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# Insights into the prospects of nanobiomaterials in the treatment of cardiac arrhythmia

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**Abstract**

Cardiac arrhythmia, a disorder of abnormal electrical activity of the heart that disturbs the rhythm of the heart, thereby affecting its normal function, is one of the leading causes of death from heart disease worldwide and causes millions of deaths each year. Currently, treatments for arrhythmia include drug therapy, radiofrequency ablation, cardiovascular implantable electronic devices (CIEDs), including pacemakers, defibrillators, and cardiac resynchronization therapy (CRT). However, these traditional treatments have several limitations, such as the side effects of medication, the risks of device implantation, and the complications of invasive surgery. Nanotechnology and nanomaterials provide safer, effective and crucial treatments to improve the quality of life of patients with cardiac arrhythmia. The large specific surface area, controlled physical and chemical properties, and good biocompatibility of nanobiomaterials make them promising for a wide range of applications, such as cardiovascular drug delivery, tissue engineering, and the diagnosis and therapeutic treatment of diseases. However, issues related to the genotoxicity, cytotoxicity and immunogenicity of nanomaterials remain and require careful consideration. In this review, we first provide a brief overview of cardiac electrophysiology, arrhythmia and current treatments for arrhythmia and discuss the potential applications of nanobiomaterials before focusing on the promising applications of nanobiomaterials in drug delivery and cardiac tissue repair. An in-depth study of the application of nanobiomaterials is expected to provide safer and more effective therapeutic options for patients with cardiac arrhythmia, thereby improving their quality of life.

**Keywords** Nanobiomaterials, Cardiac arrhythmia, Atrial fibrillation, Nanodrug delivery systems, Cardiac tissue engineering, Biosensors

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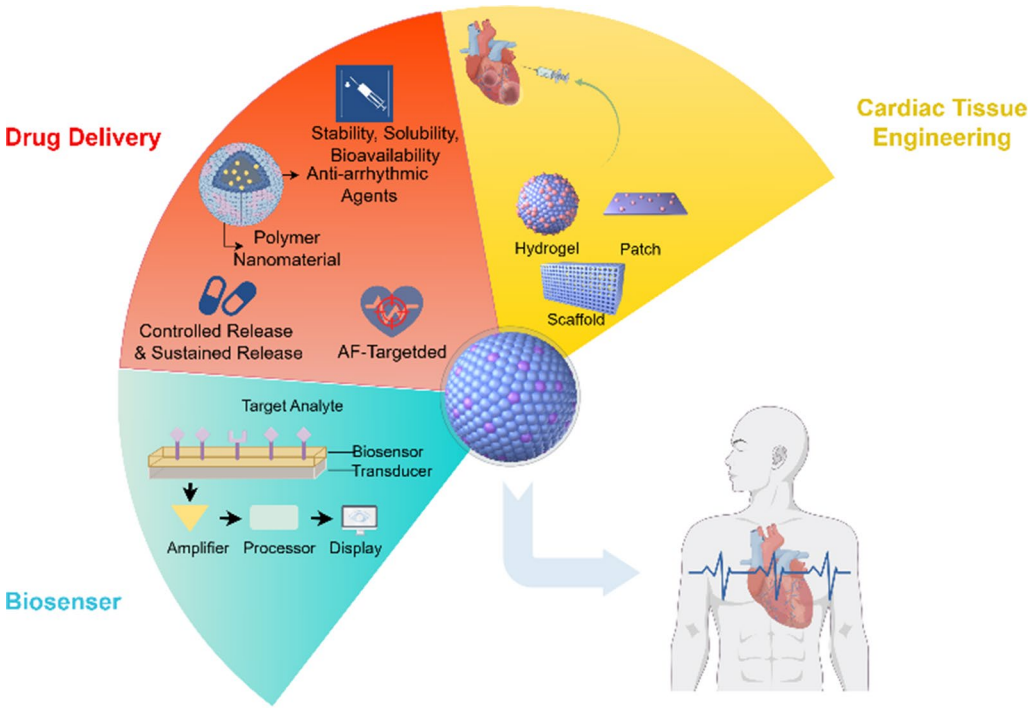
**Graphical Abstract**




## Introduction

Cardiovascular diseases (CVDs) have been the leading cause of death worldwide for almost half a century. In 2021, 20.5 million people died from CVDs, a figure that accounts for approximately one-third of all global deaths [1]. The number of deaths is projected to increase to 23.6 million by 2030, accounting for 31% of all deaths globally and even higher than the mortality of different tumors [2]. Importantly, CVD risk factors promote structural changes in the heart, and these changes usually lead to episodes of arrhythmia and electrophysiological dysfunction [3].

Cardiac arrhythmia is defined as an abnormality in the frequency, rhythm, site of origin, conduction velocity, and sequence of excitation of cardiac impulses [4]. Arrhythmia is characterized by abnormalities in the rhythm and frequency of the heartbeat caused by dysfunctions in cardiac pacing and conduction. As one of the primary reasons for mortality in individuals with cardiovascular conditions, arrhythmia presents a significant danger to human well-being [5–7]. The spectrum of arrhythmia ranges from less harmful premature beats to life-threatening cardiac arrests, and from rare familial syndromes to common atrial fibrillation (AF). According to the American Heart Association (AHA), the overall prevalence of arrhythmia is approximately 3.4% (1.4% for individuals < 18 years of age and 10.1% for individuals > 75 years of age) [2].

The predominant strategies for managing cardiac arrhythmias include pharmacological treatment, radiofrequency ablation, and the implementation of cardiovascular implantable electronic devices (CIEDs) [8–11]. Pharmacological intervention is the most extensively utilized method because of its proven efficacy and cost-effectiveness [12]. Antiarrhythmic drugs are categorized into five classes: sodium channel blockers, beta-blockers, potassium channel blockers, calcium channel blockers, and other miscellaneous antiarrhythmic agents. However, the nonselective distribution of these drugs can affect nontarget organs and tissues, potentially leading to a range of side effects, such as gastrointestinal toxicity, liver damage, cardiac toxicity, and allergic reactions [13]. Catheter ablation, which includes thermal energy sources such as radiofrequency current (RFC) or cryoballoon/laser balloon, is a second effective treatment method for controlling arrhythmias, especially atrial fibrillation. This procedure permanently disrupts atrial reentrant pathways or isolates triggers of atrial fibrillation, thereby shielding the ventricles from arrhythmogenic signals originating in the atria [14–16]. However, its success rate

remains limited, and the potential for rare but energy-related complications involving adjacent tissues, such as esophageal injury or phrenic nerve paralysis, exists [17–20]. The third therapeutic approach involves the use of CIEDs, which encompass pacemakers, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy devices. This method is invasive and can lead to discomfort and the risk of complications. Moreover, repeated shocks from an ICD can diminish quality of life, potentially leading to posttraumatic stress disorder, and may increase the risk of mortality [21, 22].

Nanoscience and nanotechnology are new areas of study that are becoming increasingly important in the fields of communication technology, medical technology, and biotechnology. Nanoscience involves researching, controlling, creating, and using materials that are smaller than 100 nm in size [23]. Nanoparticles are intensively studied in the medical field because of their unique physical and chemical characteristics that enhance biological activities, such as responsiveness, texture, elevated surface energy, and large surface area relative to volume. The application of nanotechnology in cardiovascular disease consists of three main components: targeted drug delivery, cardiac tissue engineering and biosensors. The knowledge, implementation and application of nanoscience in medicine are innovative tools for the treatment of cardiac arrhythmia [24].

Emerging innovative strategies based on nanomaterials are being developed to restore cardiac function and relieve disease symptoms, addressing the limitations of traditional methods such as drugs, pacemakers, defibrillators, and transplantation. Different types of nanoparticles have been used to improve the electrical, mechanical, and biological properties of damaged cardiac tissues. In the first part of this review, we briefly describe the electrophysiological basis of the cardiac conduction system and the pathogenesis of cardiac arrhythmia. The second part of this paper briefly describes the potential of nanobiomaterials for application, design and preparation. It then covers the applications of nanobiomaterials in drug delivery, cardiac tissue engineering, and biosensors. The last part examines the existing deficiencies and constraints of nanobiomaterials in cardiovascular use, as well as the ongoing initiatives to resolve these challenges and transition nanobiomaterials from the laboratory to the clinic.

## An overview of cardiac electrophysiology

The normal function of the human heart relies on its intricate conduction system. Therefore, action potential conduction plays a crucial role in intercellular communication between cardiomyocytes (CMs). The action potential originates from cells in the sinoatrial node and propagates throughout the heart via an active electrophysiological conduction process, which is measurable as the electrical potential difference across the intracellular and extracellular spaces. Cardiac action potentials represent transmembrane potential changes with amplitudes ranging between 60 and 120 mV [25]. Excitation–contraction coupling is a fundamental cellular process essential for the contraction and relaxation of the heart chambers. It links the electrical excitation of cardiac myocytes to the mechanical response, namely, the contractile action. In cardiac muscle, excitation–contraction coupling initiates when the action potential reaches the sarcolemma and propagates into the cell interior through the transverse (T) tubules [26].

The cardiac action potential follows a precise conduction pathway, initiating at the sinoatrial node (SAN), which serves as the primary pacemaker of the heart. From the SAN, the electrical impulse travels through the atria to the atrioventricular node (AVN), where it is briefly delayed. The impulse then continues down the His bundle, bifurcating into the right and left bundle branches, which further divide into the Purkinje fibers. These specialized fibers facilitate the rapid spread of the impulse throughout the ventricles, ensuring coordinated and efficient contraction (Fig. 1A) [27, 28].

The myocardium's continuous, rhythmic contraction and diastole, which facilitate unidirectional blood flow at adequate pressures, require close interactions between specially differentiated CMs (autoregulatory cells) and ordinary CMs (working cells).

Intercellular electrical coupling is essential for the transmission of pulses among CMs. This process refers to the capacity of a single cell to move ions directly from its sarcoplasm to adjacent cells. Gap junctions, which are composed of two precisely matched half-channels, one for each connected cell, consist of six connexin (Cx) protein subunits and constitute the primary method of achieving this connection. In cardiac muscle, the main isoforms expressed are Cx43, Cx40, and Cx45 [30]. Cx43 is the predominant isoform in adult working CMs [31, 32], whereas Cx40 is expressed in Purkinje fibers and atrial working CMs [33, 34]. Cx45 is expressed mainly at the AVN [35]. These three Cx isoforms exhibit different levels of conductance, with Cx40 having the highest conductance and Cx45 having the lowest conductance [36]. These properties correlate with the speed of pulse propagation in different structures. For example, the Purkinje fiber is a fast-conducting structure, whereas the AVN is associated with a time delay in the propagation of action potentials [35, 37].

