, M.T.; Silva, B.M.; Esteves, F.; Leitão, H.S.; Bragança, J.; Calado, S.M. Human Stem Cells for Cardiac Disease Modeling and Preclinical and Clinical Applications-Are We on the Road to Success? *Cells* **2023**, *12*, 1727. [CrossRef] [PubMed]
105. Sobota, R.; Kelm, M.; Merx, M.W.; Weber, C. Transplantation of endothelial progenitor cells improves neovascularization and left ventricular function after myocardial infarction in a rat model. *Basic Res. Cardiol.* **2008**, *103*, 69–77. [CrossRef]
106. Xiao, S.T.; Kuang, C.Y. Endothelial progenitor cells and coronary artery disease: Current concepts and future research directions. *World J. Clin. Cases* **2021**, *9*, 8953–8966. [CrossRef]
107. Janic, B.; Arbab, A.S. Cord blood endothelial progenitor cells as therapeutic and imaging probes. *Imaging Med.* **2012**, *4*, 477–490. [CrossRef]
108. Kawamoto, A.; Losordo, D.W. Endothelial progenitor cells for cardiovascular regeneration. *Trends Cardiovasc. Med.* **2008**, *18*, 33–37. [CrossRef]
109. Zhang, M.; Malik, A.B.; Rehman, J. Endothelial progenitor cells and vascular repair. *Curr. Opin. Hematol.* **2014**, *21*, 224–228. [CrossRef] [PubMed]
110. Huang, H.; Huang, W. Regulation of Endothelial Progenitor Cell Functions in Ischemic Heart Disease: New Therapeutic Targets for Cardiac Remodeling and Repair. *Front. Cardiovasc. Med.* **2022**, *9*, 896782. [CrossRef]
111. Dzau, V.J.; Gnecchi, M.; Pachori, A.S.; Morello, F.; Melo, L.G. Therapeutic potential of endothelial progenitor cells in cardiovascular diseases. *Hypertension* **2005**, *46*, 7–18. [CrossRef]
112. Wang, Y.; Yin, P.; Bian, G.L.; Huang, H.Y.; Shen, H.; Yang, J.J.; Yang, Z.Y.; Shen, Z.Y. The combination of stem cells and tissue engineering: An advanced strategy for blood vessels regeneration and vascular disease treatment. *Stem Cell Res. Ther.* **2017**, *8*, 194. [CrossRef] [PubMed]
113. Peters, E.B. Endothelial Progenitor Cells for the Vascularization of Engineered Tissues. *Tissue Eng. Part B Rev.* **2018**, *24*, 1–24. [CrossRef]
114. Xu, S.; Qiu, Y.; Tao, J. The challenges and optimization of cell-based therapy for cardiovascular disease. *J. Transl. Int. Med.* **2021**, *9*, 234–238. [CrossRef]
115. Al-Omar, M.T.; Alnajjar, M.T.; Ahmed, Z.T.; Salaas, F.M.I.; Alrefaei, T.S.M.; Haider, K.H. Endothelial progenitor cell-derived small extracellular vesicles for myocardial angiogenesis and revascularization. *J. Clin. Transl. Res.* **2022**, *8*, 476–487. [PubMed]
116. Han, Y.; Li, X.; Zhang, Y.; Han, Y.; Chang, F.; Ding, J. Mesenchymal Stem Cells for Regenerative Medicine. *Cells* **2019**, *8*, 886. [CrossRef] [PubMed]
117. Musiał-Wysocka, A.; Kot, M.; Majka, M. The Pros and Cons of Mesenchymal Stem Cell-Based Therapies. *Cell Transplant.* **2019**, *28*, 801–812. [CrossRef]
118. Nazari-Shafti, T.Z.; Neuber, S.; Garcia Duran, A.; Xu, Z.; Beltsios, E.; Seifert, M.; Falk, V.; Stamm, C. Human mesenchymal stromal cells and derived extracellular vesicles: Translational strategies to increase their proangiogenic potential for the treatment of cardiovascular disease. *Stem Cells Transl. Med.* **2020**, *9*, 1558–1569. [CrossRef] [PubMed]
119. Daltro, P.S.; Barreto, B.C.; Silva, P.G.; Neto, P.C.; Sousa Filho, P.H.F.; Santana Neta, D.; Carvalho, G.B.; Silva, D.N.; Paredes, B.D.; de Alcantara, A.C.; et al. Therapy with mesenchymal stromal cells or conditioned medium reverse cardiac alterations in a high-fat diet-induced obesity model. *Cytotherapy* **2017**, *19*, 1176–1188. [CrossRef]
120. Almeria, C.; Kreß, S.; Weber, V.; Egger, D.; Kasper, C. Heterogeneity of mesenchymal stem cell-derived extracellular vesicles is highly impacted by the tissue/cell source and culture conditions. *Cell Biosci.* **2022**, *12*, 51. [CrossRef]

121. Meng, Q.S.; Liu, J.; Wei, L.; Fan, H.M.; Zhou, X.H.; Liang, X.T. Senescent mesenchymal stem/stromal cells and restoring their cellular functions. *World J. Stem Cells* **2020**, *12*, 966–985. [CrossRef]
122. Cashman, T.J.; Gouon-Evans, V.; Costa, K.D. Mesenchymal stem cells for cardiac therapy: Practical challenges and potential mechanisms. *Stem Cell Rev. Rep.* **2013**, *9*, 254–265. [CrossRef]
123. Mehanna, R.A.; Essawy, M.M.; Barkat, M.A.; Awaad, A.K.; Thabet, E.H.; Hamed, H.A.; Elkafrawy, H.; Khalil, N.A.; Sallam, A.; Kholief, M.A.; et al. Cardiac stem cells: Current knowledge and future prospects. *World J. Stem Cells* **2022**, *14*, 1–40. [CrossRef]
124. Amini, H.; Rezaie, J.; Vosoughi, A.; Rahbarghazi, R.; Nouri, M. Cardiac progenitor cells application in cardiovascular disease. *J. Cardiovasc. Thorac. Res.* **2017**, *9*, 127–132. [CrossRef] [PubMed]
125. Gonzales, C.; Ullrich, N.D.; Gerber, S.; Berthonneche, C.; Niggli, E.; Pedrazzini, T. Isolation of cardiovascular precursor cells from the human fetal heart. *Tissue Eng. Part A* **2012**, *18*, 198–207. [CrossRef] [PubMed]
126. Bollini, S.; Smart, N.; Riley, P.R. Resident cardiac progenitor cells: At the heart of regeneration. *J. Mol. Cell. Cardiol.* **2011**, *50*, 296–303. [CrossRef]
127. Nurzynska, D.; Di Meglio, F.; Romano, V.; Miraglia, R.; Sacco, A.M.; Latino, F.; Bancone, C.; Della Corte, A.; Maiello, C.; Amarelli, C.; et al. Cardiac primitive cells become committed to a cardiac fate in adult human heart with chronic ischemic disease but fail to acquire mature phenotype: Genetic and phenotypic study. *Basic Res. Cardiol.* **2013**, *108*, 320. [CrossRef] [PubMed]
128. Romano, V.; Belviso, I.; Sacco, A.M.; Cozzolino, D.; Nurzynska, D.; Amarelli, C.; Maiello, C.; Sirico, F.; Di Meglio, F.; Castaldo, C. Human Cardiac Progenitor Cell-Derived Extracellular Vesicles Exhibit Promising Potential for Supporting Cardiac Repair in Vitro. *Front. Physiol.* **2022**, *13*, 879046. [CrossRef]
129. Stastna, M.; Abraham, M.R.; Van Eyk, J.E. Cardiac stem/progenitor cells, secreted proteins, and proteomics. *FEBS Lett.* **2009**, *583*, 1800–1807. [CrossRef]
130. Barreto, S.; Hamel, L.; Schiatti, T.; Yang, Y.; George, V. Cardiac Progenitor Cells from Stem Cells: Learning from Genetics and Biomaterials. *Cells* **2019**, *8*, 1536. [CrossRef]
131. Jiang, Y.; Lian, X.L. Heart regeneration with human pluripotent stem cells: Prospects and challenges. *Bioact. Mater.* **2020**, *5*, 74–81. [CrossRef]
132. Chong, J.J.; Murry, C.E. Cardiac regeneration using pluripotent stem cells—Progression to large animal models. *Stem Cell Res.* **2014**, *13*, 654–665. [CrossRef]
133. Liu, G.; David, B.T.; Trawczynski, M.; Fessler, R.G. Advances in Pluripotent Stem Cells: History, Mechanisms, Technologies, and Applications. *Stem Cell Rev. Rep.* **2020**, *16*, 3–32. [CrossRef] [PubMed]
134. Menasché, P.; Vanneaux, V.; Hagège, A.; Bel, A.; Cholley, B.; Parouchev, A.; Cacciapuoti, I.; Al-Daccak, R.; Benhamouda, N.; Blons, H.; et al. Transplantation of Human Embryonic Stem Cell-Derived Cardiovascular Progenitors for Severe Ischemic Left Ventricular Dysfunction. *J. Am. Coll. Cardiol.* **2018**, *71*, 429–438. [CrossRef]
135. He, J.Q.; Ma, Y.; Lee, Y.; Thomson, J.A.; Kamp, T.J. Human embryonic stem cells develop into multiple types of cardiac myocytes: Action potential characterization. *Circ. Res.* **2003**, *93*, 32–39. [CrossRef]
136. Wong, S.S.; Bernstein, H.S. Cardiac regeneration using human embryonic stem cells: Producing cells for future therapy. *Regen. Med.* **2010**, *5*, 763–775. [CrossRef]
