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Review Article

Electrochemical biomaterials for self-powered implantable "tissue batteries": A tutorial review

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ABSTRACT

Currently, due to improvements in living standards, people are paying more attention to all-around disease prevention and health care. Self-powered implantable "tissue batteries" integrated with electrochemical materials are essential for disease prevention, diagnosis, treatment, postoperative therapy, and healthcare applications. We propose and define new concepts of "tissue batteries"—self-powered tissue batteries (SPTBs)—are flexible self-powered implantable systems or platforms based on electroactive biomaterials, acting at the interface of biological tissue. Based on the electrical phenomenon of living organisms in life activities, there has been an increased attention to SPTBs for tissue repair promotion. SPTBs take advantages of both the preeminent biocompatibility of biomaterials and the promotion of time-honored electrical stimulation therapy for tissue recovery, which are very promising for human illness treatment. However, studies on clinical applications of SPTBs are impeded by a lack of comprehensive cognitive assessment of SPTBs. Herein, SPTBs for life and health applications are comprehensively reviewed. First, electrochemical materials and their across-the-board applications for several types of SPTBs are introduced and compared with regard to disease prevention, diagnosis, precision therapy, and personalized health monitoring. Then, the potential mechanisms for SPTBs for tissue repair promotion are discussed. Finally, the prospective challenges are summarized and recommendations for future research are provided. This review elucidates on the significance and versatility of SPTBs for various medical applications.

KEYWORDS

electrochemical biomaterials, self-powered, implantable, tissue batteries, medical applications

1 Introduction

Electroactive biomaterials (EBMs), which are fourth-generation biomaterials, contain regions of electron density and/or exhibit an electronic active phase. Moreover, they exhibit the ability to directly transmit electrical, electrochemical, and electromechanical stimulation to various electroactive cells [1–4]. By integrating antibodies, enzymes, and other biological moieties, the chemical, electrical, and physical characteristics of EBMs may be tuned to the specific demands of their applications, or regulated by stimulation (e.g., electricity, light, and pH) [5, 6]. Similar to the electrochemical material, the interior of a noumenal organism has a bioelectric current. Bioelectricity is the electrical phenomenon of living organisms in the process of life activities. Biological organs, tissues, cells, and biomolecules change their potential and polarity, including resting potential, action potential, and the potential caused by pressure. Therefore, bioelectricity transmits, conducts, transfers, and codes information, that is, bioelectricity is highly significant for adapting to surrounding environments to maintain life activities. For instance, as the largest organ of the human body, undamaged healthy skin is regarded as a "skin battery" for maintaining a steady state. Other human organs, such as nerves, hearts, blood vessels, bone cartilages, and tendons can also be regarded as "tissue batteries". When a tissue is injured, the epithelial barrier is disrupted, and trans-epithelial potentials are short-circuited by wounds. Due to current flow to the wound edge, the electrical potential of the wound area is reduced. Laterally oriented wound electric fields are formed via potential gradients [7, 8], and driven by the so-called "skin battery", the natural direct current comes into being on the damaged area [9–11]. This type of micro direct current bioelectricity, which is different from action potential, is also called endogenous electric fields [12]. Endogenous electric fields are of significant biological implications in wound healing [13], tissue regeneration [14], tumor formation [15, 16], and embryonic development [17]. Thus, exogenous electric fields established by electrical stimulation (ES) are promising candidates for exciting the damaged endogenous electric fields and accelerating damaged skin repair. They have the potential for a sustained non-pharmacological therapy system [18]. Under the synergy of endogenous electric fields, external ES can regulate and mediate the diverse physical activities of cells.

Compared to chemical and mechanical stimulation, ES is associated with various technological advantages, including a moderate stimulation state that causes less harm, is easier to execute, and is more accurate for parameter control [19]. Furthermore, when combined with other treatment procedures (e.g., optogenetics, sonodynamic therapy, and photodynamic therapy), ES has the potential for significant performance improvements, which are extremely desired [20].

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The electrical activity of biological tissues can be utilized to reflect the health conditions of life activities of organisms and for disease diagnosis. Monitoring of various bioelectric signals is beneficial for disease diagnosis as well as treatment. Accordingly, various wearable and implantable medical devices (IMDs) for tissue repair and personalized healthcare have been developed. Studies are evaluating the positive contribution of wearable and IMDs for tissue repair and personalized healthcare [21]. For instance, the abilities of the physical ES system [22] (direct current, pulsed current, and electric and electromagnetic fields, etc.), sonodynamic systems, photodynamic systems, and electric sensitive-based drug containment systems [19] to elicit cell growth and division, and promoting growth factor expression have been evaluated.

However, wearable and IMDs lacking self-charging abilities should be bulky enough to accommodate a large battery to avoid frequent recharging, or be replaced/disposed in a short time. Applications of self-powered system techniques in medical science will enhance clinical applications of wearables and IMDs. Herein, from the perspective of bio-electrochemistry and biological science, we refer to the self-powered multifunctional, flexible, or biodegradable IMDs as self-powered tissue batteries (SPTBs), which can load cells, peptides [23], growth factors, enzymes, drugs, and small molecular active substances, which mean they do not simply act as simple electronic products. Moreover, the softness, deformability, self-power property, biosensing, and high biocompatibility of SPTBs should be considered. An increasing number of SPTBs, such as pacemakers, nerve stimulators, and drug pumps are available for diagnosis and therapeutics (Fig. 1).

SPTBs combine implantability and electroactivity properties of biomaterials, which is a new treatment concept for diagnosis, treatment, and monitoring in clinical medicine. All SPTBs are associated with challenges in designs as well as applications, and their standardization is even more complex. For future medical applications, the challenges associated with shape and size, energy consumption, and biocompatibility as well as long-term biofouling should be solved.

2 Electroactive biomaterials

EBMs are a type of biological materials that may change their physicochemical properties upon electrical signals or generate electrical signals in response to external stimuli (Fig. 2). As next-generation biomaterials [24] for biomedical applications, EBMs can directly transfer electrical, electrochemical, and mechanical signals to cells and tissues. Electric fields associated with ion and macromolecule transportation play a significant role in the biological processes of various tissues (e.g., heart, muscle, nerve, and skin), such as promotion of angiogenesis, cell division, cell signaling, nerve growth, embryonic development, and wound healing.

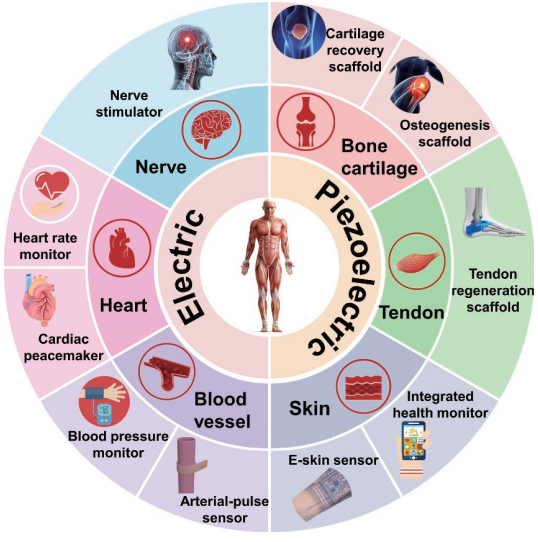

Figure 1 Medical applications for wearable and SPTBs on different electric and piezoelectric human tissues, including nerve stimulator, heart rate monitor, cardiac pacemaker, pulse and blood pressure monitor, arterial-pulse sensor, e-skin sensor, integrated health monitor, tendon regeneration scaffold, osteogenesis scaffold, and cartilage recovery scaffold.

Based on whether they require a power supply, electroactive biomaterials can be divided into semi-conductive biomaterials, conductive biomaterials, and piezoelectric biomaterials (Fig. 3). Semi-conductive and conductive biomaterials require an external power source to control ES. Dissimilarly, piezoelectric biomaterials allow ES to be transmitted through material deformation without an external power supply, which is suitable for self-powered tissue engineering scaffolds and devices. Semiconductor [25] nanocrystals and semiconductor minerals such as nanowires [26], dots [27, 28], and silicates [29–31] are the most common semiconductor biomaterials. Conductive biomaterials include shape memory alloy [32] conductive polymers, such as polyaniline [33], polypyrrole [34, 35], and polythiophene [36]. Piezoelectric ceramics [37, 38] and piezoelectric polymers [39] (polyvinylidene fluoride (PVDF) [40, 41] and polylactic acid (PLA) [42]), are candidates for nanogenerator preparation in nanomedicine applications. In addition, electroactive composite biomaterials are mainly composed of conductive biomaterials and piezoelectric biomaterials, which simultaneously possess piezoelectricity and semiconductor properties, for instance, the complex of piezoelectric ceramics and conductive polymers.

3 Construction and power approaches of SPTBs

SPTBs refer to flexible self-powered implantable systems or platforms based on EMBs, acting at the interface of biological tissue. EBMs ensure the electroactive and self-powered properties of SPTBs. SPTBs contain four types of blocks: energy harvesters, sensing blocks, signal processing blocks, and signal communication blocks [43, 44]. At first, various environmental changes and physiological stimuli that are detected by sensing blocks can be converted into electrical signals with the help of signal communication blocks, which will be finally transmitted to the outside of the human body through signal communication blocks. Power harvesters are required to power these blocks [45].

Depending on whether the implantable device carries power, it

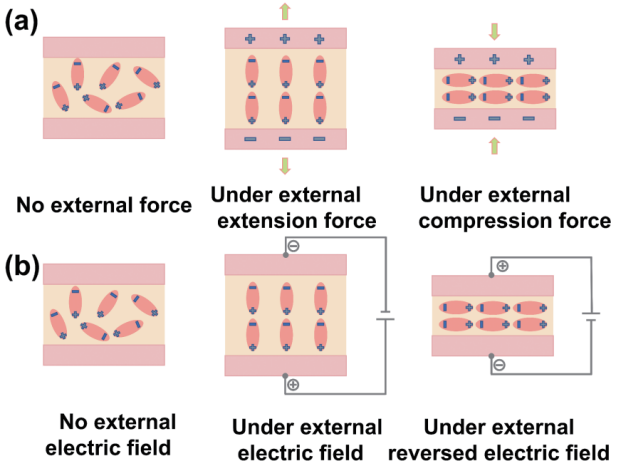

Figure 2 Mechanism of electroactive properties of electroactive biomaterials. (a) EBMs generate electrical signals or change their physicochemical properties in response to an external force. (b) EBMs generate electrical signals or change their physicochemical properties in response to external electric field.

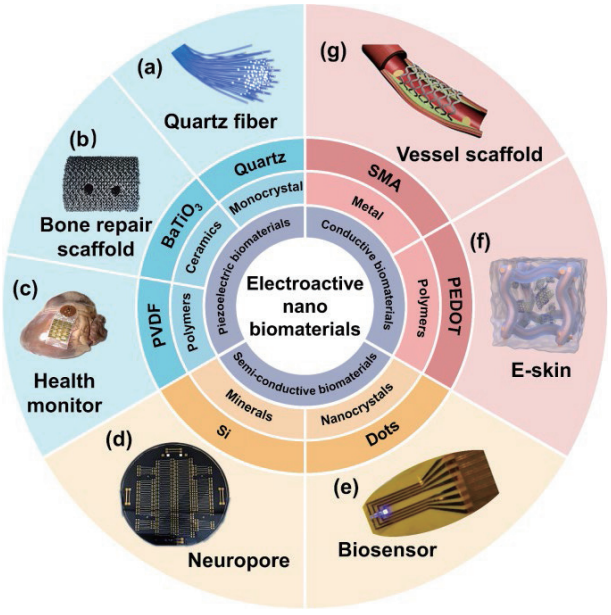

Figure 3 Typical materials and applications of electroactive nanobiomaterials, including (a) quartz fiber, (b) bone repair scaffold, (c) health monitor, (d) neuropore, (e) biosensor, (f) e-skin, reproduced with permission from Ref. [36], © Elsevier Ltd. 2021, and (g) vessel scaffold.

can be a SPTBs or wireless SPTBs. Compared to the traditional power supply approach, development of IMDs with a long lifetime, efficiency, and flexible recharging is a significant challenge [46]. There are various ways through which SPTBs generate energy: mechanical energy harvester [47], biochemical energy harvester, photovoltaic energy harvester, radio frequency harvesters, and shape memory alloy. Based on their exceptional capacity to convert tiny and irregular mechanical energy into electricity, such as friction, vibration, wind, temperature, walking, water wave, heartbeats [48, 49], and respiration movements [50], mechanical energy harvester nanogenerators can be classified into piezoelectric nanogenerators (PENGs), triboelectric nanogenerators (TENGs) [51], and pyroelectric nanogenerator [52, 53]. Biofuel cells and endocochlear potentials are good biochemical energy harvesters with a high efficiency for biochemical energy conversion [54–56]. Wireless SPTBs are powered by electromagnetic transformers and ultrasonic transducers [57, 58]. Due to their greater power conversion efficiencies and tiny sizes, photovoltaic cells are one of the most attractive alternatives for implantable applications [45].

In recent years, a new generation of SPTBs has progressively supplanted traditional portable medical devices and has become a hotspot in global medical exploration and development. Compared to traditional portable medical devices, SPTBs have a flexible convenient appearance and usage, and they can monitor health status in real time and anticipate illnesses [18]. Traditional portable medical devices are classified into domestic and portable medical electronic devices, e.g., domestic sphygmomanometers, blood glucose, hearing aids, electrocardiograph, and multiparameter monitors [59, 60]. SPTBs are represented by nerve stimulators and implantable cardiac pacemakers. Although SPTBs have rapidly developed during the last decades, it might not always be easy for SPTBs to be safe and substantive during use. Different power approaches of SPTBs for different applications are listed in Table 1.

4 Applications of SPTBs

With the fast rise of microelectronics and nanofabrication, the popularity of SPTBs in prevention and diagnosis, precision therapy, and in personalized health monitoring systems is increasing [61, 62]. Various SPTBs are versatile. They include pacemakers [63, 64], nerve stimulators [65, 66], retinal implants [67], drug pumps [68], biosensors [69], cochlear implants [70], and artificial tissues [71] as well as organ replacements, which are now being used in clinical applications [72].

4.1 Prevention and diagnosis

4.1.1 Cardiovascular risk detection

Terms selected for cardiovascular diseases include thromboembolic disease, myocardial infarction, coronary artery disease, and stroke, among others. Up to 90% of cardiovascular diseases can be prevented. Heart monitoring [41, 49, 73–75] is important for evaluating cardiac system performance and to prevent or detect cardiovascular diseases. Ye Ma et al. [76] proposed the implantable triboelectric active sensor (iTEAS) (Fig. 4(a)), a self-powered and implantable triboelectric active sensor that can provide continuous monitoring of multiple physiological and pathological signs, including heart rates, ventricular premature contraction, blood flow velocity, and respiratory rate. Figure 4(b) shows that iTEAS is comprised of triboelectric layers, electrodes, and spacers. The iTEAS was directly connected with a multichannel data acquisition system by lead wires, which may restrict its practical and clinical applications. Meanwhile, Qiang Zheng et al. [77] designed a self-powered wireless transmission system powered by an iTENG for *in vivo* cardiac healthcare monitoring (Fig. 4(c)). The iTENG, as a biomechanical energy harvesting, is used to power the implantable wireless transmitter. Compared with iTEAS proposed by Ye Ma et al., the accuracy of the output signal and the long-term biocompatibility of the wireless transmission system are worthy of careful consideration. What's more, monitoring of neurotransmission, inflammatory reactions, cardiovascular systems, and other physiological systems requires real-time NO detection. Rongfeng Li et al. [78] constructed a flexible and physically transient electrochemical sensor for real-time wireless NO monitoring in chondrocytes, livers of Sprague-Dawley rats, and the heart as well as joint cavity of New Zealand rabbits. Based on wireless control and data transmission technology, the NO sensor provided critical therapeutic and diagnostic information for assessing immune/inflammatory responses.