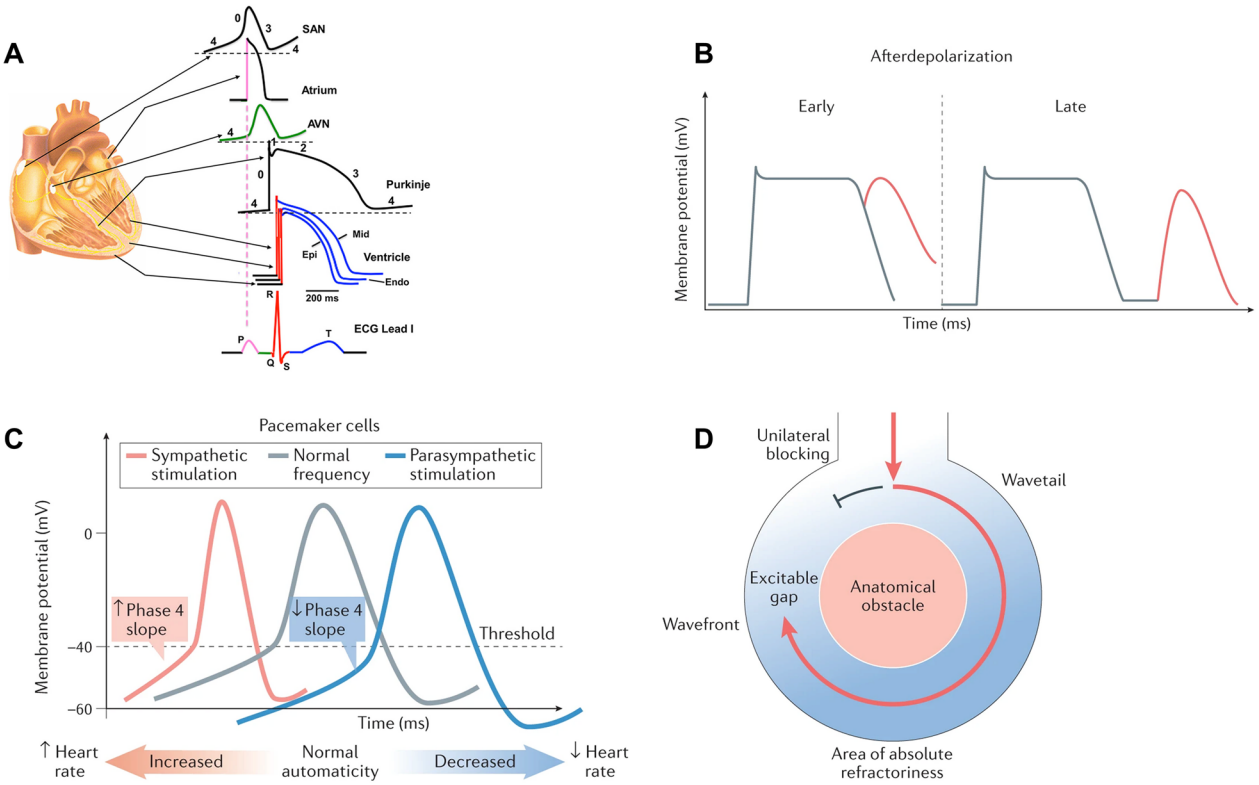



**Fig. 1** Electrophysiological principles related to the propagation of electrical signals and the development of abnormal heart rhythms. **A** Regional variations in cardiac action potential configurations are illustrated in a schematic cross-section of the heart, with different regions indicated by arrows. The color-coded sections on the action potentials correspond to sections on the electrocardiogram [ECG]. *SAN* sinoatrial node, *AVN* Atrio-ventricular node, *Epi* epicardial, *MID* midmyocardial, *Endo* endocardial. Reproduced with permission from Ref. [25]. Copyright American Physiological Society, 2021. **B** Triggered activity usually results from prematurely activated cardiac tissue, causing early or late afterdepolarizations. **C** Increased automaticity. **D** Re-entry. ECG, electrocardiogram; LV, left ventricular. Reproduced with permission from Ref. [29]. Copyright Springer Nature, 2021

## Mechanisms of cardiac arrhythmia

Cardiac arrhythmia typically arises from a combination of genetic predisposition, environmental factors (such as food-induced and physicochemical stimuli), and cardiovascular or other diseases. Arrhythmia involves three primary pathophysiological mechanisms: abnormalities in automaticity [38], triggered activity [39, 40], and re-entry [41, 42] (Fig. 1B, D).

Automaticity refers to the ability of specialized cardiac tissues, notably the sinoatrial node and Purkinje fibers, to autonomously generate electrical impulses that direct the rhythmic contractions of the heart. Therefore, increased automaticity indicates that the frequency of electrical impulse generation by certain automatic rhythmic points in the heart is abnormally high [38]. Moreover, triggered activity describes the additional electrical impulses that are initiated by the internal electrophysiological processes of the cardiac myocytes outside the normal cardiac cycle. These impulses may be triggered by an overload of calcium within the myocytes, where an unusually high concentration of intracellular calcium ions leads to the abnormal opening of calcium release channels. Such triggered activity can lead to premature contractions or tachycardias, including premature ventricular beats or ventricular tachycardia [39, 40]. Re-entry is another hallmark of arrhythmogenesis and is the most common mechanism for sustaining ventricular and supraventricular tachyarrhythmia, such as atrial fibrillation. Re-entry occurs when a shortening of the refractory period exists [43]. Additionally, a slowing of conduction can lead to foldback, as the cell is re-excited upon the arrival of the delayed impulse [44]. Changes in structure, such as dilatation and fibrosis, can extend the pathways for conduction, decrease the conduction speed, and prevent conduction, which could promote the start and continuation of re-entry [45]. In healthy myocardium, repolarization is fairly homogeneous. During illness, remodeling procedures can cause variations in electrical properties throughout the myocardium, particularly in terms of different action potential durations, due to repolarization

differences. The dispersion of repolarization has been categorized into two dimensions: the temporal dispersion, which promotes the onset of arrhythmia, and spatial dispersion, which is more significant for the persistence of arrhythmia [46, 47].

## Advanced properties of nanobiomaterials

Nanobiomaterials provide significant advantages over traditional materials, including targeting effects, large specific surface areas, biocompatibility, and in vivo biodegradability. As a result, they have broad potential applications in antiarrhythmia and improving cardiac electrophysiological function [48].

Nanomaterials exhibit a targeting effect due to their nanoscale size. Conventional therapies often have significant side effects due to their intrinsic toxicity, broad-spectrum activity, and poor control of drug delivery [49]. Nanobiomaterials are promising alternatives to conventional therapies because of their ability to penetrate cell membranes, enter the cell interior, and interact with biomolecules in specific ways [50, 51]. Targeted drug delivery can reduce the drug dosage and toxic side effects, improve the therapeutic efficacy, and provide several advantages over standard therapies.

Additionally, nanomaterials possess a large specific surface area, which allows them to carry more drug molecules, thus improving drug delivery efficiency. Nanobiomaterials can be utilized as drug carriers for arrhythmia therapy. They can encapsulate antiarrhythmic drugs on their surface or inside, achieving sustained therapeutic effects by controlling the release rate. Various types of nanoparticles have been used to load miRNAs, lncRNAs [52] and drugs such as amiodarone [53].

Furthermore, nanobiomaterials exhibit excellent biocompatibility because of their similarity to biological tissues and low toxicity. As a result, they elicit a weak immune response and minimal tissue rejection in cardiac tissues. This characteristic makes nanobiomaterials highly compatible with surrounding tissues, reduces immunogenicity, prevents premature drug destruction [54], and enhances therapeutic efficacy.

Finally, nanobiomaterials are biodegradable, which is the ability of these materials to break down into harmless byproducts within the human body. This attribute is crucial in medical and health care applications, especially when these materials may be implanted or interact with tissues over long periods. The ideal degradation process should occur through natural, nontoxic metabolic pathways or enzymatic reactions, avoiding adverse immune responses or toxicity [55]. Anticardiovascular disease drug delivery nanoplatforms composed of biodegradable polymers can be fabricated through electrospinning deposition, yielding fibrous scaffolds capable of sustained and controlled drug release [56].

Nanobiomaterials have great potential in the repair of cardiac tissue. They can facilitate the regeneration [57] and repair of cardiac tissue by providing scaffolding structures to direct the growth of cardiac cells and tissue reconstruction [58, 59].

However, the poor electrical conductivity of biomaterials has been a major obstacle for achieving physiological functions in cardiac tissue engineering (cTE). Researchers have investigated a new class of conductive biomaterials to address this issue. These biomaterials include gold nanoparticles (AuNPs), carbon-based nanomaterials (CBNs), silicon-derived nanomaterials, conductive polymers, iron oxide nanoparticles, and silver nanoparticles (as shown in Fig. 2). As replicating extracellular matrix (ECM) nanostructures is challenging using traditional fabrication methods, micro/nanofabrication techniques such as photolithography, 3D printing, and electrostatic spinning [60] are commonly employed to create biomimetic structures with ECM-like nanostructures.

## Novel strategies to improve cardiac electrophysiology

Cardiac regeneration is challenging because of the termination phase and low turnover rate of cardiomyocytes after maturation. Drug delivery, cardiac tissue engineering, and biosensors have been extensively investigated to restore the conduction properties of the diseased heart and treat arrhythmia (Fig. 3). Numerous studies have documented the effectiveness of in vivo nanodelivery systems in stabilizing drug properties and increasing the drug loading capacity [61–64].

### Application of nanobiomaterials in drug delivery systems

Antiarrhythmic drugs often have side effects on other tissues due to their poor selectivity and low bioavailability caused by poor aqueous solubility and/or poor first-pass metabolism. Researchers have developed novel hybrid nanomaterials, such as nanobodies, polymers, carbon nanotubes, silica nanoparticles, and magnetic nanoparticles [65, 66], to achieve the desirable properties and overcome these limitations. The use of nanoparticles, which have a large surface area, as a component of nanotechnology can create a more efficient drug delivery system. This approach can improve the bioavailability of drugs and allow for targeted delivery, as well as continuous controlled release of a single dose of drug. As a result, it can decrease drug-induced harm and enhance patient adherence by decreasing the frequency of drug dosing (Fig. 4) [67, 68].

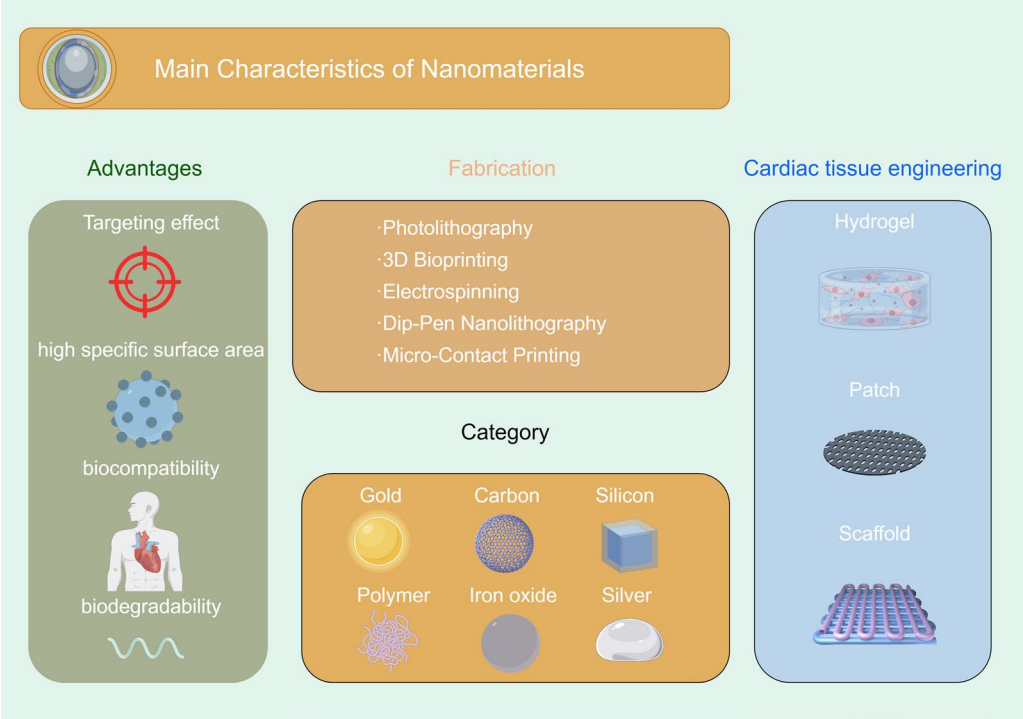



**Fig. 2** Main characteristics of nanomaterials

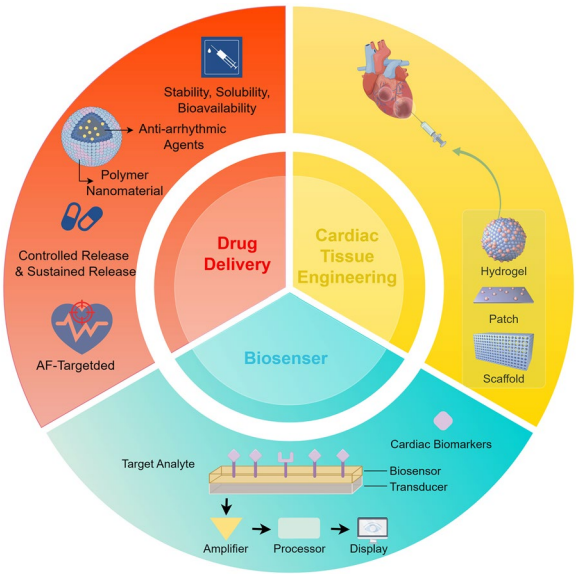



**Fig. 3** Nanobiomaterials in improving cardiac electrophysiology and treating arrhythmias

***Improving drug stability, solubility, and bioavailability***

Carvedilol (CRV) is an FDA-approved treatment for cardiac arrhythmia, including atrial fibrillation [69]. It inhibits the generation of spontaneous $Ca^{2+}$ waves, which suppresses arrhythmia. However, CRV has poor water solubility and is strongly influenced by precursor metabolism in the gastrointestinal tract, resulting in an absorption rate of only 25% [70]. Research has demonstrated that nanoparticles with a positive charge are more easily absorbed by cell membranes with a negative charge. Additionally, bile salts have been found to enhance the penetration of nanobodies through biological barriers. Gelareh et al. constructed electrically modified liposome carriers using bile salts, which significantly increased the bioavailability of CRV, reduced drug toxicity, and improved therapeutic efficacy in a rat model (Fig. 4A) [71].

