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Emerging Bioelectronic Strategies for Cardiovascular Tissue Engineering and Implantation

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Heart diseases are currently the leading cause of death worldwide. The ability to create cardiovascular tissue has numerous applications in understanding tissue development, disease progression, pharmacological testing, bio-actuators, and transplantation; yet current cardiovascular tissue engineering (CTE) methods are limited. However, there have been emerging developments in the bioelectronics field, with the creation of biomimetic devices that can intimately interact with cardiac cells, provide monitoring capabilities, and regulate tissue formation. Combining bioelectronics with cardiac tissue engineering can overcome current limitations and produce physiologically relevant tissue that can be used in various areas of cardiovascular research and medicine. This review highlights the recent advances in cardiovascular-based bioelectronics. First, cardiac tissue engineering and the potential of bioelectronic therapies for cardiovascular diseases are discussed. Second, advantageous bioelectronic materials for CTE and implantation and their properties are reviewed. Third, several representative cardiovascular tissue-bioelectronic interface models and the beneficial functions that bioelectronics can demonstrate in in vitro and in vivo applications are explored. Finally, the prospects and remaining challenges for clinical application are discussed.

1. Introduction

The cardiovascular system is made up of the heart, blood vessels, and blood. These provide the body with essential nutrients and oxygen (O_2), while removing carbon dioxide (CO_2) and metabolic waste. Heart diseases are a group of diseases and conditions causing cardiovascular problems and result in about one-third of deaths globally.[1] They include coronary heart disease, arrhythmia, heart valve disease, heart failure, cardiomyopathy, etc. With no cure, current therapeutic options such as medication and surgery can only slow disease progression. Cardiovascular tissue engineering (CTE) is considered a key approach to current therapies, being used to elucidate heart and cardiovascular disease development, for drug screening,[2] or transplantation to repair and/or replace damaged cardiovascular tissue.[3]

CTE combines a scaffold, cells, and signaling to form physiologically relevant functioning tissue.[4] However, currently available CTE methods struggle to engineer tissue that is truly representative of endogenous myocardium and blood vessels. A major drawback is that the produced tissue is often immature and non-functioning. Another issue is the lack of monitoring methods in traditional CTE particularly for transplantation applications.[5] These issues can potentially be overcome by using bioelectronics in CTE.

The bioelectronics field combines biology and electronic engineering to produce devices able to understand the complexity of the body, manipulate cell behavior, and deliver therapeutic support.[6] The introduction of electronic components in tissue engineering could provide a greater level of control over the generation of tissue by sensing, detecting, and acting in real-time to the environment the cells and tissue require to develop successfully. The cardiovascular tissue that is created can then be used in a number of in vitro and in vivo applications, including but not limited to: cardiac morphogenesis, pathogenesis, drug testing,[3] bio-actuator power source,[7,8] or implantation to improve cardiac function.[3]

Rapid advances in bioelectronics for cardiology have enabled the development of soft, flexible, and biocompatible devices that can be porous and smaller than traditional strategies to provide a seamless tissue-electronic interface, in addition to providing structural support for tissue creation, continuous monitoring of electrophysiology and cell status, electrical stimulation, and drug delivery. Compared with traditional CTE methods, the introduction of bioelectronics can play an active role in developing physiologically relevant cardiac tissue or implantable devices for cardiovascular research and heart disease medicine (**Table 1**).

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Table 1. Summary of common heart diseases along with conventional and bioelectronic therapeutic options.

Common heart diseases	Description	Conventional therapies	Bioelectronic cardiac medicine options
Coronary artery disease	Plaque build-up reducing blood flow	Blood thinning, lipid lowering, and/or blood pressure reducing medications.Artery and heart replacement surgeries.	Electronic blood vessel and heart grafts that could provide continuous monitoring of cardiac state, while providing electrical stimulation that can potentially reduce hypertension.
Heart Failure	Reduction in heart function efficiency	Blood thinning, lipid lowering, and/or blood pressure reducing medications. Artery and heart transplant and device implantation surgeries	Currently used devices include pacemakers, cardiac resynchronization therapy (CRT) devices, and implantable cardioverter defibrillators (ICDs). These are continually being improved to provide both simultaneous monitoring and electrical stimulation as therapy.
Pericarditis	Inflamed pericardium	Anti-inflammatory painkillers, and/or antibiotics	Future bioelectronic devices with sensors monitoring inflammation levels, electrical stimulation and drug delivery to be created.
Cardiomyopathy	Weak heart muscle that can lead to heart failure	Blood thinning, lipid lowering, and/or blood pressure reducing medications. Surgeries can include septal myectomy.	Pacemakers and ICDs are currently in use. These are continually being improvedto provide both simultaneous monitoring and electrical stimulation as a therapeutic option.
Cardiac arrhythmia	Disorganised electrical signals causing an unusual heartbeat that can lead to sudden cardiac death	Arrhythmia controlling medication. Catheter ablation.	Pacemakers and ICDs are currentlyin use. These devices are continually being improved to provide both simultaneous monitoring and electrical stimulation as a therapeutic option. Future devices such as electronic blood vessels/sensors/ grafts could be transplanted for monitoring of cardiac rhythm and repair of disrupted electrical activity.
Aortic aneurysm	Distention of the aorta due to wall weakness	Ultrasound scans to determine size. Surgery recommended if at high risk of bursting.	Future devices could be an electronic blood vessel replacing damaged areas and monitoring blood flow.
Valve disease	Inefficient valves that affect blood flow	Blood pressure reducing medication. Surgery to repair or replace the valve.	Future devices could be electronic valves that can open/close in response to changes in blood pressure.

In this review, we present recent bioelectronics advances that can be applied within cardiac tissue engineering and implantation, with a particular focus on materials, fabrication, bioelectronics-cell interface, and innovations in bioelectronics functions with potential to improve CTE methods. Overall, the advances and application of bioelectronics could significantly enhance the success and biomedical applications of in vitro and in vivo cardiac tissue models (**Figure 1**).

2. Advantageous Bioelectronic Materials for Cardiovascular Tissue Engineering and Implantation

2.1. Flexible and Porous Bioelectronic Materials

Traditional bioelectronics used in cardiology are large and bulky; yielding an elastic modulus in the range of 100 MPa to 10 GPa,[9] which is incomparable to the elastic modulus of heart tissue (≈10–15 kPa).[10] The heart and blood vessels are incredibly soft and bendable to allow pumping of blood around the body. Therefore, the continued in vitro and in vivo use of stiff electronics results in tissue deformation, constraint, and lasting damage. Long-term in vivo use of rigid bioelectronics is also prone to infection, inflammation, and fibrotic encapsulation of the bioelectronic device, which reduces performance and increases implant rejection risk.[11] **Figure 2**A shows an automated implantable cardioverter-defibrillator that has eroded through the skin and become partially exposed.[12]

Cardiac cells are sensitive to their environment. Heart cells need to move freely to contract and organize themselves into a mature, well-aligned structure with a striated phenotype characteristic of cardiac tissue. Therefore, cell movement is an essential process for effective cardiac tissue formation and maintenance, as well as in vivo wound healing, during heart disease and after transplantation. The introduction of flexibility and pores allows cell shape changes, migration, adhesion, efficient diffusion of O_2, nutrients, and CO_2 and metabolic waste removal.[13]

Porosity also supports angiogenesis and engineered heart tissue vascularisation,[14] which are critical to overcoming the limit of O_2 diffusion that is considerably smaller than the thickness of heart muscle. Hence, the introduction of flexibility and pores would improve effective cardiac tissue creation and its survival not only in vitro but also in vivo.[13,15]

For cardiovascular-based bioelectronics to be beneficial, materials and processing techniques that better match the soft, bendable, and porous environment of the cardiovascular system need to be adopted to guarantee greater application in cardiac tissue engineering and implantation.[14]

Figure 2B–I illustrates research that has successfully created stretchable and flexible bioelectronics able to withstand the deformations of the heart while minimising the cell movement restriction. The figure also includes studies incorporating porosity within their CTE device design for cardiac cell culture and transplantation, improving their ability to support the cells during tissue engineering.

