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Recent Advances in Nanogenerator-Driven Self-Powered Implantable Biomedical Devices

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Implantable medical devices (IMDs) have experienced a rapid progress in recent years to the advancement of state-of-the-art medical practices. However, the majority of this equipment requires external power sources like batteries to operate, which may restrict their application for in vivo situations. Furthermore, these external batteries of the IMDs need to be changed at times by surgical processes once expired, causing bodily and psychological annoyance to patients and rising healthcare financial burdens. Currently, harvesting biomechanical energy in vivo is considered as one of the most crucial energy-based technologies to ensure sustainable operation of implanted medical devices. This review aims to highlight recent improvements in implantable triboelectric nanogenerators (iTENG) and implantable piezoelectric nanogenerators (iPENG) to drive self-powered, wireless healthcare systems. Furthermore, their potential applications in cardiac monitoring, pacemaker energizing, nerve-cell stimulating, orthodontic treatment and real-time biomedical monitoring by scavenging the biomechanical power within the human body, such as heart beating, blood flowing, breathing, muscle stretching and continuous vibration of the lung are summarized and presented. Finally, a few crucial problems which significantly affect the output performance of iTENGs and iPENGs under in vivo environments are addressed.

1. Introduction

Implantable electronic devices are pivotal medical technologies for observing, evaluating, and recording physical actions in vivo. Recently, the increased reliability, biocompatibility, biodegradability, miniaturization, and smaller energy requirement of IMDs have hugely promoted their application as physiological sensors, cardiac pacemakers, cochlear implants,

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and tissue stimulators.^[1,2] Therefore, millions of people depend on such devices for better quality of life.^[3,4] Jiang and Zhou have stated that 5% to 6% of the population in industrialized countries and 8% to 10% of people in the USA have relied on IMDs for reviving body functions, or expanding longevity.^[5] A vital prerequisite for sustainable function of implantable systems is a long-lasting uninterrupted energy source. Two crucial developments in the power supply area are the availability of lithium-ion batteries and reactive powering. The development and commercialization of lithium-ion batteries for IMDs was first achieved by a renowned scientist named Wilson Greatbatch.^[6,7] However, over time one of the major challenges for IMDs is the battery-based power supply,^[8–11] owing to the small power density, limited lifetime, chemical recycling problems, and bulk. An additional surgery is usually required for replacing the battery of in vivo medical devices, which is not only expensive but also causes risk and suffering for patients. Therefore, it is a matter of high demand to harvest ambient available biomechanical energy from the biological systems of the human body to build self-powered IMDs for sustainable driving of micro/nanosystems.^[12–16]

Many investigations highlight biomechanical energy harvesting approaches to replace batteries. Various energy-harvesting systems based on mechanical, chemical, thermal, and electrical methods inside the human body have been investigated such as using breathing, heart beating, blood flowing, muscle stretching, lung vibration, glucose oxidation, and movements of the inner ear.^[12,17–21] Among all these methods small-scale movements of organs are the most abundant energy sources in a living environment. Implantable piezoelectric nanogenerators (iPENG) and implantable triboelectric nanogenerators (iTENG) are a potential route for electromechanical energy conversion with numerous benefits.^[22–34] The first demonstration of iPENG and iTENG was established by Z. L. Wang's group in 2010 and 2014, respectively.^[26] However, the application of a nanogenerator in vivo is more complicated and challenging than with in vitro environments.^[4,35,36] The in vivo power output, reliability, and biocompatibility of these energy-harvesting devices are still inadequate for applications in real implantable medical systems.^[34,37] For in vivo application, several crucial issues need to be resolved. For instance, the material of the implantable nanogenerator requires to be biocompatible, as the in vivo environment is immersed in body liquid, which remarkably influences the functioning of the device.^[38] Then, the size of the nanogenerator requires to be designed for an available narrow and irregular space inside the human body. Moreover, the in vivo motion is so gentle that the nanogenerator must be hypersensitive to respond to such tiny movements.

Herein, we introduce recent advancements in research on harvesting biomechanical energy in vivo for sustainable operation of IMDs. In **Figure 1**, a visual summary of this first review paper on nanogenerators for in vivo application is depicted. At first, in Section 2,

triboelectricity-based implantable energy harvesters are described in terms of material fabrication, device structure, output performance and practical applications. Secondly, researches on piezoelectricity-based implantable energy harvesters are summarized (Section 3). Finally, in Sections 4 and 5, the problems and future perspectives of nanogenerators as in vivo energy harvesters are highlighted. Overall, this review will highlight more realistic strategies for overcoming the present difficulties.

2. Implantable Triboelectric Nanogenerator (iTENG)

Triboelectric nanogenerators are implanted inside a live animal for powering biomedical devices utilizing ambient available energies; they are termed implantable triboelectric nanogenerators (iTENGs). These nanogenerators are a recent invention of modern energy harvesting and storage technologies which energize small in vivo medical devices.

A single cycle of the operation of the contact-mode iTENG can be explained by the coupling of contact charging and an electrostatic effect^[29], as sketched in **Figure 2**. At the initial position, no charge is generated as the contacting materials are fully separated (Figure 2A). The inhalation of live rat brings the aluminum and kapton into contact, creating positive triboelectric charges on the aluminum and negative charges on the kapton side due to triboelectrification (Figure 2B). According to the triboelectric series (**Table 1**), a material toward the bottom of the series, when making contact with a material near the top of the series, will attain a more negative charge.^[47] According to this rule, electrons which are injected from the aluminum into the kapton are retained on the kapton; thus, the aluminum becomes an electrically positively charged material and the kapton becomes a negatively charged material. Afterward, during the separating condition of the iTENG due to exhalation of the rat (Figure 2C), an electron moves back from the kapton film to the aluminum foil due to the generation of a potential difference between the conductors. The maximum current flow is obtained when the two polymers are fully separated (Figure 2D). Again In the inhalation condition of the iTENG, the electron flow occurs in a reversed direction due to the generation of electric potential with reversed polarity (Figure 2E). It is noted that the Aluminum foil with nano-surface modification served as both the contact layer and electrode of the iTENG. During this process, the iTENG acts as an electron pump that drives electrons back and forth between the two electrodes.

It is a feasible approach for sustainable driving of IMDs to replace a battery-based power supply and to reduce the cost, risk and suffering of patients. Thus iTENGs not only improve the quality of health treatment but also increase the life-time and miniaturization of in vivo medical devices.