In a separate study, Shah produced solid lipid nanoparticles (SLNs) containing CRV through thermal homogenization to prevent first-pass metabolism, resulting in increased drug bioavailability. Powder X-ray diffraction (XRD) spectroscopy was used to examine the composition of the enclosed medication, which revealed that the CRV crystals changed to an undefined state when mixed with SLNs. Cellular uptake studies indicated that the uptake of CRV from SLNs was greater than that from the drug solution. Furthermore, SLNs were able to prolong drug release. Additionally, enteric tablets containing SLNs were able to resist the acidic conditions of the stomach, thereby protecting the drug and delaying the release of carvedilol until it reached the small intestine [72].

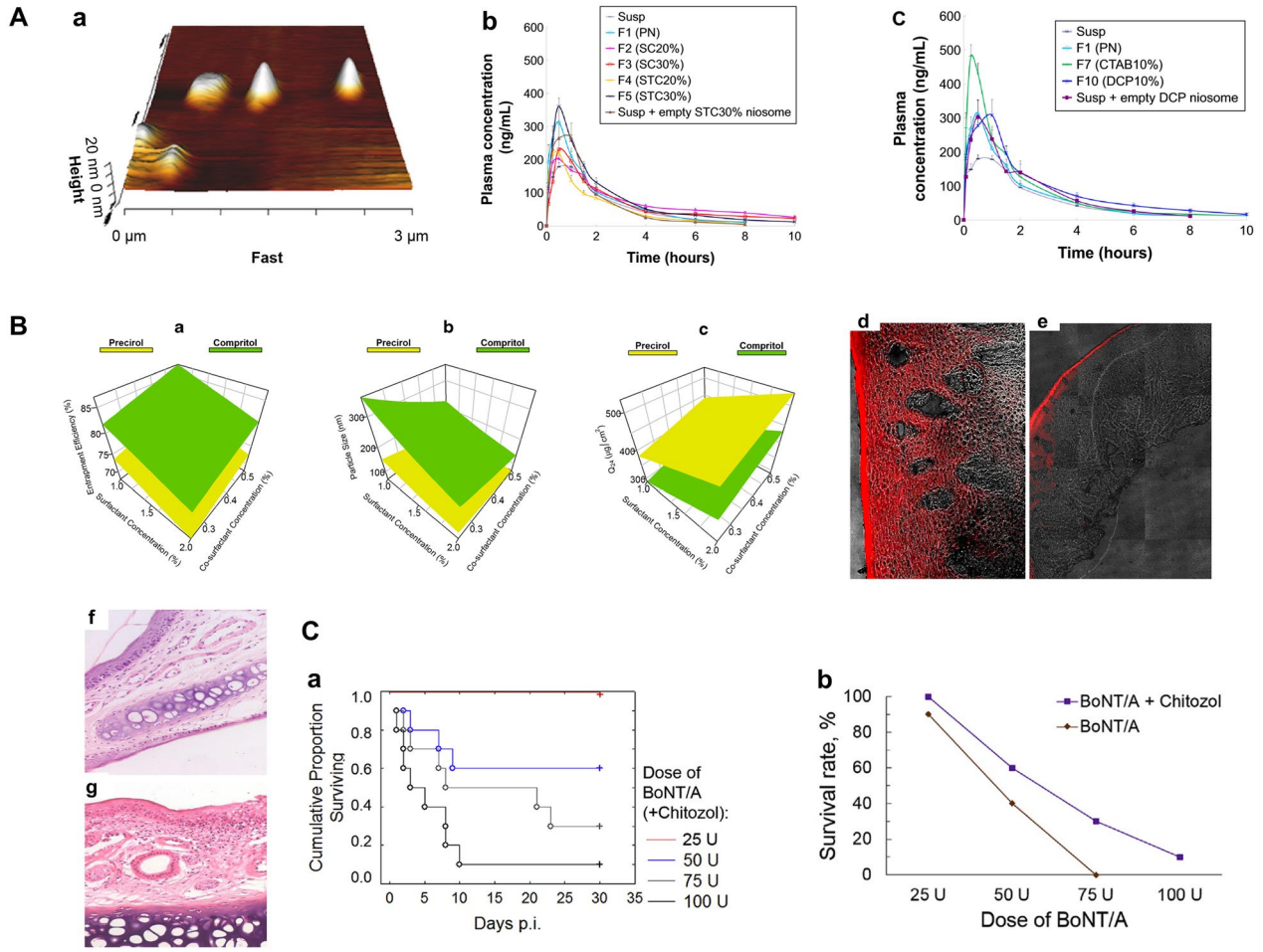



**Fig. 4** **A** (**a**) Morphology of carvedilol-loaded niosomes by AFM. (**b**) The average plasma level of carvedilol following a one-time oral administration (8 mg/kg) of bile salt-enriched (**b**) or charged niosomes (**c**) was measured against carvedilol suspension in rats (n = 6, mean ± SEM). *AFM* atomic force microscopy, *CATB* hexadecyl-trimethyl ammonium bromide, *DCP* dicetyl phosphate, *PN* plain niosomes, *Susp* suspension, *F* formulation, *SC* sodium cholate, *SEM* standard error of the mean, *STC* sodium taurocholate. Reproduced from *Arzani G, Haeri A, Daeihamed M, Bakhtiari-Kaboutaraki H, Dadashzadeh S. Niosomal carriers enhance oral bioavailability of carvedilol: effects of bile salt-enriched vesicles and carrier surface charge. Int J Nanomedicine. 2015;10(1):4797–4813* [71]. **B** Response surface graphs display how the entrapment efficiency (**a**), particle size (**b**), and Q24 (**c**) are influenced by the type of lipid, surfactant, and co-surfactant concentrations. Confocal pictures of nasal mucosa cross sections following the use of rhodamine-filled SLNs (S8) (**d**) and rhodamine liquid (**e**).Untreated rat epithelium (**f**) and rat epithelium (**g**) treated with carvedilol-loaded SLN formula S8 displayed in a light photomicrograph after in situ gelling. Reproduced with permission from Ref. [73]. Copyright Springer Nature, 2016. **C** Acute toxicity assessment of BoNT/A1 after intramuscular injection in rats. (**a**-**b**) Survival rates of rats injected intramuscularly with 0.5 mL of BoNT/A1 combined with Chitozol or BoNT/A1 in saline solution at various doses after 30 days post-injection were compared (n = 10). Reproduced with permission from Ref. [75]. Copyright Elsevier, 2018

Aboud and colleagues suggested a nasal drug delivery method utilizing SLNs to enhance the absorption of CRV (Fig. 4B). Confocal laser scanning microscopy confirmed that the developed formulation allowed the penetration of large amounts of CRV into the nasal mucosa. This increased penetration was due to the lipophilicity of the nanocarriers, causing a confinement effect that delayed water evaporation and loss. Additionally, the high specific surface area and monolayer membrane structure of the particles resulted in tight adhesion of the drug to the mucosa. A pharmacokinetic study was conducted in rabbits to compare the absolute bioavailability of CRV in nasal SLNs and oral formulations. The findings indicated that the overall bioavailability of CRV in nasal SLNs was notably greater than that of the oral formulation [73]. In addition, tolerability and toxicity studies have provided critical insights into the safety profile of drug delivery systems. The results revealed no severe reactions, such as necrosis, epithelial cell sloughing, or hemorrhage, in the studied

rat models, which underscores the potential for clinical translation without compromising patient safety.

Botulinum toxin (BoTN) is a neurotoxin that works at the synapse to inhibit autonomic remodeling by stopping the release of acetylcholine from the presynaptic membrane and decreasing the vagus nerve-induced contraction of the atrial effective refractory period. Studies of animals have shown that chitosan (CS) nanoparticles can prolong the duration of the BoTN nerve block (Fig. 4C) [74]. Therefore, CS nanoparticles are promising options for drug delivery systems. During the therapeutic process, regardless of whether the drug is injected intravenously or released in situ, it cannot be separated from the solution. Although traditional linear CS is not soluble at normal pH values, CS nanoparticles can be dispersed in water, allowing the resulting mixture to be incorporated into a solution [75]. The incorporation of CS into a nanodrug delivery system can efficiently safeguard the encapsulated BoTN, improve solubility, enhance efficacy, prolong the duration of action, and reduce toxic side effects.

#### *Controlled and prolonged release of drugs*

Systemic administration methods have deficiencies in stability, solubility, and bioavailability and are often associated with adverse side effects. Amiodarone (AM) is a class III antiarrhythmic drug [76–78]. However, due to its poor water solubility and low bioavailability, its active metabolite tends to accumulate in the body, causing damage to nontherapeutic target organs such as the lungs, liver, and thyroid. This damage can result in serious adverse effects, such as chronic interstitial pneumonia or pulmonary fibrosis [79–81]. Amira et al. encapsulated AM into polylactic-co-glycolic acid (PLGA) nanoparticles, which improved its bioavailability. The nanocarriers enabled the gradual release of AM encapsulated within them in vivo, thereby preventing toxicity to nontherapeutic target organs (Fig. 5) [82, 83].

Inflammation occurs in the myocardial tissue at the ablation site due to elevated temperatures during radiofrequency ablation. Inflammation during surgery increases the likelihood of AF recurring shortly after the operation. Budesonide, which is encapsulated within PLGA nanoparticles, has a similar effect as amiodarone. During radiofrequency ablation, the nanodrug delivery system releases budesonide at high temperatures, inhibiting the inflammatory response at the ablation site. Inactive nanoparticles can also provide prolonged anti-inflammatory benefits at the site of ablation by slowly releasing the medication, improving the efficiency of radiofrequency ablation and decreasing the likelihood of atrial fibrillation recurrence after the procedure [84].

Polymer hydrogels are a commonly used medium for controlled drug release. Nanoparticle outer coatings based on polymer hydrogels provide stable protection and can be degraded under certain triggering conditions, such as specific pH values and temperatures. PLGA is a polymer gel that is sensitive to temperature, becoming hydrated at temperatures below body temperature and becoming hydrophobic at body temperature [85]. A nanocontrolled release system has been developed to break down the outer coating once it enters the body, allowing the drug to be released. Moreover, the critical disintegration temperature can be modified by incorporating residues. If the critical temperature is set to be high, preventing natural disintegration, the outer layer disintegrates only when exposed to high temperatures in a local and instantaneous manner, such as during radiofrequency ablation. The aforementioned drugs that target the ganglion plexus (GP) can be encapsulated within a drug carrier to improve the efficacy of radiofrequency ablation and reduce the rate of AF recurrence.

Intravenously administered liposomal amiodarone showed a longer-lasting and consistent drug release and extended drug circulation time in rats than free amiodarone hydrochloride. Research on the distribution of the suggested compound revealed that the levels of the medication in the hearts of rats that underwent cardiac radiofrequency ablation (CRA) and received liposomal amiodarone were 4.1 times higher than those in a control group that underwent a sham operation and received the same treatment. This study suggested the use of liposomal amiodarone as a method of delivering the medication for the specific treatment of arrhythmia following CRA [86].