137. Lo, B.; Parham, L. Ethical issues in stem cell research. *Endocr. Rev.* **2009**, *30*, 204–213. [CrossRef]
138. Swijnenburg, R.J.; Schrepfer, S.; Govaert, J.A.; Cao, F.; Ransohoff, K.; Sheikh, A.Y.; Haddad, M.; Connolly, A.J.; Davis, M.M.; Robbins, R.C.; et al. Immunosuppressive therapy mitigates immunological rejection of human embryonic stem cell xenografts. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 12991–12996. [CrossRef] [PubMed]
139. Pearl, J.I.; Kean, L.S.; Davis, M.M.; Wu, J.C. Pluripotent stem cells: Immune to the immune system? *Sci. Transl. Med.* **2012**, *4*, 164ps25. [CrossRef] [PubMed]
140. Chambers, I.; Smith, A. Self-renewal of teratocarcinoma and embryonic stem cells. *Oncogene* **2004**, *23*, 7150–7160. [CrossRef]
141. Volarevic, V.; Markovic, B.S.; Gazdic, M.; Volarevic, A.; Jovicic, N.; Arsenijevic, N.; Armstrong, L.; Djonov, V.; Lako, M.; Stojkovic, M. Ethical and Safety Issues of Stem Cell-Based Therapy. *Int. J. Med. Sci.* **2018**, *15*, 36–45. [CrossRef] [PubMed]
142. Shiba, N.; Sakamoto, K.; Ido, D.; Shiina, T.; Ohkura, M.; Nakai, J.; Uno, N.; Kazuki, Y.; Oshimura, M.; Minami, I.; et al. Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts. *Nature* **2016**, *538*, 388–391. [CrossRef] [PubMed]
143. Belviso, I.; Sacco, A.M.; Romano, V.; Schonauer, F.; Nurzynska, D.; Montagnani, S.; Di Meglio, F.; Castaldo, C. Isolation of Adult Human Dermal Fibroblasts from Abdominal Skin and Generation of Induced Pluripotent Stem Cells Using a Non-Integrating Method. *J. Vis. Exp.* **2020**, *155*, e60629. [CrossRef]
144. Ye, L.; Swingen, C.; Zhang, J. Induced pluripotent stem cells and their potential for basic and clinical sciences. *Curr. Cardiol. Rev.* **2013**, *9*, 63–72. [CrossRef] [PubMed]
145. Park, M.; Yoon, Y.S. Cardiac Regeneration with Human Pluripotent Stem Cell-Derived Cardiomyocytes. *Korean Circ. J.* **2018**, *48*, 974–988. [CrossRef] [PubMed]
146. Paik, D.T.; Chandy, M.; Wu, J.C. Patient and Disease-Specific Induced Pluripotent Stem Cells for Discovery of Personalized Cardiovascular Drugs and Therapeutics. *Pharmacol. Rev.* **2020**, *72*, 320–342. [CrossRef] [PubMed]
147. Musunuru, K.; Sheikh, F.; Gupta, R.M.; Houser, S.R.; Maher, K.O.; Milan, D.J.; Terzic, A.; Wu, J.C.; American Heart Association Council on Functional Genomics and Translational Biology; Council on Cardiovascular Disease in the Young; et al. Induced Pluripotent Stem Cells for Cardiovascular Disease Modeling and Precision Medicine: A Scientific Statement From the American Heart Association. *Circ. Genom. Precis. Med.* **2018**, *11*, e000043. [CrossRef]

148. Moretti, A.; Laugwitz, K.L.; Dorn, T.; Sinnecker, D.; Mummery, C. Pluripotent stem cell models of human heart disease. *Cold Spring Harb. Perspect. Med.* **2013**, *3*, a014027. [CrossRef]
149. Cho, S.; Lee, C.; Skylar-Scott, M.A.; Heilshorn, S.C.; Wu, J.C. Reconstructing the heart using iPSCs: Engineering strategies and applications. *J. Mol. Cell. Cardiol.* **2021**, *157*, 56–65. [CrossRef]
150. Fanizza, F.; Campanile, M.; Forloni, G.; Giordano, C.; Albani, D. Induced pluripotent stem cell-based organ-on-a-chip as personalized drug screening tools: A focus on neurodegenerative disorders. *J. Tissue Eng.* **2022**, *13*, 20417314221095339. [CrossRef]
151. Funakoshi, S.; Yoshida, Y. Recent progress of iPSC technology in cardiac diseases. *Arch. Toxicol.* **2021**, *95*, 3633–3650. [CrossRef]
152. Masumoto, H.; Nakane, T.; Tinney, J.P.; Yuan, F.; Ye, F.; Kowalski, W.J.; Minakata, K.; Sakata, R.; Yamashita, J.K.; Keller, B.B. The myocardial regenerative potential of three-dimensional engineered cardiac tissues composed of multiple human iPS cell-derived cardiovascular cell lineages. *Sci. Rep.* **2016**, *6*, 29933. [CrossRef]
153. Liang, Y.; Zhang, H.; Feng, Q.S.; Cai, M.B.; Deng, W.; Qin, D.; Yun, J.P.; Tsao, G.S.; Kang, T.; Esteban, M.A.; et al. The propensity for tumorigenesis in human induced pluripotent stem cells is related with genomic instability. *Chin. J. Cancer* **2013**, *32*, 205–212. [CrossRef]
154. Medvedev, S.P.; Shevchenko, A.I.; Zakian, S.M. Induced Pluripotent Stem Cells: Problems and Advantages when Applying them in Regenerative Medicine. *Acta Nat.* **2010**, *2*, 18–28. [CrossRef]
155. Otsuka, R.; Wada, H.; Murata, T.; Seino, K.I. Immune reaction and regulation in transplantation based on pluripotent stem cell technology. *Inflamm. Regen.* **2020**, *40*, 12. [CrossRef] [PubMed]
156. Sackett, S.D.; Brown, M.E.; Tremmel, D.M.; Ellis, T.; Burlingham, W.J.; Odorico, J.S. Modulation of human allogeneic and syngeneic pluripotent stem cells and immunological implications for transplantation. *Transplant. Rev.* **2016**, *30*, 61–70. [CrossRef] [PubMed]
157. Fuerstenau-Sharp, M.; Zimmermann, M.E.; Stark, K.; Jentsch, N.; Klingenstein, M.; Drzymalski, M.; Wagner, S.; Maier, L.S.; Hehr, U.; Baessler, A.; et al. Generation of highly purified human cardiomyocytes from peripheral blood mononuclear cell-derived induced pluripotent stem cells. *PLoS ONE* **2015**, *10*, e0126596. [CrossRef] [PubMed]
158. Bizy, A.; Klos, M. Optimizing the Use of iPSC-CMs for Cardiac Regeneration in Animal Models. *Animals* **2020**, *10*, 1561. [CrossRef]
159. Huang, C.Y.; Peres Moreno Maia-Joca, R.; Ong, C.S.; Wilson, I.; Di Silvestre, D.; Tomaselli, G.F.; Reich, D.H. Enhancement of human iPSC-derived cardiomyocyte maturation by chemical conditioning in a 3D environment. *J. Mol. Cell. Cardiol.* **2020**, *138*, 1–11. [CrossRef]
160. Burnett, S.D.; Blanchette, A.D.; Chiu, W.A.; Rusyn, I. Human induced pluripotent stem cell (iPSC)-derived cardiomyocytes as an in vitro model in toxicology: Strengths and weaknesses for hazard identification and risk characterization. *Expert Opin. Drug Metab. Toxicol.* **2021**, *17*, 887–902. [CrossRef]
161. Buikema, J.W.; Van Der Meer, P.; Sluijter, J.P.; Domian, I.J. Concise review: Engineering myocardial tissue: The convergence of stem cells biology and tissue engineering technology. *Stem Cells* **2013**, *31*, 2587–2598. [CrossRef] [PubMed]
162. Hattori, F.; Fukuda, K. Strategies for ensuring that regenerative cardiomyocytes function properly and in cooperation with the host myocardium. *Exp. Mol. Med.* **2010**, *42*, 155–165. [CrossRef]
163. Zheng, Y.L. Some Ethical Concerns About Human Induced Pluripotent Stem Cells. *Sci. Eng. Ethics* **2016**, *22*, 1277–1284. [CrossRef]
164. Moradi, S.; Mahdizadeh, H.; Šarić, T.; Kim, J.; Harati, J.; Shahsavarani, H.; Greber, B.; Moore, J.B. 4th. Research and therapy with induced pluripotent stem cells (iPSCs): Social, legal, and ethical considerations. *Stem Cell Res. Ther.* **2019**, *10*, 341. [CrossRef] [PubMed]
165. Salem, T.; Frankman, Z.; Churko, J.M. Tissue Engineering Techniques for Induced Pluripotent Stem Cell Derived Three-Dimensional Cardiac Constructs. *Tissue Eng. Part B Rev.* **2022**, *28*, 891–911. [CrossRef] [PubMed]
166. Tomov, M.L.; Gil, C.J.; Cetnar, A.; Theus, A.S.; Lima, B.J.; Nish, J.E.; Bauser-Heaton, H.D.; Serpooshan, V. Engineering Functional Cardiac Tissues for Regenerative Medicine Applications. *Curr. Cardiol. Rep.* **2019**, *21*, 105. [CrossRef]
167. Shan, S.; Li, Q.; Criswell, T.; Atala, A.; Zhang, Y. Stem cell therapy combined with controlled release of growth factors for the treatment of sphincter dysfunction. *Cell Biosci.* **2023**, *13*, 56. [CrossRef] [PubMed]