For example, the Lieber group fabricated flexible macroporous nanoelectronic scaffolds (nanoES) to aid the creation of synthetic tissues. As shown in Figure 2B, individual Si nanowire

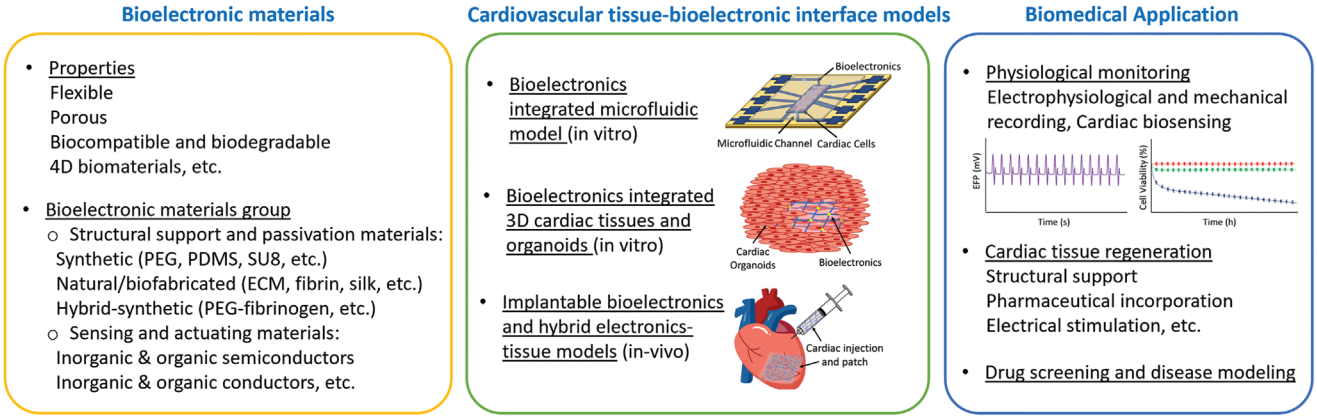

Figure 1. Summary of bioelectronic materials, interface models, and biomedical application for CTE and implantation.

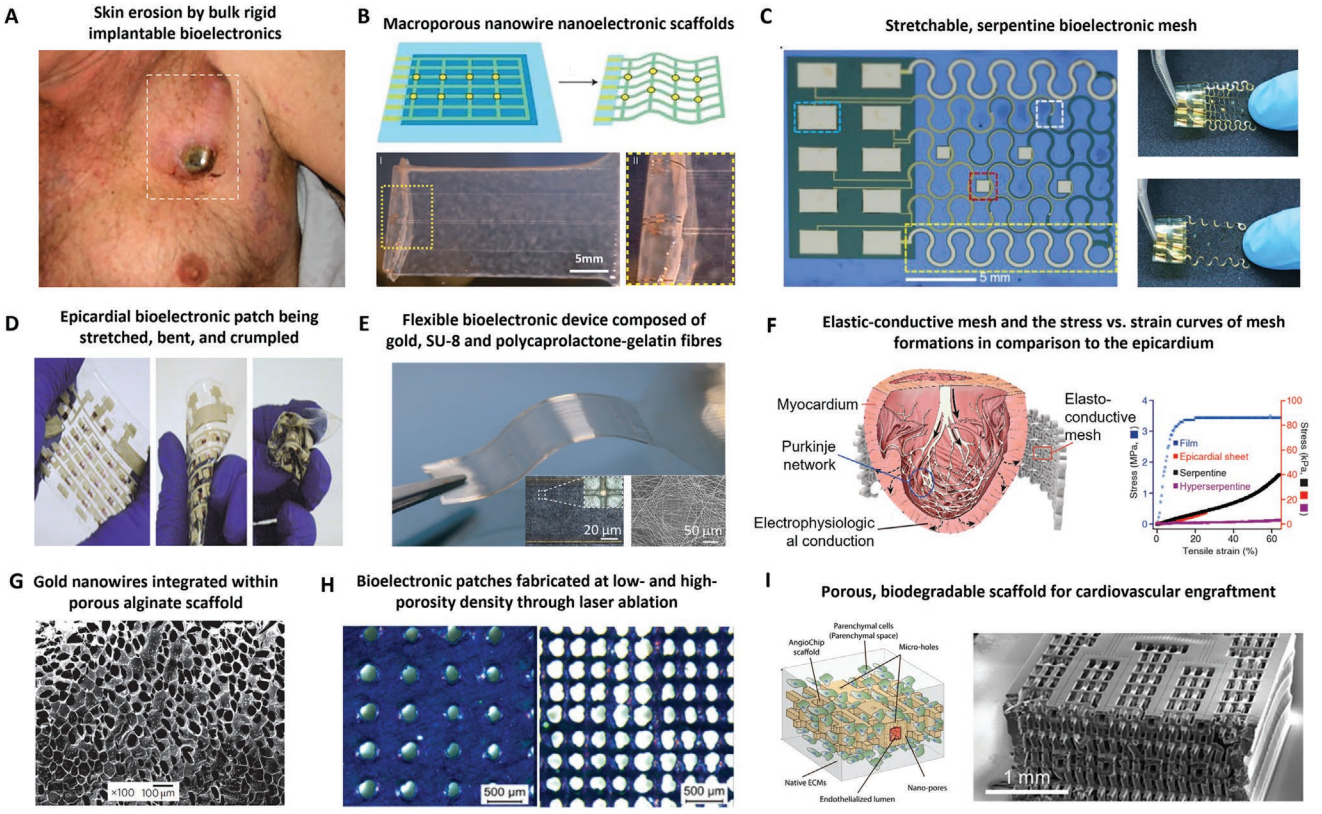

Figure 2. Macroporous, flexible, and free-standing bioelectronic devices for CTE and implantation. A) Automated implantable cardioverted defibrillator (AICD) erosion through the skin. Reproduced with permission.[12] Copyright 2004, Elsevier. B) Device fabrication schematics of nanoES (blue: nickel sacrificial layers; green: nanoES; yellow dots: individual nanowire transistors) and photograph of a single muscle cells sheet cultured with nanoES. Reproduced with permission.[16] Copyright 2012, Nature Publishing Group. C) A microelectronic device before release from sacrificial layer wafer, and a freestanding electronic device before and after manual extension. Reproduced with permission.[17] Copyright 2019, WILEY-VCH. D) An epicardial bioelectronic patch under different mechanical deformations. Reproduced with permission.[18] Copyright 2020, Nature Publishing Group. E) A flexible electronic device composed of gold electrodes within a SU-8 mesh and a scanning electron microscopy (SEM) image of a recording/stimulating electrode covered by electrospun fibers of polycaprolactone-gelatin (inset). Reproduced with permission.[20] Copyright 2016, Nature Publishing Group. F) Stress versus strain curves of mesh formations compared to those of the epicardium and a schematic and image of an elastic-conductive mesh composed of conductive nanowires and styrene-butadiene-styrene rubber wrapping around the heart. Reproduced with permission.[21] Copyright 2016, American Association for the Advancement of Science. G) Schematic and SEM image of gold nanowires incorporated within an alginate hydrogel. Reproduced with permission.[22] Copyright 2011, Nature Publishing Group. H) Optical microscope images of the porous and sutureless bioelectronic patches fabricated at low- and high-porosity density. Reproduced with permission.[24] Copyright 2019, Elsevier. I) Schematic and SEM of the AngioChip, a biodegradable scaffold containing nanopores and micro-holes. Reproduced with permission.[25] Copyright 2016, Nature Publishing Group.