Propranolol, a nonselective β-blocker commonly used to treat cardiovascular diseases such as arrhythmia, has a half-life of approximately 4 h and requires frequent administration to maintain its therapeutic effects [87]. A study was conducted on pig ear skin to investigate the permeation of nanoparticles using a gel delivery system. The results showed that the delivery system exhibited thixotropic behavior, which prolonged drug release. The authors reported delayed release of the drug due to the hydrophobic interaction between CS and propranolol hydrochloride. Only 11% of propranolol was released from the nanoparticle–gel formulation within 24 h [88]. In contrast, buffered solutions containing propranolol showed very rapid release, with approximately 65% of the drug released within 24 h. Furthermore, scanning electron microscopy (SEM) images revealed that CS nanoparticles were taken up by the skin, possibly forming drug reservoirs that extended the therapeutic effect of propranolol. Nanoparticle gels have potential as an

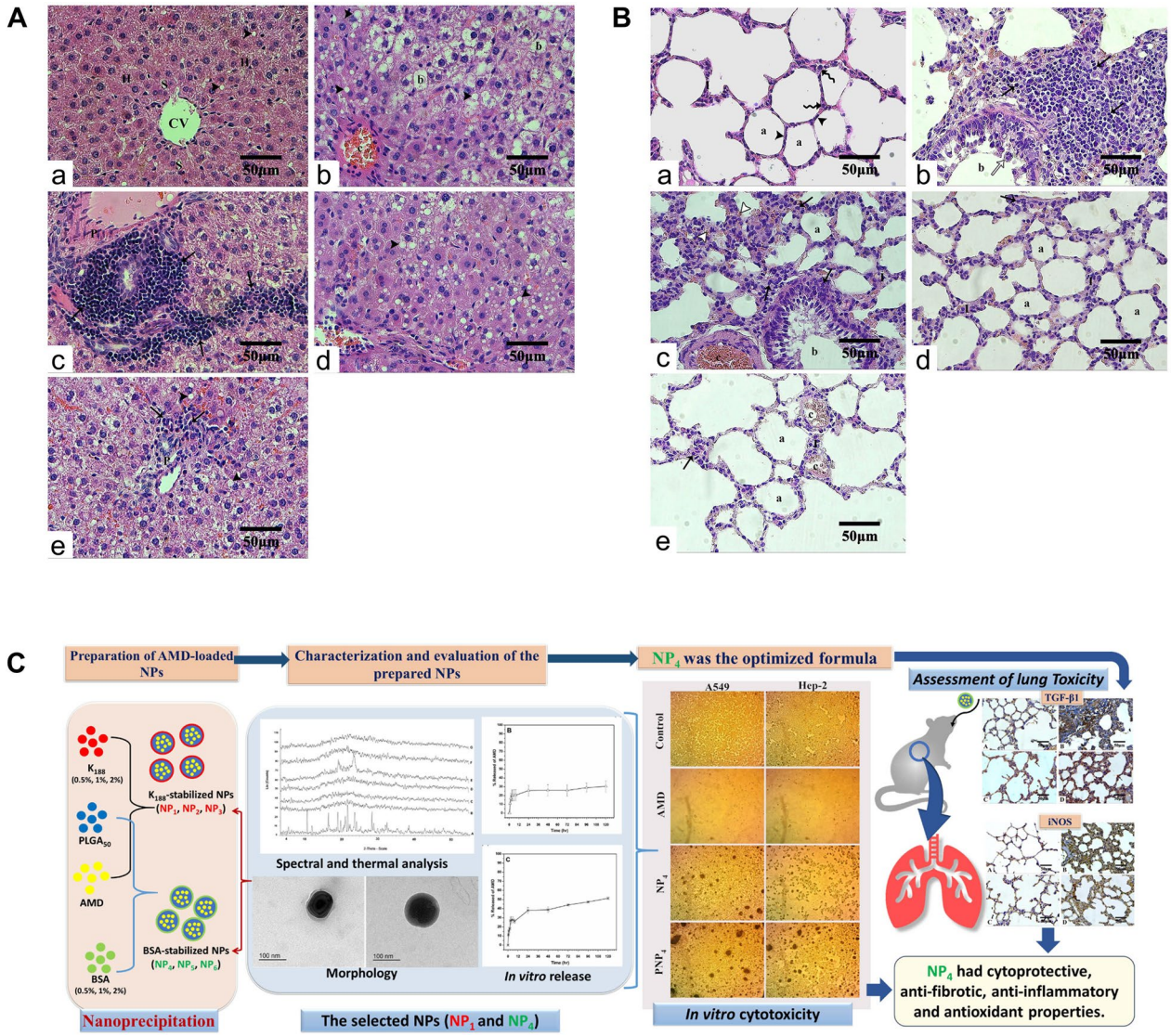



**Fig. 5** **A** Liver sections from the control group (**a**), AM-treated groups (**b**, **c**), plain nanoparticles (PNPs) group (**d**), and AM-loaded nanoparticles (NPs) group (**e**) are analyzed using photomicrographs.The PNPs group exhibits slight fatty infiltration in contrast to the control group, whereas the AM-loaded NPs group displayed less pronounced fatty and cellular infiltrations than the AM group. (H&E, × 400, scale bar = 50 μm). **B** The photomicrographs show lung sections from the control group (**a**), AM groups (**b**, **c**), PNPs group (**d**), and AM-loaded NPs group (**e**).The PNPs group exhibits thickening of interalveolar septa.Cellular infiltration and septal thickening are less prominent in the group treated with AM-loaded NPs compared to the group treated with AM. (H&E, × 400, scale bar = 50 μm). **A**, **B** Reproduced with permission from Ref. [82]. Copyright Elsevier, 2021. **C** Diagram of the important role of PLGA nanoparticles in attenuating amiodarone-induced lung toxicity. Reproduced from *Motawea A, Ahmed DAM, El-Mansy AA, Saleh NM. Crucial Role of PLGA Nanoparticles in Mitigating the Amiodarone-Induced Pulmonary Toxicity. Int J Nanomedicine. 2021;16:4713–4737* [83]

effective method for delivering propranolol through the skin, increasing its overall availability in the body.

### *Targeted therapy for atrial fibrillation (AF)*

Traditional medication treatment and ablation procedures for atrial fibrillation result in restricted effectiveness, frequent reoccurrence, and the potential for severe complications. Nanoparticle drug delivery systems have distinct physical and chemical characteristics, providing a safer, more efficient, and economical approach to treating AF. They can be used as an adjunct to enhance ablation or for targeted therapy.

Heart rate control is the cornerstone of atrial fibrillation treatment. Barium titanate nanoparticles (BTNPs) are piezoelectric nanomaterials capable of generating a localized electromagnetic field under ultrasound,

stimulating the right inferior ganglionated plexus (IRGP) of the heart in beagle dogs and reducing the ventricular rate during rapid atrial pacing (RAP)-induced atrial fibrillation. Moreover, the activation of BTNPs did not induce inflammatory or thermal damage in the IRGP. These findings suggest that ultrasound-mediated BTNP neuromodulation is a potential therapy for controlling heart rate in patients with atrial fibrillation (Fig. 6A) [89].

AM induces phospholipid deposition, which is the accumulation of phospholipids in organelles of the endosomal lysosomal system. Extracellular vesicles (EVs) are nanoparticles that are released into the extracellular compartment. They are characterized by a heterogeneous size and shape. Originally identified as a system for the disposal of cellular waste, they have also been suggested as an additional mode of intercellular signaling. A study demonstrated that EVs can contribute to the cellular response to amiodarone-induced phospholipid accumulation, aiding in the removal of deposits and alleviating this phenotype. Additionally, overexpression of TFEB, the master gene for lysosomal biogenesis, can impede the release of EVs induced by amiodarone, making it a potential target for mitigating drug-induced abnormalities (Fig. 6B) [90].

A recent study investigated formulated nanoparticles (NPs) loaded with AM and examined their potential in mitigating off-target toxicity. Polymer nanoparticles were synthesized using polylactic-co-glycolic acid, and their physicochemical attributes were comprehensively characterized. In a rodent model, a comparison of AM and AM-loaded NP exposure revealed that the latter led to diminished liver damage and enzyme levels. Similarly, animals treated with AM-loaded NPs presented less cell infiltration and interstitial thickening in the lungs than did those in the AM treatment group. The findings of this study suggest that AM-loaded NPs hold promise as a novel avenue to mitigate off-target toxicity induced by AM [82].

Studies have indicated that overactivity of the cardiac autonomic nervous system may result in AF. Atrial fibrillation not only leads to changes in electrical patterns but also worsens the function of the heart's autonomic nervous system, resulting in a harmful cycle known as 'AF promotes AF' [92]. Therefore, regulating the activity of the cardiac autonomic nervous system has become a potential target for AF treatment. Research has shown that $CaCl_2$ suppresses cardiac autonomic activity [93], whereas the N-isopropylacrylamide monomer can inhibit the cardiac autonomic nervous system by suppressing glycolytic enzymes such as enolase [94, 95]. Based on these mechanisms, a therapeutic strategy for AF was developed [85, 94, 95] in which a drug ($CaCl_2$, an N-isopropylacrylamide monomer) was encapsulated in magnetic nanoparticles and a permanent magnet was placed on the epicardial surface. Following catheter intervention, the drug is released into the coronary artery. The permanent magnet generates an external magnetic field that pulls the drug-loaded magnetic nanoparticles toward the prepositioned GPs [91], enabling targeted drug delivery (Fig. 6C).

## The application of nanobiomaterials in cardiac tissue engineering

Cardiac tissue engineering (cTE) emerged from the convergence of engineering and life sciences approximately forty years ago [96]. The process includes creating and restoring heart tissue through the integration of expertise and methods from materials science, micro/nanoengineering, cell biology, and biochemistry [97]. Efforts have been made to restore the damaged myocardium and regenerate it using bioengineered hydrogels, cardiac patches, and stents [98]. The adult heart lacks a regenerative capacity. However, ideal engineered cardiac tissues (ECTs) must exhibit not only suitable mechanical properties but also meet the electrical signal propagation requirements. However, many engineered cardiovascular scaffolds are insulated and unable to transmit electrical signals between cells in porous structures. This limitation results in poor integration between the host and ECTs, particularly in terms of electrical integration [99].

As a method to overcome this issue, various nanoparticles have been employed to enhance the electrical, mechanical, and biological properties of tissue-engineered scaffolds [100]. Nanostructures, either alone or in combination with polymers, are utilized to support CMs and facilitate regenerative processes. Numerous studies have reported the successful application of conductive nanobiomaterials in promoting the maturation of CMs and improving electrophysiology [101, 102]. In general, nanomaterials that are used in cardiac tissue engineering can be classified as injectable hydrogels, patches, or scaffolds. Recently, a significant increase in research focused on the application of electroactive substances such as conductive polymers, piezoelectric materials, carbon nanotubes (CNTs), carbon nanofibers, graphene, and gold nanostructures in the field of cardiac tissue engineering has occurred.