So far, iTENGs have been employed to convert the biomechanical energy from heart beating^[40], breathing of rat^[29], muscle stretching^[3], blood flow^[26], respiratory motion^[41], the pressure of systolic and diastolic blood vessels^[26,40] into electricity. The electricity generated by iTENGs has been used for clinical therapy of bone remodeling and orthodontic treatment^[3], nerve cell stimulation^[41,96], and a hematoxylin and eosin (H&E) staining^[39], with independent blood pressure estimation and blood flow velocity calculations^[40]. **Figure 3** shows a typical self-powered implantable triboelectric active sensor, which provides precise, continuous and real-time biomedical monitoring of multiple physiological signals. The power conversion by the iTENG can be enhanced by controlling the electron affinity, surface work function, chemical structure of the triboelectric material, contacting-separating speed, pressure, surface roughness of materials.^[42] Therefore, iTENGs hold a great potential in the future of the health care industry in real-time or continuous power-harvesting biomedical devices that are do not require an external power supply.

2.1. iTENG Material Selection and Fabrication

Triboelectrification has not been used for many indispensable applications for a long time, although it has been well-known for hundreds of years. In recent times the triboelectric effect has been successfully used for transforming ambient biomechanical energy inside the body into electrical energy, and as self-driven IMDs.^[33] The choice of materials for iTENG is limited to flexible materials with a triboelectrification effect. However, the potentiality of a material for sourcing or sinking electrons relies on its polarization. In 1757, John Carl Wilcke published the foremost triboelectric series of semiconductor materials.^[47] A material located at the lower end of the series, when in contact with a material near the upper end of the series, will gain electrons. The further two materials are situated apart on the series, the higher the amount of electrons created and transmitted.

Along with choosing materials from the triboelectric series, the surface morphologies require to be adjusted by physical methods with the formation of line, pyramid, pillar, hemisphere based nanopatterns, which are useful for augmenting the triboelectrification. The contacting areas of the triboelectric materials need to be modified chemically utilizing

different combinations of molecules, nanoparticles, nanotubes, nanowires, to improve the power production.^[43] Thus the surface potential can be largely augmented by modification of the contacting surfaces.^[43,44] Moreover, the inclusion of micro/nanopatterns on the touching surfaces not only enhances the surface electrification but also changes the effective permittivity of the constituents, so that the device is efficient for electrostatic induction.

Zheng et al. used nanostructured polytetrafluoroethylene (n-PTFE, 50 μm) as the triboelectric layer to increase the output signals as shown in **Figure 4A**. A Kapton film (150 μm) was fixed on the n-PTFE layer to increase the flexibility of the device and an ultra-thin Al foil (100 μm) employed as both triboelectric layer and electrode. Moreover, Figure 4B shows how two biodegradable polymer (BDP) layers of poly(lactide-co-glycolide) (PLGA), poly(vinyl alcohol) (PVA), poly(caprolactone) (PCL), and poly(3-hydroxybutyric acid-co-3-hydroxyvaleric acid) (PHB/V) with nano-patterns were connected as contacting portions. A tinny magnesium layer of 50 nm was placed on the back of both contact areas as a conducting film. The entire arrangement was enveloped in BDP to stop it from touching the ambient in vivo physiological atmosphere.

Likewise, Figure 4C demonstrates that spacers combined with an elastic titanium strip were integrated on Kapton film to guarantee the contact of the triboelectric layers more effectively. It also presents SEM images of the n-PTFE film, which was modified by dry-etching to create nanopatterns to augment the surface triboelectric charge density. A core-shell covering strategy was used to obtain biocompatible and flexible packaging. A flexible Polydimethylsiloxane (PDMS) layer was employed by spin-coating to enhance the leak-proof properties. To avoid potential erosion in the humid and corrosive in vivo environment, a Parylene film was placed to form a high-density coating layer. In addition, the rubber surface has a wrinkled structure (Figure 4D). Sodium chloride solution and water were utilized to perform as electrode materials because they are renewable, cheap, and environment-friendly. Overall, all the iTENG materials were fabricated with nanostructures of various shapes to increase the triboelectric coefficient.

2.2. iTENG Device Structure Formation

Although any structure of iTENG materials exhibit triboelectricity, selecting the right shape of the device can give maximum output. Researchers have introduced different device structures for convenient operation and better performance of the product.^[3, 29, 39, 40] An effective contact and separation process of the iTENG is one of the challenges for efficiently producing electricity when implanted. To address this issue, W. Tang et al. utilized an arch shape nanostructured polytetrafluoroethylene (n-PTFE, 50 μm) thin film as a substrate for its excellent strength and elastic capability as depicted in **Figure 5A**.^[3] Furthermore, Prof. Zheng and his research group fabricated a flexible Shell type iTENG structure, where PDMS and ITO (indium tin oxide) were used as the contacting surfaces (Figure 5B).^[29] They also developed a resilient titanium strip as the keel structure as shown in Figure 5E, which significantly enhanced the mechanical behaviour of the total structure and guaranteed solid contact and separation of the iTENG.^[40] To further augment the reliability of the iTENG and to avoid adhesion in the physiological environment, parylene C was deployed on the surface as a shell structure to form a hole-free coating layer. This “layer by layer” encapsulation strategy ensured the structural stability of the iTENG and its resistance to a complex internal environment. Basically, the PDMS layer was used to ensure the flexibility of the overall device to bend conveniently in response to the tiny movements made by the rat’s breathing.

The core-shell covering strategy was employed by Y. Ma et al. to achieve the hermetic and flexible packaging.^[39] To augment the stability of the overall device and to avoid potential erosion in the humid in vivo environment, a parylene film was utilized as shown in Figures 5C,D. Therefore, for the device structure selection, it was ensured that all the devices were shaped in such a manner that automatic cyclic contact between anodes and cathodes occur time to time by little movement. Moreover, the cylindrical or arc shape of the device guaranteed an enhancement in robustness and allowed it to perform efficiently for gentle in vivo motion with tiny amplitude.

2.3. iTENG Output Performance

Different triboelectric nanogenerators have been implemented for self-powered medical systems since 2014. In Table 1, firstly, various soft materials such as PDMS, PTFE, PLGA, PCL, Kapton^[8] were utilized for sustainable and continuous powering of implantable medical

devices inside the body. Secondly, the contacting surfaces of the iTENG were modified by means of fabricated nanopatterns and nanostructures to increase the triboelectric coefficient and output performance of the device. Thirdly, different types of iTENG implementations have been highlighted, particularly for self-energized medical systems. The trend in the advancement of iTENG is for flexible, viable, economical, efficient, biocompatible, biodegradable materials, which can be applied to construct the self-energized biomedical devices for utilization in an in vivo environment.