168. Sabra, M.; Karbasiafshar, C.; Aboulgheit, A.; Raj, S.; Abid, M.R.; Sellke, F.W. Clinical Application of Novel Therapies for Coronary Angiogenesis: Overview, Challenges, and Prospects. *Int. J. Mol. Sci.* **2021**, *22*, 3722. [CrossRef] [PubMed]
169. Guo, Y.; Yu, Y.; Hu, S.; Chen, Y.; Shen, Z. The therapeutic potential of mesenchymal stem cells for cardiovascular diseases. *Cell Death Dis.* **2020**, *11*, 349. [CrossRef]
170. Wang, L.; Serpooshan, V.; Zhang, J. Engineering Human Cardiac Muscle Patch Constructs for Prevention of Post-infarction LV Remodeling. *Front. Cardiovasc. Med.* **2021**, *8*, 621781. [CrossRef]
171. Chang, Y.C.; Mirhaidari, G.; Kelly, J.; Breuer, C. Current Challenges and Solutions to Tissue Engineering of Large-scale Cardiac Constructs. *Curr. Cardiol. Rep.* **2021**, *23*, 47. [CrossRef]
172. Cashman, T.J.; Josowitz, R.; Gelb, B.D.; Li, R.A.; Dubois, N.C.; Costa, K.D. Construction of Defined Human Engineered Cardiac Tissues to Study Mechanisms of Cardiac Cell Therapy. *J. Vis. Exp.* **2016**, *109*, e53447. [CrossRef]
173. Tenreiro, M.F.; Louro, A.F.; Alves, P.M.; Serra, M. Next generation of heart regenerative therapies: Progress and promise of cardiac tissue engineering. *npj Regen. Med.* **2021**, *6*, 30. [CrossRef]
174. Grigorian Shamagian, L.; Madonna, R.; Taylor, D.; Climent, A.M.; Prosper, F.; Bras-Rosario, L.; Bayes-Genis, A.; Ferdinandy, P.; Fernández-Avilés, F.; Izpisua Belmonte, J.C.; et al. Perspectives on Directions and Priorities for Future Preclinical Studies in Regenerative Medicine. *Circ. Res.* **2019**, *124*, 938–951. [CrossRef]

175. Vasu, S.; Zhou, J.; Chen, J.; Johnston, P.V.; Kim, D.H. Biomaterials-based Approaches for Cardiac Regeneration. *Korean Circ. J.* **2021**, *51*, 943–960. [CrossRef]
176. Cui, Z.; Yang, B.; Li, R.K. Application of biomaterials in cardiac repair and regeneration. *Engineering* **2016**, *2*, 141–188. [CrossRef]
177. Tariq, U.; Gupta, M.; Pathak, S.; Patil, R.; Dohare, A.; Misra, S.K. Role of Biomaterials in Cardiac Repair and Regeneration: Therapeutic Intervention for Myocardial Infarction. *ACS Biomater. Sci. Eng.* **2022**, *8*, 3271–3298. [CrossRef] [PubMed]
178. Scafa Udriște, A.; Niculescu, A.G.; Iliuță, L.; Bajeu, T.; Georgescu, A.; Grumezescu, A.M.; Bădilă, E. Progress in Biomaterials for Cardiac Tissue Engineering and Regeneration. *Polymers* **2023**, *15*, 1177. [CrossRef]
179. Majid, Q.A.; Fricker, A.T.R.; Gregory, D.A.; Davidenko, N.; Hernandez Cruz, O.; Jabbour, R.J.; Owen, T.J.; Basnett, P.; Lukasiewicz, B.; Stevens, M.; et al. Natural Biomaterials for Cardiac Tissue Engineering: A Highly Biocompatible Solution. *Front. Cardiovasc. Med.* **2020**, *7*, 554597. [CrossRef]
180. BaoLin, G.; Ma, P.X. Synthetic biodegradable functional polymers for tissue engineering: A brief review. *Sci. China Chem.* **2014**, *7*, 490–500. [CrossRef]
181. Bolan, F.; Louca, I.; Heal, C.; Cunningham, C.J. The Potential of Biomaterial-Based Approaches as Therapies for Ischemic Stroke: A Systematic Review and Meta-Analysis of Pre-clinical Studies. *Front. Neurol.* **2019**, *10*, 924. [CrossRef]
182. McMahan, S.; Taylor, A.; Copeland, K.M.; Pan, Z.; Liao, J.; Hong, Y. Current advances in biodegradable synthetic polymer based cardiac patches. *J. Biomed. Mater. Res. A* **2020**, *108*, 972–983. [CrossRef]
183. Mohammadi Nasr, S.; Rabiee, N.; Hajebi, S.; Ahmadi, S.; Fatahi, Y.; Hosseini, M.; Bagherzadeh, M.; Ghadiri, A.M.; Rabiee, M.; Jajarmi, V.; et al. Biodegradable Nanopolymers in Cardiac Tissue Engineering: From Concept Towards Nanomedicine. *Int. J. Nanomed.* **2020**, *15*, 4205–4224. [CrossRef]
184. Zhang, Y.; Mu, W.; Zhang, Y.; He, X.; Wang, Y.; Ma, H.; Zhu, T.; Li, A.; Hou, Q.; Yang, W.; et al. Recent Advances in Cardiac Patches: Materials, Preparations, and Properties. *ACS Biomater. Sci. Eng.* **2022**, *8*, 3659–3675. [CrossRef] [PubMed]
185. Mariani, E.; Lisignol, I.G.; Borzì, R.M.; Pulsatelli, L. Biomaterials: Foreign Bodies or Tuners for the Immune Response? *Int. J. Mol. Sci.* **2019**, *20*, 636. [CrossRef] [PubMed]
186. Chen, F.M.; Liu, X. Advancing biomaterials of human origin for tissue engineering. *Prog. Polym. Sci.* **2016**, *53*, 86–168. [CrossRef] [PubMed]
187. Tortorici, M.; Petersen, A.; Duda, G.N.; Checa, S. The Degradation of Synthetic Polymeric Scaffolds With Strut-like Architecture Influences the Mechanics-dependent Repair Process of an Osteochondral Defect in Silico. *Front. Bioeng. Biotechnol.* **2022**, *10*, 846665. [CrossRef] [PubMed]
188. Echeverria Molina, M.I.; Malollari, K.G.; Komvopoulos, K. Design Challenges in Polymeric Scaffolds for Tissue Engineering. *Front. Bioeng. Biotechnol.* **2021**, *9*, 617141. [CrossRef] [PubMed]
189. Labarrere, C.A.; Dabiri, A.E.; Kassab, G.S. Thrombogenic and Inflammatory Reactions to Biomaterials in Medical Devices. *Front. Bioeng. Biotechnol.* **2020**, *8*, 123. [CrossRef]
190. Ashok, K.; Babu, M.; Kavitha, G.; Jeyanthi, R.; Ladchumanandasivam, R.; da Silva, O.; Manikndan, E. Fabrication of Textile-Based Scaffolds Using Electrospun Nanofibers for Biomedical Applications. In *Electrospun Polymeric Nanofibers. Advances in Polymer Science*; Jayakumar, R., Ed.; Springer: Cham, Switzerland, 2022; Volume 291. [CrossRef]
191. Pedersen, D.D.; Kim, S.; Wagner, W.R. Biodegradable polyurethane scaffolds in regenerative medicine: Clinical translation review. *J. Biomed. Mater. Res. A* **2022**, *110*, 1460–1487. [CrossRef]
192. Scheuer-Leeser, M.; Irnich, W.; Kreuzer, J. Polyurethane leads: Facts and controversy. *Pacing Clin. Electrophysiol.* **1983**, *6*, 454–463. [CrossRef]
193. Naureen, B.; Haseeb, A.S.M.A.; Basirun, W.J.; Muhamad, F. Recent advances in tissue engineering scaffolds based on polyurethane and modified polyurethane. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2021**, *118*, 111228. [CrossRef]
194. Guerin, P. Use of synthetic polymers for biomedical application. *Pacing Clin. Electrophysiol.* **1983**, *6*, 449–453. [CrossRef]
195. Chiono, V.; Mozetic, P.; Boffito, M.; Sartori, S.; Gioffredi, E.; Silvestri, A.; Rainer, A.; Giannitelli, S.M.; Trombetta, M.; Nurzynska, D.; et al. Polyurethane-based scaffolds for myocardial tissue engineering. *Interface Focus* **2014**, *4*, 20130045. [CrossRef]
196. Griffin, M.; Castro, N.; Bas, O.; Saifzadeh, S.; Butler, P.; Hutmacher, D.W. The Current Versatility of Polyurethane Three-Dimensional Printing for Biomedical Applications. *Tissue Eng. Part B Rev.* **2020**, *26*, 272–283. [CrossRef]
197. Raeisdasteh Hokmabad, V.; Davaran, S.; Ramazani, A.; Salehi, R. Design and fabrication of porous biodegradable scaffolds: A strategy for tissue engineering. *J. Biomater. Sci. Polym. Ed.* **2017**, *28*, 1797–1825. [CrossRef]
198. Dulińska-Molak, I.; Lekka, M.; Kurzydłowski, K.J. Surface properties of polyurethane composites for biomedical applications. *Appl. Surf. Sci.* **2013**, *270*, 553–560. [CrossRef]
199. Lin, C.C.; Anseth, K.S. PEG hydrogels for the controlled release of biomolecules in regenerative medicine. *Pharm. Res.* **2009**, *26*, 631–643. [CrossRef]
200. Willerth, S.M.; Sakiyama-Elbert, S.E. Combining stem cells and biomaterial scaffolds for constructing tissues and cell delivery. In *StemBook*; Harvard Stem Cell Institute: Cambridge, MA, USA, 2008.