### *Hydrogels*

Hydrogels are the most commonly used cellular scaffolds. They are composed of polymeric materials with a 3D lattice structure that preserves the mechanical integrity of the tissue, its elasticity, and the specific biochemical properties of the cells [103]. Hydrogels can absorb significant quantities of water and expand while maintaining their structure, resulting in soft, flexible, and porous

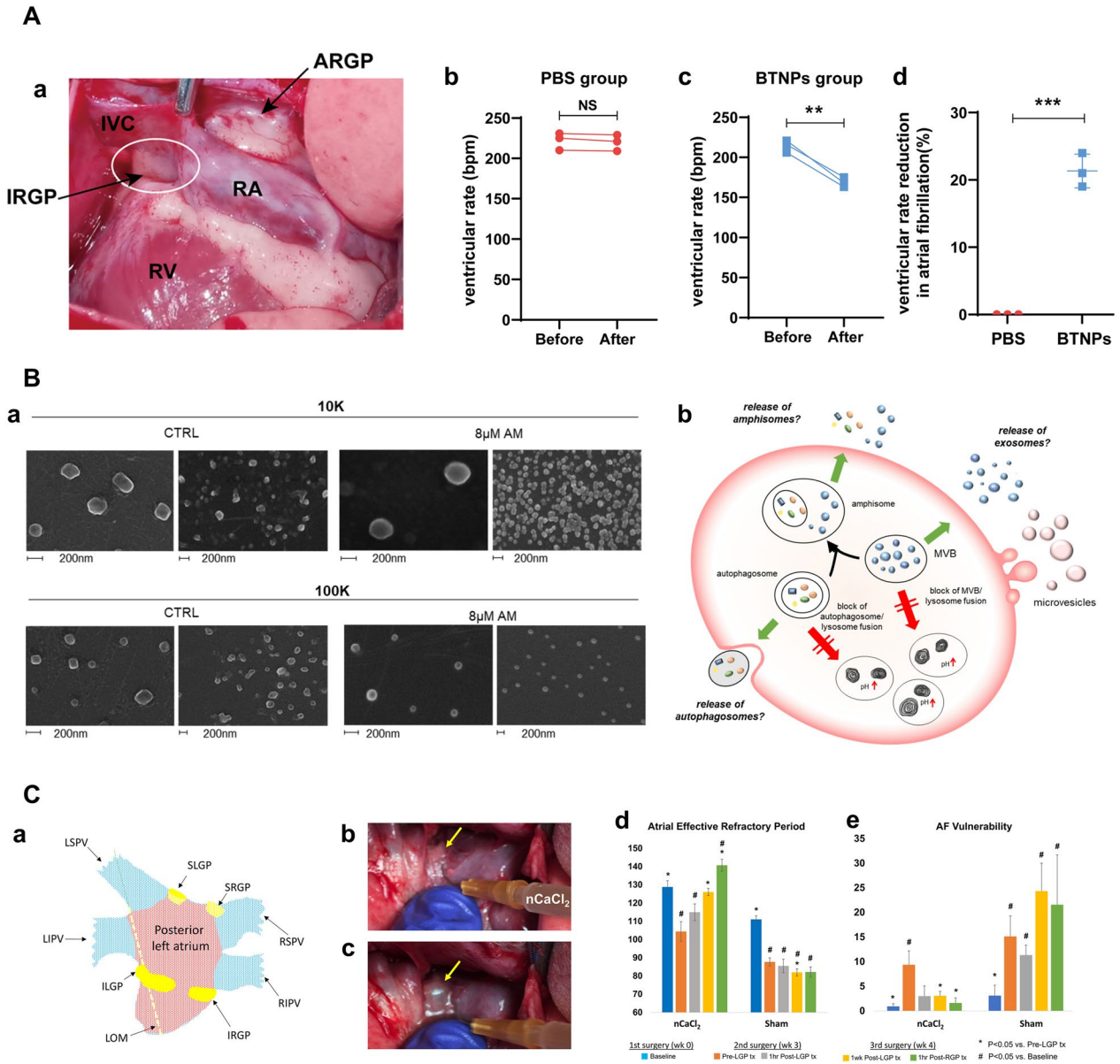



**Fig. 6** **A** The ultrasound stimulation of the piezoelectric nanoparticles in the IRGP. (**a**) The location of the IRGP in vivo, highlighted by the white circle. The ventricular rate reduction during atrial fibrillation and ultrasound treatment in the (**b**) PBS group and (**c**) BTNP group. (**d**) The ventricular rate reduction during ultrasound treatment between the PBS and BTNP groups. Reproduced from *Han J, Zhang Y, Wang X,* et al. *Ultrasound-mediated piezoelectric nanoparticle modulation of intrinsic cardiac autonomic nervous system for rate control in atrial fibrillation. Biomater Sci. 2023;11(2):655–665* [89]. **B** (**a**) Scanning electron micrographs (SEM) of EVs. Electric vehicles were separated using differential ultracentrifugation, treated with 2.5% glutaraldehyde in phosphate-buffered saline, deposited onto glass coverslips, and left to air dry at ambient temperature. (**b**) Illustration depicting the processes of Drug-induced phospholipidosis (DIPL) and the release of EVs. Reproduced *from Sagini K, Buratta S, Delo F, Pellegrino RM, Giovagnoli S, Urbanelli L, Emiliani C. Drug-Induced Lysosomal Impairment Is Associated with the Release of Extracellular Vesicles Carrying Autophagy Markers. International Journal of Molecular Sciences. 2021; 22(23):12922*[90]. **C** (**a**) View of LA structures from the posterolateral perspective. LAA and ALA are located anterolateral to LGP. Abbreviations: LSPV and LIPV: left superior and inferior pulmonary veins; SLGP and ILGP: superior and inferior left GP; LOM: Ligament of Marshall; PLA, ALA, LAA: posterior LA, anterior LA, LA appendage, respectively. GP (yellow arrow) prior to (**b**) and after injection of $nCaCl_2$ (**c**), showing the characteristic bleb. (**d**, **e**): Effects of $nCaCl_2$ on Atrial Effective Refractory Period (AERP) and Atrial Fibrillation Vulnerability (AFV). Mean AERP and AFV values represented the respective average of 3 LA regions. Reproduced with permission from Ref. [91]. Copyright Elsevier, 2019

frameworks that imitate the extracellular matrix characteristics of the natural microenvironment [104]. Electrical conductivity plays a vital role in the effectiveness of tissue engineering. Cardiac tissue, for example, requires enhanced electrical conduction to facilitate the exchange of electrical signals between cells [105]. Combining conductive materials with degradable polymers such as polylactic acid (PLA), PLGA, and CS is crucial for developing electrically conductive biomaterials for tissue engineering scaffolds [106].

Ali's group published the first report on multifunctional cardioprotective scaffolds. Simultaneously, cardiac scaffolds began transitioning from two-dimensional to three-dimensional structures. The addition of multiwalled carbon nanotubes to photocrosslinked gelatin methacrylate (GelMA) produced hybrid hydrogels (CNT-GelMA) with significantly different electrophysiological and mechanical properties (Fig. 7). The conductive and nanofibrous network formed by CNTs within the porous gelatin framework is the key feature of CNT-GelMA. It mechanically strengthens the gel, promotes cardiomyocyte adhesion and maturation, and improves cellular electrical coupling. The electrophysiological function of the tissues was optimal at a CNT concentration of 3 mg/mL. Additionally, a CNT concentration of 5 mg/mL had the greatest protective effect. CNT-GelMA not only provides structural support but also prevents or reduces damage to cardiac tissue caused by cytotoxic drugs (doxorubicin) and inhibitors (heptanol) [107].

Poly-3-amino-4-methoxybenzoic acid (PAMB) is a type of polyaniline with a carboxyl functionality [108] that acts as a conductive polymer. At physiological pH, the distinct characteristic of this product is its ability to sustain conductivity in biological tissues through self-doping. Gelatin was modified with PAMB and then crosslinked with carbodiimide to create an injectable hydrogel (PAMB-G) composed of a conductive polymer copolymer to improve the compatibility with living tissues. Following myocardial infarction in rats, the injection of the PAMB-G hydrogel into the scar area increased electrical signals in the heart and synchronized cardiac contraction. Compared with gelatin hydrogels, the PAMB-G hydrogels protected ventricular function and reduced arrhythmia [109].

A biohybrid hydrogel is made from collagen, alginate, and conductive poly (3,4-ethylenedioxythiophene): polystyrene sulfonate (PEDOT: PSS). It mimics the structure of extracellular matrix fibers, enhances electrical coupling, and promotes cardiomyocyte maturation. The addition of PEDOT: PSS to the hydrogels improves the conductivity of the tissue structures with neonatal rat cardiomyocytes and helps prevent arrhythmias. Furthermore, the CMs in these constructs exhibit an increase in alignment and density, an improvement in myotome organization, and an increase in the expression of connexin 43, which indicates the maturation of cardiac tissue. The biohybrid hydrogels developed in this study improved the maturation and pacing properties of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-derived cardiomyocytes). As a result, these cells exhibited a myotome length close to the adult myotome length of 1.9 μm, an increased pacing frequency, enhanced contraction velocity, and greater contraction amplitude [110]. Importantly, these improvements were achieved objectively and without bias.

Roshanbinfar et al. aimed to treat arrhythmia resulting from cell implantation by utilizing nonconductive substrates. They created a biohybrid hydrogel using a matrix of CNTs and pericardium, which provides a suitable environment for the maturation of hiPSC-derived cardiomyocytes. Compared with the standard culture medium Matrigel®, the hydrogel improved cardiomyocyte maturation, as evidenced by the increased cell alignment, increased expression of connexin 43, and improved organization of myofibroblasts. This quality makes the

(See figure on next page.)

**Fig. 7** Structural and physical characteristics of CNT-GelMA hydrogels have been investigated to improve cardiac cell adhesion, maturation, alignment and electrophysiological functions on CNT-GelMA. (**a**) Method for preparing fractal CNT networks within GelMA hydrogel. (**b**) TEM image showing carbon nanotubes coated with GelMA. (**c**) SEM images reveal the porous texture of a thin film made of CNT-GelMA at a concentration of 1 mg/mL. (**d**) Confocal pictures of cardiomyocytes (CMs) grown for 5 days on pure GelMA and 1 mg/mL CNT-GelMA displayed a consistent cell spread and some cell orientation on CNT-GelMA. At higher levels of magnification, it was observed that cardiac cells were elongated and had well-defined F-actin cross-striations on CNT-GelMA, while these features were absent on pristine GelMA. (**e**) The correlation coefficient calculated from FFT images exhibited a significant correlation with CNT concentrations (*$p < 0.05$). (**f**) Strong interactions between cells and CNT that cause stretching forces may impact the organization of CMs and enhance the formation of myotube striations. (**g**) CMs exhibited improved cell retention and more uniform seeding on CNT-GelMA in comparison to pure GelMA. (**h**) Cell retention and viability on hydrogel surfaces were significantly influenced by the concentration of CNTs (*$p < 0.05$). (**j**) The levels of DNA on day 3 and day 6 were not noticeably impacted by the concentration of CNT. (**k**) Cardiac tissue beating frequencies were monitored each day between day 3 and day 9. Phase contrast imaging showed that the cardiac tissues ruptured when cultured on pristine GelMA (**l**), while they remained undamaged when cultured on CNT-GelMA (**m**) after 5 days. Reproduced with permission from Ref. [107]. Copyright American Chemical Society, 2013