Driven by the heartbeat of a Yorkshire porcine, the open-circuit voltage (V_{oc}) soared to 14 V^[40], and the corresponding short-circuit current (I_{sc}) increased to as much as 5 μ A, which were enhanced by factors of 3.5 and 25, respectively, compared with the previous in vivo outputs of energy-transformation equipment based on the triboelectric effect.^[27–29] Owing to its excellent in vivo performance, a self-powered wireless transmission system (SWTS) was fabricated and the electrical signal associated with the in vivo heartbeat was successfully transmitted, showing its applicability for actual-time distant cardiac monitoring.^[40] Moreover, a large dimension iTENG (3 cm $\times$ 2 cm) was tested by Zheng et al. and transformed biomechanical energy from a rat's normal inhalation into electrical energy, having an energy density as high as 8.44 mW cm⁻².^[29]

In work performed by Zheng et al., a transient biodegradable property of an iTENG employing hydrophobic action at the surface of the PVA-covered nanogenerator was demonstrated.^[41] Tang et al. fixed an iTENG (1.5 cm $\times$ 1.0 cm) to the arm of a live rat and demonstrated the practical capability of a self-energized small-power laser cure system.^[3] Then, the nanogenerator was placed between the liver and diaphragm. A periodic touching between the triboelectric films of the iTENG caused by the inhalation and exhalation of the rat generated electric energy. The inhalation of the rat was run by a respirator at a fixed rate of 50 times min⁻¹ and the current and voltage were observed with values of 0.06 nA and 0.2 V, respectively. The ability of the self-powered sensor was evaluated by Ma et al. and it was found that the in vivo output performance of the device could reach to 10 V and 4 μ A.^[39] Although the in vivo electrical output performances were lower than those of in vitro tests, it was still higher than the majority of earlier reported devices for implanted energy harvesting.^[27,29,46]

2.4. Practical Applications of iTENG

Due to the interesting properties of iTENGs such as low cost and high performance, practical application of these devices has gained significant attention. The applications of iTENGs in energy and sensor systems have been studied earlier.^[47–50] In this part, we highlight the most important practical in vivo applications of iTENGs in cardiac monitoring, pacemaker powering, nerve cell stimulation, a laser cure system for osteogenesis, and monitoring real-time respiratory rate, heart rate, and blood pressure.

2.4.1. Energy Harvesting from the Heartbeat of a Yorkshire for Real-Time Wireless Cardiac Monitoring

Wireless transmission is essential for real-time and constant monitoring of physiological signals, which is of great importance for timely diagnosis and treatment of some severe or chronic diseases. Zheng et al. fabricated a self-powered wireless transmission system (SWTS) and successfully transmitted an electrical signal associated with the in vivo heartbeat, showing its feasibility for real-time remote cardiac monitoring (**Figure 6A,D**)^[40]. A capacitor in a power management unit was charged by heartbeat-related electrical energy, transmitted through the implantable wireless transmitter, and received by the external receiving coil as electromagnetic waves (Figure 6B,C). The wireless transmitted signal was subsequently recorded with an oscilloscope for further data analysis. They investigated the potential application of the SWTS as a motion frequency sensor at a fixed charging time of 10 s.

As shown in Figure 6, the different heart rates (60, 80, and 120 bpm) generated by the electronic pacemaker were successfully monitored by the SWTS ($R_2 = 0.983$); the results were consistent with the simultaneously recorded ECG signal (Figure 6F). Moreover, by charging for only 3 s at the heart rate of 60 bpm, the stored energy in the power management unit was sufficient to transmit wireless data, which indicates the outstanding sensitivity of the SWTS (Figure 6E).

The heart is one of the most powerful organs inside the body; so that the iTENG was set with care between the heart and the pericardium by fixing it on the inner side of the pericardium, which can effectively drive the iTENG. The integrated keel structure of a Ti strip with a Kapton substrate strengthens the mechanical properties of the iTENG and effectively guarantees the contact and separation process of the iTENG in vivo. Here, to offer both long-time reliability and flexibility, the iTENG was packaged by soft materials layer by layer,

forming a robust core/shell/shell structure. The iTENG exhibited good leak immunity for in vivo tests. The encapsulation layer also plays an important role for defending the host soft tissue from possibly toxic components of the apparatus. The selected encapsulation materials in this work were proven to be biocompatible and resistant to chemically harsh environments.^[51]

2.4.2. Harvesting Energy from the Breathing of a Rat for Powering Pacemaker

Zheng et al. utilized an iTENG for powering in vivo biomedical equipment and formed a self-energized system.^[29] The iTENG was inserted beneath the left chest membrane of the rat (Figure 7C,D). The breathing of the rat created contraction and extension of the thorax, which in turn bent the narrow Kapton film, resulting in the periodical contact between the PDMS nano-pattern and the Al film. Thus electricity produced by the contact electrification and electrostatic induction caused electrons to flow backward and forward in an outer circuit in sympathy with the breathing vibration. A constant breathing rate of 50 times minute^{-1} was utilized by a regulated respirator to calculate the open-circuit voltage and short-circuit current. During the one-cycle operation of the iTENG, a positive current peak was delivered by inhalation, and after that a negative current peak was generated by exhalation.

The average magnitudes of the voltage and current output were almost 3.73 V and 0.14 μA , respectively (Figure 7A,B). In the typical forced-vital-capacity (FVC) curve (Figure 7E, left), the proportion between the inspiratory reserve volume (IRV) and expiratory reserve volume (ERV) was similar to that between the positive and negative current peaks and, moreover, a noticeable synchronization was also revealed by matching the FVC curve and the current curve as presented in Figure 7E.

They proposed and fabricated the self-energized pacemaker model like a 555 timer IC (Figure 8A,B). The outcome of a particular stimulation pulse of the developed pacemaker model was almost 25 μA (I_p), and the pulse width was about 2 ms (t_p), which was analogous to commercial pacemakers. After that the charged capacitor was used to drive the pacemaker and stimulation pulses with various frequencies were successfully verified (Figure 8C). Moreover, they also employed the iTENG-driven pacemaker model to control the heart beating rate of the rat (Figure 8E). Stimulation pulses at different frequencies (2 Hz, 3 Hz and 5 Hz) generated by the pacemaker were applied to the heart, and the heart beating rate was controlled to match the frequency of the stimulation beat.

They re-designed the iTENG to locate it between the diaphragm and the liver (**Figure 9A,B**). The expansion and contraction during respiration of rat can drive the iTENG, and generated an AC output (0.6 μ A) (Figure 9C). These devices suffer from several drawbacks that to be resolved. For instance, firstly, the in vivo environment greatly influences the output performance of the iTENG as it is filled with body fluid,^[29] secondly, careful packaging is required via biocompatible and flexible polymers, thirdly, the in vivo movement is so mild and the amplitude is so small that the iTENG need to be finely tuned to work from small movements.

2.4.3. Energy Harvesting from the Subdermal Region of a Rat to Stimulate Nerve Cells

A basic understanding of the in vivo degradation procedure and the evaluation of tissue reactions performs an important part in the modeling and improvement of biodegradable systems for therapeutic use. Zheng et al. conducted several experiments examining the degradation characteristics of a biodegradable triboelectric nanogenerator (BD-TENG) at different time durations. Two BD-TENGs were made up using PVA and PLGA encapsulation, respectively.^[41] Those devices were then inserted in the subdermal area of rats (**Figure 10A,E**). Figure 10A shows the case of the covered BD-TENG. 9 weeks after insertion, no actual infection was observed, indicating a good biocompatibility of the BD-TENGs (Figure 10B).