201. Knop, K.; Hoogenboom, R.; Fischer, D.; Schubert, U.S. Poly(ethylene glycol) in drug delivery: Pros and cons as well as potential alternatives. *Angew. Chem. Int. Ed.* **2010**, *49*, 6288–6308. [CrossRef]
202. Riewruja, K.; Aguglia, A.M.; Hines, S.; Makarcyzk, M.J.; Honsawek, S.; Lin, H. PEG Reinforced Scaffold Promotes Uniform Distribution of Human MSC-Created Cartilage Matrix. *Gels* **2022**, *8*, 794. [CrossRef]

203. Siddiqui, N.; Asawa, S.; Birru, B.; Baadhe, R.; Rao, S. PCL-Based Composite Scaffold Matrices for Tissue Engineering Applications. *Mol. Biotechnol.* **2018**, *60*, 506–532. [CrossRef]
204. Wunner, F.M.; Bas, O.; Saidy, N.T.; Dalton, P.D.; Pardo, E.M.D.; Hutmacher, D.W. Melt Electrospinning Writing of Three-dimensional Poly(ε-caprolactone) Scaffolds with Controllable Morphologies for Tissue Engineering Applications. *J. Vis. Exp.* **2017**, *130*, 56289. [CrossRef]
205. Wanjare, M.; Hou, L.; Nakayama, K.H.; Kim, J.J.; Mezak, N.P.; Abilez, O.J.; Tzatzalos, E.; Wu, J.C.; Huang, N.F. Anisotropic microfibrous scaffolds enhance the organization and function of cardiomyocytes derived from induced pluripotent stem cells. *Biomater. Sci.* **2017**, *5*, 1567–1578. [CrossRef]
206. Ko, J.; Mohtaram, N.K.; Ahmed, F.; Montgomery, A.; Carlson, M.; Lee, P.C.; Willerth, S.M.; Jun, M.B. Fabrication of poly (ε-caprolactone) microfiber scaffolds with varying topography and mechanical properties for stem cell-based tissue engineering applications. *J. Biomater. Sci. Polym. Ed.* **2014**, *25*, 1–17. [CrossRef]
207. Xu, Y.; Kim, C.S.; Saylor, D.M.; Koo, D. Polymer degradation and drug delivery in PLGA-based drug-polymer applications: A review of experiments and theories. *J. Biomed. Mater. Res. B Appl. Biomater.* **2017**, *105*, 1692–1716. [CrossRef]
208. Yu, J.; Lee, A.R.; Lin, W.H.; Lin, C.W.; Wu, Y.K.; Tsai, W.B. Electrospun PLGA fibers incorporated with functionalized biomolecules for cardiac tissue engineering. *Tissue Eng. Part A* **2014**, *20*, 1896–1907. [CrossRef] [PubMed]
209. Park, H.; Radisic, M.; Lim, J.O.; Chang, B.H.; Vunjak-Novakovic, G. A novel composite scaffold for cardiac tissue engineering. *In Vitro Cell. Dev. Biol. Anim.* **2005**, *41*, 188–196. [CrossRef] [PubMed]
210. Xing, Y.; Shi, S.; Zhang, Y.; Liu, F.; Zhu, L.; Shi, B.; Wang, J. Construction of engineered myocardial tissues in vitro with cardiomyocyte-like cells and a polylactic-co-glycolic acid polymer. *Mol. Med. Rep.* **2019**, *20*, 2403–2409. [CrossRef]
211. Senatov, F.S.; Niaza, K.V.; Zadorozhnyy, M.Y.; Maksimkin, A.V.; Kaloshkin, S.D.; Estrin, Y.Z. Mechanical properties and shape memory effect of 3D-printed PLA-based porous scaffolds. *J. Mech. Behav. Biomed. Mater.* **2016**, *57*, 139–148. [CrossRef]
212. Phutane, P.; Telange, D.; Agrawal, S.; Gunde, M.; Kotkar, K.; Pethe, A. Biofunctionalization and Applications of Polymeric Nanofibers in Tissue Engineering and Regenerative Medicine. *Polymers* **2023**, *15*, 1202. [CrossRef] [PubMed]
213. Santoro, M.; Shah, S.R.; Walker, J.L.; Mikos, A.G. Poly(lactic acid) nanofibrous scaffolds for tissue engineering. *Adv. Drug Deliv. Rev.* **2016**, *107*, 206–212. [CrossRef] [PubMed]
214. Sencadas, V.; Sadat, S.; Silva, D.M. Mechanical performance of elastomeric PGS scaffolds under dynamic conditions. *J. Mech. Behav. Biomed. Mater.* **2020**, *102*, 103474. [CrossRef]
215. Kharaziha, M.; Nikkhah, M.; Shin, S.R.; Annabi, N.; Masoumi, N.; Gaharwar, A.K.; Camci-Unal, G.; Khademhosseini, A. PGS: Gelatin nanofibrous scaffolds with tunable mechanical and structural properties for engineering cardiac tissues. *Biomaterials* **2013**, *34*, 6355–6366. [CrossRef]
216. Jeffries, E.M.; Allen, R.A.; Gao, J.; Pesce, M.; Wang, Y. Highly elastic and suturable electrospun poly(glycerol sebacate) fibrous scaffolds. *Acta Biomater.* **2015**, *18*, 30–39. [CrossRef] [PubMed]
217. Rai, R.; Tallawi, M.; Barbani, N.; Frati, C.; Madeddu, D.; Cavalli, S.; Graiani, G.; Quaini, F.; Roether, J.A.; Schubert, D.W.; et al. Biomimetic poly(glycerol sebacate) (PGS) membranes for cardiac patch application. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2013**, *33*, 3677–3687. [CrossRef] [PubMed]
218. Pushp, P.; Gupta, M.K. Cardiac Tissue Engineering: A Role for Natural Biomaterials. In *Bioactive Natural Products for Pharmaceutical Applications*; Pal, D., Nayak, A.K., Eds.; Advanced Structured Materials; Springer: Cham, Switzerland, 2021; Volume 140, pp. 617–641. [CrossRef]
219. Christman, K.L.; Lee, R.J. Biomaterials for the treatment of myocardial infarction. *J. Am. Coll. Cardiol.* **2006**, *48*, 907–913. [CrossRef]
220. Hasan, A.; Waters, R.; Roula, B.; Dana, R.; Yara, S.; Alexandre, T.; Paul, A. Engineered Biomaterials to Enhance Stem Cell-Based Cardiac Tissue Engineering and Therapy. *Macromol. Biosci.* **2016**, *16*, 958–977. [CrossRef]
221. Liu, S.; Yu, J.M.; Gan, Y.C.; Qiu, X.Z.; Gao, Z.C.; Wang, H.; Chen, S.X.; Xiong, Y.; Liu, G.H.; Lin, S.E.; et al. Biomimetic natural biomaterials for tissue engineering and regenerative medicine: New biosynthesis methods, recent advances, and emerging applications. *Mil. Med. Res.* **2023**, *10*, 16. [CrossRef] [PubMed]
222. Tarafdar, A.; Gaur, V.K.; Rawat, N.; Wankhade, P.R.; Gaur, G.K.; Awasthi, M.K.; Sagar, N.A.; Sirohi, R. Advances in biomaterial production from animal derived waste. *Bioengineered* **2021**, *12*, 8247–8258. [CrossRef]
223. Wang, L.; Wang, C.; Wu, S.; Fan, Y.; Li, X. Influence of mechanical properties of biomaterials on degradability, cell behaviors and signaling pathways: Current progress and challenges. *Biomater. Sci.* **2020**, *8*, 2714–2733. [CrossRef]
224. Salthouse, D.; Novakovic, K.; Hilkens, C.M.U.; Ferreira, A.M. Interplay between biomaterials and the immune system: Challenges and opportunities in regenerative medicine. *Acta Biomater.* **2023**, *155*, 1–18. [CrossRef]
225. Nikolova, M.P.; Chavali, M.S. Recent advances in biomaterials for 3D scaffolds: A review. *Bioact. Mater.* **2019**, *4*, 271–292. [CrossRef]
226. Wu, W.Q.; Peng, S.; Song, Z.Y.; Lin, S. Collagen biomaterial for the treatment of myocardial infarction: An update on cardiac tissue engineering and myocardial regeneration. *Drug Deliv. Transl. Res.* **2019**, *9*, 920–934. [CrossRef]
227. Dong, C.; Lv, Y. Application of Collagen Scaffold in Tissue Engineering: Recent Advances and New Perspectives. *Polymers* **2016**, *8*, 42. [CrossRef] [PubMed]
228. Cen, L.; Liu, W.; Cui, L.; Zhang, W.; Cao, Y. Collagen tissue engineering: Development of novel biomaterials and applications. *Pediatr. Res.* **2008**, *63*, 492–496. [CrossRef] [PubMed]

229. Shi, C.; Li, Q.; Zhao, Y.; Chen, W.; Chen, B.; Xiao, Z.; Lin, H.; Nie, L.; Wang, D.; Dai, J. Stem-cell-capturing collagen scaffold promotes cardiac tissue regeneration. *Biomaterials* **2011**, *32*, 2508–2515. [CrossRef] [PubMed]
230. Rashedi, I.; Talele, N.; Wang, X.H.; Hinz, B.; Radisic, M.; Keating, A. Collagen scaffold enhances the regenerative properties of mesenchymal stromal cells. *PLoS ONE* **2017**, *12*, e0187348. [CrossRef]