transistors were created from metal contacts and embedded into SU-8, a biocompatible polymer structure on nickel sacrificial layers by lithography. After etching the sacrificial layer, the 2D mesh nanoES had an overall thickness of ≈1 μm and allowed culturing of electroactive cells including neurons and cardiomyocytes.[16] The Dvir group developed the potential of freestanding electronic devices consisting of six separate serpentine filaments that allowed for extension while minimizing stress (Figure 2C).[17] The ability for device manipulation is an important design feature as seen in Figure 2D. Sim et al. assessed the effects of mechanical deformations on an epicardial bioelectronic patch, which is key to suitability for the cardiovascular system's moving microenvironment. The patch was created from silver nanowires and polydimethylsiloxane (PDMS) and was successfully placed on a porcine heart.[18] It is worth noting that the device structure did not allow deeper understanding of the cells within the tissue. Only exploration of the epicardium, which is predominately composed of connective and adipose tissue[19] rather than cardiomyocytes was possible. The Dvir group explored the creation of porous hybrids composed of electronics and 3D scaffolds. Electrospun polycaprolactone (PCL)-gelatin fibers were used to provide an extracellular matrix (ECM) equivalent when culturing on recording/stimulating electrodes that could then fold to form a cardiac patch (Figure 2E).[20] Park et al. developed an elasto-conductive mesh by pouring a silver nanowire and styrene-butadiene-styrene rubber solution into a serpentine-shaped PDMS. The flexible device was designed to match the stress-strain curve of the epicardium (Figure 2F). Although preliminary studies were done in cancer cells and rat myoblasts, the work provided a promising platform suitable for human cardiac cells.[21] Bioelectronic constructs composed of gold nanowires within alginate hydrogel by Dvir et al. improved cell growth, while the porosity of alginate promoted cell survival and a more physiologically relevant culture environment. The seamless addition of metal components further improved tissue creation by aiding electrical conduction (Figure 2G). The construct allowed close monitoring of neonatal rat cardiac cell-electronic interface over several days in vitro.[22] The device was made of SU-8 encapsulating a chromium and gold layer, defined by photolithography and reactive ion etching. This device allowed for close interaction with cells when incorporated within a nanofibrous 3D scaffold. One possible concern is the use of 10 nm chromium as an adhesion layer for gold, the main electronic component of the device, as degradation of chromium could lead to the production of Cr_2O_3 nanoparticles known for their poisonous effects on biological systems.[23] Hoang et al. demonstrated a greater level of porosity control by using laser ablation to create holes within a chitosan film, which was covered in polyaniline to create a conductive surface (Figure 2H). The various porous bioelectronic patches also retained their electronic properties despite deformations such as cyclic stretching, mimicking cardiac contraction rhythm allowing a successful electro-coupling in a rat heart model.[24] Indeed, the addition of porosity allowed refined control, as shown in Figure 2I, where Zhang and colleagues created a nanopore/micropore biodegradable scaffold allowing direct anastomosis using a built-in vasculature. The group demonstrated that this implant established blood perfusion in rat hindlimbs. Although more research is needed in larger animal models, the study supports the promising idea of seamless integration of porous bioelectronics in the cardiovascular system.[25,26] Fabrication of devices that can withstand relatively large deformations is an important feature when working with moving and contracting cells.

Overall, these publications demonstrate the potential of creating devices with porous and flexible bioelectronic materials, however, it must be noted that to be commercially distributed as medical devices, these materials must obtain safety qualification certification (e.g., FDA approval (US market), CE mark (European economic area), among others). Therefore, future works would have to include verification that these materials meet high safety, health, and environment protection requirements for specific medical product applications.

2.2. Biocompatible and Biodegradable Bioelectronic Materials

Cardiac tissue has a very poor regenerative capacity, meaning it is unlikely to repair and restore complete healthy functioning. Hence, damage and scarring remain for life, reducing contraction efficiency and adding strain to the remaining heart muscle. This, in turn, leads to more damage and a higher risk of arrhythmias, heart failure, and sudden cardiac death.[5] Arguably, the most important property a material can have when introduced into a biological system is biocompatibility, as it is crucial for cells to survive on and around the bioelectronic device in vitro and in vivo. Therefore, the materials used to create bioelectronic devices must be carefully considered, to prevent inadvertently causing harm when introduced into a cell culture or the cardiovascular system.

Consequently, biocompatible bioelectronic materials should be non-toxic and should not elicit an inflammatory response, to minimise cell death and tissue scarring. This encourages an intimate interaction between the device and the cardiac tissue, significantly improving long-term performance[27,28] and allowing continuous physiological studies and therapeutic applications.[29,30]

Both natural (such as biofabricate) and artificial synthetic materials have the potential to be biocompatible. For example, PDMS, low-density polyethene (LDPE), polyvinyl alcohol (PVA), natural silk, shellac, hard gelatin, etc. have been shown to provide acceptable substrates for bioelectronic devices fabrication. In addition, ECM coatings, such as poly-D-lysine, gelatin, fibronectin, as well as treating bioelectronics with oxygen plasma to increase hydrophilicity, have the ability to improve the device biocompatibility and therefore increase cellular adhesion.[31]

Figure 3 summarises studies that have created biocompatible and biodegradable bioelectronic devices with potential in cardiovascular biology applications. Ju et al. used photo-cross-linkable silk fibroin (PSF) to promote cellular adhesion on freestanding bioelectronic scaffolds. Figure 3A shows a biocompatibility study of human-induced neural stem cells (hiNSCs) grown on PSF compared to a frequently used biocompatible photoresist polymer, SU-8. Despite poly-D-lysine was used on both surfaces, there was greater cellular adhesion to PSF, highlighting it as a promising material for bioelectronics,[32] and potentially culture of cardiac cells.

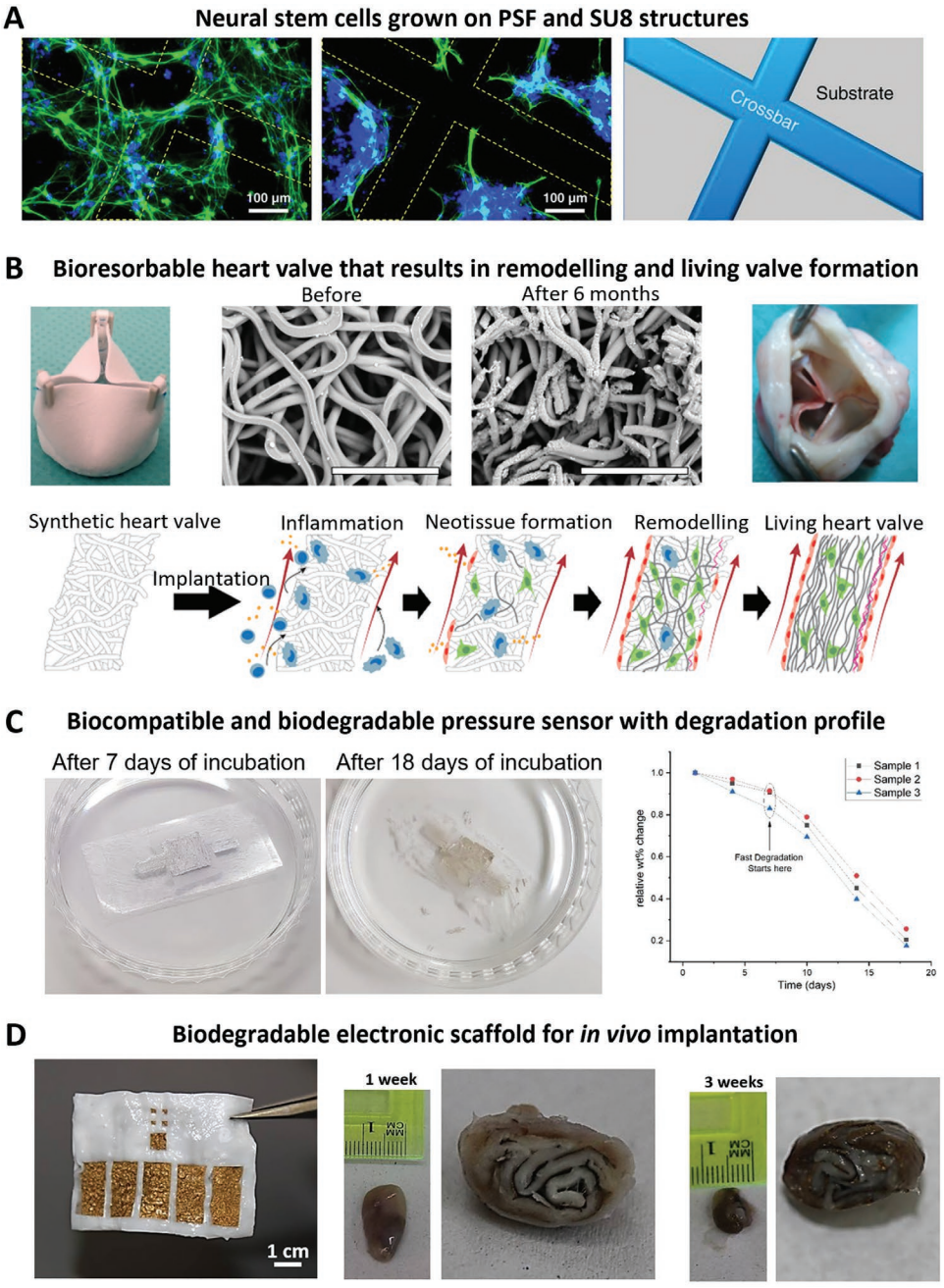

Figure 3. Biocompatible and Biodegradable bioelectronic devices. A) hiNSC adhesion study on microfabricated PSF and SU8 structures. Cells stained with neuron-specific marker antibody TUJ1 (green) and DAPI (blue). Reproduced with permission.[32] Copyright 2020, PNAS. B) Heart valve tissue engineering using bioresorbable supramolecular elastomer and a schematical representation of valve remodeling process after implantation. Reproduced with permission.[35] Copyright 2017, Elsevier. C) Biocompatible pressure sensor degradation and the corresponding degradation profile of the device ($n = 3$) over 18 days. Reproduced with permission.[36] Copyright 2019, Elsevier. D) Reduction of the size of a biodegradable electronic scaffold after in vivo implantation for 1 and 3 weeks. Reproduced with permission.[37] Copyright 2018, Elsevier.