No significant inflammatory reaction was detected when the BD-TENG was applied between the muscle and the subdermal layers (Figure 10F). A few neutrophilic granulocytes were noticed at the fourth week, but the rate was not increased at time which shows a good biocompatibility of the device.

The output response of the system was significantly diminished from 4 to 1 V after 2 weeks insertion (Figure 10G). Moreover, the TENGs were tested as implantable devices (Figure 10J,K). They worked for more than 1 day in vivo after applying hydrophobic treatment (output, about 3 V) and nearly dissipated within 3 days (Figure 10I).

The application of electrical stimulation to cells offers a promising direction for tissue operations.^[25] Different electric stimulation methods have been established as effective in medical and study sceneries.^[25,52–54] Zheng et al. united the BD-TENG with stimulation equipment to illustrate the utilization of a BD-TENG for neuron tissue alignment.^[41] The entire system was enclosed with a tiny PDMS surface (100 nm) to avoid a probable electrochemical reaction, while Cu conductors were submerged in the culture area (Figure

11C). The metal bands were equally displaced and the widths of the bands were about 100 nm as outlined in Figure 11D. The BD-TENG, with an output of 1V, was joined to the conductors by a bridge rectifier (Figure 11A,B). Therefore, the electric field at the 2 bends was about 10 V mm^{-1} . The principal neurons were sewn on to the stimulation equipment coated with by polylysine, and exposed to repetitive electric stimulation after 1 day of culture. Electric field alternations of 0 and 10 V mm^{-1} at 1 Hz were used for 30 min per day. After 5 days of culturing, the nucleus and cytoskeleton were tarnished. As shown in **Figure 11**, the majority of the stimulated neurons were fairly aligned (Figure 11F). The cytoskeleton of the neurons was observably parallel to the electric field, whereas the cell organization and cytoskeleton in the regulator group had no obvious alignment (Figure 11G).

The neuron cell orientation was driven by the electric field from the BD-TENG and was vital for neural healing. Due to its notable biocompatibility, and its adjustable degradation characteristic, the BD-TENG represented in this task is a vital energy source for implant electric stimulation.

2.4.4. Implementation of iTENG in the Liver of a Rat to Build a Self-Powered Laser Cure (SPLC) System for Osteogenesis

Tang et al. fixed an iTENG (1.5 cm x 1.0 cm) to the arm of a live rat and demonstrated the real-world application ability of the self-energized laser treatment method.^[3] An iTENG was attached to a human and charged a capacitor to 5 V in 60 s by harvesting energy from an arm through walking (**Figure 12B**). The SPLC structure can perform well, operated by people's normal walking, with a laser radiation rate of 1 pulse min^{-1} . Additionally, they examined the possibility of implanting the system in an adult rat. The iTENG was located between the diaphragm and the liver as shown in Figure 12D (inset). The breathing of the rat produces a regular movement of the diaphragm. The distortion of the iTENG produced by the touching of the ITO layer to the PDMS film produced electricity. The short-circuit current and open-circuit voltage output of the iTENG were 0.06 nA and 0.2 V, respectively (Figure 12D,E).

Tang et al. employed the system on a human arm and found that the laser was adequately stimulated by 60 s of walking. This performance reveals a great development in the application of iTENGs in IMDs for the clinical treatments of bone remodeling and orthodontic cure.

2.4.5. Harvesting Triboelectric Energy for Monitoring Respiratory Rate, Heart Rate, and Blood Pressure

The ability of the self-powered sensor was evaluated by Ma et al. and they found that the in vivo output performance of the implantable triboelectric active sensor (iTEAS) could reach 10 V.^[39] An arterial pressure tube was fixed in the right femoral blood vessel and linked to the data acquisition (DAQ) system. The peak output voltage of the device increased when the blood pressure (BP) was increased by an infusion of epinephrine (**Figure 13A**). To minimize the interference of respiratory movement with the voltage and blood pressure, a detailed examination of the relationship between the two involved averaging the values of six consecutive peaks was made by the same research group.

Although there is a correlation between the systolic blood pressure (sBP) and output voltage, with a sensitivity of $17.8 \text{ mV mmHg}^{-1}$, the linearity is not strong ($R_2 = 0.78$) (**Figure 13B**). This can be interpreted by the issue that the sBP is not only related to the heart but also depends on various other physiological attributes. As schematically depicted in **Figure 13C**, the peak voltage occurs when blood is pumping out from the heart, and the recorded BP elevates to the culmination (sBP) when the blood flows through the femoral artery; thus a leading time (LT) exists between two corresponding peaks (**Figure 13D**). Further study under different sBPs shows that the velocity of blood flow rose and the leading time dropped when the sBP was high, as shown in **Figure 13E**.

The respiratory rate (RR) presents another pivotal sign that is important for examining the function of the respiratory system.^[55,56] Traditional methods for RR measurement are time-consuming, costly, and overly sensitive to artefacts brought on by the movements of patients.^[57–59] Ma et al. also observed an interesting phenomenon, that the magnitude of the output voltage was significantly affected by respiratory motion, characterized by cyclic variations of the voltage peaks. In consideration of the effect of the motion of the lungs, three sites of implantation were selected to assess the monitoring function for respiration: left lateral wall (LLW), right lateral wall (RLW), and posterior wall (PW) of the heart (**Figure 14A,B**). The highest output voltages of the iTEAS at the LLW and RLW presented stable periodical changes along with the respiration (**Figure 14C,D**). The peak output voltage changed uncertainly and irregularly at the place of PW (**Figure 14D**), thus showing that the lateral walls of the heart are the optimal positions for monitoring respiration.

Further analysis under the fluctuations revealed that the highest output voltage was attained at various phases of the respiratory cycle (RC). **Figure 14E** demonstrates that the

output voltages increase from ≈ 4.8 to ≈ 6.3 V at the time of inhalation and reduce to the baseline during the time of exhalation. This excellent outcome guaranteed the potential of iTEAS to be a precise self-powered respiratory monitor.