4.1.2 Blood glucose, pressure, and oxygen detection

SPTBs have been used for blood glucose, pressure, and oxygen detection [79, 80]. Symptomatic instances of diabetes may be difficult to diagnose since they may occur without clinical signs in the early stages [81, 82]. During treatment, continuous self-monitoring of glucose is critical for therapeutic assessment and detecting incipient hypoglycemia [83]. Wanglinhan Zhang et al. created a self-powered implantable skin-like glucometer that can detect blood glucose levels in real-time *in vivo*. The working mechanism is based on the piezo-enzymatic-reaction coupling effects of GOx@ZnO nanowires. Under applied force, the device actively produces a piezoelectric signal with the glucose-detecting information, and converts the mechanical energy into the piezoelectric impulse, which is significantly influenced by blood glucose concentration [84]. Strictly speaking, this glucometer is not completely implantable because lacking transport block of the electric signal. In addition, lifespan, stability, and recycled usability are not further discussed in this research. Therefore, significant efforts are still needed to develop a fully implantable, high-precision, and long-lifetime glucometer for real-time monitoring of blood glucose.

Given the imminent danger of secondary diseases, patients should be able to assess long-term and intensive monitoring. Previously, Xiaoliang Cheng [85] found that the electric output

Table 1 Summary of materials and applications of SPTBs based on kinds of power supply

Application type		Type of power supply	Typical materials and structure	Evaluation	Cell and animals experimental design	References
Heart monitors		TENG	(1) Integrated multilayer structure including polydimethylsiloxane (PDMS), polytetrafluoroethylene (PTFE), and Kapton, etc. (2) Directly connected with a multichannel data acquisition system by lead wires	(1) *In vitro* open-circuit voltage (V_{OC}): ~ 10 V; *in vivo* short-circuit current (I_{SC}): ~ 4 μA. (2) Quantified accuracies of heart rate monitoring implanted after 72 h: 99%. (3) Sensitivity of the average velocity of blood flow: 17.8 mV/mmHg; R^2: 0.78	Yorkshire pigs	2016 [76]
			(1) TENG has a multilayered structure: core/shell/shell package, "keel structure", electrode layers (Au and Al layer), and triboelectric layers (n-PTFE, 50 μm). (2) Wireless transmission system: implantable wireless transmitter and external receiving coil	(1) *In vivo* V_{OC}: 14 V; *in vivo* I_{SC}: 5 μA. (2) At a heart rate of 80 bpm, a 1 μF capacitor was charged from 0.2 to 2.8 V beat by beat within 200 s by the TENG. (3) R^2 of the linear relationship between the heart rate and the normalized wireless transmission signal is 0.983	Yorkshire pigs	2016 [77]
Cardiac pacemakers		PENG	The integrated multilayer structure consisted of a piezoelectric transducer, pacing probe, pulse generator circuit, and external encapsulation unit: PDMS, poly(ethylene terephthalate) (PET), and PLA, etc.	(1) *In vitro* output maximum power was 6.9 μW at an optimal external resistance of 400 kΩ, under a peak loading force of 0.5 N and frequency of 2 Hz, and could be rectified by a rectifier to charge a 47 μF capacitor. (2) *In vivo* output current: 30 μA; voltage: 8.1 V	Swine	2020 [91]
			A capsular structure like "8" consists of a piezoelectric layer, beryllium–bronze foil, and Cr/Au electrodes	(1) *In vivo* maximal V_{OC}: ~ 20 V; *in vivo* I_{SC}: ~ 15 μA. (2) PENG can power a modern and full-function cardiac pacemaker with the built-in lithium battery removed	Yorkshire pigs	2019 [49]
Stimulators		PENG	Indium modified crystalline thin (PIMNT) thin film on a PET substrate	Maximum I_{out}: 0.57 mA; maximum V_{out}: 11 V	The primary motor cortex of mice	2015 [197]
			It is consisting of a TENG (PTFE and Al) and a PET	(1) V_{OC}: 100 V; I_{SC}: 1.6 μA. (2) The transferred charge was around 2.2 μC within 23 s' charges after rectification	Sprague Dawley rats	2019 [105]
		TENG	It is consisting of a TENG (PTFE, Al, and Au) and a PET	(1) Induced by respiration: V_{OC}: 0.4 V. The frequency of voltage pulses was 1.5 Hz. (2) Driven by heartbeats: V_{OC} < 5 V	Japanese big-ear rabbits and Sprague Dawley rats	2022 [198]
Glucose meters		Electrochemical cell	Integrated multilayer structure: platinum nanotree microelectrode (three-electrode configuration), flexible circuit patch, and NFC antenna	(1) The detection range of glucose *in vitro*: range of 1–5 mV and sensitivity of 7.42 μA/(mM·cm^2); range of 5–20 mM and sensitivity of 4.26 μA/(mM·cm^2); range of 5 ~ 20 mM, R^2 of 0.9964 and limit of detection of 0.0539 mM. (2) The detection range of glucose *in vivo*: only compared the peak values of response current after the injection of different volumes of 2.5 M glucose	Peritoneal cavities of Sprague Dawley rats	2021 [199]
Biosensors	Neural dynamics GECIs recorder	Radio frequency harvester	Integrated multilayer structure including micro-inorganic light-emitting diode, microscale inorganic photodetector, microcontroller, and infrared, etc.	The detection range of Ca^{2+} *in vitro*: range of 0.0625 ~ 32 μM with an average SD (14.24 arbitrary units (a.u.))	CD1 and C57BL/6 mice	2020 [200]
	Arterial-pulse sensor	Capacitor	Cuff-type based on bilayer coil structure: poly(glycerol sebacate), polyhydroxyvalerate, polyhydroxybutyrate, poly(octamethylene maleate (anhydride) citrate), and poly(lactic acid) (PLLA)	Lifespan: partially degraded after 12 weeks	Femoral artery of Sprague Dawley rats	2019 [98]
	Force sensor	PENG	Integrated multilayer structure: PLA and PLLA	Pressure measure range: 0–18 kPa; lifespan: 4 days	Abdominal cavity of mice	2018 [201]
Drug delivery systems		Magnet TENG	Two friction layers: PTFE, titanium and PDMS	(1) V_{OC}: 70 V; I_{SC}: 0.55 μA; transferred charge (Q_{SC}): 25 nC. (2) The amount of drug released under electric fields exceeded that of the control by threefold	Red blood cells, Hela cells, and tumor-bearing nude mice	2019 [129]
Cochlear implants		Piezoelectric micro-electromechanical system	Cantilever array: Si-on-insulator and AlN	V_{out}: 3–10 mV	None	2017 [202]

(V_{out}) of the piezoelectric film wrapped over the aorta is proportional to the blood pressure (BP). Thus, they theorized that if there is a linear correlation between the electric output and blood pressure, a piezoelectric thin film (PETF) wrapped around the aorta may be used for blood pressure monitoring. They evaluated the feasibility and efficacy of an implantable and self-

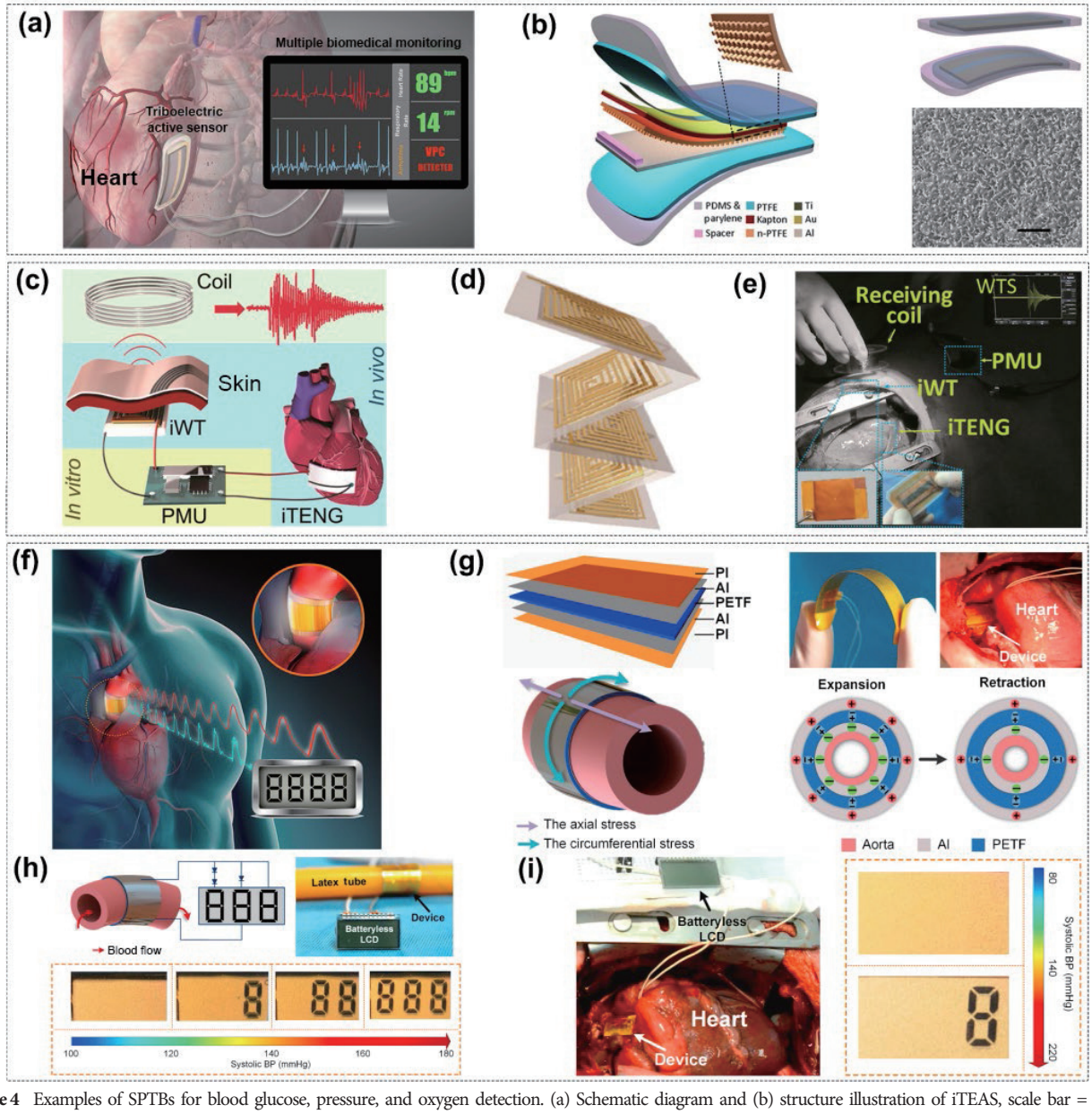

Figure 4 Examples of SPTBs for blood glucose, pressure, and oxygen detection. (a) Schematic diagram and (b) structure illustration of iTEAS, scale bar = 5 μm. Reproduced with permission from Ref. [76], © American Chemical Society 2016. (c) Schematic diagram of the self-powered wireless transmission system based on the iTENG. (d) Photograph of the implantable wireless transmitter. (e) *In vivo* heart rate monitoring. Reproduced with permission from Ref. [77], © American Chemical Society 2016. (f) Diagrammatic drawing of an implantable and self-powered BP monitor. (g) Structure and working principle illustration of multilayer thin film of the blood pressure monitoring device. (h) Blood pressure monitoring experiment of the visualized blood pressure monitoring system. (i) The digital photograph of the blood pressure monitoring device was implanted *in vivo* (left) and the liquid crystal display (LCD) was turned on when the systolic blood pressure was higher than 140 mmHg (right). Reproduced with permission from Ref. [85], © Elsevier Ltd. 2016.

powered blood pressure monitor (Fig. 4(f)) with multilayer configuration, and found that it was capable of scavenging biomechanical energy and indicating the real-time blood pressure (Fig. 4(g)). An implanted, self-powered, and visible blood pressure monitoring system was developed as a proof-of-concept research, and its viability was proven, providing hypertension patients with the convenience of real-time alert and in-time therapy (Figs. 4(h) and 4(i)). This research has clear implications for future development of real-time blood pressure monitoring.

4.2 Precision therapy

4.2.1 Cardiovascular diseases

The pillars of bradyarrhythmia treatment are implantable cardiac pacemakers [63, 86]. Implanted temporary systems provide atrial and ventricular pacing to patients whose bradyarrhythmia are expected to be short-lived [87]. In terms of energy harvesting approaches, the mechanisms of cardiac pacemakers can be classified into triboelectrification [48, 50, 77, 86], piezoelectricity [49, 88–91], mass imbalance oscillations [92], electrostatic interactions [93], and electromagnetic radiations [94]. Yeon Sik Choi et al. [95] established a bio-resorbable and temporary cardiac pacemakers (Fig. 5(a)) and demonstrated its performance in various small and large animal models (Figs. 5(b)–5(d)). They found that it remains stable during use, and its removal upon therapeutic completion is not necessary because all implanted portions of the pacemaker are entirely bioabsorbable (Fig. 5(e)). The working mechanism of the system is wireless energy transfer via resonant inductive coupling the delivers power to the system. The Rx coil transforms the received waveform to an approximately direct current output via the adio frequency (RF) diode, and the heart begins to pace under electrical stimuli delivered by a strip of a double-layered electrode. Although battery-less and bioresorbable properties circumvent the need for batteries