231. Wang, Q.; He, X.; Wang, B.; Pan, J.; Shi, C.; Li, J.; Wang, L.; Zhao, Y.; Dai, J.; Wang, D. Injectable collagen scaffold promotes swine myocardial infarction recovery by long-term local retention of transplanted human umbilical cord mesenchymal stem cells. *Sci. China Life Sci.* **2021**, *64*, 269–281. [CrossRef]
232. He, S.; Zhang, Z.; Luo, R.; Jiang, Q.; Yang, L.; Wang, Y. Advances in Injectable Hydrogel Strategies for Heart Failure Treatment. *Adv. Healthc. Mater.* **2023**, *12*, e2300029. [CrossRef]
233. Rinkevich-Shop, S.; Landa-Rouben, N.; Epstein, F.H.; Holbova, R.; Feinberg, M.S.; Goitein, O.; Kushnir, T.; Konen, E.; Leor, J. Injectable collagen implant improves survival, cardiac remodeling, and function in the early period after myocarditis in rats. *J. Cardiovasc. Pharmacol. Ther.* **2014**, *19*, 470–480. [CrossRef]
234. Barsotti, M.C.; Felice, F.; Balbarini, A.; Di Stefano, R. Fibrin as a scaffold for cardiac tissue engineering. *Biotechnol. Appl. Biochem.* **2011**, *58*, 301–310. [CrossRef]
235. Roura, S.; Gálvez-Montón, C.; Bayes-Genis, A. Fibrin, the preferred scaffold for cell transplantation after myocardial infarction? An old molecule with a new life. *J. Tissue Eng. Regen. Med.* **2017**, *11*, 2304–2313. [CrossRef]
236. Jockenhoevel, S.; Zund, G.; Hoerstrup, S.P.; Chalabi, K.; Sachweh, J.S.; Demircan, L.; Messmer, B.J.; Turina, M. Fibrin gel—Advantages of a new scaffold in cardiovascular tissue engineering. *Eur. J. Cardiothorac. Surg.* **2001**, *19*, 424–530. [CrossRef]
237. Echave, M.C.; Saenz del Burgo, L.; Pedraz, J.L.; Orive, G. Gelatin as Biomaterial for Tissue Engineering. *Curr. Pharm. Des.* **2017**, *23*, 3567–3584. [CrossRef] [PubMed]
238. Lukin, I.; Erezuma, I.; Maeso, L.; Zarate, J.; Desimone, M.F.; Al-Tel, T.H.; Dolatshahi-Pirouz, A.; Orive, G. Progress in Gelatin as Biomaterial for Tissue Engineering. *Pharmaceutics* **2022**, *14*, 1177. [CrossRef] [PubMed]
239. Nakajima, K.; Fujita, J.; Matsui, M.; Tohyama, S.; Tamura, N.; Kanazawa, H.; Seki, T.; Kishino, Y.; Hirano, A.; Okada, M.; et al. Gelatin Hydrogel Enhances the Engraftment of Transplanted Cardiomyocytes and Angiogenesis to Ameliorate Cardiac Function after Myocardial Infarction. *PLoS ONE* **2015**, *10*, e0133308. [CrossRef] [PubMed]
240. Kundu, B.; Rajkhowa, R.; Kundu, S.C.; Wang, X. Silk fibroin biomaterials for tissue regenerations. *Adv. Drug Deliv. Rev.* **2013**, *65*, 457–470. [CrossRef] [PubMed]
241. Song, Y.; Wang, H.; Yue, F.; Lv, Q.; Cai, B.; Dong, N.; Wang, Z.; Wang, L. Silk-Based Biomaterials for Cardiac Tissue Engineering. *Adv. Healthc. Mater.* **2020**, *9*, e2000735. [CrossRef]
242. Motta, A.; Barone, R.; Macaluso, F.; Giambalvo, F.; Pecoraro, F.; Di Marco, P.; Cassata, G.; Puleio, R.; Migliaresi, C.; Guercio, A.; et al. Silk-Based Matrices and c-Kit-Positive Cardiac Progenitor Cells for a Cellularized Silk Fibroin Scaffold: Study of an in vivo Model. *Cells Tissues Organs* **2023**, *212*, 258–271. [CrossRef]
243. Kim, Y.; Zharkinbekov, Z.; Raziyeva, K.; Tabyldiyeva, L.; Berikova, K.; Zhumagul, D.; Temirkhanova, K.; Saparov, A. Chitosan-Based Biomaterials for Tissue Regeneration. *Pharmaceutics* **2023**, *5*, 807. [CrossRef]
244. Beleño Acosta, B.; Advincula, R.C.; Grande-Tovar, C.D. Chitosan-Based Scaffolds for the Treatment of Myocardial Infarction: A Systematic Review. *Molecules* **2023**, *28*, 1920. [CrossRef]
245. Kazemi Asl, S.; Rahimzadegan, M.; Ostadrahimi, R. The recent advancement in the chitosan hybrid-based scaffolds for cardiac regeneration after myocardial infarction. *Carbohydr. Polym.* **2023**, *300*, 120266. [CrossRef]
246. Liberski, A.; Latif, N.; Raynaud, C.; Bollensdorff, C.; Yacoub, M. Alginate for cardiac regeneration: From seaweed to clinical trials. *Glob. Cardiol. Sci. Pract.* **2016**, *2016*, e201604. [CrossRef]
247. Ruvinov, E.; Cohen, S. Alginate biomaterial for the treatment of myocardial infarction: Progress, translational strategies, and clinical outlook: From ocean algae to patient bedside. *Adv. Drug Deliv. Rev.* **2016**, *96*, 54–76. [CrossRef] [PubMed]
248. Cattelan, G.; Guerrero Gerbolés, A.; Foresti, R.; Pramstaller, P.P.; Rossini, A.; Miragoli, M.; Caffarra Malvezzi, C. Alginate Formulations: Current Developments in the Race for Hydrogel-Based Cardiac Regeneration. *Front. Bioeng. Biotechnol.* **2020**, *8*, 414. [CrossRef] [PubMed]
249. Bonafè, F.; Govoni, M.; Giordano, E.; Caldarera, C.M.; Guarnieri, C.; Muscari, C. Hyaluronan and cardiac regeneration. *J. Biomed. Sci.* **2014**, *21*, 100. [CrossRef]
250. Xu, X.; Jha, A.K.; Harrington, D.A.; Farach-Carson, M.C.; Jia, X. Hyaluronic Acid-Based Hydrogels: From a Natural Polysaccharide to Complex Networks. *Soft Matter* **2012**, *8*, 3280–3294. [CrossRef]
251. Abdalla, S.; Makhoul, G.; Duong, M.; Chiu, R.C.; Cecere, R. Hyaluronic acid-based hydrogel induces neovascularization and improves cardiac function in a rat model of myocardial infarction. *Interact Cardiovasc. Thorac. Surg.* **2013**, *17*, 767–772. [CrossRef] [PubMed]
252. Le, L.V.; Mohindra, P.; Fang, Q.; Sievers, R.E.; Mkrtschjan, M.A.; Solis, C.; Safranek, C.W.; Russell, B.; Lee, R.J.; Desai, T.A. Injectable hyaluronic acid based microrods provide local micromechanical and biochemical cues to attenuate cardiac fibrosis after myocardial infarction. *Biomaterials* **2018**, *169*, 11–21. [CrossRef]
253. Mendibil, U.; Ruiz-Hernandez, R.; Retegi-Carrion, S.; Garcia-Urquia, N.; Olalde-Graells, B.; Abarrategi, A. Tissue-Specific Decellularization Methods: Rationale and Strategies to Achieve Regenerative Compounds. *Int. J. Mol. Sci.* **2020**, *21*, 5447. [CrossRef]

254. Eitan, Y.; Sarig, U.; Dahan, N.; Machluf, M. Acellular cardiac extracellular matrix as a scaffold for tissue engineering: In vitro cell support, remodeling, and biocompatibility. *Tissue Eng. Part C Methods* **2010**, *16*, 671–683. [CrossRef]
255. Di Meglio, F.; Nurzynska, D.; Romano, V.; Miraglia, R.; Belviso, I.; Sacco, A.M.; Barbato, V.; Di Gennaro, M.; Granato, G.; Maiello, C.; et al. Optimization of Human Myocardium Decellularization Method for the Construction of Implantable Patches. *Tissue Eng. Part C Methods* **2017**, *23*, 525–539. [CrossRef]
256. Belviso, I.; Sacco, A.M.; Cozzolino, D.; Nurzynska, D.; Di Meglio, F.; Castaldo, C.; Romano, V. Cardiac-derived extracellular matrix: A decellularization protocol for heart regeneration. *PLoS ONE* **2022**, *7*, e0276224. [CrossRef]
257. Lockhart, M.; Wirrig, E.; Phelps, A.; Wessels, A. Extracellular matrix and heart development. *Birth Defects Res. A Clin. Mol. Teratol.* **2011**, *91*, 535–550. [CrossRef]
258. Belviso, I.; Angelini, F.; Di Meglio, F.; Picchio, V.; Sacco, A.M.; Nocella, C.; Romano, V.; Nurzynska, D.; Frati, G.; Maiello, C.; et al. The Microenvironment of Decellularized Extracellular Matrix from Heart Failure Myocardium Alters the Balance between Angiogenic and Fibrotic Signals from Stromal Primitive Cells. *Int. J. Mol. Sci.* **2020**, *21*, 7903. [CrossRef]