3. Implantable Piezoelectric Nanogenerator (iPENG)

Biomechanical energy such as the natural contraction and extraction of the internal organs of live animals can be transformed into electricity by piezoelectric materials. When a piezoelectric nanogenerator can be a stable and reliable power source for operating implantable medical devices, it is termed as implantable piezoelectric nanogenerator (iPENG). The working principle of a typical iPENG is schematically illustrated in **Figure 15**. A high electric field is applied to create and align dipoles in the thin film of piezoelectric material (PMN-PT) as shown in the upper side of Figure 15A. Once the iPENG is bent by means of any kind of movement piezo-potential is produced inside the PMN-PT layer (Figure 15B), causing electron flow in the outer circuit to equilibrium the electric field created by dipoles and accumulate at the upper Au electrode. When the iPENG come back to the initial flat state, the charges tend to return to their initial locations. Therefore, under periodic movements of bending and unbending, positive and negative electrical signals are produced from the iPENG.^[25] Different methods of harvesting ambient mechanical energy utilizing piezoelectric elements have been introduced previously.^[20,60,61] Later piezoelectric devices have shown numerous advantages^[18,25,62–66] and have become a potential route for transduction of ambient mechanical energy to electricity. Some piezoelectric materials are biocompatible and applicable for in vivo power harvesting.^[67–69] The first demonstration of an iPENG was made by Wang's group in 2010^[26] and the device was further modified more recently.^[29] However, the uses of nanogenerators for in vitro and in vivo environments are different. Some critical issues are essential to be solved prior to utilizing them inside the body, for instance, biocompatibility, biodegradability, nontoxicity etc.

3.1. iPENG Material Selection and Fabrication

Piezoelectric nanogenerators are promising for the self-energizing of micro-systems used for in vivo bio-detecting, observing, and treatment.^[25, 34] The effective materials in an iPENG have crystal-like structures with the ability to efficiently convert ambient mechanical power into electricity. This behavior of these materials offers the capability to capture even very tiny biomechanical power from their surroundings, and convert it into electric charges which can be utilized to energize electronics.^[26,71,72] Wang et al. first introduced the iPENG in 2010 by investigating the piezoelectric characteristics of ZnO nanowire by implanting it in a live rat and energy harvesting from the breath and heartbeat.^[25] Since then, various piezoelectric

materials, for example lead zirconate titanate (PZT)^[73], barium titanate^[43], polyvinylidene fluoride (PVDF)^[71], have been considered for powering IMDs. The power production in iPENGs depends on their piezoelectric characteristics, and they generate alternating current. When the piezoelectric material experiences a strain, an equivalent current output crest can be achieved.^[23]

For the application of iPENGs in IMDs, biocompatibility of the material is critically important. From that point of view, ZnO has a good biocompatibility^[34], but because of the low piezoelectric coefficient the output energy of ZnO-based iPENGs is small, which confines their uses to various implantable devices. On the other hand, the lead zirconatetitanate (PZT) family offers a high piezoelectric coefficient, but the toxicity of Pb causes serious pollution to the environment inside an animal body, which restricts the uses of Pb-related materials for IMDs. Therefore, a combination of piezoelectric materials named $0.5\text{Ba}(\text{Zr}_{0.2}\text{Ti}_{0.8})\text{O}_3 - 0.5(\text{Ba}_{0.7}\text{Ca}_{0.3})\text{TiO}_3$ (BZT-BCT) has replaced the PZT family (200–710 pC/N) because of its lead-free property and extraordinary piezoelectric coefficient value (≈ 620 pC/N).^[61,74,75]

Yuan et al. used this BZT-BCT material for the first time for building iPENGs and verified the biocompatibility of its nanowires (NWs).^[33] Due to the intrinsic superior flexibility and elasticity, high piezoelectric coefficients^[76], good mechanical behavior and excellent biocompatibility^[27,34,61,74,75,77,78] of PMN-PT polymers were directly used in iPENG design by Keon Jae Lee and his research team.^[25] iPENG is also used for diagnostic ultrasound imaging and investigating geometric design in diaphragms by ultrasonic energy transducer with a wide frequency bandwidth.^[97–98] Moreover, Qiongfeng Shi et al. utilized a dual-in-line package (DIP) for covering a Piezoelectric Ultrasonic Energy Harvester (PUEH) and used a PZT transducer as a transmitter in the acoustic energy transfer (AET) system as illustrated in **Figure 16E**^[73]. Overall, researchers have chosen a combinations of piezoelectric materials in building iPENG due to better flexibility, compatibility, and piezoelectric coefficient rate of the device.

3.2. iPENG Device Structure Formation

Structural modification plays a vital role in an efficient iPENG outcome. Shin et al. first fabricated vertically aligned phages by a prototype-based self-assembly method and termed as phage nanopillars (PNPs) (**Figure 17A**).^[80] These PNPs were surrounded by a PDMS layer, and the porous prototype was totally dissipated which shows its good biodegradability. A bendable and cost-effective power harvester, supported by a crystal-like piezoelectric $(1-x)\text{Pb}(\text{Mg}_{1/3}\text{Nb}_{2/3})\text{O}_3 - x\text{PbTiO}_3$ (PMN-PT) thin layer on a flexible substrate to achieve a self-energized artificial pacemaker was reported by Hwang et al.^[25] It has a piezoelectric charge constant of 2500 pC N^{-1} , about 4 times as great as for PZT, 20 times as great as for BaTiO_3 , and 90 times as great as for ZnO .^[80,81] The stress-controlled exfoliating technique was enhanced for relocating the PMN-PT thin layer from a bulk material onto a bendable substrate without any mechanical loss by utilizing the latent remaining pressure of the Ni layer.^[82] The schematic of such a nanogenerator is shown in Figure 17D. A cyclic outer stress was applied to the device to obtain piezoelectricity.^[25]

Figure 17C provides the graphic illustrations of a bendable PZT mechanical energy harvester (MEH). The main active material is a capacitive structured PZT layer (500 nm) between the bottom (Ti/Pt, 20 nm/300 nm) and top (Cr/Au, 10 nm/200 nm) conductors. In an MEH unit 12 sets of 10 such assemblies are joined in parallel. Each of the 12 sets is also joined in series with its adjacent set to increase the response. A tiny layer of polyimide (PI) is utilized as encapsulation of the device to isolate it from bodily fluids and tissue.

3.3. iPENG Output Performance

Various piezoelectric nanogenerators have been devised for self-powered medical devices since 2010. **Table 2** depicts a comparison of iPENG performance and their applications for IMDs. Different materials such as ZnO, PZT, PMN-PT, PVDF^[20,25,27,33,71,73,80,83] were used for building iPENGs using various synthesis techniques such as physical vapor deposition, sputtering, electron beam evaporation and polarization. Numerous applications based on iPENG have been reported, especially for implantable medical systems. The research

progress of iPENG toward being efficient, biocompatible and biodegradable can be expected to develop more self-powered IMDs for applications for in vivo environments.