Another method for reducing long-term negative effects is degradation of the devices over time, known as biodegradability. The degradation by-products from the device must also be biocompatible. Ellis and Kolek developed a bioresorbable, antibacterial envelope that could encase a cardiac pacemaker and become absorbed by the body 9 weeks after implantation.[33] Despite its promise, more work is required to ensure the biocompatibility and biodegradability of both bioelectronic devices and coatings.

Biodegradability is an exciting area in tissue engineering and bioelectronics, with several devices capable of degrading once therapeutic support has been provided.[34] For example, Kluin et al. demonstrated the progression of a synthetic heart valve using a biodegradable supramolecular elastomer that

underwent remodeling into a living and functional heart valve (Figure 3B). The graft was accepted into the cardiovascular systems of sheep, producing a beneficial cell-prosthetic interface over a 12-month period.[35] Another study by Khalid et al. fabricated a piezocapacitative pressure sensor using polylactic-co-glycolic acid (PLGA) and PCL that degraded over several weeks without harmful products[36] (Figure 3C). The pressure sensor was developed as a wearable electronic device; however, biodegradable implantable devices have increasing potential to provide care with a reduced risk of infection due to minimized chronic use. Finally, Figure 3D shows electronic scaffold biodegradability over time, with a clear reduction in scaffold size at 1 week and 3 weeks after implantation in vivo.[37] Future work in larger animal models may aid in greater human translation of this promising study.

The emerging developments in the field of bioelectronics have allowed creation of "cyborg" cardiac tissue with embedded electronics for monitoring and manipulating cellular activity.[20] To create effective hybrid tissue, the devices need to be biocompatible. The properties of both natural and artificial materials have been exploited for use within bioelectronics. For example, widely used hydrogels are 3D networks primarily consisting of waterable to provide a level of flexibility and biocompatibility during cardiac cell culture. Natural hydrogels can be created from polysaccharides (e.g., alginate, chitosan, agarose) and ECM components (e.g., collagen, gelatin, fibronectin, and laminin). Their properties improve cellular adhesion and proliferation but lack the mechanical strength for creation of large-scale scaffolds. Synthetic hydrogels (e.g., polyethylene glycol diacrylate (PEGDA)) have tunable mechanical and electrical characteristics but are usually not favored over natural equivalents by cells.[38] These advances in biocompatible natural and artificial materials and processing approaches could lead to fabricate functional bionic tissues.

3. Cardiovascular Tissue-Bioelectronics Interface and Biosensing

3.1. Bioelectronics Integrated Microfluidic Model for In Vitro Application

Microfluidics allows exploration of cell culture models at microscale, by investigating individual cells in vitro. These devices offer increased spatio-temporal resolution, and experimental design flexibility.[39]

Wei et al. developed a multifunctional hybrid integrated cardiomyocyte biosensor, which can detect bitter receptor-induced cardiotoxicity by synchronously recording extracellular field potentials and mechanical beating signals from the cultured cardiomyocytes (**Figure 4**A).[40] This microchip is a promising solution to explore cardiotoxicity in the laboratory. A similar system was developed by Liu et al.[41] who established a heart-on-a-chip composed of PDMS microfluidic channels, gold, and cardiac cells, which proved to be a suitable platform for exploring in real-time the electrophysiological properties of cells under disease conditions, such as hypoxia (Figure 4B). Healthy cardiac function relies on effective electrical and mechanical activity. Therefore understanding electrophysiological and mechanical abnormalities that occur during disease progression may allow for development of better treatment strategies and provide mechanistic insights into cardiac healing responses.

Despite the limited number of cells employed in microfluidic models (ranging from a few thousands to single cells), integrated bioelectronics have successfully recorded high-amplitude low-noise extracellular signals (electrical and mechanical)[40–43] and intracellular action potentials (via Pt nanopillars)[41] (Figure 4A,B). Nanopillar microelectrodes are a recent important development in electrophysiology sensing as, unlike

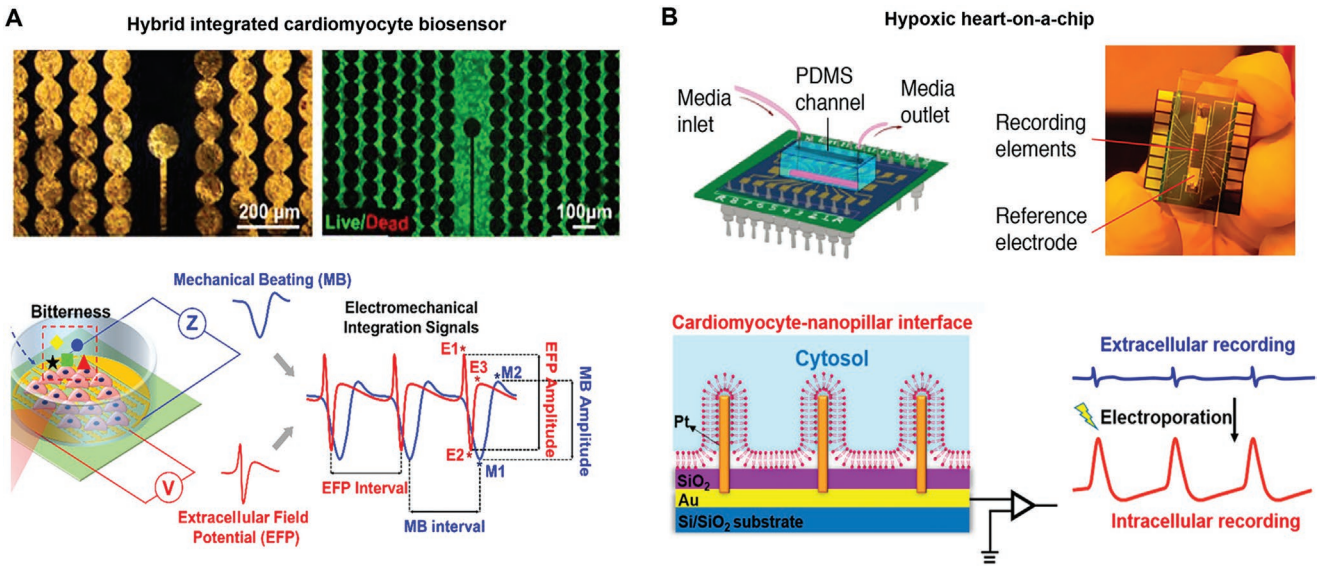

Figure 4. In vitro bioelectronic microfluidic models. A) (Upper) Optical microscopy images of cardiomyocytes and live/dead staining results of cardiomyocytes on a hybrid integrated cardiomyocyte biosensor. (Bottom) Schematics of synchronised recordings of extracellular field potentials and mechanical beating signals from cultured cardiomyocytes using a hybrid integrated cardiomyocyte biosensor. Reproduced with permission.[40] Copyright 2021, American Chemical Society. B) Heart-on-a-chip allowing both extracellular and intracellular recordings to explore cell status under hypoxic conditions. Reproduced with permission.[41] Copyright 2020, ACS publications.

extracellular bioelectronics, these provide accurate action potential measurements at a single-cell level. As nanopillar microelectrodes are similar to commencialized multi-electrode assay systems, they could be easily implemented after minor circuit and instrument design adjustments.

It is worth noting that cells cultured in microfluidic systems are at the microscale, and there is a need for revised culture protocols when reducing media volumes and culture areas. It must be considered that cells cultured in an artificial microscale device in vitro are likely to respond differently to those in a 3D macroscale culture. Therefore, different device-cell interface systems need to be created depending on the application,[39] and care must be taken when translating results from micro-scale to 3D macroscale cultures.