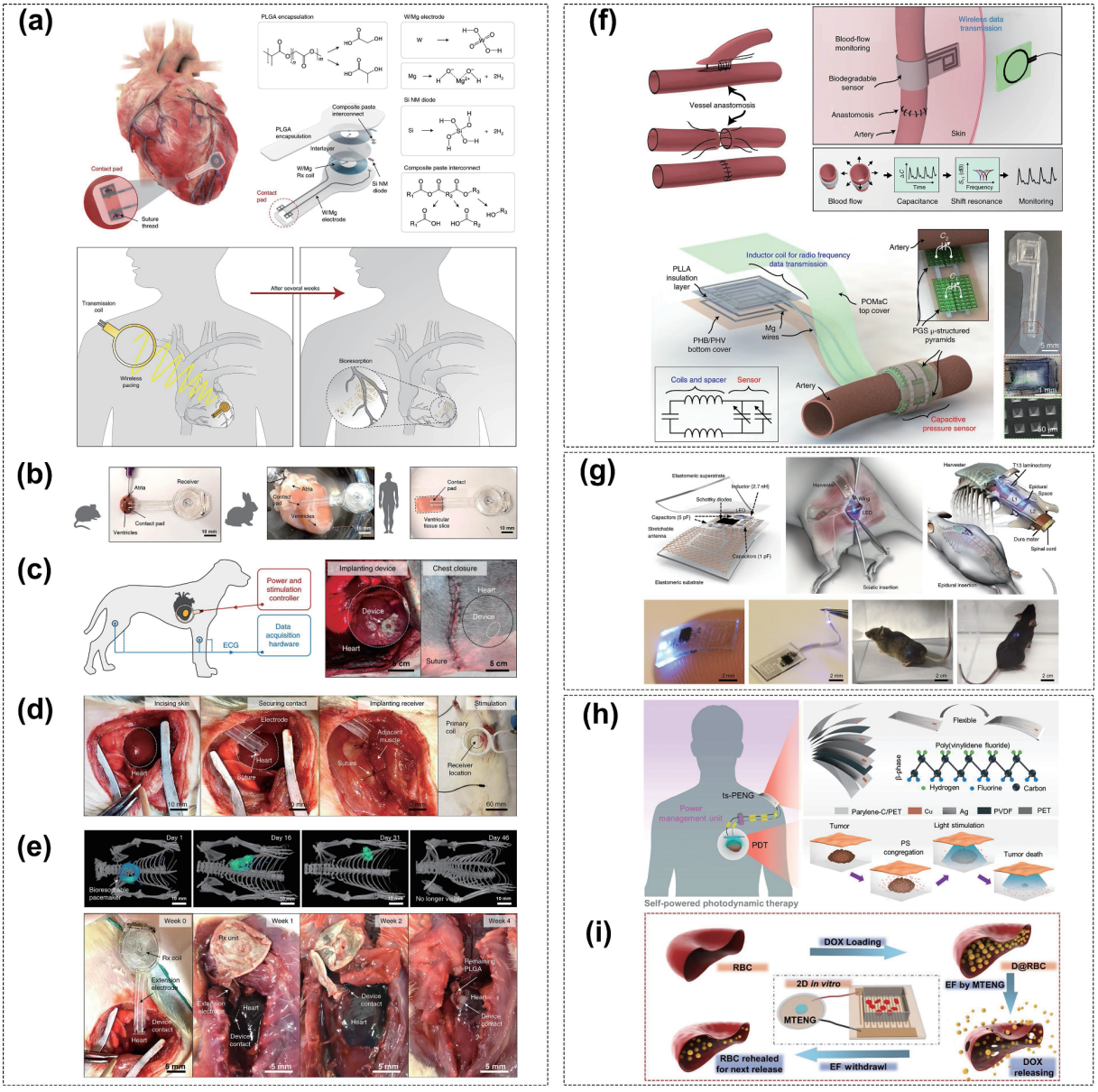

Figure 5 Examples of SPTBs for precision therapy of cardiovascular diseases, neuromodulation, and neuroregeneration. (a) Schematic diagram of the bioresorbable, implantable, leadless, and battery-free cardiac pacemakers, including its materials and structural construction. (b) The experiment of bioresorbable cardiac pacemakers on mouse and rabbit hearts and human cardiac tissue *in vitro*. (c) Demonstration of a bioresorbable and leadless cardiac pacemakers in an *in vivo* canine model. (d) Digital photographs of the chronic *in vivo* rat model implanted with a bioresorbable cardiac pacemakers. (e) Bioresorbability of the cardiac pacemakers. Reproduced with permission from Ref. [95], © Choi, Y. S. et al. 2021. (f) The design and working principle of the biodegradable, flexible, and passive arterial-pulse sensor. Reproduced with permission from Ref. [98], © Boutry, C. M. et al. 2019. (g) Schematic diagram, application model, and photos of the fully implantable and soft optoelectronic systems for wireless optogenetics. Reproduced with permission from Ref. [102], © Nature America, Inc 2015. (h) The materials, structure, and design features of the self-powered photodynamic therapy (s-PDT) system. Reproduced with permission from Ref. [120], © American Chemical Society 2020. (i) Schematic illustration showing the process of loading DOX into RBCs and release of DOX. Reproduced with permission from Ref. [129], © WILEY-VCH Verlag GmbH & Co. KGaA, Weimheim 2019.

and their associated mass, physical bulk, and hazardous constituent materials, further exploration of the adaptation between biodegradation rate and efficiency of cardiac pacemakers should be much more involved and deeper.

Using various fully bioabsorbable natural materials, Wen Jiang et al. [96] prepared a triboelectric nanogenerator (BN-TENGs) to increase cell contraction regularity. A wireless powered implantable atrial defibrillator consisting of a radio frequency power transmitter (*ex vivo*) and a battery-less implantable power receiver (*in vivo*) were reported by Philip Walsh et al. [97]. In addition, Clementine M. Boutry et al. [98] designed and created an arterial-pulse sensor for wireless short-term monitoring of blood flow, which can be biodegraded after treatment (Fig. 5(f)). The device, which consists of a fringe-field capacitive sensor and a bilayer coil structure, can be used in both small and large vessels after surgical procedures that require vessel anastomosis. In summary, SPTBs have excellent potential for future therapeutic applications, accurate diagnosis of disease location, and precision treatment.

4.2.2 *Neuromodulation and neuroregeneration*

Based on versatile biosensors, advances in electronic, optoelectronic, and microfluidic interfaces with living bio-systems have laid the foundations for peripheral and central neural activities, i.e., neuromodulation [99, 100]. As a non-destructive and reversible therapeutic strategy that involves stimulating neural networks to change physiological signals [65], neuromodulation has significant effects on some illnesses [57, 101].

Sung Il Park et al. [102] assembled a wireless optoelectronic system as the radio frequency power, which was minimally invasively implanted over multiple neural interfaces (Fig. 5(g)). Its implantation underneath muscles and in the epidural space for optogenetic stimulation of peripheral nerves and optogenetic control in the spinal cord revealed that it can specifically and reversibly activate both peripheral and spinal pain circuits as well as modulate pain-related behaviors of mice. Jahyun Koo et al. introduced a platform for wireless and programmable electric peripheral nerve stimulation. Multiple ES rounds of the damaged nerve tissue enhanced neuroregeneration and functional recovery in mice models, indicating a unique non-pharmacological and bioelectric type of treatment that might complement the existing surgical techniques [18].

4.2.3 *Bone remodeling and regeneration*

Osteoporosis is a chronic disease that is characterized by a loss of bone density and quality, as well as increased degradation of bone microstructures and fragility, which enhances the risk of bone fractures [103, 104]. It has been shown that ES has the ability to facilitate bone restoration and osseointegration [105–109]. Guang Yao et al. [108] assembled a self-powered, implantable, and bioresorbable bone fracture electrostimulation device that comprises a TENG and a pair of dressing electrodes for direct administration of electrostimulations to the fracture. The electricity generation mechanism of the TENG followed the vertical contact–separation mode between the bottom micropyramid-structured poly(lactic-co-glycolic acid) (P-PLGA) and top Mg triboelectric layers. A pair of interdigitated dressing electrodes converted the collected energy to biphasic electric pulses, and provided ES to the fracture site. Due to the positive regulatory and promotion effects of the biphasic electric pulses to osteoclast cells, the fracture healing process of rats implanted with fracture electrostimulation device was completed at 6 weeks, whereas the controls were more than 10 weeks.

4.2.4 *Cancer therapy*

Cancer therapy and recovery is a long-standing, formidable, and complex process. Among the most common causes of cancer-associated mortality, metastatic spread and recurrence are of significance [110]. Therefore, improvement in early cancer diagnosis is helpful for its effective treatment and for decreasing the mortality rates [111].

Currently, various therapeutic strategies, including photothermal therapy [112, 113], photodynamic therapy [114, 115], photobiomodulation [116], and optogenetic therapy [117, 118] are widely applied in medical clinics. These approaches are associated with advantages of low toxicity, small wounds, and high selectivity. Given the severe side-effects of photodynamic therapy, which are attributed to excessive exposures, development of photodynamic therapy devices with low irradiation is vital [119]. For cancer treatment, a self-powered photodynamic therapy system that is based on nanogenerators is capable of converting biomechanical energies into electricity, which provides a promising approach for efficient and convenient management of various cancers. Based on PENG, Zhuo Liu et al. [120] formulated self-powered photodynamic therapy system, which could transform biomechanical energy from joint motion into electricity as a power source (Fig. 5(h)). Ai Lin Chin et al. engineered an implantable miniature optical fiber device for local administration of immune checkpoint blockade antibodies and tumor impedance measuring to monitor clinical outcomes [121]. Besides, Chao He et al. [122] assembled an ultrathin two-dimensional (2D) inorganic ancient pigment Egyptian blue decorated three-dimensional (3D)-printing scaffold (CaPCu) with deep photothermal therapy efficacy against osteosarcoma and improved osteogenesis performance.

4.2.5 *Drug pumps*

Even though the significance of the intelligent drug delivery system and the need for greater focuing on drug doses, timing, and administration routes have been revealed, they are still underappreciated in current medical practice [123]. Compared to the conventional drug administration routes (e.g., oral, intravenous administration, and transdermal drug delivery [124]), on-demand medication release and delivery might allow for accurate control of drug concentrations at illness locations, eliminating peripheral and off-target adverse effects [125, 126]. Bioinspired designs and manufacture of drug pumps enable drugs to be custom released at satisfying rates and at certain time points [127, 128]. Due to the development of diverse stimulus-responsive materials and technologies, it is now feasible to control medication release using various external or internal stimulation [53].

Chaochao Zhao et al. [129] established a nanogenerator-controlled drug delivery system that is based on a magnet triboelectric nanogenerator and successfully applied it in cancer therapy. Red blood cells were used as anti-tumor drug delivery system of magnet triboelectric nanogenerator to load doxorubicin hydrochloride (DOX), and DOX release was markedly increased under stimulation of electric fields from magnet triboelectric nanogenerator (Fig. 5(i)). In this way, controllable drug delivery system created as a result of cell membrane stability was reversibly altered by electric fields. The drug delivery system controlled by magnet triboelectric nanogenerator can be applicable in cancer therapy *in vitro* and *in vivo*, at low DOX dosing. In diabetic mice models, Myung-hwan Choi et al. applied light-controlled treatment using a cell-containing optical hydrogel to enhance glucose homeostasis [130]. Since the hydrogel is transparent enough, the light-responsive protein (melanopsin) is activated in the plasma membrane, which drives the production of an antidiabetic secretory protein (glucagon-like peptide-1 (GLP-1)). It is worth mentioning that light-guiding hydrogels avoid photoelectric energy conversion, which favors light delivery and collection.

4.3 Personalized health monitoring bio-systems

Development of health monitoring bio-systems is enhanced by the current trend of flexible electronics and national biotechnology development strategies [131]. Wearable electronic devices show remarkable real-time prospects, continuous monitoring of several physiological parameters [44], including vital signs, electrophysiological signals (e.g., electroencephalogram, electrocardiogram, and electromyography) [132], and biochemical analyses [133]. However, the batteries of wearable electronic devices can be poisonous, unwieldy, and require frequent replacing. Fortunately, implantable biodevices provide long-term and continuous health supervision through efficient energy harvesters. For instance, Lei Zhang et al. [134] fabricated a fully-organic, self-adhesive, and stretchable dry electrode with high conductivity, which had adhesive and stretchable dry electrodes for epidermal biopotentials, including electrocardiogram, electromyogram, and electroencephalogram (Fig. 6(a)). Non-implantable wearable electronic devices require no implantation surgery, thereby reducing patient suffering.

4.3.1 *Biosensors*

With regards to biosensors [135], SPTBs can analyze biofluids such as interstitial fluids, saliva, tears, and perspiration in a continuous and multiplexed manner [136]. Moreover, the benefits of continuous glucose monitoring for blood glucose control in

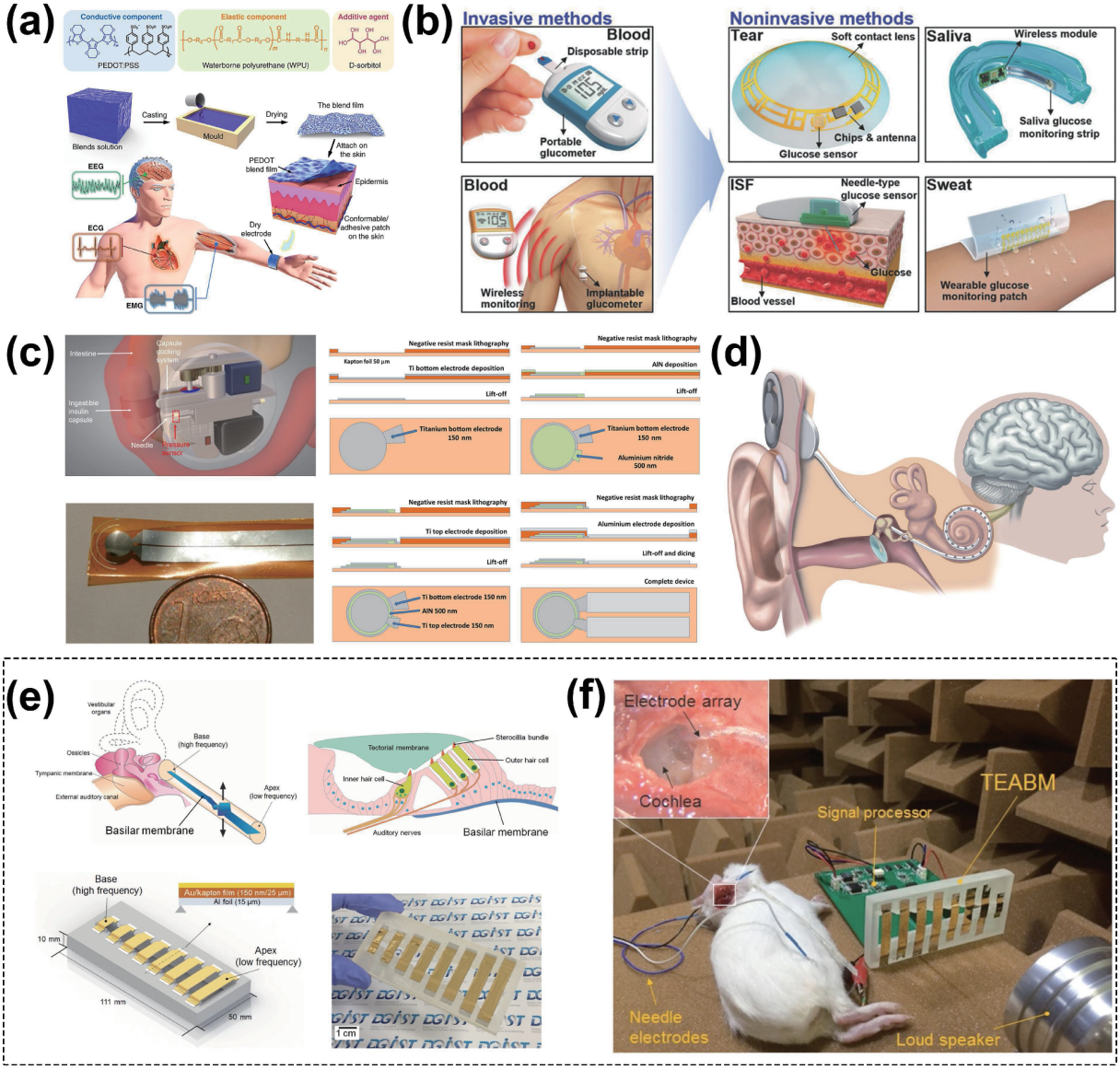

Figure 6 Examples of personalized health monitoring bio-systems. (a) Fabrication and applications of the blend films based on PEDOT:PSS, WPU, and D-sorbitol. Reproduced with permission from Ref. [134], © Zhang, L. et al. 2020. (b) Developmental evolution of glucose biosensors for glucose monitoring system. Reproduced with permission from Ref. [138], © WILEY-VCH Verlag GmbH & Co. KGaA, Weimheim 2018. (c) The schematic illustration of implantable artificial pancreas prototype and the manufacturing of the AlN-based flexible pressure sensor. Reproduced with permission from Ref. [141], © Signore, M. A. et al. 2019. (d) Schematic illustration of the position of a no totally cochlear implant. Reproduced with permission from Ref. [142], © Kral, A. et al. 2013. (e) Schematic drawing of the triboelectric-based artificial basilar membrane with eight beams. (f) Photographs of experiment of triboelectric-based artificial basilar membrane applied *in vivo*. Reproduced with permission from Ref. [70], © WILEY-VCH Verlag GmbH & Co. KGaA, Weimheim 2016.

diabetic patients have been recognized [137]. Based on the principles of electrochemical glucose sensing, glucose biosensors are divided into three types: enzymatic glucose biosensors [138], non-enzymatic glucose sensors [139], and nanomaterials-based electrochemical glucose sensors. Invasive and noninvasive electrochemical glucose monitoring systems such as Guardian Sensor 3 (Medtronic) and SugarBEATs (ISF glucose monitoring) have been commercialized and applied for diversification (Fig. 6(b)) [138]. Implantable glucose sensors are capable of real-time noninvasive or minimally invasive monitoring of blood glucose levels by analyzing skin tissue fluids [82]. Compared to percutaneous glucose sensors, implantable subcutaneous glucose biosensors have longer monitoring abilities [140]. A powerful example is a completely implantable biosensor that is composed of a flexible piezoelectric pressure sensor and the electronic interface, developed by M. A. Signore et al., which could be integrated into an implantable artificial pancreas for diabetic patients (Fig. 6(c)) [141]. To a certain extent, they solved the dilemma of using implantable flexible biosensors to replace or augment lost natural organ functionalities, which is a promising and creative method for artificial organ fabrication to cure disorders or diseases.