259. Bayomy, A.F.; Bauer, M.; Qiu, Y.; Liao, R. Regeneration in heart disease-Is ECM the key? *Life Sci.* **2012**, *91*, 823–827. [CrossRef] [PubMed]
260. Guyette, J.P.; Charest, J.M.; Mills, R.W.; Jank, B.J.; Moser, P.T.; Gilpin, S.E.; Gershlak, J.R.; Okamoto, T.; Gonzalez, G.; Milan, D.J.; et al. Bioengineering Human Myocardium on Native Extracellular Matrix. *Circ. Res.* **2016**, *118*, 56–72. [CrossRef]
261. McInnes, A.D.; Moser, M.A.J.; Chen, X. Preparation and Use of Decellularized Extracellular Matrix for Tissue Engineering. *J. Funct. Biomater.* **2022**, *13*, 240. [CrossRef] [PubMed]
262. Smith, L.R.; Cho, S.; Discher, D.E. Stem Cell Differentiation is Regulated by Extracellular Matrix Mechanics. *Physiology* **2018**, *33*, 16–25. [CrossRef]
263. Watt, F.M.; Huck, W.T. Role of the extracellular matrix in regulating stem cell fate. *Nat. Rev. Mol. Cell Biol.* **2013**, *14*, 467–473. [CrossRef] [PubMed]
264. Parmaksiz, M.; Dogan, A.; Odabas, S.; Elçin, A.E.; Elçin, Y.M. Clinical applications of decellularized extracellular matrices for tissue engineering and regenerative medicine. *Biomed. Mater.* **2016**, *11*, 022003. [CrossRef]
265. Mesquita, F.C.P.; Morrissey, J.; Monnerat, G.; Domont, G.B.; Nogueira, F.C.S.; Hochman-Mendez, C. Decellularized Extracellular Matrix Powder Accelerates Metabolic Maturation at Early Stages of Cardiac Differentiation in Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes. *Cells Tissues Organs* **2023**, *212*, 32–44. [CrossRef]
266. Ott, H.C.; Matthiesen, T.S.; Goh, S.K.; Black, L.D.; Kren, S.M.; Netoff, T.I.; Taylor, D.A. Perfusion-decellularized matrix: Using nature's platform to engineer a bioartificial heart. *Nat. Med.* **2008**, *14*, 213–221. [CrossRef]
267. Zhang, X.; Chen, X.; Hong, H.; Hu, R.; Liu, J.; Liu, C. Decellularized extracellular matrix scaffolds: Recent trends and emerging strategies in tissue engineering. *Bioact. Mater.* **2021**, *10*, 15–31. [CrossRef]
268. Perea-Gil, I.; Gálvez-Montón, C.; Prat-Vidal, C.; Jorba, I.; Segú-Vergés, C.; Roura, S.; Soler-Botija, C.; Iborra-Egea, O.; Revuelta-López, E.; Fernández, M.A.; et al. Head-to-head comparison of two engineered cardiac grafts for myocardial repair: From scaffold characterization to pre-clinical testing. *Sci. Rep.* **2018**, *8*, 6708. [CrossRef]
269. Romano, V.; Belviso, I.; Cozzolino, D.; Sacco, A.M.; Schonauer, F.; Nurzynska, D.; Di Meglio, F.; Castaldo, C. Decellularization for the Preparation of Highly Preserved Human Acellular Skin Matrix for Regenerative Medicine. *J. Vis. Exp.* **2021**, *175*, e62935. [CrossRef] [PubMed]
270. Jiang, Y.; Zhang, L.L.; Zhang, F.; Bi, W.; Zhang, P.; Yu, X.J.; Rao, S.L.; Wang, S.H.; Li, Q.; Ding, C.; et al. Dual human iPSC-derived cardiac lineage cell-seeding extracellular matrix patches promote regeneration and long-term repair of infarcted hearts. *Bioact. Mater.* **2023**, *28*, 206–226. [CrossRef] [PubMed]
271. Lee, P.F.; Chau, E.; Cabello, R.; Yeh, A.T.; Sampaio, L.C.; Gobin, A.S.; Taylor, D.A. Inverted orientation improves decellularization of whole porcine hearts. *Acta Biomater.* **2017**, *49*, 181–191. [CrossRef]
272. Rouwkema, J.; Khademhosseini, A. Vascularization and Angiogenesis in Tissue Engineering: Beyond Creating Static Networks. *Trends Biotechnol.* **2016**, *34*, 733–745. [CrossRef] [PubMed]
273. Gao, L.P.; Du, M.J.; Lv, J.J.; Schmull, S.; Huang, R.T.; Li, J. Use of human aortic extracellular matrix as a scaffold for construction of a patient-specific tissue engineered vascular patch. *Biomed. Mater.* **2017**, *12*, 065006. [CrossRef] [PubMed]
274. Taghizadeh, B.; Ghavami, L.; Derakhshankhah, H.; Zangene, E.; Razmi, M.; Jaymand, M.; Zarrintaj, P.; Zarghami, N.; Jaafari, M.R.; Moallem Shahri, M.; et al. Biomaterials in Valvular Heart Diseases. *Front. Bioeng. Biotechnol.* **2020**, *8*, 529244. [CrossRef]
275. Lee, J.H.; Rim, Y.S.; Min, W.K.; Park, K.; Kim, H.T.; Hwang, G.; Kim, H.J. Biocompatible and biodegradable neuromorphic device based on hyaluronic acid for implantable bioelectronics. *Adv. Funct. Mater.* **2021**, *31*, 2107074. [CrossRef]
276. Todros, S.; Todesco, M.; Bagno, A. Biomaterials and their biomedical applications: From replacement to regeneration. *Processes* **2021**, *9*, 1949. [CrossRef]
277. Smith, L.J.; Li, P.; Holland, M.R.; Ekser, B. FABRICA: A Bioreactor Platform for Printing, Perfusing, Observing, & Stimulating 3D Tissues. *Sci. Rep.* **2018**, *8*, 7561. [CrossRef]
278. Ovando-Roche, P.; West, E.L.; Branch, M.J.; Sampson, R.D.; Fernando, M.; Munro, P.; Georgiadis, A.; Rizzi, M.; Kloc, M.; Naeem, A.; et al. Use of bioreactors for culturing human retinal organoids improves photoreceptor yields. *Stem Cell Res. Ther.* **2018**, *9*, 156. [CrossRef] [PubMed]
279. Jomezadeh Kheibary, N.; Abolfazli Esfahani, J.; Mousavi Shaegh, S.A. Analysis of oxygen transport in microfluidic bioreactors for cell culture and organ-on-chip applications. *Eng. Rep.* **2020**, *2*, e12062. [CrossRef]

280. Chen, A.M.; Lashmet, M.; Isidan, A.; Sterner, J.L.; Walsh, J.; Koehler, C.; Li, P.; Ekser, B.; Smith, L. Oxygenation Profiles of Human Blood, Cell Culture Medium, and Water for Perfusion of 3D-Bioprinted Tissues using the FABRICA Bioreactor Platform. *Sci. Rep.* **2020**, *10*, 7237. [CrossRef]
281. Lee, J. Development of a model to determine mass transfer coefficient and oxygen solubility in bioreactors. *Heliyon* **2017**, *3*, e00248. [CrossRef]
282. Ginai, M.; Elsby, R.; Hewitt, C.J.; Surry, D.; Fenner, K.; Coopman, K. The use of bioreactors as in vitro models in pharmaceutical research. *Drug Discov. Today* **2013**, *18*, 922–935. [CrossRef] [PubMed]
283. Williams, J.K.; Yoo, J.J.; Atala, A. Regenerative medicine approaches for tissue engineered heart valves. In *Principles of Regenerative Medicine*, 3rd ed.; Academic Press: Cambridge, MA, USA, 2019; pp. 1041–1058. [CrossRef]
284. Dupard, S.J.; Garcia, A.G.; Bourgine, P.E. Customizable 3D printed perfusion bioreactor for the engineering of stem cell microenvironments. *Front. Bioeng. Biotechnol.* **2023**, *10*, 1081145. [CrossRef]
285. Schmid, J.; Schwarz, S.; Meier-Staude, R.; Sudhop, S.; Clausen-Schaumann, H.; Schieker, M.; Huber, R. A Perfusion Bioreactor System for Cell Seeding and Oxygen-Controlled Cultivation of Three-Dimensional Cell Cultures. *Tissue Eng. Part C Methods* **2018**, *24*, 585–595. [CrossRef] [PubMed]
286. Lerman, M.J.; Lembong, J.; Gillen, G.; Fisher, J.P. 3D printing in cell culture systems and medical applications. *Appl. Phys. Rev.* **2018**, *5*, 041109. [CrossRef] [PubMed]
287. Putame, G.; Gabetti, S.; Carbonaro, D.; Di Meglio, F.; Romano, V.; Sacco, A.M.; Belviso, I.; Serino, G.; Bignardi, C.; Morbiducci, U.; et al. Compact and tunable stretch bioreactor advancing tissue engineering implementation. Application to engineered cardiac constructs. *Med. Eng. Phys.* **2020**, *84*, 1–9. [CrossRef] [PubMed]