Zhou Li et al. tightly fixed the iPENG to the surface of the heart and obtained the current and voltage outputs about 30 pA and 3 mV, respectively.^[83] They also stated that a heartbeat comprises the ventricle and auricle beating; that accounts for the bigger and slighter peaks during the process. Frequency adjustment of the piezoelectric energy harvester was performed by Chengkuo Lee's research group to minimize the effect of standing waves for any given distance, or even distance fluctuations during the energy transfer process. By only adjusting the frequency from 250 kHz to 240 kHz, the output power was enhanced from 0.59 $\mu\text{W cm}^{-2}$ to 3.75 $\mu\text{W cm}^{-2}$.^[73] Moreover, Hwang et al. performed a real-time electrical stimulation using the artificial heartbeat of a living rat, employing the well-performing PMN-PT power energizer.^[25] The peak output voltage and current of the bendable PMN-PT thin-layer energizer were 8.2 V and 0.223 mA, respectively^[25], utilizing the cardiac motion of the rat which is enough for powering a pacemaker. The converted electricity can drive 50 LEDs and recharge batteries for operating moveable electronics.

3.4. iPENG Practical Application

Recent progress in implantable piezoelectric nanogenerators opens many doors for power transduction from ambient biomechanical energy to electrical charge for real-world in vivo applications. Considerable research and effort have been made to augment power production through iPENGs to commercialize their application to power implanted bio-devices. A few of these are highlighted below.

3.4.1. Harvesting Piezoelectric Energy from the Breath and Heartbeat of a Live Rat

To unite nano-structured piezo-materials with tissues in vivo, Li et al. pointed out that ZnO nanolines can be safely used as they are biocompatible.^[26] They harvested biomechanical power for the very first time and built an AC nanogenerator in 2010, which was implemented in a living rat to employ power produced by its heart beating and breathing.

The ZnO nanowire was formed by the physical vapor deposition (PVD) technique with a diameter of 100–800 nm and a length of about 100–500 nm. Because of the existence of bodily liquids around the implant, the whole equipment was enclosed by a bendable polymer to isolate it from the nearby medium and to augment its strength. To test the performance of the nanogenerator output electrical responses like voltage and current values were measured.

The mechanical deformation associated with the regular movement of the diaphragm was converted into electrical power (**Figure 18A**). Adult rats (Hsd: Sprague Dawley SD, male, 200–224g) were employed for the experimentation. The stomach cavity of the rat was unwrapped to implanting a nanogenerator at the ventral side of the diaphragm (Figure 18B).

Before placing the nanogenerator within the body, the voltage and current responses were measured to test the existence of a schottky barrier, as displayed in Figure 18C. After that the nanogenerator was joined to the diaphragm by a biocompatible cell adhesive, as shown in Figure 18A. The breathing of the rat resulted in movement of the diaphragm, which in response created periodical expansion and contraction of the device. The piezoelectric potential produced in the nanowire caused electrons to drift back and forth in an outer circuit in sympathy with the physical stretching and releasing of the diaphragm. The output current is shown in Figure 18D.

3.4.2. Piezoelectric Energy Harvester Integrated with a Pacemaker

Sound energy conversion is a rising energy harvesting method for in vivo biomedical equipment. However, it does not have much potential for energizing self-powered in vivo biomedical equipment for two main reasons – the bulk of piezoelectric acoustic transducers and response inconstancy with transmitted displacement due to stationary waves. Qiongfeng Shi et al. reported an MEMS-based piezoelectric ultrasonic energy harvester (PUEH) to create self-energized in vivo biomedical electronics.^[74] The PUEH is a micro-fabricated PZT diaphragm array which has a large active bandwidth. Displacement variation for in vivo biomedical equipment is obvious due to the manual surgical procedure and it intensely affects the coupling performance of the device. This problem can be greatly resolved by active frequency regulation. The developed PUEH revealed a great promise to find application with in vivo biomedical platforms as an energy harvester.

Figure 19A shows a schematic of the proposed PUEH driving a pacemaker inside a body. The PUEH is developed from a small PZT micro-diaphragm array, making it suitable to be integrated with an implantable pacemaker without notably increasing the device volume. Owing to the optimized design of the PZT micro-diaphragm, two resonant modes are overlapped, providing an extra-wide operation bandwidth. Distance fluctuations during the energy transfer process caused by breathing or muscle movement can be overcome by this

frequency adjustment. When the distance slightly deviates (i.e., from 1 cm to 1.1 cm) at 370 kHz, the output power density drops dramatically from $4.10 \mu\text{W cm}^{-2}$ to $0.18 \mu\text{W cm}^{-2}$. The power and efficiency loss can be restored to $4.06 \mu\text{W cm}^{-2}$ by changing the ultrasound frequency to 340 kHz. The proposed MEMS-based broadband PUEH showed great potential as a power source for various IMDs.

The overall device structure of the PUEH consists of 7 PZT diaphragms that are joined in parallel to increase the output performance (Figure 19B). The PZT diaphragm array is manufactured on a silicon wafer. Each PZT diaphragm contains Si, SiO_2 , a lower Pt conductor, PZT, and an upper Pt conductor as shown in Figure 19C, with dimensions $500 \mu\text{m} \times 250 \mu\text{m}$. The optimized length-to-width ratio and thickness provide the PZT diaphragm with useful device performance and robustness. A dicing chip having a size of $5 \text{ mm} \times 5 \text{ mm}$ is shown in Figure 19D on a human finger.

Figure 20 shows an in vitro test of the PUEH to transmit power through a slice of pork tissue. When the ultrasound frequency is 370 kHz, the output power is only 16.5 nW (Figure 20B). By adjusting the frequency to 330 kHz, the output power is augmented to 85.2 nW. The ultrasound intensity through a pork tissue decreases because of the impedance mismatch of pork tissue and the water medium, ultrasound attenuation through the pork tissue, and ultrasound reflection at the interfaces.

The PUEH is fabricated from a PZT diaphragm array with miniaturized size and optimized length-to-width ratio. Frequency adjustment of the PUEH was performed to minimize the effect of standing waves for the given distances, or even distance fluctuations during the energy transfer process. Thus distance fluctuation was overcome by adjusting the ultrasound frequency for the fluctuating distance. The proposed MEMS-based broadband PUEH has a high potential to be integrated into various IMDs for diversified applications.

3.4.3. Investigation of iPENG Biocompatibility and Biosafety

Abundant in vivo biomechanical energy is available and can be harvested to solve the challenge of energizing IMDs. iPENGs can be combined with other tiny useful electronics to build a self-energized system. After producing current from the movement of a rabbit quadriceps in one investigation,^[77] a piezoelectric nanogenerator showed a significant prospect to be amalgamated with IMDs. Furthermore, iPENGs have been implanted inside an animal body to gather power from the movement of various organs, for instance lung, diaphragm and heart.^[27] Additionally, in comparison to a battery, a nanogenerator can energize in vivo devices for an extended period as it can nonstop translate ambient

biomechanical motion into electricity. Though ZnO has excellent biocompatibility,^[34] owing to its relatively low piezoelectric coefficient its use is restricted for driving implant systems. Although PZT has large piezoelectric coefficient value but it is not applicable in iPENGs as Pb toxicity attributes serious contamination inside the human body by the chemical synthesis technique. However, a lead-free piezoelectric-material, $0.5\text{Ba}(\text{Zr}_{0.2}\text{Ti}_{0.8})\text{O}_3 - 0.5(\text{Ba}_{0.7}\text{Ca}_{0.3})\text{TiO}_3$ (BZT-BCT) exhibits a piezoelectric coefficient of about 620 PC/N^[75] which is higher than the conventional PZT family (200–510 PC/N)^[61,74].