4.3.2 *Cochlear implants*

Modern cochlear implants are complicated electrical systems with external and internal components (Fig. 6(d)) [142]. Totally implantable cochlear implants can overcome the challenges associated with non-implantable cochlear implants: (1) Adolescents often struggle with speech processors and suffer low self-esteem; (2) speech processors of cochlear implants should be removed during special contact and water-based activities, including swimming, showering, and bathing [143]; (3) speech processors are easily lost and damaged, thereby causing inconvenience to the user; (4) the battery often requires frequent recharging or replacement [144].

In the design processes of implantable cochlear implants, the essential problems faced by researchers include implantation of

power sources, speech processors, and microphones [145]. Power sources for implantable cochlear implants can be categorized into piezoelectric energy harvester [146], triboelectric energy harvester [147], electromagnetic harvester [148], and micro-electromechanical system harvester. Jongmoon Jang et al. [70] developed a triboelectric-based artificial basilar membrane to mimic cochlear tonotopy (Fig. 6(e)). Moreover, an animal model was used to characterize the triboelectric-based artificial basilar membrane tonotopy in order to confirm the viability of a self-powered acoustic sensor for an experimental prototype (Fig. 6(f)). With regards to clinical trials, on 24th September 2020, the first implantable cochlear implants implantation surgery was performed in Belgium, Europe, performed by Prof. Philippe Lefebvre and the MED-EL Medical Electronics Company, which was a big milestone in the area of implantable cochlear implants.

5 Mechanisms and applications of SPTBs for tissue repair promotion

5.1 Mechanisms of SPTBs for tissue repair promotion

Physiological endogenous electric fields are located ubiquitously in cells and tissues of microorganisms, plants, and animals [149]. The strength of endogenous electric fields ranges from tens to hundreds of mV/mm [150]. Endogenous electric fields modulate physiological processes by the transport of macromolecules and ions across membranes and the control of the axis of membrane voltage as well as asymmetric cell division [151]. The human body contains many electro-sensitive tissues such as bone, skin, nerves, heart, and vessels [152]. Customized ES, generated by various types of SPTBs based on EMBs, regulates cell growth, differentiation, metabolism, and migration, enhancing the repair and regeneration of cardiac, skin, bone, cartilage, and nerve tissue [153–156].

5.1.1 Mechanisms of SPTBs for skin wound healing

Endogenous electric fields in the wound area typically last for several hours to days, and point uniformly to the skin wound center from the wound edge, which can induce cells to move toward the wound center, a process known as galvanotaxis [157]. The electrical signal disappears completely until the skin wound is fully covered by epithelial cells. The signal in the skin wound area could be controlled through the use of EBMs, and equipped ES. Researchers are devoted to exploring the complex interface between cells and a biomaterial surface, and have conjectured that a critical aspect of this pathway for the electric microenvironment to regulate cell behavior is biological ion channels (Fig. 7(a)) [158, 159], including the L-type voltage-gated calcium channel (L-VGCC) [160] and the TWIK-related K^+ channel 1 (TREK-1) [161]. In addition, ES upregulates the expression of growth factors [162] and the production of ROS [163].

5.1.2 Mechanisms of SPTBs for regulation and regeneration of nerves

The antidromic action potential is the crucial factor of the promotion of ES for nerve regeneration [164]. Under normal physiological conditions, the action potential began at the soma hillock and the initial axon, where the density of voltage-gated ion channels is higher than another site of the soma [165]. As shown in Fig. 7(b), when ES is applied to the distal axon, voltage-gated ion channels are activated [166]. Influx of sodium ion from extracellular to intracellular initiates action potentials. Subsequently, action potentials are traveled to the soma from the distal axon, and a process termed antidromic transmission. Therefore, ES can activate remote projection neurons. Besides, ES

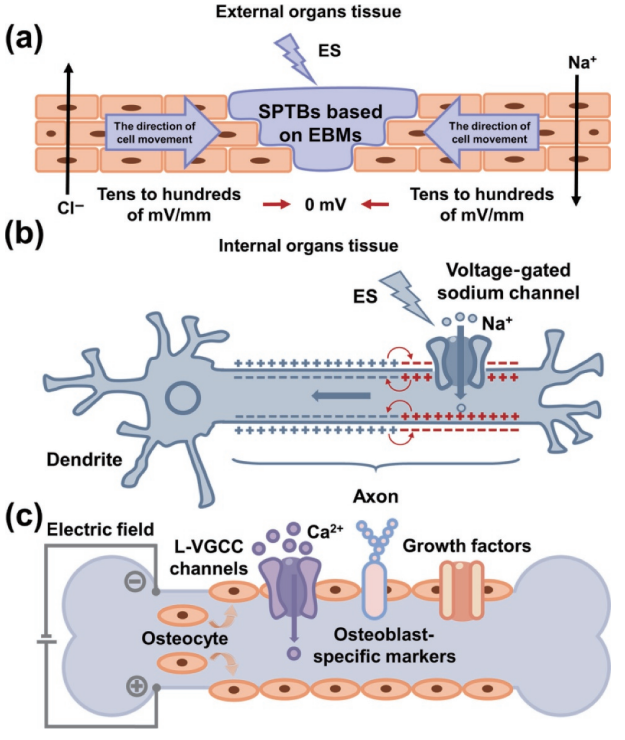

Figure 7 Mechanisms of SPTBs for tissue repair promotion: (a) mechanisms of SPTBs for skin wound healing; (b) mechanisms of SPTBs for regulation and regeneration of nerves; (c) mechanisms of SPTBs for bone remodeling and regeneration.

further enhanced cell proliferation, cell migration [167], and the formation of intracellular connections [168].

5.1.3 Mechanisms of SPTBs for bone remodeling and regeneration

Hydroxyapatite and collagen are the main components in natural bone with piezoconductivity [169]. As shown in Fig. 7(c), ES for osseointegration has been used for thirty years [170], which can be summarized in the following points: (1) Enhance osteoclastogenesis adhesion and proliferation, levels of mineralized nodule formation, and synthesis of extracellular matrix proteins [171, 172]; (2) upregulates the expression of osteoblast-specific markers (alkaline phosphatase (ALP), Runt-related transcription factor-2 (Runx2), and osteocalcin (OCN), etc.) and cytokines (bone morphogenetic protein 2 (BMP-2), insulin-like growth factors-1 (IGF-1), and vascular endothelial growth factor (VEGF), etc.) [173, 174]; (3) stimulates fibroblast activity and calcium influx [175].

5.2 Pathways combination of SPTBs to promote tissue repair

As previously mentioned, ES can excite the damaged endogenous electric fields and accelerate damaged skin repair through changes in various cellular mechanisms. SPTBs systems for promoting tissue repair under electrical microenvironments can be: sonodynamic systems, photodynamic systems, electric sensitive-based drug containment systems, and physical ES systems, such as direct current, alternating current, pulsed current, electric fields, and electromagnetic fields among others. The combination approaches of SPTBs have been a continuous research focus in recent years.

5.2.1 SPTBs combined with sonodynamic systems

Sonodynamic therapy is a new non-invasive treatment method, which utilizes exogenous ultrasound to activate the sonosensitizer to generate reactive oxygen species, leading to oxidative damage and cell death. Equally important is that exogenous ultrasonic

waves can also activate the piezoelectric effect [176] and the piezocatalysis can create reactive oxygen species by the reaction of the generated charge carriers with surrounding molecular H_2O and O_2 (Fig. 8(a)). Consequently, piezoelectric biomaterials might be used to build effective sonosensitizers for sonodynamic therapy. Mengqi Wu et al. fabricated a new kind of sonosensitizer using a piezoelectric nanocomposite (Au@BTO NCs) for sonodynamic bacterial killing and wound repair. They found that during the sonodynamic process *in vivo,* it could kill bacteria and promote fibroblast migration as well as wound repair [20].

5.2.2 *SPTBs combined with photodynamic systems*

Photodynamic therapy is a minimally invasive therapeutic approach that involves photosensitizers-mediated reactive oxygen species formation, such as H_2O_2, $\bullet O_2^-$, $\bullet OH$, and $^1O_2$ to combat multidrug resistant bacteria. Piezoelectric and ferroelectric nanomaterials have the ability for electrical modulation and are commonly used in the manufacture of photovoltaic and energy-harvesting devices, via promoting photoinduced electron–hole separation for photocatalysis and building an internal piezoelectric electric potential (Fig. 8(b)) [177]. Beyond that, for practical antibacterial applications, stimulation of charge separation and transfer to further boost photochemical reactive oxygen species formation is highly sought. As a result, photodynamic bacterial death and tissue healing may be possible using nanocomposites containing piezoelectric potentials.

Xin Yu et al. prepared a multilayered coaxial heterostructured antibacterial coating that is based on nanorod array for photodynamic bacterial killing and infectious tissue wound recovery [177]. Zongguang Liu et al. developed a self-powered cardiac stimulator, which could effectively control porcine hearts by external photoelectric stimulations *in vivo* pacing evaluations [4].

5.2.3 *Electric sensitive-based drug containment systems*

External stimulating signals (e.g., temperature, magnetic, electrical, optical, and ultrasound) as well as internal stimulating signals (e.g., glucose and pH) are supposed to induce or control drug release and achieve on-demand drug delivery (Fig. 8(c)). Thus, PENGs-, TENGs-, pyroelectric nanogenerators-, biofuel cells-, galvanic cell-, solar cell-, and photovoltaic cell-based drug delivery systems are becoming more widespread. Among them, the ES system has gotten a lot of interest since electrical signals are simple to manage and can provide consistent and dependable medication release for therapeutic purposes. The goal of drug delivery system with ES is to load the drug into the electric-responsive carrier and employ an electric field or current to regulate drug release, which may be classified into two types: pulsed drug delivery and continuous constant speed drug delivery. Self-powered ES drug delivery system formulated by electroactive biomaterials can induce drug release without any external power source.

Moonjeong Bok et al. combined a dissolving microneedle device base on salmon deoxyribonucleic acid and a triboelectric device for drug delivery. TENG converted the mechanical energy into alternating current. *In vitro*, the drug release model confirmed that the drug delivery rate increased along with triboelectricity [178].

5.2.4 *Physical ES systems based on SPTBs*

Physiotherapy means applying diverse physical factors, including electropathy (e.g., electrostatic potential therapy, direct current therapy, low/medium/high-frequency therapy [179], and iontophoresis), magnetotherapy, actinotherapy, hydrotherapy, and cupping therapy on the human body to prevent and cure diseases. Physiotherapy can be divided into two types: direct ES and electroactive biomaterials-based ES. Exogenous ES cannot directly participate in regulation of animals in the electrophysiological microenvironment, therefore, it is necessary to continuously apply external electric fields, resulting in poor portability, easy infection, and increased pain intensity during treatment. Self-powered electroactive biomaterial-based ES does not require energy from the battery, physically connected power supply, or any wire connection, which favors implantation into the body for various therapeutic applications.

In the 18th century, John Wesley was the first to demonstrate the use of electricity for treatment of illness [180]. However, the

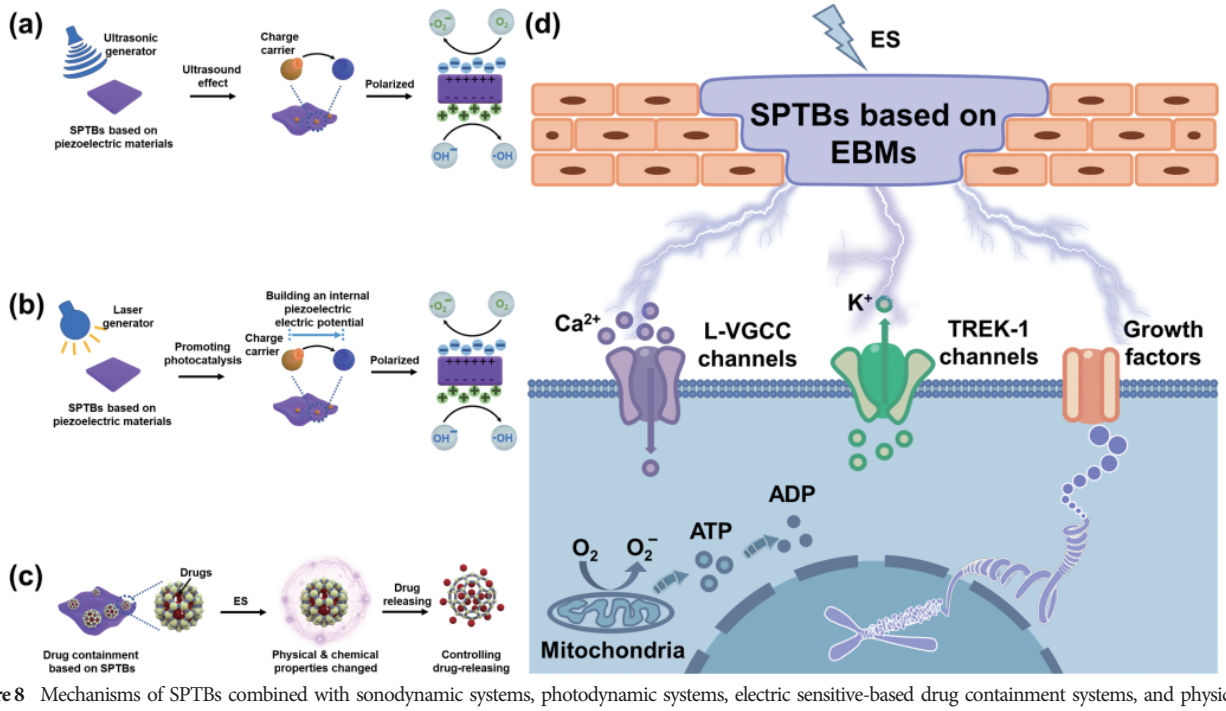

Figure 8 Mechanisms of SPTBs combined with sonodynamic systems, photodynamic systems, electric sensitive-based drug containment systems, and physical ES systems for tissue repair promotion. (a) SPTBs combined with sonodynamic systems; (b) SPTBs combined with photodynamic systems; (c) electric sensitive-based drug containment systems; (d) physical ES systems based on SPTBs.

mechanisms of ES on cell proliferation and differentiation activation are poorly understood. As shown in Fig. 8(d), the mechanisms of ES for tissue recovery can be concluded as: (1) complex regulation of cell behaviors by EBMs, including cell adhesion, proliferation, differentiation, and signal transduction by recreating natural tissue microenvironments and stem cell niches at the cell–substrate or cell–cell interfaces [181, 182]; (2) external ES has an impact on cell membrane potential, membrane receptors, gap junctions, and ion channels among others, including activating the voltage-gated calcium channels [183], and inducing intracellular calcium stores to release Ga^{2+} [184]; (3) regulating the expressions and distribution of membrane receptors [185] (such as growth factor receptors [186] among others); (4) accelerating metabolism by expediting ATP depletion [187, 188]; (5) controlling reactive oxygen species generation to trigger signaling pathways associated with cell proliferation and differentiation regulation [189]; (6) affecting calcium, potassium, cyclic nucleotides, and inositol phosphate exchanges by adjusting cell gap junctions [190]; (7) promoting cell attachment by altering local electric fields of the extracellular matrix molecules and changing protein adsorption [191, 192]. Shuo Du et al. developed a mussel-inspired, self-adhesive, and PENG-based hybrid patch with the property of promoting skin wound healing [193]. Experimentally, a pulsed voltage (from 0.1 to 0.5 V, on average) was produced by moving, breathing, or muscles shaking *in situ*.