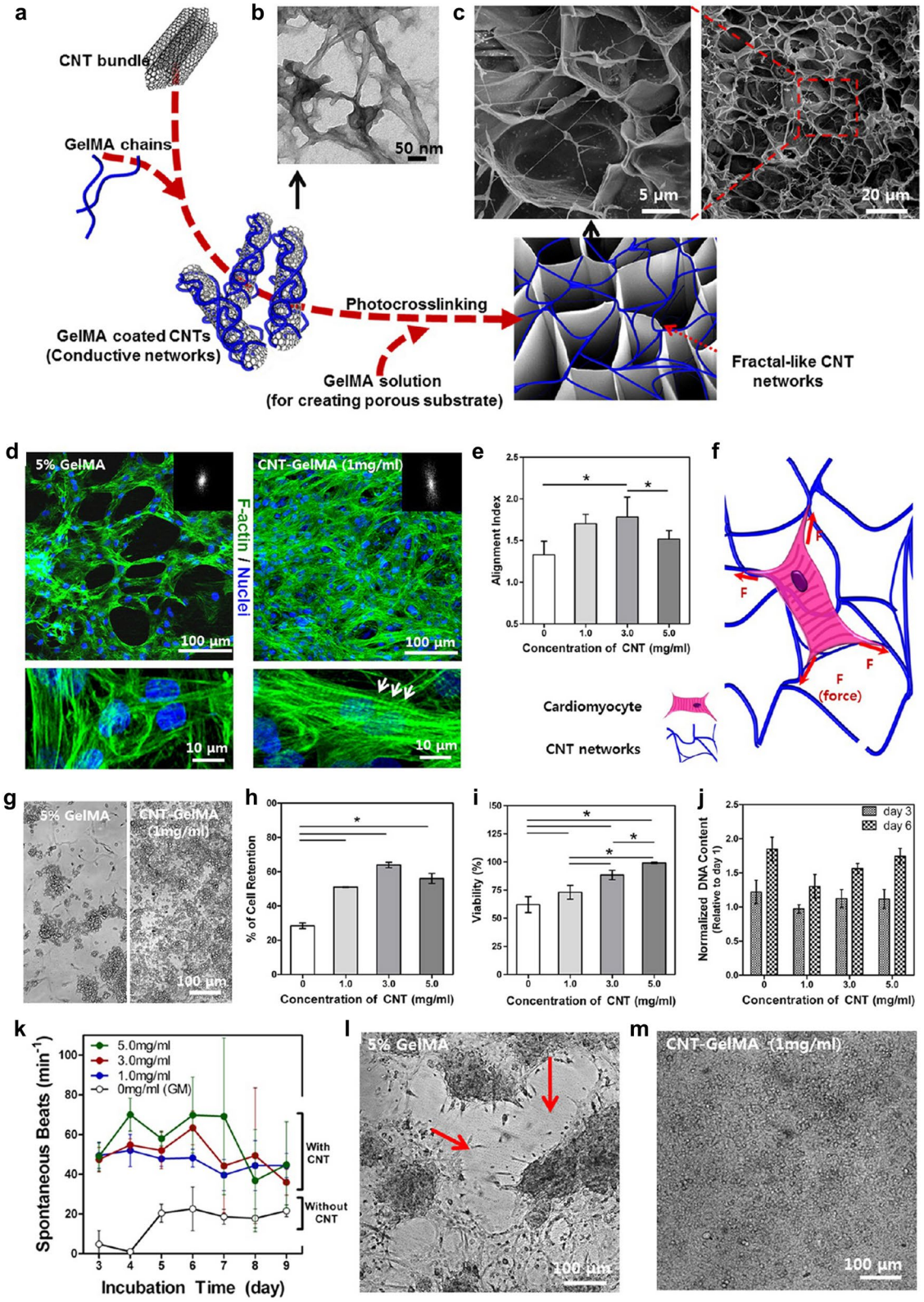



**Fig. 7** (See legend on previous page.)

hydrogel a promising substance for cTE using stem cells [111].

CMs exhibit double the amplitude of their intracellular calcium transients when grown on a conductive hydrogel infused with graphene. The rhythm of the beating matches the frequency of the electrical stimulus being applied (0.5 Hz) [112].

After the integration of conductive reduced graphene oxide (rGO) sheets into the GelMA substrate, a marked improvement in the electrical conductivity of the hydrogel was observed. Compared with the original GelMA samples, the CMs cultured on the rGO-GelMA hydrogel demonstrated a greater degree of organization and enhanced intercellular coupling. Additionally, the rate of spontaneous contraction of CMs seeded on the rGO-GelMA hydrogel significantly exceeded that of CMs seeded on the GelMA gel alone [113].

Incorporating AuNPs into the decellularized retinal matrix resulted in a two-fold increase in the amplitude of contraction and a faster calcium transient in the CMs [114]. Adding gold nanowires to the alginate patches improved electrical conductivity, leading to a 2.4-fold increase in Cx43 expression and well-coordinated calcium transients, in contrast to the weak transients observed in cells grown on pure alginate. Similarly, researchers have combined collagen, a natural polymer, with CNTs to create hydrogels that are conductive. Neonatal rat left ventricular myocytes grown in collagen-CNT hydrogels showed better compatibility and rhythmic contraction than the cells grown in collagen-only hydrogels [115]. In addition to the abovementioned smart hydrogels, supramolecular hydrogels formed through only noncovalent interactions among hydrogel molecules serve as innovative carriers for transporting therapeutic substances. The adaptable nature of the building blocks allows for greater customization of sol–gel transitions and release kinetics [116].

#### *Patches*

After myocardial infarction (MI), CM necrosis occurs due to persistent ischemia. This process leads to the replacement of damaged tissue with fibrotic tissue at the site of injury, resulting in subsequent ventricular remodeling [117, 118]. Fibrotic tissue is nonconductive, which causes the infarcted myocardium to lose its ability to maintain normal excitation–contraction coupling. This loss of coupling produces an arrhythmogenic and heterogeneous environment [119, 120]. Thus, restoring electrical connections within the heart is crucial for restoring the normal function of the infarcted heart. By electrically reconnecting the CMs in fibrotic tissue to healthy myocardium and restoring impulse propagation across the infarct scar, contraction can be resynchronized and adverse ventricular remodeling can be prevented [109, 121].

Tissue-engineered cardiomyoplasty using engineered cardiac patch diaphragms was first introduced in the early 2000s [122–128]. Cardiac patches for treating damaged cardiac tissue after a heart attack are typically created by cultivating cardiomyocytes in a three-dimensional porous biomaterial scaffold [122, 123, 129]. However, this approach is limited by the fact that the pore walls of the porous matrix restrict cell–cell interactions and delay the propagation of electrical signals [130]. Dvir et al. doped gold nanowires in alginate scaffolds to address the poor electrical conductivity of the original material, which restricts electrical conduction to neighboring CMs in the patch. The gold nanowires increased the expression of the electrically coupled protein Cx43 and improved the electrical communication between neighboring CMs. Compared with cells cultured on pure alginate, the cells cultured on the altered sections contracted simultaneously and exhibited improved alignment when subjected to electrical stimulation [131].

Li's group has been working on building engineered heart tissue for over two decades. Fetal rat myocytes were inoculated onto a biodegradable gelatin mesh ($15\times15\times5$ $mm^3$). After 1 week of incubation, the mesh was implanted into the myocardial scar tissue of freeze-damaged rat hearts. After 5 weeks, blood vessels grew into the grafts from the periphery, and the cells within the grafts survived and formed connections with the recipient cardiac cells [132]. Li's group combined polypyrrole (PPy) and CS to form a conductive patch by mixing them into a gelatin sponge (Gel) [133]. Neonatal rat cardiomyocytes (NRCMs) grown on PPy/CS/Gel patches presented a $Ca^{2+}$ transient velocity that was 2.5 times faster than that of NRCMs grown on Gel or CS/Gel patches. Four weeks after implantation, in vivo testing revealed rapid conduction speeds on the outer layer of the heart with no abnormal heart rhythms in the group treated with the PPy/CS/Gel patch. Like gelatin hydrogels grafted with PAMB [90], the electrical activity of fibrotic tissues was significantly increased by the epicardial implantation of cardiac muscle cells seeded on PAMB-Gel patches. This property enhanced the transmission of electrical signals and coordinated the contraction of CMs in the scarred area, resulting in a reduced susceptibility to arrhythmia [134].

Conducting polymers (CPs) are potential candidates for cardiac tissue engineering because of their inherent electroactivity and flexibility. However, CPs transition from an oxidized (conductive) form to a neutral (nonconducting) form when exposed to air or in contact with physiological media [135], creating barriers to their application. Compared with injectable cell/hydrogel systems, patches

retain more cells at the delivered dose and provide structural support. Therefore, they offer some advantages. Nevertheless, implanting the patch onto the cardiac surface is challenging and complex [136] and often requires invasive suturing techniques.

Phytate dopants were immobilized in the conducting scaffolds to produce patches of polyaniline (PANI)/CS, to increase the electrical stability of the CPs, and to prevent invasive damage to the patch. These patches remain electrically stable in physiological media for more than two weeks. Additionally, the CS membrane demonstrated bioadhesive properties upon the addition of the photoactivatable dye Rose Bengal (RB). After green laser irradiation ($\lambda = 532$ nm), the RB-CS membrane adhered to the tissue, providing an alternative to the commonly used surgical sutures. This discovery formed the basis for the development of electrically stable CP-based patches [137].

The objective of these researchers was to develop stretchable, flexible nanofibrillar cellulose/single-walled carbon nanotube ink patches with high electrical conductivity. These patches were intended to activate and restore conduction in regions where electrical signals are disrupted. Experiments conducted on the epicardial surface of the canine heart revealed that the 3D custom-printed conductive carbon nanopatch was able to perfectly compensate for disrupted cardiac conduction [138].

Cardiac arrhythmia is a leading cause of early death after MI and heart failure. Abnormalities in electrical conduction in the infarcted myocardium not only cause undesirable myocardial remodeling but also impede tissue repair. Optimal anisotropic conductivity and improved penetrability have been achieved by optimizing the biomaterials of electrostatically spun filamentous silk protein (rGO/silk) functionalized with reduced graphene oxide (rGO). Compared with nonconducting spun silk and isotropically conducting rGO/silk patches, the anisotropically conducting rGO/silk patch resulted in an enhanced pumping function, decreased arrhythmia susceptibility, a thickened left ventricular wall, and improved survival of functional CMs [139]. These findings highlight its significant therapeutic effect on repairing the infarcted myocardium.

#### *Scaffolds*

Due to their unique structures and surface properties, nanomaterials can act as scaffolds for cardiomyocytes, creating a suitable environment for the growth, differentiation, and regeneration of myocardial tissue. The structure of nanomaterials can mimic the characteristics of myocardial tissue, as they possess a nanoscale pore structure and surface texture similar to the microstructure of myocardial tissue. When scaffold materials come into contact with CMs, their structures can provide a microenvironment similar to that required by CMs, enabling better attachment and growth of CMs. The fabrication of scaffolds is influenced by a combination of chemical, biological, and physical properties [140, 141]. For successful myocardial tissue engineering, the scaffold material must possess several key characteristics, including electrical conductivity, mechanical stability, biocompatibility, topological adaptability, and elasticity, similar to those of the natural myocardium [142, 143]. Furthermore, it must be capable of propagating electrical impulses and translating them into synchronized contractions to maintain circulation [144].

Decellularized frameworks are valuable supports for creating operational patches to address arrhythmia. Nevertheless, the lack of rapid and efficient electrical coupling between neighboring cells may hinder the success of this therapy. Shevach et al. developed a conductive scaffold for cardiac tissue engineering by depositing AuNPs on a decellularized greater omental matrix (see Fig. 8A). The CMs in the hybrid AuNP/greater omental engineered scaffolds exhibited an elongated and aligned morphology, increased Cx43 expression, enhanced contractility, lower excitation thresholds, and faster calcium transients [114].

This study revealed that gold nanostructures can be added to alginate scaffolds to improve matrix conductivity and enhance electrical signaling between cardiomyocytes. These properties lead to better cell–cell coupling at the electrical level [145]. Fleischer et al. created electrically conductive nanocomposite scaffolds for myocardial tissue engineering by integrating AuNPs into poly-ϵ-caprolactone electrospun fibers. In the presence of AuNPs, CMs displayed an aligned and elongated morphology, stronger contractility, and lower excitation thresholds when exposed to electric fields. The addition of AuNPs further enhanced the performance of the cardiac patch, ensuring the anisotropic transmission of electrical signals throughout the engineered cardiac tissue (see Fig. 8B).

Superparabolic carbon nanotube sheets (SA-CNTs) were studied for their ability to cultivate cardiomyocytes, replicating the parabolic structure and electrical impulse transport behavior of the natural myocardium. The scaffolds of the SA-CNTs were aligned with the morphology of the CMs, resulting in a well-defined elongated and aligned morphology similar to that of natural CMs (Fig. 8C). In contrast, CMs cultured on coverslips exhibited an irregular distribution in random orientations. CMs grown on SA-CNTs presented increased cell-to-cell communication and decreased variability in heartbeats and intercellular repolarizations that are essential for maintaining normal rhythms and potentially reducing

the incidence of arrhythmia [146]. SA-CNTs also showed pacing functions through a rapid signaling pathway and were further developed into flexible monolithic pacing electrodes, suggesting their potential application in cardiac resynchronization therapy.

One major limitation of using engineered cardiac tissue for cardiac defect repair is the use of insulating polymer scaffold walls. These walls impede the transmission of electrical signals between cardiomyocytes, which can result in a susceptibility to arrhythmia during scaffold implantation. Due to their conductive nature, CNTs have been shown to significantly enhance electrical coupling between cultured cells. They can be used alone or in combination with other biomaterials to form scaffolds. In one study, subtoxic concentrations of single-walled carbon nanotubes (SWCNTs) were added to gelatin CS hydrogels to act as electrical nanobridges between CMs. Compared with CMs cultured on nonconducting structures, the cells grown on these scaffolds produced synchronized contractions with a high beat frequency and had an excitatory conduction velocity similar to that of natural cardiac muscle tissue (22 ± 9 cm/s) [147]. Nanotube structures significantly increase communication between cultured CMs by increasing the presence of gap junction proteins and intercellular coupling through the propagation of electrical signals [146, 148]. Nevertheless, CMs can experience arrhythmia when they are grown on surfaces containing elevated levels of nanotubes, indicating that the nanotubes could have cytotoxic effects when utilized in relatively high amounts [113].