3.2. Bioelectronics Integrated Cardiac Tissues and Organoids for In Vitro Applications

Macroscopic cardiac models include organoids, which have applications in in vitro, ex vivo, and in vivo setups. To a large extent, these systems represent and retain the biological characteristics and functions of cells.[44] Matching the properties of the bioelectronics to those of cardiac models enables a seamless and non-disruptive interface between the cells and the device. Hence the risk of detrimental morphological and functional changes triggering a signalling cascade that induces or furthers cell death, diseased states, and immune response is reduced.[45] Therefore, macroscopic models permits reliable, long-term cell recording; provide electrical stimulation for synchronous cell contraction and improve tissue growth; and efficiently release drugs.[20,29,30,37,46,47]

Figure 5 presents various studies investigating the interface between bioelectronics and cardiac cells within an organoid system. For example, Tian et al. designed flexible and free-standing 2D nanoelectronics that can be integrated with cells to create hybrid tissue (Figure 5A).[16] Liu's group also reported the creation of stretchable "cyborg" organoids entirely covered with soft, stretchable mesh nanoelectronics. The group demonstrated their stretchable serpentine mesh nanoelectronics can migrate with and integrate into the initial 2D cell layers to form 3D organoid structures with minimal impact on tissue growth or differentiation (Figure 5B).[48] Integrating cardiac cells into 3D scaffolds is desired, as these can mimic the ECM. Therefore, there is focus on 2D meshes folding to form 3D electronic scaffolds with condensed attachment sites for tissue creation. Introducing scaffold support can be done through includingalternative biomaterials such as hydrogels (Figure 5C).[49] However, hydrogels often degrade with time, therefore, their use must be tailored for the desired study.

The creation of a seamless interface allows monitoring of cellular activity within the organoid. For example, Cohen-Karni's group developed 3D self-rolled biosensor arrays of either active field-effect transistors (FETs) or passive microelectrodes that interface with human cardiac spheroids in 3D.[50] The arrays provided continuous and stable multiplexed field potential recordings with high sensitivity and spatio-temporal resolution, supported with simultaneous calcium imaging (Figure 5D). Their ability to fold provides structural support, attachment areas, and innervation of the cardiac cell culture. To ensure cell survival within the organoid and improve long-term studies with such devices, a porous bioelectronic design could be considered, as described in Section 2.1.

On the other hand, for greater understanding and monitoring capability, future work should include the introduction of various sensor types, such as mechanical, chemical, and/or temperature, or capabilities for intracellular recording. For example, Zhao et al. fabricated an ultrasmall U-shaped nanowire FET to record intracellular electrophysiology. Figure 5E shows schematics of simultaneous multisite and multiplexed intracellular recordings from human induced pluripotent stem cell-derived cardiomyocytes measured by the probe array.[51]

Advanced biosensors allow high sensitivity, while monitoring extracellular and intracellular signaling provides label-free, real-time information of cell behavior and survival.[52] This is important as understanding the status of the cellsindicate how well the cells adapt to the conditions they are experiencing, for example, during initial tissue development or when responding to certain therapeutics in clinical trials. It can also provide real-time feedback to aid in tailoring electrical stimulation, growth conditions, and drug release for more effective cardiovascular tissue creation.[37]

3.3. Implantable Bioelectronics and Hybrid Electronics-Tissue Models for In Vivo Application

Engineered cardiac tissue and emerging bioelectronics can be combined for in vivo applications, with the ultimate goal of restoring healthy cardiac function.

During common heart diseases, the cardiovascular system will lose areas of mechanical and electrical function, however, this can be re-established using integrated electronic components. For example, Park et al. developed an epicardial mesh from electrically conductive and mechanically elastic material to restore cardiac tissue mechanics and conduction after myocardial infarction in rat hearts (**Figure 6**A).[21] Cardiovascular function can also be improved through the use of implanted electronics to mimic blood vessels (Figure 6B).[53] However, these rat and rabbit in vivo studies need to be complemented by larger animal studies to provide greater translation to human hearts. Overall, the integration of bioelectronics can provide support to cells on and around the device to improve success rates of tissue engineering and transplantation.

The use of bioelectronics and hybrid tissue also allows the integration of sensing activity to understand disease conditions at a greater level. For example, the Rogers group developed an ultrathin and flexible needle-type polymer substrate, which can be inserted into the myocardium of a rabbit heart in a minimally invasive manner, to monitor both radiofrequency ablation and cryoablation, in a manner that has no measurable effects on the natural mechanical motions of the heart (Figure 6C).[54] These flexible needle-type temperature sensors made from polyethylene terephthalate (PET), chromium, gold, SU-8, and PDMS could overcome the current limitations with traditional sensors that only allow for temperature monitoring at the myocardial surface.

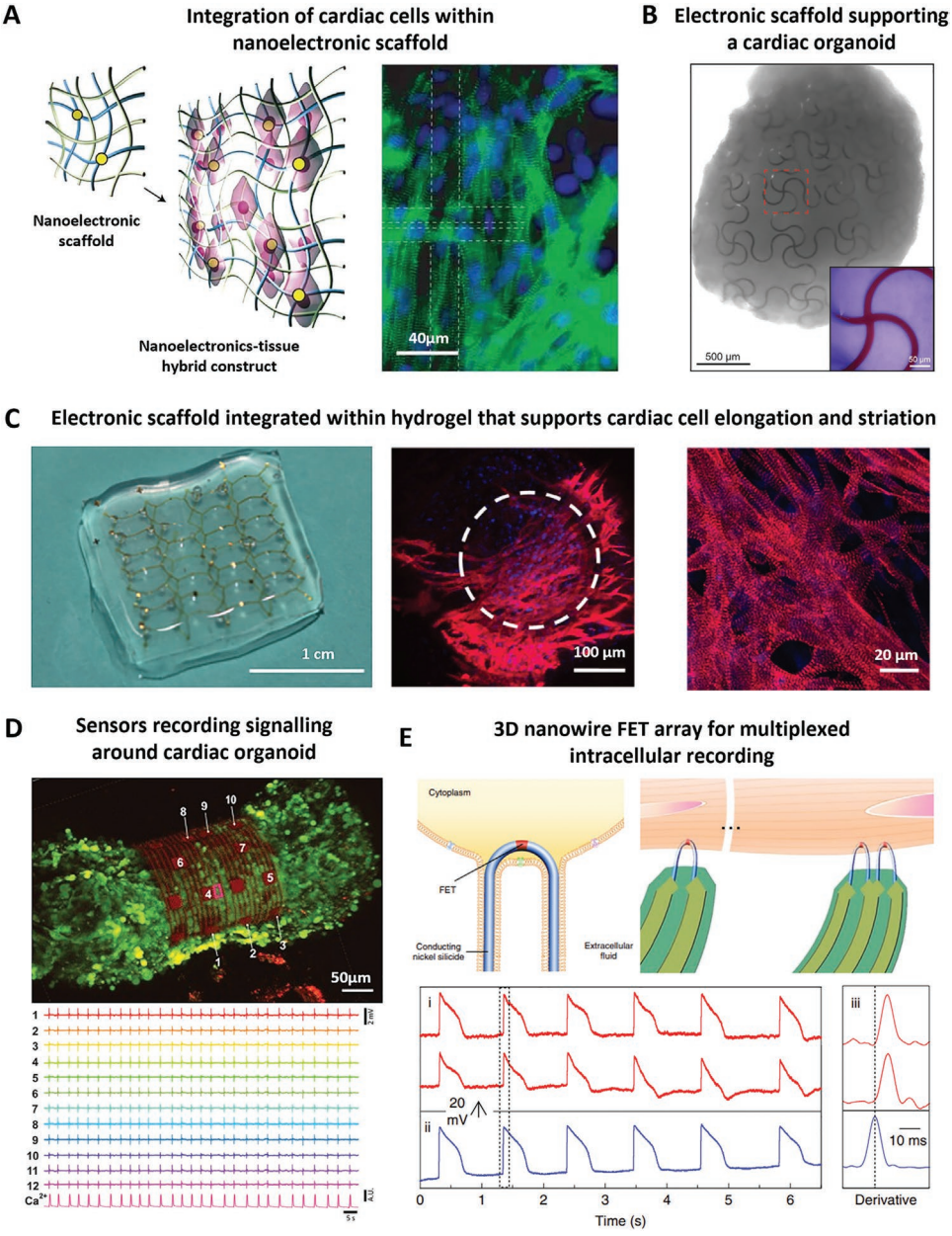

Figure 5. Bioelectronic-integrated organoids. A) (Left) Schematic of the integration of cells and nanoelectronics to create hybrid tissue; (Right) Epifluorescence image of the hybrid tissue (α-actinin (green), cell nuclei (blue)). The electrodes are outlined with dashed lines. Reproduced with permission.[16] Copyright 2012, Nature Publishing Group. B) Bright-field image of electronic scaffold integrated within a cardiac organoid after 10 days of culture. Reproduced with permission.[48] Copyright 2019, American Chemical Society. C) (Left) 3D electronic scaffold integrated within the hydrogel. Scale bar, 1 cm. (Right) Confocal images of cardiac cells illustrating cell elongation and striations after culture on and around a 3D electronic scaffold. Sarcomeric actinin (red), nuclei (blue), stimulating electrode (dashed white circle). Reproduced with permission.[49] Copyright 2020, Elsevier. D) 3D confocal microscopy image of a cardiac spheroid (green) encapsulated by bioelectronic sensors (red) and field potential traces recorded by electronic sensors. Reproduced with permission.[50] Copyright 2019, American Association for the Advancement of Science. E) Intracellular recording from cardiomyocytes by 3D U-shaped nanowire field-effect transistor (FET) arrays. Reproduced with permission.[51] Copyright 2019, Nature Publishing Group.