Yuan et al. constructed BZT-BCT nanowires by an electrospinning process,^[78] and tested the decomposability of nanowires by means of a 3-(4,5)-dimethylthiazol-2-yl-4-methyl-5-phenyltetrazolium bromide (MTT) test, a scanning electron microscope (SEM), and a laser scanning confocal microscope (LSCM). Chang liver cells and L929 cells grow well in a culture solution with BZT-BCT NWs and on the surface of a film composed of BZT-BCT NWs, respectively. Chang liver tissues could cultivate well on the top face of the entire nanogenerator, and the implant tests also established the biocompatibility of the whole device.

The iPENG was implanted into a rabbit's rear to examine the implant biocompatibility (**Figure 21A**). Portions of BZT-BCT nanowires were exposed to the neighboring cells. By systematically pressing the rear of the rabbit, the partially packed iPENG could provide an output current of 0.13 nA (Figure 21B). After 5 weeks, the device with the adjacent cells was cautiously released from the rabbit (Figure 21C). By checking the slices of tissue and comparing the cell morphology surrounding the nanogenerator (Figure 21E–F) with that unleashed from parts remote from the device (Figure 21G–H), no cell destroy, scratching were obtained, that verified there were no damages. This outcome also confirms that the nanogenerator has a good decomposability for implant usage. Overall, the BZT-BCT NW iPENG has valuable implant biosafety, which eases its path to potentially energize in vivo devices.

3.4.4. Piezoelectric Energy Harvesting from Motion of Heart, Lung, and Diaphragm

Dagdeviren et al.^[28] reported piezoelectric energy-harvesting elements that perform very efficient electromechanical power transduction from the normal expansion and contraction

movements of the diaphragm, heart, and lung, tested in various animals with body parts like human. An integrated usage of those harvesters with converters and batteries offers a flexible system, feasible amalgamation with the heart by operation with efficiencies of around 2%. It offered much improvement in nano-material based autonomous power harvesters.

An article on implants described attaching nanogenerators to epicardial locations on the left ventricle (LV), right ventricle (RV) base, and free wall of bovine and ovine hearts as presented in **Figure 22A(a)**. The PZT MEH maintains conformal contact through the complete period of cardiac movement from expansion to contraction. The size and beat rate of the heart affect the overall performance²⁶. Figure 22A(e) shows that increasing the bovine heart beat rate using a pacemaker raises the outcome in proportion to the heart rate.

Outcomes for mounting on the ovine lung (Figure 22B) are persistent with expectation. Specifically, in both types respiratory motion can be transformed into voltage (Figure 22B). Similar realizations with the heart and responses from the lung demonstrate weak interspecies variations (Figure 22B). These findings reveal that bendable PZT-based structures are able to harvest energy from various bodily organs. Records gathered from the chest, open (Figure 22C(a)) and close (Figure 22C(b)), also depict identical competencies in energization, as shown in Figure 22 C(c).

The reported outcomes proof that piezoelectric power harvesters can yield critical electricity from movements of bodily organs for practical application in implants. Furthermore, similar structures can be applied in skin-attached arrangements for health condition observations.

3.4.5. Powering Pacemaker by Cardiac Motion of Live Rat

Artificial cardiac pacemakers have made a crucial contribution to control heart beating utilizing electronic signals for contracting the heart muscles of individuals who are ill with heart block or abnormal heartbeat rate.^[81,86] Hwang et al. fabricated high-performance crystalline $(1-x) \text{Pb}(\text{Mg}_{1/3} \text{Nb}_{2/3})\text{O}_3 - x\text{PbTiO}_3$ (PMN-PT) for real-time powering of a cardiac pacemaker, which has an exceptional piezoelectric charge constant of 2500 PC/N, that is about four times as great as for PZT, twenty times as great as for BaTiO_3 , and ninety times as

great

as

for

ZnO.^[80,82]

They used the electrical response of the implanted iPENG to stimulate the heartbeat of a live rat without any other energy supply. **Figure 23A** shows a graphic presentation of self-powered cardiac pacemaking utilizing a PMN-PT energy harvester. Figure 23B displays the in vivo test with unwrapping the chest of an anesthetized rat for stimulating the heart. Figure 23C illustrates that the rat had the normal QRS complex P and T waves in the electrocardiogram amplitude having a 6 beats per second heart rate. When the PMN-PT was stretched and released repeatedly, the corresponding outputs were revealed on the usual heartbeat of the rat in the electrocardiogram, as displayed in Figure 23D. The produced energy ($2.7 \mu\text{J}$) from one twisting movement of the harvester was greater than the threshold energy ($1.1 \mu\text{J}$) to drive the heart.^[25] The outcome shows that the flexible iPENG has a prospective biomedical application for the normalization of cardiac operation.^[88]

4. Discussion

There has been a rising demand for flexibly and sustainably energized in vivo wireless biomedical devices for implantable use, preferably free from the integration of batteries. One feasible tactic is to harvest biomechanical power associated with body movement, muscle action, and metabolic techniques from the ambient in vivo physiological environment. Several iTENGs and iPENGs have been developed since 2010 to highlight the above implementation issues through the direct utilization of biomechanical power in vivo condition.

In terms of the choice of triboelectric materials, various soft materials such as PDMS, PTFE, PLGA, PCL, Kapton^[3,29,39–41] were utilized for sustainable and real-time operation of implantable medical devices inside the body. Then the contacting surfaces of the materials were modified by fabricating nanopatterns and nanostructures to augment the triboelectric coefficient and output performance of the device. PDMS is also widely used due to its highly stretchable features.

A notable point is that the contact and separation process of the iTENG rely on the mechanical resilience of the material used. For in vivo application, both the narrow space of the implantation site and the encapsulation structure are required to recover from their deformation when an external mechanical load is released. Long-term reliability is another

crucial factor for implantation in an active body, which is very dependent on the encapsulation strategy. The encapsulation layers have two roles. First, the hermetic packaging ensures the in vivo response of the system and protects the iTENG over its lifetime under certain biological situations. Second, the encapsulation layer plays an important role for shielding the host cells from possibly toxic components of the system. Thus, the biocompatibility and biodegradation properties of the materials should be carefully considered.