6 Summary

The emergence of SPTBs has revolutionized the application of personalized healthcare monitoring and precise medicine. Flexible electroactive nanomaterials for self-powered implantable devices have been widely applied in the field of biomedical research for the diagnosis and prevention of disease due to their high flexibility, biocompatibility, and multifunctionality. Novel self-powered implantable devices serve as the tissue batteries and differ from conventional battery-based implantable devices in that they are smaller, convenient, and consume low amount of electricity. Notwithstanding these advantages, the biocompatibility, stability, and accuracy of these devices need to be improved through further research. There is need to optimize these parameters to improve the clinical effect and industrial use of these devices.

6.1 Challenges and recommendations

6.1.1 Biocompatibility

The biocompatibility of SPTBs is evaluated based on *in vitro* cytotoxicity tests and *in vivo* biocompatibility tests. However, most studies reported so far performed *in vitro* cytotoxicity tests for 7 days and *in vivo* biocompatibility test for 14 days. Therefore, future long-term tests should be conducted to establish the biocompatibility of implanted devices (including degradation products and ions and their physiological metabolic process) [194]. The *in vitro* cytotoxicity tests should be conducted for 21 days and *in vivo* biocompatibility tests should be conducted for 6 months to provide more conclusive findings regarding the therapeutic potential and the possible side effects of the devices.

6.1.2 The long-term stability of SPTBs

The physiological properties of human tissues are complex [195]. The long-term stability of SPTBs is influenced by the following two aspects: (1) power consumption in different functional blocks; (2) mechanical match at the device–tissue interface. These two aspects can be improved as follows: (1) minimizing the power consumption in functional blocks and increasing the power generation density of the energy harvester; (2) enhancing interfacial bonding properties between electroactive biomaterials and living organisms or biological substances, by modifying the device to meet the requirements of the wetting theory, adsorption theory, chemical bonding theory, molecular conjugation theory, acid-base combination theory, mechanical adhesion theory, and interfacial stress conduction theory of bio-interface.

6.1.3 Detection accuracy of SPTBs

The detection accuracy of SPTBs for medical applications can be improved through the following approaches. (1) Their anti-interference ability can be enhanced by encapsulating SPTBs in a thinner soft highly biocompatible reliable encapsulation layer (e.g., silicone, polydimethylsiloxane, and polyimide) to prevent the electronic circuitry from corrosion and degradation. The signal-to-noise ratio of the signal processing block can be increased to obtain an acceptable error range. (2) The output performance can be optimized by connecting multiple devices and reserving energy in capacitors or rechargeable batteries.

6.1.4 ES conditions

The ES conditions of electroactive biomaterials should match the electrophysiological properties of the target tissue, including voltage, pulse width, and frequency. Cells always change dramatically and dynamically during wound healing. Therefore, the SPTBs should be intelligent enough to stimulate electroactive biomaterials and induce favorable changes in the implanted system in line with the cell endogenous adjustments.

6.2 Future perspectives

As mentioned above, several problems face the SPTBs ranging from device integration to biological research, all of which need to be improved. The SPTBs have been widely investigated for their application in medical research. Inspired by the Internet of Things (IoT) [196], the body sensor network (bodyNET) will be established in future for disease diagnosis and monitoring of therapy, recovery, postoperative care, and health. In this way, everyone is capable of possessing an individualized health database collecting biosensors at various parts of the body. Doctors can give more comprehensive and precise treatment plans for upcoming and existing chronic diseases through diverse physiological signals. More desirably, home health care and nonpharmacological therapy will be successfully achieved and developed day by day.

Acknowledgements

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References

[1] Balint, R.; Cassidy, N. J.; Cartmell, S. H. Conductive polymers: Towards a smart biomaterial for tissue engineering. *Acta Biomater.* **2014**, *10*, 2341–2353.

[2] Lakard, B.; Ploux, L.; Anselme, K.; Lallemand, F.; Lakard, S.; Nardin, M.; Hihn, J. Y. Effect of ultrasounds on the electrochemical synthesis of polypyrrole, application to the adhesion and growth of biological cells. *Bioelectrochemistry* **2009**, *75*, 148–157.

[3] Ghasemi-Mobarakeh, L.; Prabhakaran, M. P.; Morshed, M.; Nasr-Esfahani, M. H.; Baharvand, H.; Kiani, S.; Al-Deyab, S. S.;

Ramakrishna, S. Application of conductive polymers, scaffolds and electrical stimulation for nerve tissue engineering. *J. Tissue Eng. Regen. Med.* **2011**, *5*, e17–e35.

[4] Liu, Z. G.; Wen, B.; Cao, L. Y.; Zhang, S. B.; Lei, Y. K.; Zhao, G. Z.; Chen, L.; Wang, J. Z.; Shi, Y.; Xu, J. et al. Photoelectric cardiac pacing by flexible and degradable amorphous Si radial junction stimulators. *Adv. Healthcare Mater.* **2020**, *9*, 1901342.

[5] Olvera, D.; Monaghan, M. G. Electroactive material-based biosensors for detection and drug delivery. *Adv. Drug Delivery Rev.* **2021**, *170*, 396–424.

[6] Tapeinos, C.; Gao, H.; Bauleth-Ramos, T.; Santos, H. A. Progress in stimuli-responsive biomaterials for treating cardiovascular and cerebrovascular diseases. *Small* **2022**, *18*, 2200291.

[7] Kloth, L. C. Electrical stimulation technologies for wound healing. *Adv. Wound Care* **2014**, *3*, 81–90.

[8] Gomes, R. C.; Guirro, E. C. O.; Gonçalves, A. C.; Farina Junior, J. A.; Murta Junior, L. O.; Guirro, R. R. J. High-voltage electric stimulation of the donor site of skin grafts accelerates the healing process. *A randomized blinded clinical trial. Burns* **2018**, *44*, 636–645.

[9] Galvani, L. De viribus electricitatis in motu musculari commentarius. In *De Bonoiensi Scientiarum et Artium Intituo atque Academie Commentarii*; Galvani, L., Ed.; Bologna, 1791; Vol. 7, pp 363–418.

[10] Matteucci, C. *Traité des Phénomènes Électro-Physiologiques des Animaux,* Fortin, Masson: Paris, 1844.

[11] Bois-Reymond, E. D. *Untersuchungen über tierische Elektrizität II.* Berlin, 1860.

[12] Borgens, R. B.; Vanable, J. W., Jr.; Jaffe, L. F. Bioelectricity and regeneration: Large currents leave the stumps of regenerating newt limbs. *Proc. Natl. Acad. Sci. USA.* **1977**, *74*, 4528–4532.

[13] Ud-Din, S.; Sebastian, A.; Giddings, P.; Colthurst, J.; Whiteside, S.; Morris, J.; Nuccitelli, R.; Pullar, C.; Baguneid, M.; Bayat, A. Angiogenesis is induced and wound size is reduced by electrical stimulation in an acute wound healing model in human skin. *PLoS One* **2015**, *10*, e0124502.

[14] Becker, R. O. Stimulation of partial limb regeneration in rats. *Nature* **1972**, *235*, 109–111.

[15] Djamgoz, M. B. A.; Mycielska, M.; Madeja, Z.; Fraser, S. P.; Korohoda, W. Directional movement of rat prostate cancer cells in direct-current electric field: Involvement of voltagegated Na^+ channel activity. *J. Cell Sci.* **2001**, *114*, 2697–2705.

[16] Cuzick, J.; Holland, R.; Barth, V.; Davies, R.; Faupel, M.; Fentiman, I.; Frischbier, H. J.; LaMarque, J. L.; Merson, M.; Sacchini, V. et al. Electropotential measurements as a new diagnostic modality for breast cancer. *Lancet* **1998**, *352*, 359–363.

[17] McCaig, C. D.; Song, B.; Rajnicek, A. M. Electrical dimensions in cell science. *J. Cell Sci.* **2009**, *122*, 4267–4276.

[18] Koo, J.; MacEwan, M. R.; Kang, S. K.; Won, S. M.; Stephen, M.; Gamble, P.; Xie, Z. Q.; Yan, Y.; Chen, Y. Y.; Shin, J. et al. Wireless bioresorbable electronic system enables sustained nonpharmacological neuroregenerative therapy. *Nat. Med.* **2018**, *24*, 1830–1836.

[19] Hu, W. T.; Wei, X. L.; Zhu, L.; Yin, D.; Wei, A. M.; Bi, X. Y.; Liu, T.; Zhou, G. M.; Qiang, Y. H.; Sun, X. H. et al. Enhancing proliferation and migration of fibroblast cells by electric stimulation based on triboelectric nanogenerator. *Nano Energy* **2019**, *57*, 600–607.

[20] Wu, M. Q.; Zhang, Z. Y.; Liu, Z. R.; Zhang, J. M.; Zhang, Y. L.; Ding, Y. M.; Huang, T.; Xiang, D. L.; Wang, Z.; Dai, Y. J. et al. Piezoelectric nanocomposites for sonodynamic bacterial elimination and wound healing. *Nano Today* **2021**, *37*, 101104.

[21] Guk, K.; Han, G.; Lim, J.; Jeong, K.; Kang, T.; Lim, E. K.; Jung, J. Evolution of wearable devices with real-time disease monitoring for personalized healthcare. *Nanomaterials* **2019**, *9*, 813.

[22] Long, Y.; Li, J.; Yang, F.; Wang, J. Y.; Wang, X. D. Wearable and implantable electroceuticals for therapeutic electrostimulations. *Adv. Sci.* **2021**, *8*, 2004023.

[23] Luo, X. M.; Huo, Q. Q.; Liu, X. H.; Zheng, C.; Liu, Y. Effect of hydrophilic or hydrophobic interactions on the self-assembly behavior and micro-morphology of a collagen mimetic peptide. *J. Leather Sci. Eng.* **2021**, *3*, 11.

[24] Chen, H. X.; Xue, L. Q.; Gong, G. D.; Pan, J. Z.; Wang, X. L.; Zhang, Y. Y.; Guo, J. L.; Qin, L. Collagen-based materials in reproductive medicine and engineered reproductive tissues. *J. Leather Sci. Eng.* **2022**, *4*, 3.

[25] Zhu, B.; Fan, L. D.; Mushtaq, N.; Raza, R.; Sajid, M.; Wu, Y.; Lin, W. F.; Kim, J. S.; Lund, P. D.; Yun, S. N. Semiconductor electrochemistry for clean energy conversion and storage. *Electrochem. Energy Rev.* **2021**, *4*, 757–792.

[26] Song, Y.; Kim, S.; Heller, M. J. An implantable transparent conductive film with water resistance and ultrabendability for electronic devices. *ACS Appl. Mater. Interfaces* **2017**, *9*, 42302–42312.

[27] Wang, L. D.; Xu, D.; Gao, J.; Chen, X.; Duo, Y. H.; Zhang, H. Semiconducting quantum dots: Modification and applications in biomedical science. *Sci. China Mater.* **2020**, *63*, 1631–1650.

[28] Choi, C.; Colón-Berríos, A. R.; Hamachi, L. S.; Owen, J. S.; Schwartz, T. H.; Ma, H. T.; Kymissis, I. Localizing seizure activity in the brain using implantable micro-LEDs with quantum dot downconversion. *Adv. Mater. Technol.* **2018**, *3*, 1700366.

[29] Jiang, Y. W.; Tian, B. Z. Inorganic semiconductor biointerfaces. *Nat. Rev. Mater.* **2018**, *3*, 473–490.

[30] Zhao, C. Z.; Cheung, K. M.; Huang, I. W.; Yang, H. Y.; Nakatsuka, N.; Liu, W. F.; Cao, Y.; Man, T. X.; Weiss, P. S.; Monbouquette, H. G. et al. Implantable aptamer-field-effect transistor neuroprobes for *in vivo* neurotransmitter monitoring. *Sci. Adv.* **2021**, *7*, eabj7422.

[31] Sun, L. Y.; Li, S.; Yang, K. F.; Wang, J. C.; Li, Z. J.; Dan, N. H. Polycaprolactone strengthening keratin/bioactive glass composite scaffolds with double cross-linking networks for potential application in bone repair. *J. Leather Sci. Eng.* **2022**, *4*, 1.

[32] Ang, Y. X.; Khudzari, A. Z. M.; Ali, M. S. M. Non-invasive treatment for coronary in-stent restenosis via wireless revascularization with nitinol active stent. *IEEE Trans. Biomed. Eng.* **2021**, *68*, 3681–3689.

[33] Liu, P. B.; Yan, J.; Guang, Z. X.; Huang, Y.; Li, X. F.; Huang, W. H. Recent advancements of polyaniline-based nanocomposites for supercapacitors. *J. Power Sources* **2019**, *424*, 108–130.

[34] Alshammary, B.; Walsh, F. C.; Herrasti, P.; de Leon, C. P. Electrodeposited conductive polymers for controlled drug release: Polypyrrole. *J. Solid State Electrochem.* **2016**, *20*, 839–859.

[35] Wu, C. J.; Wang, J. P.; Bai, Y.; Li, X. F. Significant effect of cations on polypyrrole cycle stability. *Solid State Ionics* **2020**, *346*, 115216.

[36] Zheng, M. H.; Wang, X. C.; Yue, O. Y.; Hou, M. D.; Zhang, H. J.; Beyer, S.; Blocki, A. M.; Wang, Q.; Gong, G. D.; Liu, X. H. et al. Skin-inspired gelatin-based flexible bio-electronic hydrogel for wound healing promotion and motion sensing. *Biomaterials* **2021**, *276*, 121026.

[37] Dhall, A.; Islam, S.; Park, M.; Zhang, Y.; Kim, A.; Hwang, G. Bimodal nanocomposite platform with antibiofilm and self-powering functionalities for biomedical applications. *ACS Appl. Mater. Interfaces* **2021**, *13*, 40379–40391.

[38] Liu, W. W.; Yang, D.; Wei, X. H.; Guo, S.; Wang, N.; Tang, Z.; Lu, Y. J.; Shen, S. N.; Shi, L.; Li, X. K. et al. Fabrication of piezoelectric porous $BaTiO_3$ scaffold to repair large segmental bone defect in sheep. *J. Biomater. Appl.* **2020**, *35*, 544–552.

[39] Li, J.; Long, Y.; Yang, F.; Wang, X. D. Degradable piezoelectric biomaterials for wearable and implantable bioelectronics. *Curr. Opin. Solid State Mater. Sci.* **2020**, *24*, 100806.