4. Bioelectronic Functions for Cardiovascular Tissue Engineering and Implantation

4.1. Bioelectronic Scaffolds and Sensors for Tissue Regeneration

Cardiac tissue is dynamic, with the ECM providing structural support and spatial organization, while allowing signal communication to influence cell behavior. There are great advantages of creating biomimetic and dynamic scaffolds for tissue organization and generation. The closer the scaffold is in representing the ECM, the higher is the likelihood that cardiac cells will adhere, migrate, grow, and vascularize it. The development of such scaffolds allows generation of cardiovascular tissue for applications in drug screening, disease models,

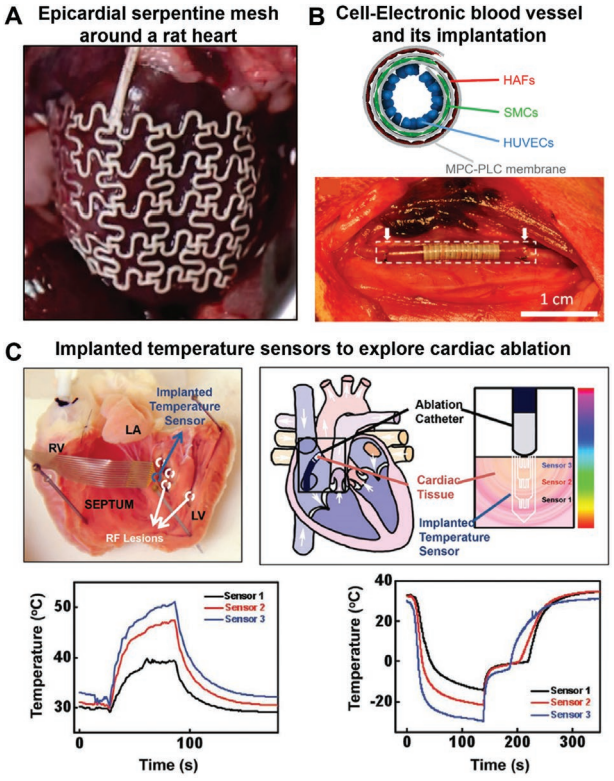

Figure 6. Implantable bioelectronics for in vivo cardiac application. A) An elastic-conductive epicardial mesh wrapped around a rat heart. Reproduced with permission.[21] Copyright 2016, American Association for the Advancement of Science. B) (Top) Blood vessel-mimicking electronics supporting different cells across different layers of the structure. (Bottom) Implantation of an electronic blood vessel. The dotted frame outline the edge of the native carotid artery and the implanted electronic blood vessel. The white arrows specify two ends of the electronic blood vessel. Reproduced with permission.[53] Copyright 2020, Cell Press. C) (Upper) Ultrathin injectable, multimodal thermal sensors for monitoring cardiac ablation in the transmural direction. (Bottom) Thermographic monitoring during both radiofrequency ablation (10W) and cryoablation. Reproduced with permission.[54] Copyright 2016, WILEY-VCH.

bio-actuators, or patient-specific transplants. However, current tissue engineering methods are limited as they create static scaffolds unable to adapt to changes of the in vitro and in vivo cardiac environment.[37,38,55]

As the field is developing, novel methods to create dynamic scaffolds are emerging. An example are 4D "smart" biomaterials that respond to the microenvironment and adapt their properties accordingly. Such materials can be responsive to biological stimuli, magnetic stimuli, electrical stimuli, light, temperature, ultrasound, pH, ultraviolet light, or osmotic pressure. 4D printing uses these intelligent materials to create complex, biomimetic, 3D scaffolds capable of changing conformation when exposed to external stimuli, thus better mimicking the dynamic environment of cardiac tissue.[55,56] **Figure 7** illustrates recent advances within this field in relation to CTE and implantation. Figure 7A demonstrates the potential of using polymers with shape memory (bisphenol A diglycidyl ether, poly(propylene glycol) bis(2-aminopropyl) ether, and decylamine) to create a support for dynamic myocardial tissue. In this example, cell culture is performed on a flat surface to promote alignment. Instead of a normal flat substrate, a temperature-sensitive shape memory material was used, which curves as temperature increases to better match the heart for myocardial repair applications.[57] Temperature manipulation was also used by Ma et al. who 4D printed a temperature-sensitive drug release system based on Polylactic acid (PCL)-PLA that results in the "opening" of the device at different times depending on the PLA-PCL concentration (Figure 7B).[58] Manipulation of device "opening" could benefit cell therapy applications with devices encapsulating and then releasing cells (Figure 7C). Pedron et al. explored the use of PLA-PEG-PLA and poly(N-isopropyl acrylamide) (PIPAAm) to create constructs that could be delivered as a form of cardiac microtissue transplantation to improve heart dysfunction.[59]

The biosensors field is becoming well-established, however, 4D biomaterials and printing is an emerging area. The use of this technology in combination with bioelectronics holds great promise for creating dynamic constructs for cardiology. However, numerous limitations related to material development, macro- and micro- structural design, and printing techniques environment still remain.[37,38,55]

On the other hand, scaffolds that include integrated bioelectronics allow for greater applications and responses to the dynamic microenvironment, as the devices can provide additional functions important to promote tissue regeneration and biosensing. The cardiovascular system, in particular the heart, relies on cell signaling networks and complex electrical circuitry to function correctly. The ability to reliably sense and monitor this information is a valuable tool to influence CTE and implantation. This can be achieved through bioelectronic sensors, which monitor and transform biological signals into recordable signals, for processing and analysis.[60] This presents an opportunity for continuous, real-time monitoring of heart cells,[61,62] including their response to the bioelectronics, the scaffold, and the culture conditions. Indeed, monitoring of patients has proven to significantly shorten the time of diagnosis and targeted treatment.[63]

The incorporation of sensors is needed to provide greater understanding both in vitro and in vivo when exploring cells environment and maturation, pathogenesis, pharmaceutical efficacy, and healing processes.

Creating a dynamic bioelectronic-scaffold system allows the development of a close interface with the cells, which provides the opportunity to gather label-free, real-time information on cell behavior and survival during tissue development, disease progression, pharmacological treatments, clinical trials, and trauma and healing after hybrid tissue engraftments.[37,52,64,65] The combined use of 4D biomaterials and biosensors and their continuous development will rapidly improve the seamless integration of scaffolds within biological systems. The future of this work includes the possibility of "smart" materials adapting to the data collected from the biosensors.