288. Scholp, A.J.; Jensen, J.; Chinnathambi, S.; Atluri, K.; Mendenhall, A.; Fowler, T.; Salem, A.K.; Martin, J.A.; Sander, E.A. Force-Bioreactor for Assessing Pharmacological Therapies for Mechanobiological Targets. *Front. Bioeng. Biotechnol.* **2022**, *10*, 907611. [CrossRef] [PubMed]
289. Ganeeva, I.; Zmievskaya, E.; Valiullina, A.; Kudriaeva, A.; Miftakhova, R.; Rybalov, A.; Bulatov, E. Recent Advances in the Development of Bioreactors for Manufacturing of Adoptive Cell Immunotherapies. *Bioengineering* **2022**, *9*, 808. [CrossRef] [PubMed]
290. Yang, C.; Kong, L.; Zhang, Z. Bioreactor: Intelligent platform for drug delivery. *Nano Today* **2022**, *44*, 101481. [CrossRef]
291. Wang, B.; Wang, Z.; Chen, T.; Zhao, X. Development of Novel Bioreactor Control Systems Based on Smart Sensors and Actuators. *Front. Bioeng. Biotechnol.* **2020**, *8*, 7. [CrossRef]
292. Figallo, E.; Cannizzaro, C.; Gerecht, S.; Burdick, J.A.; Langer, R.; Elvassore, N.; Vunjak-Novakovic, G. Micro-bioreactor array for controlling cellular microenvironments. *Lab Chip* **2007**, *7*, 710–719. [CrossRef] [PubMed]
293. Ahmed, S.; Chauhan, V.M.; Ghaemmaghami, A.M.; Aylott, J.W. New generation of bioreactors that advance extracellular matrix modelling and tissue engineering. *Biotechnol. Lett.* **2019**, *41*, 1–25. [CrossRef]
294. O'Mara, P.; Farrell, A.; Bones, J.; Twomey, K. Staying alive! Sensors used for monitoring cell health in bioreactors. *Talanta* **2018**, *176*, 130–139. [CrossRef]
295. Busse, C.; Biechele, P.; de Vries, I.; Reardon, K.F.; Solle, D.; Scheper, T. Sensors for disposable bioreactors. *Eng. Life Sci.* **2017**, *17*, 940–952. [CrossRef]
296. Bluma, A.; Höpfner, T.; Lindner, P.; Rehbock, C.; Beutel, S.; Riechers, D.; Hitzmann, B.; Scheper, T. In-situ imaging sensors for bioprocess monitoring: State of the art. *Anal. Bioanal. Chem.* **2010**, *398*, 2429–2438. [CrossRef]
297. Gruber, P.; Marques, M.P.C.; Szita, N.; Mayr, T. Integration and application of optical chemical sensors in microbioreactors. *Lab Chip* **2017**, *17*, 2693–2712. [CrossRef]
298. Shkilnyy, A.; Dubois, J.; Sabra, G.; Sharp, J.; Gagnon, S.; Proulx, P.; Vermette, P. Bioreactor controlled by PI algorithm and operated with a perfusion chamber to support endothelial cell survival and proliferation. *Biotechnol. Bioeng.* **2012**, *109*, 1305–1313. [CrossRef]
299. Bizon, K.; Tabiś, B. Problems in volumetric flow rate and liquid level control of a continuous stirred tank bioreactor with structured and unstructured kinetics. *Chem. Eng. Res. Des.* **2021**, *175*, 309–319. [CrossRef]
300. Ylä-Herttuala, S.; Baker, A.H. Cardiovascular Gene Therapy: Past, Present, and Future. *Mol. Ther.* **2017**, *25*, 1095–1106. [CrossRef] [PubMed]
301. Shimamura, M.; Nakagami, H.; Sanada, F.; Morishita, R. Progress of Gene Therapy in Cardiovascular Disease. *Hypertension* **2020**, *76*, 1038–1044. [CrossRef] [PubMed]
302. Wolfram, J.A.; Donahue, J.K. Gene therapy to treat cardiovascular disease. *J. Am. Heart Assoc.* **2013**, *2*, e000119. [CrossRef] [PubMed]
303. Zhang, H.; Zhan, Q.; Huang, B.; Wang, Y.; Wang, X. AAV-mediated gene therapy: Advancing cardiovascular disease treatment. *Front. Cardiovasc. Med.* **2022**, *9*, 952755. [CrossRef]
304. Cao, G.; Xuan, X.; Zhang, R.; Hu, J.; Dong, H. Gene Therapy for Cardiovascular Disease: Basic Research and Clinical Prospects. *Front. Cardiovasc. Med.* **2021**, *8*, 760140. [CrossRef]
305. Sleeper, M.M.; Bish, L.T.; Sweeney, H.L. Gene therapy in large animal models of human cardiovascular genetic disease. *ILAR J.* **2009**, *50*, 199–205. [CrossRef]
306. Korpela, H.; Siimes, S.; Ylä-Herttuala, S. Large Animal Model for Evaluating the Efficacy of the Gene Therapy in Ischemic Heart. *J. Vis. Exp.* **2021**, *175*, e62833. [CrossRef]

307. Gopinath, C.; Nathar, T.J.; Ghosh, A.; Hickstein, D.D.; Nelson, E.J.R. Contemporary Animal Models For Human Gene Therapy Applications. *Curr. Gene Ther.* **2015**, *15*, 531–540. [CrossRef]
308. Giacca, M.; Zacchigna, S. VEGF gene therapy: Therapeutic angiogenesis in the clinic and beyond. *Gene Ther.* **2012**, *19*, 622–629. [CrossRef] [PubMed]
309. del Monte, F.; Harding, S.E.; Schmidt, U.; Matsui, T.; Kang, Z.B.; Dec, G.W.; Gwathmey, J.K.; Rosenzweig, A.; Hajjar, R.J. Restoration of contractile function in isolated cardiomyocytes from failing human hearts by gene transfer of SERCA2a. *Circulation* **1999**, *100*, 2308–2311. [CrossRef] [PubMed]
310. Askari, A.T.; Unzek, S.; Popovic, Z.B.; Goldman, C.K.; Forudi, F.; Kiedrowski, M.; Rovner, A.; Ellis, S.G.; Thomas, J.D.; Di Corleto, P.E.; et al. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. *Lancet* **2003**, *362*, 697–703. [CrossRef] [PubMed]
311. Hammond, H.K.; Penny, W.F.; Traverse, J.H.; Henry, T.D.; Watkins, M.W.; Yancy, C.W.; Sweis, R.N.; Adler, E.D.; Patel, A.N.; Murray, D.R.; et al. Intracoronary Gene Transfer of Adenylyl Cyclase 6 in Patients With Heart Failure: A Randomized Clinical Trial. *JAMA Cardiol.* **2016**, *1*, 163–171. [CrossRef]
312. Raake, P.W.; Tscheschner, H.; Reinkober, J.; Ritterhoff, J.; Katus, H.A.; Koch, W.J.; Most, P. Gene therapy targets in heart failure: The path to translation. *Clin. Pharmacol. Ther.* **2011**, *90*, 542–553. [CrossRef] [PubMed]
313. Isner, J.M.; Vale, P.R.; Symes, J.F.; Losordo, D.W. Assessment of risks associated with cardiovascular gene therapy in human subjects. *Circ. Res.* **2001**, *89*, 389–400. [CrossRef]
314. Zhou, H.S.; Liu, D.P.; Liang, C.C. Challenges and strategies: The immune responses in gene therapy. *Med. Res. Rev.* **2004**, *24*, 748–761. [CrossRef]
315. Bradshaw, A.C.; Baker, A.H. Gene therapy for cardiovascular disease: Perspectives and potential. *Vasc. Pharmacol.* **2013**, *58*, 174–181. [CrossRef]
316. Zhou, J.; Ren, Z.; Xu, J.; Zhang, J.; Chen, Y.E. Gene editing therapy ready for cardiovascular diseases: Opportunities, challenges, and perspectives. *Med. Rev.* **2021**, *1*, 6–9. [CrossRef]
317. Shirley, J.L.; de Jong, Y.P.; Terhorst, C.; Herzog, R.W. Immune Responses to Viral Gene Therapy Vectors. *Mol. Ther.* **2020**, *28*, 709–722. [CrossRef]
318. Freitas, M.V.; Frâncio, L.; Haleva, L.; Matte, U.D.S. Protection is not always a good thing: The immune system's impact on gene therapy. *Genet. Mol. Biol.* **2022**, *45*, e20220046. [CrossRef]
319. Both, G.; Alexander, I.; Fletcher, S.; Nicolson, T.J.; Rasko, J.E.; Wilton, S.D.; Symonds, G. Gene therapy: Therapeutic applications and relevance to pathology. *Pathology* **2011**, *43*, 642–656. [CrossRef]
320. Ishikawa, K.; Weber, T.; Hajjar, R.J. Human Cardiac Gene Therapy. *Circ. Res.* **2018**, *123*, 601–613. [CrossRef]
321. Ishikawa, K.; Tilemann, L.; Fish, K.; Hajjar, R.J. Gene delivery methods in cardiac gene therapy. *J. Gene Med.* **2011**, *13*, 566–572. [CrossRef] [PubMed]
322. Wasala, N.B.; Shin, J.H.; Duan, D. The evolution of heart gene delivery vectors. *J. Gene Med.* **2011**, *13*, 557–565. [CrossRef] [PubMed]