[40] Badatya, S.; Bharti, D. K.; Srivastava, A. K.; Gupta, M. K. Solution processed high performance piezoelectric eggshell membrane-PVDF layer composite nanogenerator via tuning the interfacial polarization. *J. Alloys Compd.* **2021**, *863*, 158406.

[41] Sun, R. J.; Carreira, S. C.; Chen, Y.; Xiang, C. Q.; Xu, L. L.; Zhang, B.; Chen, M. D.; Farrow, I.; Scarpa, F.; Rossiter, J. Stretchable piezoelectric sensing systems for self-powered and wireless health monitoring. *Adv. Mater. Technol.* **2019**, *4*, 1900100.

[42] Morsada, Z.; Hossain, M. M.; Islam, M. T.; Mobin, M. A.; Saha, S.

Recent progress in biodegradable and bioresorbable materials: From passive implants to active electronics. *Appl. Mater. Today* **2021**, *25*, 101257.
[43] Chandrakasan, A. P.; Verma, N.; Daly, D. C. Ultralow-power electronics for biomedical applications. *Annu. Rev. Biomed. Eng.* **2008**, *10*, 247–274.
[44] Song, Y.; Min, J. H.; Gao, W. Wearable and implantable electronics: Moving toward precision therapy. *ACS Nano* **2019**, *13*, 12280–12286.
[45] Zhao, J. W.; Ghannam, R.; Htet, K. O.; Liu, Y. C.; Law, M. K.; Roy, V. A. L.; Michel, B.; Imran, M. A.; Heidari, H. Self-powered implantable medical devices: Photovoltaic energy harvesting review. *Adv. Healthcare Mater.* **2020**, *9*, 2000779.
[46] Dagdeviren, C. The future of bionic dynamos. *Science* **2016**, *354*, 1109–1109.
[47] Zhu, M. L.; Yi, Z. R.; Yang, B.; Lee, C. Making use of nanoenergy from human-nanogenerator and self-powered sensor enabled sustainable wireless IoT sensory systems. *Nano Today* **2021**, *36*, 101016.
[48] Dong, L.; Jin, C. R.; Closson, A. B.; Trase, I.; Richards, H. C.; Chen, Z.; Zhang, J. X. J. Cardiac energy harvesting and sensing based on piezoelectric and triboelectric designs. *Nano Energy* **2020**, *76*, 105076.
[49] Li, N.; Yi, Z. R.; Ma, Y.; Xie, F.; Huang, Y.; Tian, Y. W.; Dong, X. X.; Liu, Y.; Shao, X.; Li, Y. et al. Direct powering a real cardiac pacemaker by natural energy of a heartbeat. *ACS Nano* **2019**, *13*, 2822–2830.
[50] Zheng, Q.; Shi, B. J.; Fan, F. R.; Wang, X. X.; Yan, L.; Yuan, W. W.; Wang, S. H.; Liu, H.; Li, Z.; Wang, Z. L. *In vivo* powering of pacemaker by breathing-driven implanted triboelectric nanogenerator. *Adv. Mater.* **2014**, *26*, 5851–5856.
[51] Liu, Z.; Li, H.; Shi, B.; Fan, Y. B.; Wang, Z. L.; Li, Z. Wearable and implantable triboelectric nanogenerators. *Adv. Funct. Mater.* **2019**, *29*, 1808820.
[52] Gu, L.; Liu, J. M.; Cui, N. Y.; Xu, Q.; Du, T.; Zhang, L.; Wang, Z.; Long, C. B.; Qin, Y. Enhancing the current density of a piezoelectric nanogenerator using a three-dimensional intercalation electrode. *Nat. Commun.* **2020**, *11*, 1030.
[53] Xu, L. L.; Yang, Y.; Mao, Y. K.; Li, Z. Self-powerbility in electrical stimulation drug delivery system. *Adv. Mater. Technol.* **2022**, *7*, 2100055.
[54] Xiao, X. X.; McGourty, K. D.; Magner, E. Enzymatic biofuel cells for self-powered, controlled drug release. *J. Am. Chem. Soc.* **2020**, *142*, 11602–11609.
[55] Shi, B. J.; Li, Z.; Fan, Y. B. Implantable energy-harvesting devices. *Adv. Mater.* **2018**, *30*, 1801511.
[56] Zou, L.; Qiao, Y.; Li, C. M. Boosting microbial electrocatalytic kinetics for high power density: Insights into synthetic biology and advanced nanoscience. *Electrochem. Energy Rev.* **2018**, *1*, 567–598.
[57] Chen, P.; Wang, Q.; Wan, X.; Yang, M.; Liu, C. L.; Xu, C.; Hu, B.; Feng, J. X.; Luo, Z. Q. Wireless electrical stimulation of the vagus nerves by ultrasound-responsive programmable hydrogel nanogenerators for anti-inflammatory therapy in sepsis. *Nano Energy* **2021**, *89*, 106327.
[58] Bansal, A.; Yang, F. Y.; Xi, T.; Zhang, Y.; Ho, J. S. *In vivo* wireless photonic photodynamic therapy. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 1469–1474.
[59] Mukherjee, S.; Suleman, S.; Pilloton, R.; Narang, J.; Rani, K. State of the art in smart portable, wearable, ingestible and implantable devices for health status monitoring and disease management. *Sensors* **2022**, *22*, 4228.
[60] Du, X. Y. Discussing application and development of portable medical electronic equipment. In *The 26th Annual Conference of IT, Network, Information Technology, Electronics, Instrumentation Innovation in China*, Tianjin, China, 2012, pp 81–84.
[61] Cheng, M.; Zhu, G. T.; Zhang, F.; Tang, W. L.; Jianping, S.; Yang, J. Q.; Zhu, L. Y. A review of flexible force sensors for human health monitoring. *J. Adv. Res.* **2020**, *26*, 53–68.
[62] Wang, W. L.; Pang, J. B.; Su, J.; Li, F. J.; Li, Q.; Wang, X. X.; Wang, J. G.; Ibarlucea, B.; Liu, X. Y.; Li, Y. F. et al. Applications of nanogenerators for biomedical engineering and healthcare systems. *InfoMat* **2022**, *4*, e12262.
[63] Ryu, H.; Park, H. M.; Kim, M. K.; Kim, B.; Myoung, H. S.; Kim, T. Y.; Yoon, H. J.; Kwak, S. S.; Kim, J.; Hwang, T. H. et al. Self-rechargeable cardiac pacemaker system with triboelectric nanogenerators. *Nat. Commun.* **2021**, *12*, 4374.
[64] Xie, F.; Qian, X. Q.; Li, N.; Cui, D. X.; Zhang, H.; Xu, Z. Y. An experimental study on a piezoelectric vibration energy harvester for self-powered cardiac pacemakers. *Ann. Transl. Med.* **2021**, *9*, 880.
[65] Yao, G.; Kang, L.; Li, J.; Long, Y.; Wei, H.; Ferreira, C. A.; Jeffery, J. J.; Lin, Y.; Cai, W. B.; Wang, X. D. Effective weight control via an implanted self-powered vagus nerve stimulation device. *Nat. Commun.* **2018**, *9*, 5349.
[66] Lee, S.; Wang, H.; Xian Peh, W. Y.; He, T.; Yen, S. C.; Thakor, N. V.; Lee, C. Mechano-neuromodulation of autonomic pelvic nerve for underactive bladder: A triboelectric neurostimulator integrated with flexible neural clip interface. *Nano Energy* **2019**, *60*, 449–456.
[67] Ma, Y. Q.; Bao, J.; Zhang, Y. W.; Li, Z. J.; Zhou, X. Y.; Wan, C. L.; Huang, L.; Zhao, Y.; Han, G.; Xue, T. Mammalian near-infrared image vision through injectable and self-powered retinal nanoantennae. *Cell* **2019**, *177*, 243–255. e15.
[68] Zhao, C. C.; Cui, X.; Wu, Y. X.; Li, Z. Recent progress of nanogenerators acting as self-powered drug delivery devices. *Adv. Sustainable Syst.* **2021**, *5*, 2000268.
[69] Xu, J.; Wang, Y. H.; Wei, Z. N.; Wang, F. T.; Huang, K. J. Significantly improving the performance of self-powered biosensor by effectively combining with high-energy enzyme biofuel cells, N-doped graphene, and ultrathin hollow carbon shell. *Sens. Actuators B:Chem.* **2021**, *327*, 128933.
[70] Jang, J.; Lee, J.; Jang, J. H.; Choi, H. A triboelectric-based artificial basilar membrane to mimic cochlear tonotopy. *Adv. Healthcare Mater.* **2016**, *5*, 2481–2487.
[71] Chen, X. Y.; Jiang, T.; Yao, Y. Y.; Xu, L.; Zhao, Z. F.; Wang, Z. L. Stimulating acrylic elastomers by a triboelectric nanogenerator-toward self-powered electronic skin and artificial muscle. *Adv. Funct. Mater.* **2016**, *26*, 4906–4913.
[72] Yoon, H. J.; Kim, S. W. Nanogenerators to power implantable medical systems. *Joule* **2020**, *4*, 1398–1407.
[73] Kim, D. H.; Shin, H. J.; Lee, H.; Jeong, C. K.; Park, H.; Hwang, G. T.; Lee, H. Y.; Joe, D. J.; Han, J. H.; Lee, S. H. et al. *In vivo* self-powered wireless transmission using biocompatible flexible energy harvesters. *Adv. Funct. Mater.* **2017**, *27*, 1700341.
[74] Li, J.; Hacker, T. A.; Wei, H.; Long, Y.; Yang, F.; Ni, D. L.; Rodgers, A.; Cai, W. B.; Wang, X. D. Long-term *in vivo* operation of implanted cardiac nanogenerators in swine. *Nano Energy* **2021**, *90*, 106507.
[75] Zhao, D. N.; Zhuo, J. T.; Chen, Z. T.; Wu, J. J.; Ma, R.; Zhang, X. J.; Zhang, Y. F.; Wang, X.; Wei, X. S.; Liu, L. X. et al. Eco-friendly *in-situ* gap generation of no-spacer triboelectric nanogenerator for monitoring cardiovascular activities. *Nano Energy* **2021**, *90*, 106580.
[76] Ma, Y.; Zheng, Q.; Liu, Y.; Shi, B. J.; Xue, X.; Ji, W. P.; Liu, Z.; Jin, Y. M.; Zou, Y.; An, Z. et al. Self-powered, one-stop, and multifunctional implantable triboelectric active sensor for real-time biomedical monitoring. *Nano Lett.* **2016**, *16*, 6042–6051.
[77] Zheng, Q.; Zhang, H.; Shi, B. J.; Xue, X.; Liu, Z.; Jin, Y. M.; Ma, Y.; Zou, Y.; Wang, X. X.; An, Z. et al. *In vivo* self-powered wireless cardiac monitoring via implantable triboelectric nanogenerator. *ACS Nano* **2016**, *10*, 6510–6518.
[78] Li, R. F.; Qi, H.; Ma, Y.; Deng, Y. P.; Liu, S. N.; Jie, Y. S.; Jing, J. Z.; He, J. L.; Zhang, X.; Wheatley, L. et al. A flexible and physically transient electrochemical sensor for real-time wireless nitric oxide monitoring. *Nat. Commun.* **2020**, *11*, 3207.
[79] Dyson, A.; Stidwill, R.; Taylor, V.; Singer, M. The impact of inspired oxygen concentration on tissue oxygenation during progressive haemorrhage. *Intensive Care Med.* **2009**, *35*, 1783–1791.
[80] Zhang, H.; Gutruf, P.; Meacham, K.; Montana, M. C.; Zhao, X. Y.; Chiarelli, A. M.; Vázquez-Guardado, A.; Norris, A.; Lu, L.; Guo, Q. L. et al. Wireless, battery-free optoelectronic systems as