4.2. Bioelectronic Actuators for Electrical Stimulation and Pharmaceutical Incorporation

The heart relies on endogenous electrical stimuli to regulate cardiac cell behavior and encourage healthy contraction.[66]

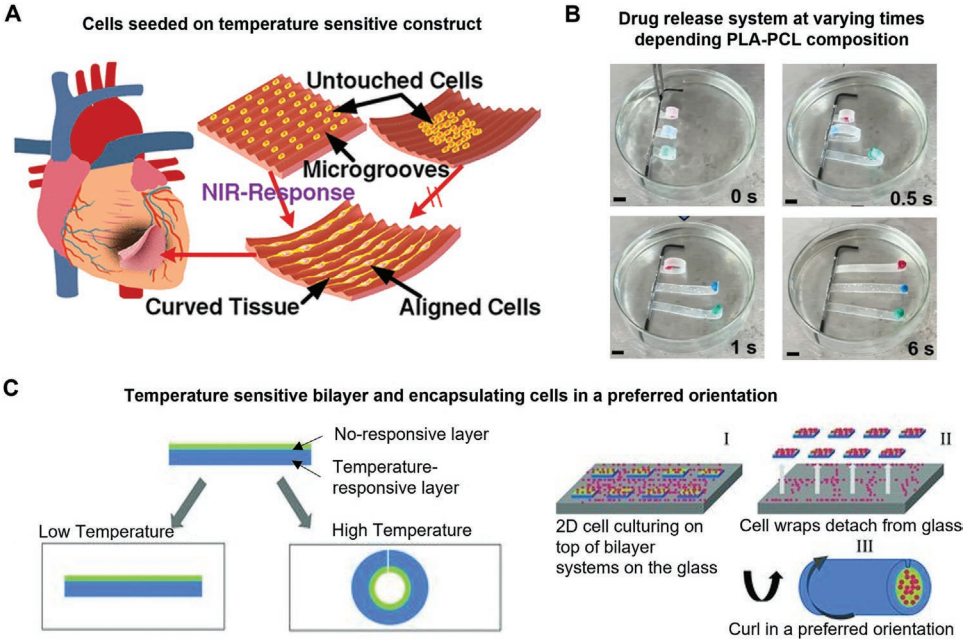

Figure 7. 4D biomaterials and printing. A) Temperature-sensitive cell-seeded tissue construct changes shape to better fit the curved myocardium. Reproduced with permission.[57] Copyright 2021, ACS publications. B) Photographs of drug release from the different PLA-PCL compositions at different times. Scale bar,1cm. PLA1.00/PCL0.00 (green), PLA0.94/PCL0.06 (blue), and PLA0.70/PCL0.30 (red). Reproduced with permission.[58] Copyright 2021, Springer Nature. C) Schematic of temperature-responsive bilayers and cells encapsulation within the construct. Adapted with permission.[59] Copyright 2011, WILEY-VCH.

For effective CTE, cell behavior must be predictably guided to create organized and functional cardiac tissue.[4,67] Current CTE advances include electronic components that electrically stimulate cardiac cells to influence their properties, promoting better tissue assembly and improving tissue regeneration in vitro.[52]

Cardiac tissue has a specific phenotype, with the major cell type, cardiomyocytes (cardiac muscle cells), being elongated, rod-like, and aligned anisotropically to allow for fast electrical conduction and synchronized contraction for effective blood pumping.[68] This phenotype and alignment must be accurately replicated for engineered tissue to be successful in vitro and in vivo.

Alongside phenotype and alignment, the engineered cardiac tissue must be representative at a molecular level. It has been demonstrated that the application of electrical stimulation on engineered cardiac tissue induces the formation of well-aligned sarcomeres (the basic contractile unit of muscle), indicating maturing cardiomyocytes; presents well-developed intercalated discs and gap junctions; and increases the amounts of mitochondria, glycogen, and cardiac proteins such as β-MHC, Cx-43, creatine kinase-MM, and cardiac Tn-I.[69]

Electrical stimulation is also beneficial for the implantation of engineered cardiac tissue. In diseased states and scar tissue development, cardiomyocytes cannot effectively communicate with one another resulting in electrical conduction slowing or block. The introduction of bioelectronic components can provide a bridge between the conducting (healthy) and non-conducting (diseased) cardiac tissue, overcoming arrhythmias observed with traditional cardiac grafts.[21] In addition, electrical stimulation demonstrates antimicrobial behavior, with the potential of fighting bacterial infections during CTE and transplantation.[70]

As described in **Figure 8**, and **Tables 2** and **3**, electrical stimulation is a promising and innovative method to promote formation of representative adult cardiac tissue for cardiac research and implantation applications. Feiner et al. developed a cardiac tissue-electronic hybrid with integrated electrical stimulation. An example of stimulation protocol and corresponding tissue contractions are illustrated in Figure 8A. The group was able to demonstrate improved neonatal rat heart tissue assembly (elongation and striation) and function depending on the stimulation pattern given.[17] Electrical stimulation can also be applied by bioelectronic meshes in vivo to cure arrhythmia issues, which often result from cardiovascular disease (Figure 8B). Park et al. designed an epicardial mesh to enable broad distribution of current flow by electrical stimulation,[21] which is an important factor to ensure cells experience the same influence. In addition, chronic electrical stimulation has the capability to increase the expression of important cardiac markers within human-based cardiac cells (Figure 8C). Importantly, to ensure reliable results, stimulation must be continuous.[71] It is also possible to use stimulation to inspire cell movement depending on the electric fields (Figure 8D).[53] While only a limited range of stimulation conditions has been explored on endothelial cells (25, 50, 75, and 100 mV mm^{-1}), electrical stimulation could still prove to be a useful tool in manipulating cell behavior for CTE and implantation. The reported impact of different stimulation conditions on cardiac cell behavior is presented in Table 2 and Table 3. The range of parameters and conditions for different reported experiments points out the need for the development of reference protocols to support the advancement of the field.

Besides, through rational design of electrode circuits and electrophysiological instruments, simultaneous stimulation