323. Katz, M.G.; Swain, J.D.; White, J.D.; Low, D.; Stedman, H.; Bridges, C.R. Cardiac gene therapy: Optimization of gene delivery techniques in vivo. *Hum. Gene Ther.* **2010**, *21*, 371–380. [CrossRef] [PubMed]
324. Jasim, S.A.; Bokov, D.O.; Suksatan, W.; Alsaikhan, F.; Jawad, M.A.; Sharma, S.K.; Chupradit, S.; Thangavelu, L. Organoid Models of Heart Diseases: Find a New Channel in Improvements of Cardiac Regenerative Medicine. *Curr. Med. Chem.* **2023**, *30*, 2726–3742. [CrossRef]
325. Mollaki, V. Ethical Challenges in Organoid Use. *BioTech* **2021**, *10*, 12. [CrossRef] [PubMed]
326. Yang, Z.; Zhang, Y.; Wang, J.; Yin, J.; Wang, Z.; Pei, R. Cardiac organoid: Multiple construction approaches and potential applications. *J. Mater. Chem. B* **2023**. [CrossRef]
327. Yaqing, W.; Jianhua, Q. Advances in human organoids-on-chips in biomedical research. *Life Med.* **2023**, *2*, lnad007. [CrossRef]
328. Zhao, X.; Xu, Z.; Xiao, L.; Shi, T.; Xiao, H.; Wang, Y.; Li, Y.; Xue, F.; Zeng, W. Review on the Vascularization of Organoids and Organoids-on-a-Chip. *Front. Bioeng. Biotechnol.* **2021**, *9*, 637048. [CrossRef] [PubMed]
329. Huang, Y.; Huang, Z.; Tang, Z.; Chen, Y.; Huang, M.; Liu, H.; Huang, W.; Ye, Q.; Jia, B. Research Progress, Challenges, and Breakthroughs of Organoids as Disease Models. *Front. Cell Dev. Biol.* **2021**, *9*, 740574. [CrossRef] [PubMed]
330. Yang, S.; Hu, H.; Kung, H.; Zou, R.; Dai, Y.; Hu, Y.; Wang, T.; Lv, T.; Yu, J.; Li, F. Organoids: The current status and biomedical applications. *MedComm* **2023**, *4*, e274. [CrossRef] [PubMed]
331. Hoang, P.; Wang, J.; Conklin, B.R.; Healy, K.E.; Ma, Z. Generation of spatial-patterned early-developing cardiac organoids using human pluripotent stem cells. *Nat. Protoc.* **2018**, *13*, 723–737. [CrossRef]
332. Mills, R.; Hudson, J. An in vitro model of myocardial infarction. *Nat. Biomed. Eng.* **2020**, *4*, 366–367. [CrossRef]
333. Hofbauer, P.; Jahnel, S.M.; Papai, N.; Giesshammer, M.; Deyett, A.; Schmidt, C.; Penc, M.; Tavernini, K.; Grdseloff, N.; Meledeth, C.; et al. Cardioids reveal self-organizing principles of human cardiogenesis. *Cell* **2021**, *184*, 3299–3317.e22. [CrossRef]
334. Lewis-Israeli, Y.R.; Wasserman, A.H.; Aguirre, A. Heart Organoids and Engineered Heart Tissues: Novel Tools for Modeling Human Cardiac Biology and Disease. *Biomolecules* **2021**, *11*, 1277. [CrossRef]
335. Rauth, S.; Karmakar, S.; Batra, S.K.; Ponnusamy, M.P. Recent advances in organoid development and applications in disease modeling. *Biochim. Biophys. Acta Rev. Cancer* **2021**, *1875*, 188527. [CrossRef]

336. Yan, J.; Li, Z.; Guo, J.; Liu, S.; Guo, J. Organ-on-a-chip: A new tool for in vitro research. *Biosens. Bioelectron.* **2022**, *216*, 114626. [CrossRef]
337. Monteduro, A.G.; Rizzato, S.; Caragnano, G.; Trapani, A.; Giannelli, G.; Maruccio, G. Organs-on-chips technologies—A guide from disease models to opportunities for drug development. *Biosens. Bioelectron.* **2023**, *231*, 115271. [CrossRef]
338. Low, L.A.; Tagle, D.A. Organs-on-chips: Progress, challenges, and future directions. *Exp. Biol. Med.* **2017**, *242*, 1573–1578. [CrossRef] [PubMed]
339. Low, L.A.; Sutherland, M.; Lumelsky, N.; Selimovic, S.; Lundberg, M.S.; Tagle, D.A. Organs-on-a-Chip. *Adv. Exp. Med. Biol.* **2020**, *1230*, 27–42. [CrossRef]
340. Ma, C.; Peng, Y.; Li, H.; Chen, W. Organ-on-a-Chip: A New Paradigm for Drug Development. *Trends Pharmacol. Sci.* **2021**, *42*, 119–133. [CrossRef] [PubMed]
341. Wu, Q.; Liu, J.; Wang, X.; Feng, L.; Wu, J.; Zhu, X.; Wen, W.; Gong, X. Organ-on-a-chip: Recent breakthroughs and future prospects. *Biomed. Eng. Online* **2020**, *19*, 9. [CrossRef] [PubMed]
342. Paloschi, V.; Sabater-Lleal, M.; Middelkamp, H.; Vivas, A.; Johansson, S.; van der Meer, A.; Tenje, M.; Maegdefessel, L. Organ-on-a-chip technology: A novel approach to investigate cardiovascular diseases. *Cardiovasc. Res.* **2021**, *117*, 2742–2754. [CrossRef] [PubMed]
343. Inbody, S.C.; Sinquefield, B.E.; Lewis, J.P.; Horton, R.E. Biomimetic microsystems for cardiovascular studies. *Am. J. Physiol. Cell Physiol.* **2021**, *320*, C850–C872. [CrossRef] [PubMed]
344. Zhang, Y.S.; Arneri, A.; Bersini, S.; Shin, S.R.; Zhu, K.; Goli-Malekabadi, Z.; Aleman, J.; Colosi, C.; Busignani, F.; Dell'Erba, V.; et al. Bioprinting 3D microfibrous scaffolds for engineering endothelialized myocardium and heart-on-a-chip. *Biomaterials* **2016**, *110*, 45–59. [CrossRef] [PubMed]
345. Lim, S.; Kim, S.W.; Kim, I.K.; Song, B.W.; Lee, S. Organ-on-a-chip: Its use in cardiovascular research. *Clin. Hemorheol. Microcirc.* **2023**, *83*, 315–339. [CrossRef] [PubMed]
346. Wu, H.; Shi, S.; Liu, Y.; Zhang, Q.; Lam, R.H.W.; Lim, C.T.; Hu, J. Recent progress of organ-on-a-chip towards cardiovascular diseases: Advanced design, fabrication, and applications. *Biofabrication* **2023**, *15*, 042001. [CrossRef]
347. Rahmani Dabbagh, S.; Rezapour Sarabi, M.; Birtek, M.T.; Mustafaoglu, N.; Zhang, Y.S.; Tasoglu, S. 3D bioprinted organ-on-chips. *Aggregate* **2023**, *4*, e197. [CrossRef]
348. Marsano, A.; Conficconi, C.; Lemme, M.; Occhetta, P.; Gaudiello, E.; Votta, E.; Cerino, G.; Redaelli, A.; Rasponi, M. Beating heart on a chip: A novel microfluidic platform to generate functional 3D cardiac microtissues. *Lab Chip* **2016**, *16*, 599–610. [CrossRef] [PubMed]
349. Yang, Q.; Xiao, Z.; Lv, X.; Zhang, T.; Liu, H. Fabrication and Biomedical Applications of Heart-on-a-chip. *Int. J. Bioprint.* **2021**, *7*, 370. [CrossRef] [PubMed]
350. Ronaldson-Bouchard, K.; Ma, S.P.; Yeager, K.; Chen, T.; Song, L.; Sirabella, D.; Morikawa, K.; Teles, D.; Yazawa, M.; Vunjak-Novakovic, G. Advanced maturation of human cardiac tissue grown from pluripotent stem cells. *Nature* **2018**, *556*, 239–243. [CrossRef] [PubMed]
351. Leung, C.M.; de Haan, P.; Bouchard, K.R.; Kim, G.A.; Ko, J.; Rho, H.S.; Chen, Z.; Habibovic, P.; Jeon, N.L.; Takayama, S.; et al. A guide to the organ-on-a-chip. *Nat. Rev. Methods Prim.* **2022**, *2*, 33. [CrossRef]
352. Skardal, A.; Murphy, S.V.; Devarasetty, M.; Mead, I.; Kang, H.W.; Seol, Y.J.; Shrike Zhang, Y.; Shin, S.R.; Zhao, L.; Aleman, J.; et al. Multi-tissue interactions in an integrated three-tissue organ-on-a-chip platform. *Sci. Rep.* **2017**, *7*, 8837. [CrossRef]
353. Clarke, G.A.; Hartse, B.X.; Niaraki Asli, A.E.; Taghavimehr, M.; Hashemi, N.; Abbasi Shirsavar, M.; Montazami, R.; Alimoradi, N.; Nasirian, V.; Ouedraogo, L.J.; et al. Advancement of Sensor Integrated Organ-on-Chip Devices. *Sensors* **2021**, *21*, 1367. [CrossRef]
354. Shirure, V.S.; Hughes, C.C.W.; George, S.C. Engineering Vascularized Organoid-on-a-Chip Models. *Annu. Rev. Biomed. Eng.* **2021**, *23*, 141–167. [CrossRef]
355. Suhito, I.R.; Kim, T.-H. Recent advances and challenges in organoid-on-a-chip technology. *Organoid* **2022**, *2*, e4. [CrossRef]
356. Park, S.E.; Georgescu, A.; Huh, D. Organoids-on-a-chip. *Science* **2019**, *364*, 960–965. [CrossRef]