subdermal implants for local tissue oximetry. *Sci. Adv.* **2019**, *5*, eaaw0873.
[81] Alberti, K. G. M. M.; Zimmet, P. Z. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1:Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet. Med.* **1998**, *15*, 539–553.
[82] Teymourian, H.; Barfidokht, A.; Wang, J. Electrochemical glucose sensors in diabetes management: An updated review (2010–2020). *Chem. Soc. Rev.* **2020**, *49*, 7671–7709.
[83] Gebremichael, G. B.; Mariye Zemicheal, T. Hypoglycemia prevention practice and associated factors among diabetic patients on follow-up at public hospitals of central zone, tigray, ethiopia, 2018. *Int. J. Endocrinol.* **2020**, *2020*, 8743531.
[84] Zhang, W.; Zhang, L. L.; Gao, H. L.; Yang, W. Y.; Wang, S.; Xing, L. L.; Xue, X. Y. Self-powered implantable skin-like glucometer for real-time detection of blood glucose level *in vivo*. *Nano-Micro Lett.* **2018**, *10*, 32.
[85] Cheng, X. L.; Xue, X.; Ma, Y.; Han, M. D.; Zhang, W.; Xu, Z. Y.; Zhang, H.; Zhang, H. X. Implantable and self-powered blood pressure monitoring based on a piezoelectric thinfilm: Simulated, *in vitro* and *in vivo* studies. *Nano Energy* **2016**, *22*, 453–460.
[86] Ouyang, H.; Liu, Z.; Li, N.; Shi, B. J.; Zou, Y.; Xie, F.; Ma, Y.; Li, Z.; Li, H.; Zheng, Q. et al. Symbiotic cardiac pacemaker. *Nat. Commun.* **2019**, *10*, 1821.
[87] Waldo, A. L.; Wells, J. L. Jr.; Cooper, T. B.; MacLean, W. A. H. Temporary cardiac pacing: Applications and techniques in the treatment of cardiac arrhythmias. *Prog. Cardiovasc. Dis.* **1981**, *23*, 451–474.
[88] Dong, L.; Closson, A. B.; Jin, C. R.; Nie, Y.; Cabe, A.; Escobedo, D.; Huang, S. C.; Trase, I.; Xu, Z.; Chen, Z. et al. Multifunctional pacemaker lead for cardiac energy harvesting and pressure sensing. *Adv. Healthcare Mater.* **2020**, *9*, 2000053.
[89] Hwang, G. T.; Park, H.; Lee, J. H.; Oh, S.; Park, K. I.; Byun, M.; Park, H.; Ahn, G.; Jeong, C. K.; No, K. et al. Self-powered cardiac pacemaker enabled by flexible single crystalline PMN-PT piezoelectric energy harvester. *Adv. Mater.* **2014**, *26*, 4880–4887.
[90] Azimi, S.; Golabchi, A.; Nekookar, A.; Rabbani, S.; Amiri, M. H.; Asadi, K.; Abolhasani, M. M. Self-powered cardiac pacemaker by piezoelectric polymer nanogenerator implant. *Nano Energy* **2021**, *83*, 105781.
[91] Yi, Z. R.; Xie, F.; Tian, Y. W.; Li, N.; Dong, X. X.; Ma, Y.; Huang, Y.; Hu, Y. L.; Xu, X. B.; Qu, D. et al. A battery-and leadless heart-worn pacemaker strategy. *Adv. Funct. Mater.* **2020**, *30*, 2000477.
[92] Zurbuchen, A.; Haeberlin, A.; Bereuter, L.; Wagner, J.; Pfenniger, A.; Omari, S.; Schaerer, J.; Jutzi, F.; Huber, C.; Fuhrer, J. et al. The Swiss approach for a heartbeat-driven lead- and batteryless pacemaker. *Heart Rhythm* **2017**, *14*, 294–299.
[93] Tashiro, R.; Kabei, N.; Katayama, K.; Tsuboi, E.; Tsuchiya, K. Development of an electrostatic generator for a cardiac pacemaker that harnesses the ventricular wall motion. *J. Artif. Organs* **2002**, *5*, 239–245.
[94] Franzina, N.; Zurbuchen, A.; Zumbrunnen, A.; Niederhauser, T.; Reichlin, T.; Burger, J.; Haeberlin, A. A miniaturized endocardial electromagnetic energy harvester for leadless cardiac pacemakers. *PLoS One* **2020**, *15*, e0239667.
[95] Choi, Y. S.; Yin, R. T.; Pfenniger, A.; Koo, J.; Avila, R.; Benjamin Lee, K.; Chen, S. W.; Lee, G.; Li, G.; Qiao, Y. et al. Fully implantable and bioresorbable cardiac pacemakers without leads or batteries. *Nat. Biotechnol.* **2021**, *39*, 1228–1238.
[96] Jiang, W.; Li, H.; Liu, Z.; Li, Z.; Tian, J. J.; Shi, B. J.; Zou, Y.; Ouyang, H.; Zhao, C. C.; Zhao, L. M. et al. Fully bioabsorbable natural-materials-based triboelectric nanogenerators. *Adv. Mater.* **2018**, *30*, 1801895.
[97] Walsh, P.; Kodoth, V.; McEneaney, D.; Rodrigues, P.; Velasquez, J.; Waterman, N.; Escalona, O. Towards low energy atrial defibrillation. *Sensors* **2015**, *15*, 22378–22400.
[98] Boutry, C. M.; Beker, L.; Kaizawa, Y.; Vassos, C.; Tran, H.; Hinckley, A. C.; Pfattner, R.; Niu, S. M.; Li, J. H.; Claverie, J. et al. Biodegradable and flexible arterial-pulse sensor for the wireless monitoring of blood flow. *Nat. Biomed. Eng.* **2019**, *3*, 47–57.
[99] Won, S. M.; Song, E. M.; Reeder, J. T.; Rogers, J. A. Emerging modalities and implantable technologies for neuromodulation. *Cell* **2020**, *181*, 115–135.
[100] Won, S. M.; Cai, L.; Gutruf, P.; Rogers, J. A. Wireless and battery-free technologies for neuroengineering. *Nat. Biomed. Eng.*, in press, https://doi.org/10.1038/s41551-021-00683-3.
[101] Iaccarino, H. F.; Singer, A. C.; Martorell, A. J.; Rudenko, A.; Gao, F.; Gillingham, T. Z.; Mathys, H.; Seo, J.; Kritskiy, O.; Abdurrob, F. et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature* **2016**, *540*, 230–235.
[102] Park, S. I.; Brenner, D. S.; Shin, G.; Morgan, C. D.; Copits, B. A.; Chung, H. U.; Pullen, M. Y.; Noh, K. N.; Davidson, S.; Oh, S. J. et al. Soft, stretchable, fully implantable miniaturized optoelectronic systems for wireless optogenetics. *Nat. Biotechnol.* **2015**, *33*, 1280–1286.
[103] Kameo, Y.; Miya, Y.; Hayashi, M.; Nakashima, T.; Adachi, T. In silico experiments of bone remodeling explore metabolic diseases and their drug treatment. *Sci. Adv.* **2020**, *6*, eaax0938.
[104] Yu, X. Y.; Zhang, H. P.; Miao, Y. L.; Xiong, S. B.; Hu, Y. Recent strategies of collagen-based biomaterials for cartilage repair: From structure cognition to function endowment. *J. Leather Sci. Eng.* **2022**, *4*, 11.
[105] Tian, J. J.; Shi, R.; Liu, Z.; Ouyang, H.; Yu, M.; Zhao, C. C.; Zou, Y.; Jiang, D. J.; Zhang, J. S.; Li, Z. Self-powered implantable electrical stimulator for osteoblasts' proliferation and differentiation. *Nano Energy* **2019**, *59*, 705–714.
[106] Tang, W.; Tian, J. J.; Zheng, Q.; Yan, L.; Wang, J. X.; Li, Z.; Wang, Z. L. Implantable self-powered low-level laser cure system for mouse embryonic osteoblasts' proliferation and differentiation. *ACS Nano* **2015**, *9*, 7867–7873.
[107] Karipott, S. S.; Nelson, B. D.; Guldberg, R. E.; Ong, K. G. Clinical potential of implantable wireless sensors for orthopedic treatments. *Expert Rev. Med. Devices* **2018**, *15*, 255–264.
[108] Yao, G.; Kang, L.; Li, C. C.; Chen, S. H.; Wang, Q.; Yang, J. Z.; Long, Y.; Li, J.; Zhao, K. N.; Xu, W. N. et al. A self-powered implantable and bioresorbable electrostimulation device for biofeedback bone fracture healing. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2100772118.
[109] Yu, B.; Qiao, Z. G.; Cui, J. J.; Lian, M. F.; Han, Y.; Zhang, X.; Wang, W. Q.; Yu, X. G.; Yu, H.; Wang, X. D. et al. A host-coupling bio-nanogenerator for electrically stimulated osteogenesis. *Biomaterials* **2021**, *276*, 120997.
[110] Qin, L.; Cao, J.; Shao, K.; Tong, F.; Yang, Z. H.; Lei, T.; Wang, Y. Z.; Hu, C.; Umeshappa, C. S.; Gao, H. L. et al. A tumor-to-lymph procedure navigated versatile gel system for combinatorial therapy against tumor recurrence and metastasis. *Sci. Adv.* **2020**, *6*, eabb3116.
[111] Chen, M. H.; Zhou, Y. K.; Lang, J. Y.; Li, L. J.; Zhang, Y. Triboelectric nanogenerator and artificial intelligence to promote precision medicine for cancer. *Nano Energy* **2022**, *92*, 106783.
[112] Zhang, X. G.; Tang, J. J.; Li, C.; Lu, Y.; Cheng, L. L.; Liu, J. A targeting black phosphorus nanoparticle based immune cells nano-regulator for photodynamic/photothermal and photo-immunotherapy. *Bioact. Mater.* **2021**, *6*, 472–489.
[113] Shao, J. D.; Xie, H. H.; Huang, H.; Li, Z. B.; Sun, Z. B.; Xu, Y. H.; Xiao, Q. L.; Yu, X. F.; Zhao, Y. T.; Zhang, H. et al. Biodegradable black phosphorus-based nanospheres for *in vivo* photothermal cancer therapy. *Nat. Commun.* **2016**, *7*, 12967.
[114] Dolmans, D. E. J. G. J.; Fukumura, D.; Jain, R. K. Photodynamic therapy for cancer. *Nat. Rev. Cancer* **2003**, *3*, 380–387.
[115] Park, J.; Lee, Y. K.; Park, I. K.; Hwang, S. R. Current limitations and recent progress in nanomedicine for clinically available photodynamic therapy. *Biomedicines* **2021**, *9*, 85.
[116] Lee, G. H.; Moon, H.; Kim, H.; Lee, G. H.; Kwon, W.; Yoo, S.; Myung, D.; Yun, S. H.; Bao, Z. N.; Hahn, S. K. Multifunctional materials for implantable and wearable photonic healthcare devices. *Nat. Rev. Mater.* **2020**, *5*, 149–165.
[117] Deisseroth, K. Optogenetics. *Nat. Methods* **2011**, *8*, 26–29.
[118] Gheorghiu, M.; Polonschii, C.; Popescu, O.; Gheorghiu, E.

Advanced optogenetic-based biosensing and related biomaterials. *Materials* **2021**, *14*, 4151.
[119] Younis, M. R.; Wang, C.; An, R. B.; Wang, S. J.; Younis, M. A.; Li, Z. Q.; Wang, Y.; Ihsan, A.; Ye, D. J.; Xia, X. H. Low power single laser activated synergistic cancer phototherapy using photosensitizer functionalized dual plasmonic photothermal nanoagents. *ACS Nano* **2019**, *13*, 2544–2557.
[120] Liu, Z.; Xu, L. L.; Zheng, Q.; Kang, Y.; Shi, B. J.; Jiang, D. J.; Li, H.; Qu, X. C.; Fan, Y. B.; Wang, Z. L. et al. Human motion driven self-powered photodynamic system for long-term autonomous cancer therapy. *ACS Nano* **2020**, *14*, 8074–8083.
[121] Chin, A. L.; Jiang, S.; Jang, E.; Niu, L. Q.; Li, L. W.; Jia, X. T.; Tong, R. Implantable optical fibers for immunotherapeutics delivery and tumor impedance measurement. *Nat. Commun.* **2021**, *12*, 5138.
[122] He, C.; Dong, C. H.; Yu, L. D.; Chen, Y.; Hao, Y. Q. Ultrathin 2D inorganic ancient pigment decorated 3D-printing scaffold enables photonic hyperthermia of osteosarcoma in NIR-II biowindow and concurrently augments bone regeneration. *Adv. Sci.* **2021**, *8*, 2101739.
[123] Lee, S. H.; Wan, Q. Q.; Wentworth, A.; Ballinger, I.; Ishida, K.; Collins, J. E.; Tamang, S.; Huang, H. W.; Li, C. C.; Hess, K. et al. Implantable system for chronotherapy. *Sci. Adv.* **2021**, *7*, eabj4624.
[124] Choi, G.; Fitriasari, E. I.; Park, C. Electro-mechanochemical gating of a metal-phenolic nanocage for controlled guest-release self-powered patches and injectable gels. *ACS Nano* **2021**, *15*, 14580–14586.
[125] Li, J. Y.; Mooney, D. J. Designing hydrogels for controlled drug delivery. *Nat. Rev. Mater.* **2016**, *1*, 16071.
[126] Brudno, Y.; Mooney, D. J. On-demand drug delivery from local depots. *J. Control. Release* **2015**, *219*, 8–17.
[127] Song, P. Y.; Kuang, S. Y.; Panwar, N.; Yang, G.; Tng, D. J. H.; Tjin, S. C.; Ng, W. J.; Majid, M. B. A.; Zhu, G.; Yong, K. T. et al. A self-powered implantable drug-delivery system using biokinetic energy. *Adv. Mater.* **2017**, *29*, 1605668.
[128] Gabrielsson, E. O.; Jung, Y. H.; Han, J. H.; Joe, D. J.; Simon, D. T.; Lee, K. J.; Berggren, M. Autonomous microcapillary drug delivery system self-powered by a flexible energy harvester. *Adv. Mater. Technol.* **2021**, *6*, 2100526.
[129] Zhao, C. C.; Feng, H. Q.; Zhang, L. J.; Li, Z.; Zou, Y.; Tan, P. C.; Ouyang, H.; Jiang, D. J.; Yu, M.; Wang, C. et al. Highly efficient *in vivo* cancer therapy by an implantable magnet triboelectric nanogenerator. *Adv. Funct. Mater.* **2019**, *29*, 1808640.
[130] Choi, M.; Choi, J. W.; Kim, S.; Nizamoglu, S.; Hahn, S. K.; Yun, S. H. Light-guiding hydrogels for cell-based sensing and optogenetic synthesis *in vivo*. *Nat. Photonics* **2013**, *7*, 987–994.
[131] Ma, Y. J.; Zhang, Y. C.; Cai, S. S.; Han, Z. Y.; Liu, X.; Wang, F. L.; Cao, Y.; Wang, Z. H.; Li, H. F.; Chen, Y. H. et al. Flexible hybrid electronics for digital healthcare. *Adv. Mater.* **2020**, *32*, 1902062.
[132] Tian, L. M.; Zimmerman, B.; Akhtar, A.; Yu, K. J.; Moore, M.; Wu, J.; Larsen, R. J.; Lee, J. W.; Li, J. H.; Liu, Y. H. et al. Large-area MRI-compatible epidermal electronic interfaces for prosthetic control and cognitive monitoring. *Nat. Biomed. Eng.* **2019**, *3*, 194–205.
[133] Yu, Y.; Nyein, H. Y. Y.; Gao, W.; Javey, A. Flexible electrochemical bioelectronics: The rise of *in situ* bioanalysis. *Adv. Mater.* **2020**, *32*, 1902083.
[134] Zhang, L.; Kumar, K. S.; He, H.; Cai, C. J.; He, X.; Gao, H. X.; Yue, S. Z.; Li, C. S.; Seet, R. C. S.; Ren, H. L. et al. Fully organic compliant dry electrodes self-adhesive to skin for long-term motion-robust epidermal biopotential monitoring. *Nat. Commun.* **2020**, *11*, 4683.
[135] Sun, J. Y.; Yang, A. P.; Zhao, C. C.; Liu, F.; Li, Z. Recent progress of nanogenerators acting as biomedical sensors *in vivo*. *Sci. Bull.* **2019**, *64*, 1336–1347.
[136] Heikenfeld, J.; Jajack, A.; Feldman, B.; Granger, S. W.; Gaitonde, S.; Begtrup, G.; Katchman, B. A. Accessing analytes in biofluids for peripheral biochemical monitoring. *Nat. Biotechnol.* **2019**, *37*, 407–419.
[137] Wang, J. Glucose biosensors: 40 years of advances and challenges. *Electroanalysis* **2001**, *13*, 983–988.
[138] Lee, H.; Hong, Y. J.; Baik, S.; Hyeon, T.; Kim, D. H. Enzyme-based glucose sensor: From invasive to wearable device. *Adv. Healthcare Mater.* **2018**, *7*, 1701150.
[139] Hwang, D. W.; Lee, S.; Seo, M.; Chung, T. D. Recent advances in electrochemical non-enzymatic glucose sensors—A review. *Anal. Chim. Acta* **2018**, *1033*, 1–34.
[140] Gough, D. A.; Kumosa, L. S.; Routh, T. L.; Lin, J. T.; Lucisano, J. Y. Function of an implanted tissue glucose sensor for more than 1 year in animals. *Sci. Transl. Med.* **2010**, *2*, 42ra53.
[141] Signore, M. A.; Rescio, G.; De Pascali, C.; Iacovacci, V.; Dario, P.; Leone, A.; Quaranta, F.; Taurino, A.; Siciliano, P.; Francioso, L. Fabrication and characterization of AlN-based flexible piezoelectric pressure sensor integrated into an implantable artificial pancreas. *Sci. Rep.* **2019**, *9*, 17130.
[142] Kral, A. Auditory critical periods: A review from system's perspective. *Neuroscience* **2013**, *247*, 117–133.
[143] Cohen, N. The totally implantable cochlear implant. *Ear Hear.* **2007**, *28*, 100S–101S.
[144] Park, S.; Guan, X. Y.; Kim, Y.; Creighton, F. X.; Wei, E.; Kymissis, I.; Nakajima, H. H.; Olson, E. S. PVDF-based piezoelectric microphone for sound detection inside the cochlea: Toward totally implantable cochlear implants. *Trends Hear.* **2018**, *22*, 2331216518774450.
[145] Mitchell-Innes, A.; Saeed, S. R.; Irving, R. The future of cochlear implant design. *Adv. Otorhinolaryngol.* **2018**, *81*, 105–113.
[146] Latif, R.; Noor, M. M.; Yunas, J.; Hamzah, A. A. Mechanical energy sensing and harvesting in micromachined polymer-based piezoelectric transducers for fully implanted hearing systems: A review. *Polymers* **2021**, *13*, 2276.
[147] Liu, Y. D.; Zhu, Y. X.; Liu, J. Y.; Zhang, Y.; Liu, J.; Zhai, J. Y. Design of bionic cochlear basilar membrane acoustic sensor for frequency selectivity based on film triboelectric nanogenerator. *Nanoscale Res. Lett.* **2018**, *13*, 191.
[148] Kim, S. H.; Yu, C.; Ishiyama, K. Rotary-type electromagnetic power generator using a cardiovascular system as a power source for medical implants. *IEEE/ASME Trans. Mech.* **2016**, *21*, 122–129.
[149] Tyler, S. E. B. Nature's electric potential: A systematic review of the role of bioelectricity in wound healing and regenerative processes in animals, humans, and plants. *Front. Physiol.* **2017**, *8*, 627.
[150] Zhao, M.; Song, B.; Pu, J.; Wada, T.; Reid, B.; Tai, G. P.; Wang, F.; Guo, A. H.; Walczysko, P.; Gu, Y. et al. Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-γ and PTEN. *Nature* **2006**, *442*, 457–460.
[151] Rajabi, A. H.; Jaffe, M.; Arinzeh, T. L. Piezoelectric materials for tissue regeneration: A review. *Acta Biomater.* **2015**, *24*, 12–23.
[152] Ning, C. Y.; Zhou, Z. N.; Tan, G. X.; Zhu, Y.; Mao, C. B. Electroactive polymers for tissue regeneration: Developments and perspectives. *Prog. Polym. Sci.* **2018**, *81*, 144–162.
[153] Zhang, X. H.; Zhang, C. G.; Lin, Y. H.; Hu, P. H.; Shen, Y.; Wang, K.; Meng, S.; Chai, Y.; Dai, X. H.; Liu, X. et al. Nanocomposite membranes enhance bone regeneration through restoring physiological electric microenvironment. *ACS Nano* **2016**, *10*, 7279–7286.
[154] Municoy, S.; Echazu, M. I. Á.; Antezana, P. E.; Galdoporpora, J. M.; Olivetti, C.; Mebert, A. M.; Foglia, M. L.; Tuttolomondo, M. V.; Alvarez, G. S.; Hardy, J. G. et al. Stimuli-responsive materials for tissue engineering and drug delivery. *Int. J. Mol. Sci.* **2020**, *21*, 4724.
[155] Qian, Y.; Song, J. L.; Zhao, X. T.; Chen, W.; Ouyang, Y. M.; Yuan, W. E.; Fan, C. Y. 3D fabrication with integration molding of a graphene oxide/polycaprolactone nanoscaffold for neurite regeneration and angiogenesis. *Adv. Sci.* **2018**, *5*, 1700499.
[156] del Monte-Nieto, G.; Fischer, J. W.; Gorski, D. J.; Harvey, R. P.;