Ahadian et al. integrated CNTs into poly (octamethylene maleate (anhydride) 1,2,4-butanetricarboxylate) (124 polymer) to produce a flexible framework for cardiac tissue engineering. The scaffold mimics the natural extracellular matrix by providing electrical conductivity and structural stability. Compared with the control group, the 124 polymer–CNT scaffold with hybridization provided superior mechanical support and increased cell survival seven days after the inoculation of neonatal rat ventricular myocytes (NRVMs). Furthermore, the scaffold produced improved contractility, and compared with nonconducting controls, the implanted NRVMs presented homogeneous syncytiotrophoblasts [149]. In summary, nanomaterials are promising materials in cardiac tissue engineering. Due to their special structures, nanomaterials can provide a suitable environment for the growth and differentiation of CMs. Nanomaterials can also promote the regeneration and repair of myocardial tissues, which can lead to new breakthroughs in the treatment of cardiac arrhythmia [150].

### The application of nanobiomaterials in biosensors

Biosensors show great potential for detecting cardiac biomarkers early and monitoring cardiovascular diseases continuously to ensure prompt treatment and safeguard function [151–153]. Nanotechnology enhances the sensitivity and durability of biosensors through increased surface-to-volume ratios, facilitating improved binding of biocatalysts. The current cardiac patches lack the ability to monitor and report the performance of engineered cardiac tissues online, as well as deliver patch-activated signals or integrate them with the host. However, a novel cardiac patch has been developed that integrates CMs with flexible, self-supporting electronics and 3D nanocomposite scaffolds. The patch identifies electrical signals produced by CMs at different points within the 3D framework and administers electrical stimulation from a distance to coordinate cell contractions. Additionally, regulating tissue function at specific times and locations could assist in connecting the patch to unaffected areas

(See figure on next page.)

**Fig. 8** **A** Altering the electrical characteristics of omental matrix with AuNPs. (**a**) AuNPs were applied to a decellularized omental matrix using an e-beam evaporator. Using cells from the identical patient, a personalized cardiac patch was created by placing them on the scaffold. Arrangement of CMs and performance of created tissue on day 5 (**b**–**d**). Immunostaining was performed on the cardiac α sarcomeric actinin (pink), connexin 43 (green), and nuclei (blue) of cardiac cells in the pristine (**b**), 4 nm (**c**), and 10 nm (**d**) scaffolds. (**e**) Spontaneous contraction amplitude, excitation threshold, and speed of calcium transients during natural contractions. Bar = 20 μm. Reproduced with permission from Ref. [114]. Copyright American Chemical Society, 2014. **B** Cardiac cell organization in the three-dimensional scaffold. (**a**) Illustration depicting the structure of a three-dimensional nanowire cardiac tissue. (**b**) Quantifying the expression of sarcomeric actinin protein using western blot analysis. (**c**) Quantification of sarcomeric actinin protein expression by western blot. (**d**-**g**) H&E stained thin sections of the engineered tissues on day 8 showed a thick tissue in the nanowire scaffold (**d**, **e**), whereas the engineered tissue in the pristine scaffolds demonstrated non-continuous tissue separated by pore walls (**f**, **g**). Scale bars, 200 mm (**d**, **f**) or 20 mm (**e**, **g**). Reproduced from *Dvir, T., Timko, B., Brigham, M.* et al. *Nanowired three-dimensional cardiac patches. Nature Nanotech 6, 720–725 (2011)* [145]. **C** (**a**) A diagram showing how the conductive SA-CNTs direct the development of CMs. (**b**–**d**) Cell morphology, CX43 expression and distribution. (**b**) Confocal images show that CMs cultured on coverglass spread randomly, whereas cardiomyocytes on SACNTs aligned with the nanotubes after 3 days of culture. (**c**) Representative images of cardiomyocytes cultured for 7 days show that cells on the coverglass increased in size while maintaining a random structure. In contrast, cardiomyocytes on SA-CNTs displayed an organized distribution with numerous sarcomeric striations perpendicular to the orientation. (**d**) A representative confocal image was superimposed to show CMs on SA-CNTs aligned along the nanotube axis. Reproduced with permission from Ref. [146]. Copyright John Wiley and Sons, 2017

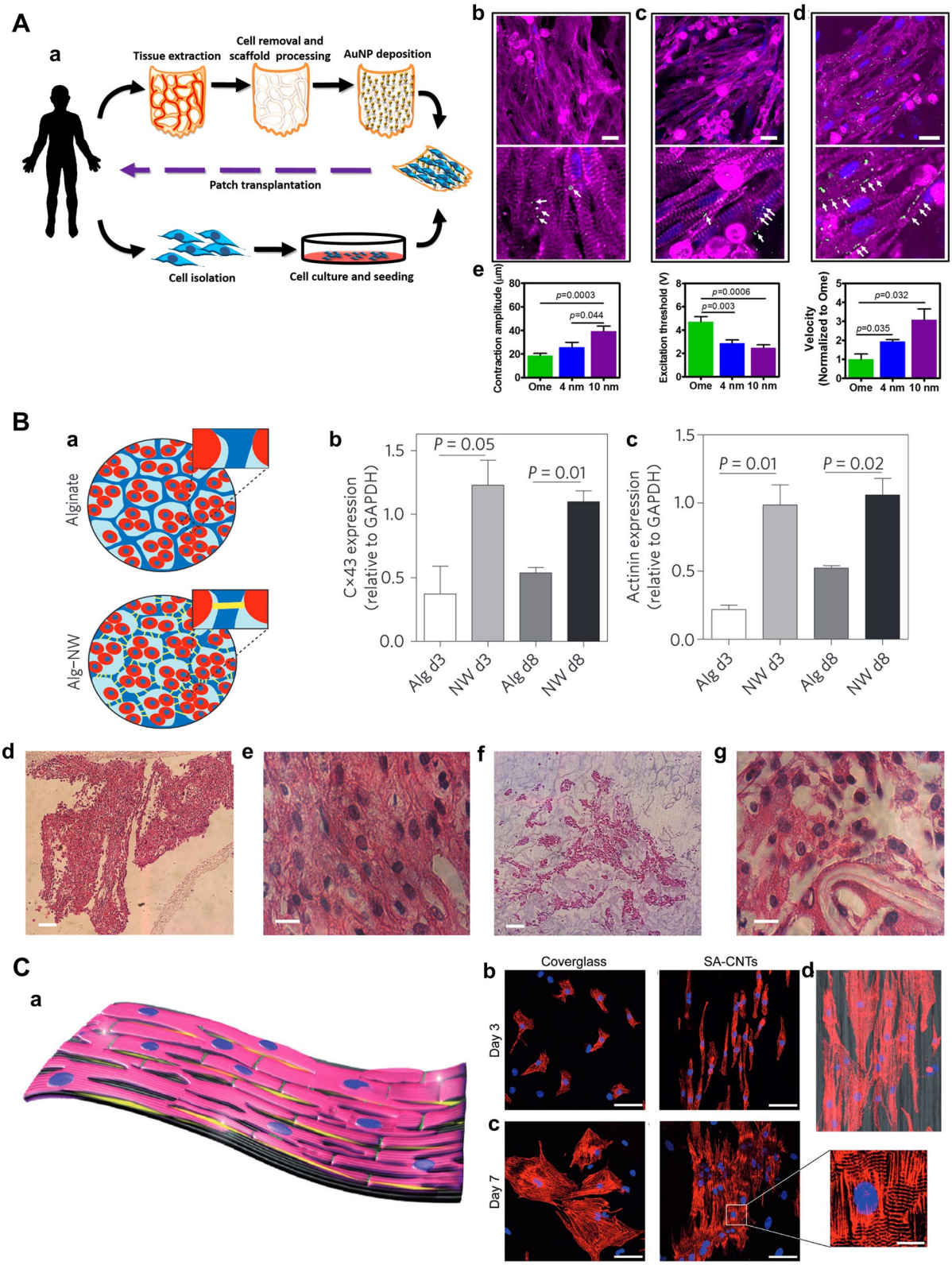



**Fig. 8** (See legend on previous page.)

of the heart, introducing a novel method for restoring the impaired cardiac conduction system (Fig. 9A) [154]. This innovation has the potential to provide doctors with early information about a patient's health, introducing a novel approach to disease management from a distance.

Lei et al. used rGO, a derivative of graphene, as a sensor in their study. The biosensor design, depicted in Fig. 9B, consisted of reduced graphene oxide modified with platinum nanoparticles and an anti-brain natriuretic peptide (BNP) antibody for detecting BNP levels in whole human blood. The immunosensor detected BNP at concentrations as low as 100 fM. The sensitivity of the biosensor to different amounts of the BNP antigen in PBS is shown in Fig. 9B. The biosensor shows better sensitivity than traditional techniques such as ELISA, surface plasmon resonance, and electrochemical methods in identifying BNP in blood samples from patients with CVDs [155]. It also has high specificity for BNP.

## Limitations and challenges of nanomaterials

### Limitations and challenges in drug delivery systems

Functionalized nanomaterials have been developed as intelligent drug delivery systems to increase their effectiveness and minimize adverse effects. Nevertheless,