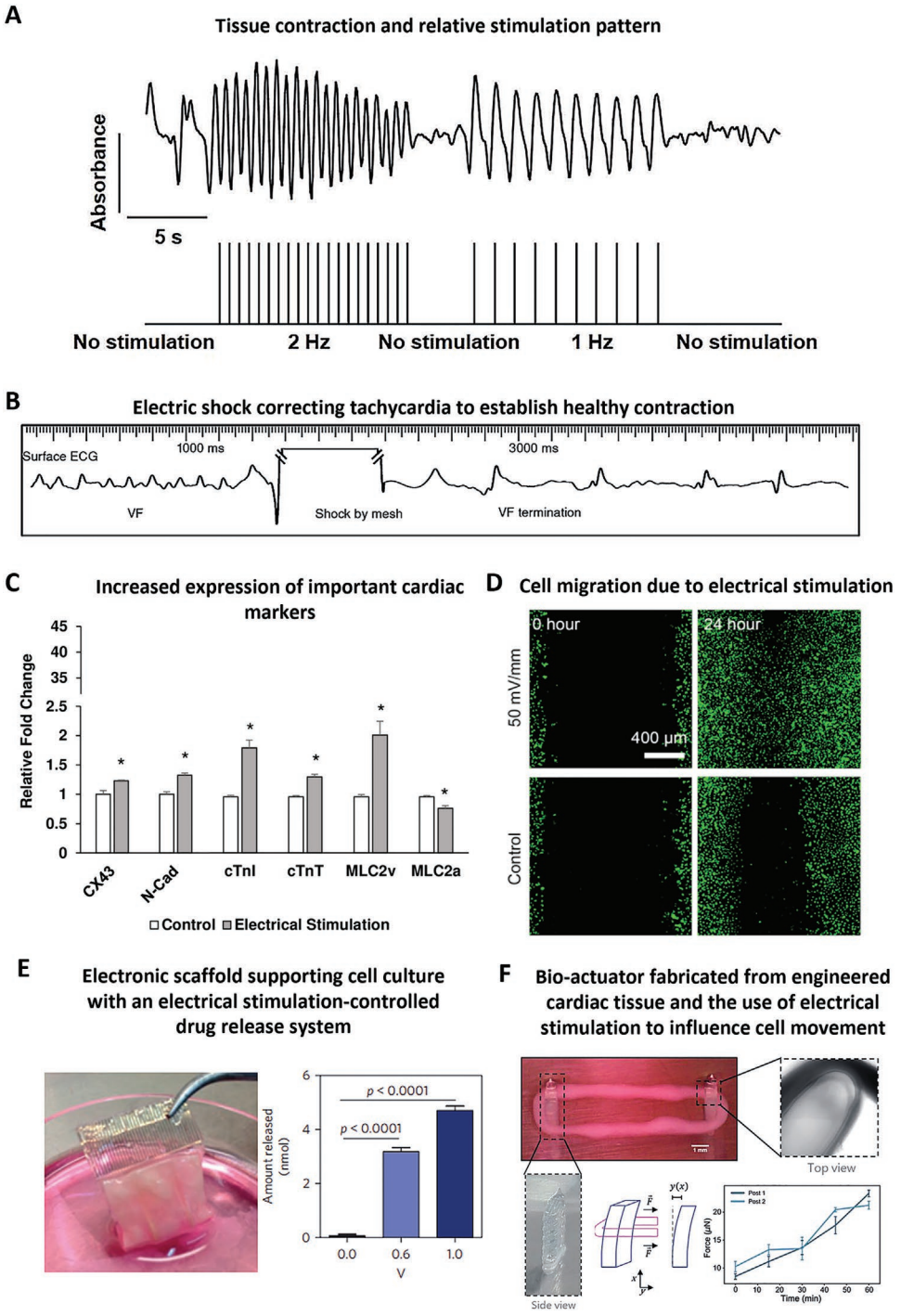

Figure 8. Bioelectronic electrical stimulation and drug delivery. A) (Top) Tissue contraction in response to stimulation via the microelectronic device. (Bottom) Stimulation pattern. Reproduced with permission.[17] Copyright 2019, Small. B) Electrocardiograph (ECG) demonstrating a biphasic electrical shock of 2 joules from an elastic-conductive epicardial mesh curing a ventricular tachycardia. Reproduced with permission.[21] Copyright 2016, Science Translational Medicine. C) Graph showing electrical stimulation of hiPSC-cardiomyocytes results in the increased expression of cardiac markers (CX42, N-Cad, cTnI, cTnT, MLC2v, and MLC2a) $*p < 0.05$. Reproduced with permission.[71] Copyright 2019, PLOS ONE. D) Confocal fluorescence images of endothelial cells migration after stimulation from different DC electric fields (50 mV mm^{-1}) (calcein-AM: green). Reproduced with permission.[53] Copyright 2020, Cell Press. E) (Left) Cardiac cell culture with integrated electronics. The inset shows a magnified image of the electrode. (Right) Schematic shows the deposition and active release of dexamethasone alongside a plot showing the amount of released drug against applied voltages. Reproduced with permission.[20] Copyright 2016, Nature Publishing Group. F) Bio-actuator created from cardiac tissue grown around two posts. (Top View) Microscope image to accurately measure post-displacement. (Side View) Image of the 3D-printed post. The graph shows the force exerted by the tissue on the posts after 1 h of electrical stimulation. Reproduced with permission.[8] Copyright 2019, WILEY.

Table 2. Electrical stimulation to manipulate cardiac cell behavior.

Paper	ES parameters	Cell type	Results
[66]	0.65–2 V cm^{-1}, 1 ms, 1 Hz, 14 days	iPS(Foreskin)-2 cell line-based cardiomyocytes	Improved motility and contractility
[69]	6 V cm^{-1}, 2 ms, monophasic, square, 1 Hz, 5 days	Neonatal rat cardiomyocytes	Cell elongation
[71]	6.5 V cm^{-1}, 5 ms, 2 Hz, 7 days	Induced pluripotent stem cell (iPSC)-derived cardiomyocytes	Improved tissue organisation, maturation, and contractility
[78]	5 V cm^{-1}, 2 ms, rectangular, 1 Hz, 5 days	Neonatal rat cardiomyocytes	Increased contractility
[79]	3.5–4 V cm^{-1}, 1 ms, biphasic, rectangular, 1.2 Hz, 4 days	Neonatal rat cardiomyocytes	Improved organisation and conductivity
[80]	6.6 V cm^{-1}, 2 ms, 1 Hz, 4 days	Embryoid bodies	Maturation, elongation
[81]	5 V cm^{-1}, 2 ms, monophasic, square, 1 Hz, 2 days	Neonatal rat cardiomyocytes	Improved contractility
[82]	5 V cm^{-1}, 2 ms, biphasic, 1 Hz, 3 days	Human cardiac progenitor cells	Improved tissue organisation, maturation, and contractility

and recording of cardiac or neuron action potentials could be achieved on different or same electrodes.[72,73] For example, Giovangrandi et al. designed high-frequency stimulation techniques with appropriate hardware and demonstrated the unique ability to record depolarization events on the same electrode used for stimulation.[72] This kind of automatic measurement could also be used to assess the electrophysiological impact of compounds for closed-loop pacemakers or drug screening.

Due to the impact of introducing electronics into either an in vivo or in vivo cardiovascular environment, it is essential to include some pharmaceutical interventions. The extent of this impact can be seen when infection leads to skin erosion and the rejection of implantable cardiac electronics (Figure 2A). Therefore, monitoring infection and fibrosis after implantation are necessary to overcome these issues. Feiner et al. described an anti-inflammatory drug release system integrated within bioelectronics that periodically releases therapeutics when stimulation is provided (Figure 8E). A polypyrrole film containing the negatively charged antibiotic drug (blue circles) was created by oxidizing the pyrrole monomers (black circles) on large electrodes intended for drug release. Application of a voltage led to polypyrrole reduction, disruption of the electrostatic bonds between polypyrrole and the drug, and subsequent drug release.[20] This novel method is an alternative way to prevent infection, however, within this system, the amount of drug is finite and ways to replanish it would have to be considered. Furthermore, the drug release was manual. To be beneficial within an in vivo environment, a feedback system would be required to monitor signs of infection and provide the relevant amount of pharmaceutical treatment when needed. Nonetheless, incorporating pharmaceuticals with bioelectronic devices can greatly improve the efficacy and the amount of support that the device can provide. The integration of drugs could be periodically released to further the therapeutic support of the electronics within CTE and implantation. Depending on the needs, various drugs and/or growth factors can be incorporated to stimulate cell proliferation and wound healing, support tissue growth, reduce implant rejection, and target inflammation.[74–77]

Figure 8 also demonstrates an application of fabricated cardiac tissue, where the cardiac cells act as a driving source for new micro-actuators. Horiguchi et al. cultured cardiac tissue within a casting mold that could wrap around two 3D-printed structures (Figure 8F). The resulting contractions from the cardiac tissue exerted a force on the posts that was measured. Changing parameters of the electrical stimulation applied to the tissue could influence contraction rates and post displacement. The use of muscle-based bio-actuators is in the early stages of development, but demonstrates another application of engineered cardiac tissue creation and stimulation.[7]

Table 3. The phenotypic effect of electrical stimulation on engineered cardiac tissue.

The effect of electrical stimulation of cardiac cells	Papers
Cell elongation and striation	[68,69,83,84]
Improved organisation and alignment	[22,68,71,79,83–85]
Maturation	[22,68,71,80,84,86]
Improved motility	[66]
Improved contractility and synchronisation	[22,66,78,81,83,85–87]

5. Conclusion and Future Prospects

Heart diseases, including coronary heart disease, arrhythmia, heart valve disease, heart failure, cardiomyopathy, etc. are a leading cause of mortality worldwide, with the number of deaths predicted to further increase due to the lack of a cure. A way to combat this growing problem is creating heart tissue that is readily available for drug screening, clinical trials, and transplantation. CTE is a vitally important field, yet traditional methods lack the ability to create physiologically relevant human tissue usable for such applications.

Nevertheless, emerging advances in bioelectronics have already and will continue to revolutionize CTE. Particularly if materials, processing techniques, design ideas, and functions are combined to produce bioelectronic platforms that can readily match the cardiac environment to explore and manipulate human cell signaling and tissue development in vitro and in vivo.[21]

This review has described how biomimetic bioelectronic devices can be readily fabricated to create a seamless interface with cardiac cells. This in turn allows the long-term application of the electronic components and a demonstration of their functions: biosensing, electrical stimulation, and drug delivery.

The main goal of regenerative medicine and tissue engineering is the fabrication of functional tissue that can be applied in drug testing, bio-actuators, or implantation to improve or replace damaged tissue so that normal, healthy function can be restored. As described, bioelectronics can be used to support the creation of cardiovascular tissue that is physiologically relevant for in vivo studies or as bioelectronic-integrated cardiovascular grafts that can maintain both structural and electrical properties,[88,89] as well as, integrate with native tissue and establish blood perfusion.[25]

However, this field is very much in its infancy and many studies employ animal-derived cells or small animal models. To fully demonstrate bioelectronics translational ability, human-derived cells, larger animal studies, and clinical trials would be required. This will be greatly supported by the development of dynamic and intelligent materials for device fabrication that will allow multidimensional responses from the bioelectronics, in turn furthering their application in creating viable cardiovascular tissue. In addition, validation methods for new integrated sensors and reference protocols to stimulate and sense will need to be created to accelerate innovation and facilitate the result reproducibility. Finally, many advanced bioelectronic materials recently developed for CTE and implantation have not been approved by the relevant agencies as a medical device for clinical use, indicating future work verifying these materials meet high safety, health, and environmental protection requirements is needed.

In conclusion, bioelectronics is emerging as a vital part of cardiology due to its novel material, design, and functional developments. Further progress in this research field will aid to reliable and effective way to create bioelectronic-integrated cardiovascular tissue for experimentation and implantation.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

bioelectronics, cardiovascular tissue engineering, cardiovascular tissue-electronics interfaces, electronic scaffolds, implantation

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