Kovacic, J. C. Basic biology of extracellular matrix in the cardiovascular system, Part 1/4: JACC focus seminar. *J. Am. Coll. Cardiol.* **2020**, *75*, 2169–2188.

[157] Huang, Y. J.; Schiapparelli, P.; Kozielski, K.; Green, J.; Lavell, E.; Guerrero-Cazares, H.; Quinones-Hinojosa, A.; Searson, P. Electrophoresis of cell membrane heparan sulfate regulates galvanotaxis in glial cells. *J. Cell Sci.* **2017**, *130*, 2459–2467.

[158] Cameron, M. A.; Al Abed, A.; Buskila, Y.; Dokos, S.; Lovell, N. H.; Morley, J. W. Differential effect of brief electrical stimulation on voltage-gated potassium channels. *J. Neurophysiol.* **2017**, *117*, 2014–2024.

[159] Naskar, S.; Kumaran, V.; Markandeya, Y. S.; Mehta, B.; Basu, B. Neurogenesis-on-chip: Electric field modulated transdifferentiation of human mesenchymal stem cell and mouse muscle precursor cell coculture. *Biomaterials* **2020**, *226*, 119522.

[160] Cho, M. R. A review of electrocoupling mechanisms mediating facilitated wound healing. *IEEE Trans. Plasma Sci.* **2002**, *30*, 1504–1515.

[161] Jing, W.; Zhang, Y. F.; Cai, Q.; Chen, G. Q.; Wang, L.; Yang, X. P.; Zhong, W. H. Study of electrical stimulation with different electric-field intensities in the regulation of the differentiation of PC12 cells. *ACS Chem. Neurosci.* **2019**, *10*, 348–357.

[162] Abedin-Do, A.; Zhang, Z.; Douville, Y.; Méthot, M.; Rouabhia, M. Effect of electrical stimulation on diabetic human skin fibroblast growth and the secretion of cytokines and growth factors involved in wound healing. *Biology* **2021**, *10*, 641.

[163] Sauer, H.; Bekhite, M. M.; Hescheler, J.; Wartenberg, M. Redox control of angiogenic factors and CD31-positive vessel-like structures in mouse embryonic stem cells after direct current electrical field stimulation. *Exp. Cell Res.* **2005**, *304*, 380–390.

[164] Pei, Y. C.; Chen, T. Y.; Hsu, P. C.; Lin, C. H.; Huang, J. J. An electroneurography-based assay for identifying injured nerve segment during surgery: Design and *in vivo* application in the rat. *J. Neural Eng.* **2019**, *16*, 026027.

[165] Garrido, J. J.; Fernandes, F.; Moussif, A.; Fache, M. P.; Giraud, P.; Dargent, B. Dynamic compartmentalization of the voltage-gated sodium channels in axons. *Biol. Cell* **2003**, *95*, 437–445.

[166] Asensio-Pinilla, E.; Udina, E.; Jaramillo, J.; Navarro, X. Electrical stimulation combined with exercise increase axonal regeneration after peripheral nerve injury. *Exp. Neurol.* **2009**, *219*, 258–265.

[167] Li, Y. C.; Weiss, M.; Yao, L. Directed migration of embryonic stem cell-derived neural cells in an applied electric field. *Stem Cell Rev. Rep.* **2014**, *10*, 653–662.

[168] Zhou, Z. F.; Liu, X. F.; Wu, W.; Park, S.; Miller II, A. L.; Terzic, A.; Lu, L. C. Effective nerve cell modulation by electrical stimulation of carbon nanotube embedded conductive polymeric scaffolds. *Biomater. Sci.* **2018**, *6*, 2375–2385.

[169] Yu, P.; Ning, C. Y.; Zhang, Y.; Tan, G. X.; Lin, Z. F.; Liu, S. X.; Wang, X. L.; Yang, H. Q.; Li, K.; Yi, X. et al. Bone-inspired spatially specific piezoelectricity induces bone regeneration. *Theranostics* **2017**, *7*, 3387–3397.

[170] Chen, L. R.; Hou, P. H.; Chen, K. H. Nutritional support and physical modalities for people with osteoporosis: Current opinion. *Nutrients* **2019**, *11*, 2848.

[171] Vila, M.; Cicuéndez, M.; Sánchez-Marcos, J.; Fal-Miyar, V.; Manzano, M.; Prieto, C.; Vallet-Regi, M. Electrical stimuli to increase cell proliferation on carbon nanotubes/mesoporous silica composites for drug delivery. *J. Biomed. Mater. Res. Part A* **2013**, *101A*, 213–221.

[172] Wiesmann, H. P.; Hartig, M.; Stratmann, U.; Meyer, U.; Joos, U. Electrical stimulation influences mineral formation of osteoblast-like cells *in vitro*. *Biochim. Biophys. Acta-Mol. Cell Res.* **2001**, *1538*, 28–37.

[173] Saberi, A.; Jabbari, F.; Zarrintaj, P.; Saeb, M. R.; Mozafari, M. Electrically conductive materials: Opportunities and challenges in tissue engineering. *Biomolecules* **2019**, *9*, 448.

[174] Shi, G. X.; Zhang, Z.; Rouabhia, M. The regulation of cell functions electrically using biodegradable polypyrrole–polylactide conductors. *Biomaterials* **2008**, *29*, 3792–3798.

[175] Sun, G. X.; Wang, L. J.; Xiang, C.; Qin, K. R. A dynamic model for intracellular calcium response in fibroblasts induced by electrical stimulation. *Math. Biosci.* **2013**, *244*, 47–57.

[176] Wu, J.; Qin, N.; Bao, D. H. Effective enhancement of piezocatalytic activity of $BaTiO_3$ nanowires under ultrasonic vibration. *Nano Energy* **2018**, *45*, 44–51.

[177] Yu, X.; Wang, S.; Zhang, X. D.; Qi, A. H.; Qiao, X. R.; Liu, Z. R.; Wu, M. Q.; Li, L. L.; Wang, Z. L. Heterostructured nanorod array with piezophototronic and plasmonic effect for photodynamic bacteria killing and wound healing. *Nano Energy* **2018**, *46*, 29–38.

[178] Bok, M.; Lee, Y.; Park, D.; Shin, S.; Zhao, Z. J.; Hwang, B.; Hwang, S. H.; Jeon, S. H.; Jung, J. Y.; Park, S. H. et al. Microneedles integrated with a triboelectric nanogenerator: An electrically active drug delivery system. *Nanoscale* **2018**, *10*, 13502–13510.

[179] Rezaei, M.; Ahmadirad, N.; Ghasemi, Z.; Shojaei, A.; Raoufy, M. R.; Barkley, V.; Fathollahi, Y.; Mirnajafi-Zadeh, J. Alpha adrenergic receptors have role in the inhibitory effect of electrical low frequency stimulation on epileptiform activity in rats. *Int. J. Neurosci.*, in press, https://doi.org/10.1080/00207454.2021.1929211.

[180] Reddy, S.; He, L. M.; Ramakrishana, S. Miniaturized-electroneurostimulators and self-powered/rechargeable implanted devices for electrical-stimulation therapy. *Biomed. Signal Process. Control* **2018**, *41*, 255–263.

[181] Liu, Z. G.; Dong, L. Q.; Cheng, K.; Luo, Z. K.; Weng, W. J. Charge injection based electrical stimulation on polypyrrole planar electrodes to regulate cellular osteogenic differentiation. *RSC Adv.* **2018**, *8*, 18470–18479.

[182] Gelmi, A.; Schutt, C. E. Stimuli-responsive biomaterials: Scaffolds for stem cell control. *Adv. Healthcare Mater.* **2021**, *10*, 2001125.

[183] Blanquer, A.; Careta, O.; Anido-Varela, L.; Aranda, A.; Ibáñez, E.; Esteve, J.; Nogués, C.; Murillo, G. Biocompatibility and electrical stimulation of skeletal and smooth muscle cells cultured on piezoelectric nanogenerators. *Int. J. Mol. Sci.* **2021**, *23*, 432.

[184] Murillo, G.; Blanquer, A.; Vargas-Estevez, C.; Barrios, L.; Ibáñez, E.; Nogués, C.; Esteve, J. Electromechanical nanogenerator–cell interaction modulates cell activity. *Adv. Mater.* **2017**, *29*, 1605048.

[185] Xu, G. Y.; Huang, L. Y. M. Ca^{2+}/calmodulin-dependent protein kinase II potentiates ATP responses by promoting trafficking of P2X receptors. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11868–11873.

[186] Gu, J. H.; He, X. Z.; Chen, X. Y.; Dong, L. Q.; Weng, W. J.; Cheng, K. Effects of electrical stimulation on cytokine-induced macrophage polarization. *J. Tissue Eng. Regener. Med.* **2022**, *16*, 448–459.

[187] Larsson, O.; Kindmark, H.; Brandstrom, R.; Fredholm, B.; Berggren, P. O. Oscillations in K-ATP channel activity promote oscillations in cytoplasmic free Ca^{2+} concentration in the pancreatic beta cell. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 5161–5165.

[188] Zhao, G. L.; Joca, H. C.; Nelson, M. T.; Lederer, W. J. ATP- and voltage-dependent electro-metabolic signaling regulates blood flow in heart. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 7461–7470.

[189] Serena, E.; Figallo, E.; Tandon, N.; Cannizzaro, C.; Gerecht, S.; Elvassore, N.; Vunjak-Novakovic, G. Electrical stimulation of human embryonic stem cells: Cardiac differentiation and the generation of reactive oxygen species. *Exp. Cell Res.* **2009**, *315*, 3611–3619.

[190] Lissoni, A.; Hulpiau, P.; Martins-Marques, T.; Wang, N.; Bultynck, G.; Schulz, R.; Witschas, K.; Girao, H.; De Smet, M.; Leybaert, L. RyR2 regulates Cx43 hemichannel intracellular Ca^{2+}-dependent activation in cardiomyocytes. *Cardiovasc. Res.* **2021**, *117*, 123–136.

[191] Kotwal, A.; Schmidt, C. E. Electrical stimulation alters protein adsorption and nerve cell interactions with electrically conducting biomaterials. *Biomaterials* **2001**, *22*, 1055–1064.

[192] Meng, S. Y.; Rouabhia, M.; Zhang, Z. Electrical stimulation and cellular behaviors in electric field in biomedical research. *Materials* **2021**, *15*, 165.

[193] Du, S.; Zhou, N. Y.; Gao, Y. J.; Xie, G.; Du, H. Y.; Jiang, H.;

Zhang, L. B.; Tao, J.; Zhu, J. T. Bioinspired hybrid patches with self-adhesive hydrogel and piezoelectric nanogenerator for promoting skin wound healing. *Nano Res.* **2020**, *13*, 2525–2533.

[194] Li, J.; Kang, L.; Yu, Y. H.; Long, Y.; Jeffery, J. J.; Cai, W. B.; Wang, X. D. Study of long-term biocompatibility and bio-safety of implantable nanogenerators. *Nano Energy* **2018**, *51*, 728–735.

[195] Rijal, G.; Li, W. M. Native-mimicking *in vitro* microenvironment: An elusive and seductive future for tumor modeling and tissue engineering. *J. Biol. Eng.* **2018**, *12*, 20.

[196] Liu, L.; Guo, X. G.; Lee, C. Promoting smart cities into the 5G era with multi-field Internet of Things (IoT) applications powered with advanced mechanical energy harvesters. *Nano Energy* **2021**, *88*, 106304.

[197] Hwang, G. T.; Kim, Y.; Lee, J. H.; Oh, S.; Jeong, C. K.; Park, D. Y.; Ryu, J.; Kwon, H.; Lee, S. G.; Joung, B. et al. Self-powered deep brain stimulation via a flexible PIMNT energy harvester. *Energy Environ. Sci.* **2015**, *8*, 2677–2684.

[198] Zhao, L. W.; Gao, Z. B.; Liu, W.; Wang, C. L.; Luo, D.; Chao, S. Y.; Li, S. W.; Li, Z.; Wang, C. Y.; Zhou, J. Promoting maturation and contractile function of neonatal rat cardiomyocytes by self-powered implantable triboelectric nanogenerator. *Nano Energy* **2022**, *103*, 107798.

[199] Xu, J.; Cheng, C.; Li, X. R.; Lu, Y. L.; Hu, S.; Liu, G.; Zhu, L. H.; Wang, N.; Wang, L. C.; Cheng, P. et al. Implantable platinum nanotree microelectrode with a battery-free electrochemical patch for peritoneal carcinomatosis monitoring. *Biosens. Bioelectron.* **2021**, *185*, 113265.

[200] Burton, A.; Obaid, S. N.; Vázquez-Guardado, A.; Schmit, M. B.; Stuart, T.; Cai, L.; Chen, Z. Y.; Kandela, I.; Haney, C. R.; Waters, E. A. et al. Wireless, battery-free subdermally implantable photometry systems for chronic recording of neural dynamics. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 2835–2845.

[201] Curry, E. J.; Ke, K.; Chorsi, M. T.; Wrobel, K. S.; Miller III, A. N.; Patel, A.; Kim, I.; Feng, J. L.; Yue, L. X.; Wu, Q. et al. Biodegradable piezoelectric force sensor. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 909–914.

[202] Udvardi, P.; Radó, J.; Straszner, A.; Ferencz, J.; Hajnal, Z.; Soleimani, S.; Schneider, M.; Schmid, U.; Révész, P.; Volk, J. Spiral-shaped piezoelectric MEMS cantilever array for fully implantable hearing systems. *Micromachines* **2017**, *8*, 311.