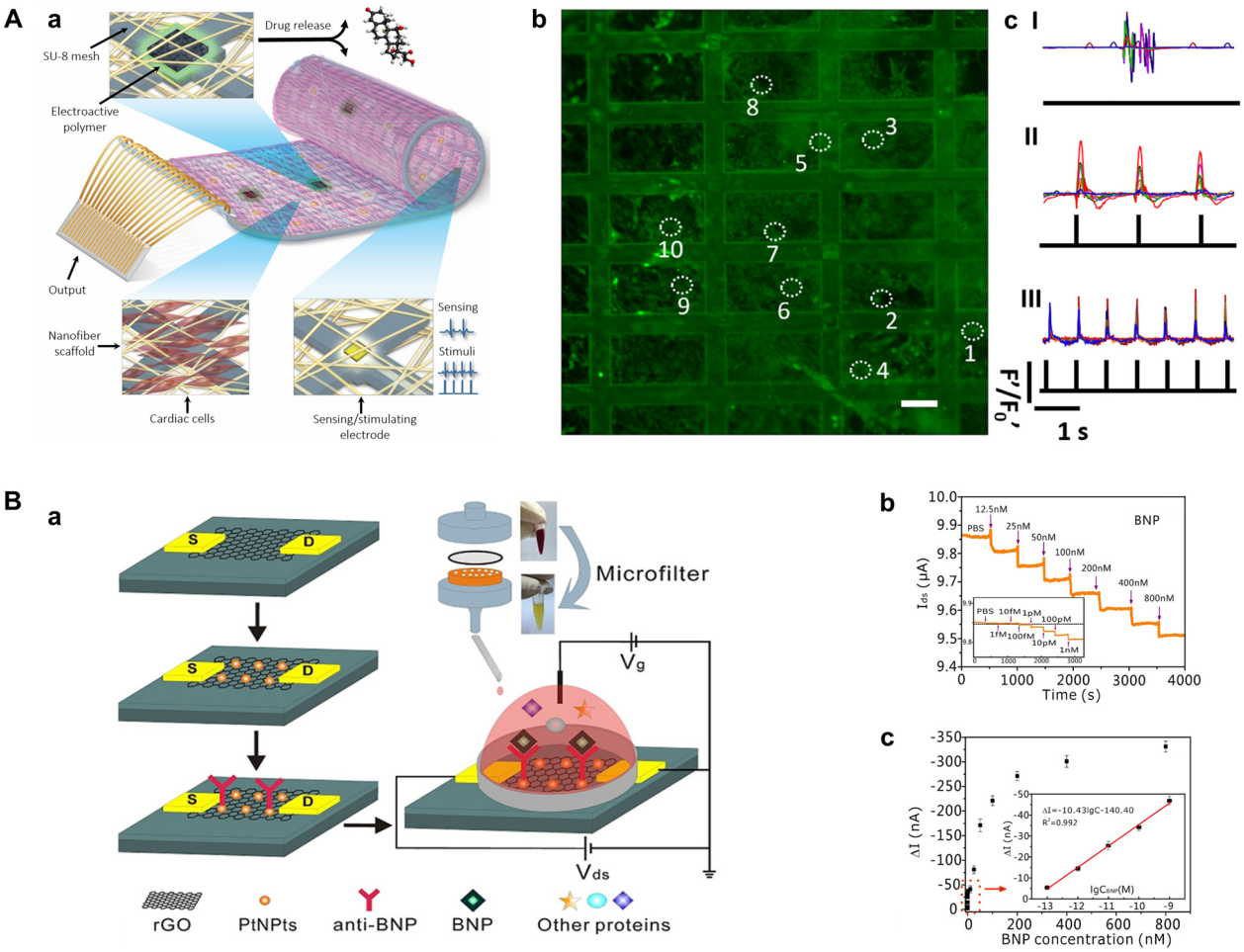



**Fig. 9** **A** A blended 3D nanocomposite blend with integrated electronics designed for real-time monitoring of engineered cardiac patches. (**a**) Illustration depicting the idea of a small electronic cardiac patch. (**b**) Fluorescence image displaying the specific areas analyzed for calcium imaging data quantification. Scale bar, 100 μm. (**c**) Calcium transients were quantified under unperturbed conditions (I) and with pacing regimes of 3 V, 50 ms, 1 Hz (II), and 2 Hz (III). Reproduced from *Feiner, R., Engel, L., Fleischer, S.* et al. *Engineered hybrid cardiac patches with multifunctional electronics for online monitoring and regulation of tissue function. Nature Mater 15, 679–685 (2016)* [154]. **B** (**a**) A diagram showing the rGO FET biosensor decorated with PtNPs and a specially designed microfilter for detecting BNP. (**b**) Real-time monitoring of electrical signals at various BNP solution concentrations in PBS, including 12.5 nM, 25 nM, 50 nM, 100 nM, 200 nM, 400 nM, and 800 nM. The PtNPs-decorated rGO biosensors' reaction to varying levels of BNP. Examine how the biosensors react to BNP within a small concentration range (100 fM, 1 pM, 10 pM, 100 pM, 1 nM). Reproduced with permission from Ref. [155]. Copyright Elsevier, 2017

because of the diversity of human nanodrug delivery systems, certain nanoparticles that have been tested in preclinical studies have been found to be toxic to cells or trigger an immune response [156, 157]. Nanomaterial toxicity encompasses both cytotoxicity and genotoxicity, although most studies have focused on cytotoxicity rather than genotoxicity. Research data on the long-term safety of nanomaterials are limited, which poses a significant barrier to their clinical translation. Upon entering the bloodstream and reaching the target, nanoparticles can accumulate and segregate in the liver due to phagocytosis by Kupffer cells, leading to severe off-target effects [158]. Furthermore, some nanoparticles may penetrate and persist in multiple organs, such as the spleen and kidney, over time [159]. Numerous studies have documented that metal nanoparticles, carbon nanostructures, and silica nanoparticles, among others, can cause severe toxicity [159–164]. These side effects are related to the size, concentration, composition, modification, and route of administration of the nanoparticles. The toxicity of metallic nanomaterials, for example, is highly dependent on their size [165]. Future research should focus on delivering therapeutic agents to the target area safely and efficiently while minimizing toxicity.

Researchers have attempted to reduce the activity of the mononuclear phagocyte system (MPS) by changing the surface of nanomaterials, and incorporating targeted mechanisms can lower the amount of medication needed and its harmful effects while encouraging its accumulation in specific target tissues [166, 167]. Currently, the introduction of polyethylene glycol (PEG) onto the surface of NPs is the standard method for reducing MPS clearance and increasing circulation time [168]. However, the use of PEG alone cannot prevent MPS clearance, and the presence of PEG antibodies may reduce performance after multiple administrations [163]. Currently, investigations of the effectiveness of different stealth polymers, such as poly(2-oxazoline) and poly(amphoteric), and confirmation of their efficacy in living organisms are needed [169]. Furthermore, as the demand for more resilient surface functionalities increases, methods for targeting ligand affixation are becoming progressively challenging, particularly for large-scale production [170]. Current research is focused on controlling the release profile of therapeutic components. However, a high risk of functional alterations of encapsulated drugs exists during stimulus-responsive changes in the properties of nanomaterials. These changes are always regulated by the dynamic microenvironment.

#### Limitations and challenges in cardiac tissue engineering

Notably, despite the great importance of nanomaterials in protecting cardiomyocytes and facilitating the recovery of cardiac electrophysiological functions, they may produce complications such as potential cytotoxicity, and nonbiodegradable fragments could lead to inflammation at specific tissue sites when used over an extended period in living organisms. The three primary critical upstream factors contributing to tissue damage resulting from nanomaterial exposure are inflammation, oxidative stress, and cytotoxicity [60]. Tissue damage caused by these factors can result in tissue dysfunction and ultimately lead to adverse outcomes, including fibrosis, emphysema, granuloma, and mesothelioma. Studies have reported that conductive nanoparticles can trigger NLRP3 inflammasome activation in different types of stem cells, resulting in lysosomal membrane permeabilization (LMP) and impaired autophagy [171]. These findings suggest that the biopersistence and biodurability of these materials may have negative effects.

Modern methods of production, such as 3D printing, lithography, and bioprinting, have successfully addressed restrictions to imitate the physicochemical characteristics of cardiomyocyte ECM elements. However, they still lack the ability to mimic the anisotropic nanostructural features of cardiac tissue. The molecular mechanisms by which engineered cardiac tissues improve electrophysiological function are not fully understood.

#### Limitations and challenges in biosensors

The limitations of biosensors encompass several critical issues. Changes in the mechanical properties due to varying temperatures and humidities can affect their performance. Gaseous diffusion across polymeric sheets can alter the chemical structure of electrodes, impacting sensor sensitivity. The prolonged retention of nanosensors in the blood may cause surface modifications, leading to nonspecific background signals [152]. Additionally, sample processing often requires the dilution of plasma samples, which can complicate field monitoring. Nonspecific adsorption in plasma samples can interfere with sensor signals and detection accuracy, and while dextran sulfate can mitigate this effect, it may also affect antibody–antigen binding. Finally, sensor stability and repeatability over continuous use present challenges, with signal degradation observed after more than 10 cycles [172], indicating a need for further optimization for long-term stability.

## Conclusions and future perspectives

This paper provides an overview of arrhythmogenesis mechanisms and current therapeutic modalities. It also examines the potential applications and challenges of nanomaterials in antiarrhythmic treatments, such as drug delivery, cardiac tissue engineering, and biosensors. Despite significant progress in drugs, cardiac implantable

devices, and catheter ablation, arrhythmia continues to be a significant global health concern. Nanotechnology and nanomedicine have significant potential in the diagnosis and treatment of arrhythmia because they provide personalized care in various ways. Advances in biotechnology, tissue engineering, bionics, and polymer science have led to the development of nanomaterials in medicine, providing additional properties such as controlled and slow release, biodegradability, long blood circulation times, and targeted drug delivery. Numerous types of nanoparticles have been shown to enhance the electrophysiological function of cardiomyocytes, reduce arrhythmia, and promote cardiomyocyte repair.

Recent research has shown that the submicron thinness and pliability of graphene when it interacts with living tissue make it a perfect material for integration with cardiac tissue. These properties enable it to attach securely to the heart while not impeding or changing its regular movement. This finding supports the use of multichannel electrical pacing for in vivo labeling, which can lead to the improved diagnosis and treatment of cardiac arrhythmia [173]. As our understanding of the pathophysiology of inherited arrhythmias deepens, gene therapy is emerging as a promising avenue for both preclinical and clinical interventions in arrhythmia syndromes. Advances in vector engineering, achieved by refining transgene constructs and employing capsid modifications, have the potential to increase the transduction efficacy and vector specificity while minimizing adverse immune responses in the host [174]. Recently, an engineered prokaryotic sodium channel with optimized codon usage was developed. This innovation has been shown to generate functional Nav channels both in laboratory settings and within living organisms. It has been reported to markedly improve excitability and electrical conduction in fibrotic cardiac tissue cultures [175], thereby reducing the incidence of conduction blocks and reentrant arrhythmias, which are often associated with severe cardiac dysfunction.

However, a number of challenges must be overcome to successfully integrate these materials into clinical practice. The potential cytotoxicity, genotoxicity, and carcinogenicity of nanomaterials in the myocardial environment, as well as after degradation, remain controversial topics. More extensive research on the synthesis and physicochemical characterization of nanoparticles is needed to achieve safer material combinations. The biocompatibility of materials is a crucial parameter determining their clinical applicability. Therefore, more validation studies on biomaterials in animal models and humans are needed to understand the safety profile of the beneficial effects mediated by biomaterials. The synthesis and optimization of theranostic nanoparticles necessitate a focus on their reproducibility and cost control. A pivotal domain for the prospective clinical adoption of nanobiomaterials lies in the innovation of machinery designed for the large-scale manufacturing of nanomaterial-based products. This advancement is crucial for translating the promise of nanobiomaterials into accessible and affordable health care solutions.

In the past few decades, only a handful of products based on nanobiomaterials have been successfully translated into viable medical applications. This lack of translation is largely due to inappropriate preclinical assessment and screening methods to detect the toxicity of nanobiomaterials. Three-dimensional (3D) culture models can serve as in vitro alternatives to traditional methods and routine in vivo animal testing for assessing the liver accumulation and toxicity of nanobiomaterials. Furthermore, a thorough comprehension of arrhythmia pathogenesis, including autoregulatory abnormalities, triggered activity, and re-entry, may aid in the identification and understanding of novel molecular markers and their functions. This information, in turn, could advance the application of nanomedicine toward more effective targets for treating arrhythmia.

**Abbreviations**

| | |
|---|---|
| CIEDs | Cardiovascular implantable electronic devices |
| CRT | Cardiac resynchronisation therapy |
| CVDs | Cardiovascular diseases |
| AF | Atrial fibrillation |
| Cx | Connexin |
| AVN | Atrioventricular node |
| AuNPs | Gold nanoparticles |
| CBNs | Carbon-based nanomaterials |
| NMs | Nanomaterials |
| ECM | Extracellular matrix |
| PLGA | Poly (lactic-co-glycolic acid) |
| CNTs | Carbon nanotubes |
| MI | Myocardial infarction |
| CMs | Cardiomyocytes |
| CPs | Conductive polymers |
| cTE | Cardiac tissue engineering |
| CRV | Carvedilol |
| SLN | Solid lipid nanoparticles |
| BoTN | Botulinum toxin |
| CS | Chitosan |
| AM | Amiodarone |
| CRA | Cardiac radiofrequency ablation |
| SEM | Scanning electron microscopy |
| I/R | Ischemic/reperfused |
| EVs | Extracellular vesicles |
| NPs | Nanoparticles |
| GPs | Ganglion plexus |
| ECTs | Engineered cardiac tissues |
| GelMA | Gelatin methacrylate |
| PAMB | Poly-3-amino-4-methoxybenzoic acid |
| PEDOT:PSS | Poly(3,4-ethylenedioxythiophene):polystyrene sulfonate |
| hiPSC-derived cardiomyocytes | Human induced pluripotent stem cell-derived cardiomyocytes |
| rGO | Reduced graphene oxide |
| SA-CNTs | Superparabolic carbon nanotube sheets |
| SWCNT | Single-walled carbon nanotubes |

| | |
|---|---|
| NRVMs | Neonatal rat ventricular myocytes |
| BNPs | Brain Natriuretic Peptides |
| MPS | Mononuclear phagocyte system |
| PEG | Polyethylene glycol |
| Polypyrrole | PPy |
| GelMA | Gelatin methacrylate |

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FXH brought forward the subject and guided the writing. LDK wrote the manuscript and prepared Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9. All authors participated in designing and revising the manuscript. All authors read and approved the final manuscript.

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## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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