For additional advancement and extensive application of the iTENG, several problems need to be resolved. Firstly, precise packaging is required utilizing flexible and biocompatible triboelectric materials. Secondly, the in vivo motion is so tiny that an iTENG must be very sensitive to respond to such a small movement. Thirdly, the implant environment is occupied by bodily liquids, which considerably influence the output of the device if they flow into the inner structure. Fourthly, flexibility is required to avoid damage to brittle tissue or compromising of the function of organs inside the body. Fifthly, for organ connectable uses, better adaptability to body interfaces requires to be examined with decomposable materials. Finally, new concepts require to be practiced in conjunction with newly devised nanogenerators to transmit wirelessly and supply power to distant medical devices.

Recent improvements in the output performance of iTENGs are highlighted in Figure 24. Within 2 years of the first application of an iTENG there have been several improvements and practical applications accomplished by various research groups all over the world. Though the in vivo electrical outputs were smaller than those of previous in vitro experiments, they were still greater than most of the prior reported systems for intracorporeal energy harvesting.^[27,29,46] The trend in the advancement of iTENGs is toward flexible, viable, high by efficient, cost effective, biocompatible, biodegradable, for development of self-powered biomedical devices for in vivo application.

In terms of the choice of piezoelectric materials, different flexible materials, such as PZT^[74], BaTiO₃^[43], PVDF^[71], have been applied for powering IMDs. The efficient application of iTENG in implanted biomedical systems depends on their piezoelectric properties, flexibility to implant inside the body, stretchability, biocompatibility, biodegradability, elasticity, durability, and low-cost processing.

Figure 25 depicts the advance of the piezoelectric energy harvester for self-energized in vivo systems in terms of material fabrication, device structure and application of implantable biomedical systems in recent years. Zhou Li et al. verified that the breathing of a rat resulted in the continuous stretching and releasing of the diaphragm, which produced cyclic expansion and contraction of the NG, respectively. The potential difference created in the piezoelectric materials pushed negative charge to drift to and fro through an outer wire in sympathy with the physical changes of the diaphragm.^[6,83] Later Shi et al. reported that, owing to the various sizes of human organs and manual medical operations, the displacement variation for in vivo biomedical equipment is obvious and greatly influences the coupling performance. This problem can be solved by using frequency regulation of the piezoelectricity generator.^[74]

Dagdeviren et al. reported piezoelectric energy-harvesting elements that perform high-efficiency electromechanical power transduction from the ordinary movements of the lung, heart, and diaphragm, validated in diverse animal models with body parts like human^[27]. The key findings of tests of iPENG in vivo include: (i) the output performance of iPENGs is better than for previous in vivo results because of material modification and device structure optimization; (ii) a rectifier circuit and a wireless transmission unit have been developed for real-time power production and storage; (iii) biocompatible, biodegradable, non-toxic forms of implanted iPENG materials have been evaluated through cell cultures on different internal organs; and (iv) nonstop action of a cardiac pacemaker by applying an iPENG showed its practical applicability; (v) stability of the device was tested by running over 20 million periods of bending and unbending in a humid, hydrogel atmosphere; and (vi) coupling of mechanical distortions and piezoelectric properties to obtain electricity was quantitatively analyzed by various models.

The reported outcomes indicate that triboelectric and piezoelectric energy harvesters can harvest critical electric power from movements of bodily parts for practical application in implants. Furthermore, very similar devices can be applied in skin-attached arrangements for health observations.

The main advantage of iTENG and iPENG is harvesting waste energy from the environment and, thus, being a sustainable energy source, which can replace battery or extend the lifetime of battery. The main disadvantage of these devices is long-term unreliability of the

device. Hence, the performance of such device needs to be evaluated using accelerated life testing (ALT) such as on/ off cycling for an extended period of time. The differences between iTENGs and iPENGs in terms of advantages and disadvantages during their application to the implantable medical devices are highlighted in **table 4**.

One of the goals for harvesting energy from the ambient environment, such as autonomous movement of different bodily organs, blood flow, muscle stretching is to build self-powered nano-systems for implantable biomedical devices. For these in vivo implications, it is important to test the biocompatibility and biosafety of the device materials. Zhou Li et al. reported the first study on the cellular level biocompatibility of piezoelectric materials (ZnO). Results revealed that ZnO nanowires (NWs) are totally biocompatible and biosafe. ZnO NWs are reliable and trustworthy material in iPENG fabrication for in vivo application.^[89]

In implantable device fabrications, PDMS is widely used as encapsulation materials.^[90–92] Belanger et al. investigated the in vivo biocompatibility of PDMS sheets by implanting them intraperitoneally in a rat.^[90] However, PDMS create biofouling when uncovered in a blood interact environment,^[93–95] which considerably degrade the device performance. Different surface treatments such as ultraviolet light, oxygen plasma, ozone and anti-fouling coatings are applicable to avoid the fouling problem by correcting the hydrophilicity of PDMS layer.

Parylene C is another widely used packaging material. It is biologically inert and mechanically robust, and it has been utilized as the packaging membrane under in vivo environment for many years. The iTENG testified by Zheng et al. utilized Parylene C as the furthestmost layer in the package.^[34] They examined the biocompatibility of Parylene C by viability experiment of mouse fibroblasts cells (L929). The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) experiment revealed that there was no change in viability between cells on Parylene C and cells on plates after day 3, which verified the exceptional biocompatibility of Parylene C.

Dagdeviren et al. tested the viability of rat smooth muscle cells (SMCs) on the encapsulated PZT capacitor structures as a screen of the biocompatibility and absence of toxicity of the component materials.^[27] Those cells readily adhere to fibronectin-coated structures, with evident spreading (**Figure 26A**), and intact detectable cytoskeletal structures, for example,

Vinculin focal contacts via fluorescence (green in Figure 26A) and cytoskeletal actin microfilaments (red in Figure 26B). The scanning electron microscope (SEM) image displays spreading cells in Figure 26C. No noticeable toxicity was observed in a live or dead test that recognizes calcein acetomethoxy derivative (green) for viable cells and ethidium homodimer (red) for injured cells, proposing that the most of SMCs are healthy (green in Figure 26A). In fact, above 96% of cells were viable after 9 d of culture. Cells developed on device structures revealed no changes from those developed on tissue culture plates at 3rd and 9th days (Figure 26D).

In general, materials selection and appropriate modifications are a crucial part for iTENG and iPENG development. The triboelectric/piezoelectric material determines the power output, while the encapsulation material dictate the lifetime of the overall device. Although the materials described above are biocompatible, it is still required to package nanogenerators with biocompatible and biosafe constituents to avoid materials damage and poisonousness inside the body.

The nanogenerator has very low efficiency in directly powering electronics for the unbalanced load matching. The bottleneck for the practicability of iTENG and iPENG is the effective power management as it plays an essential role in efficient energy utilization. Few researchers used wire connection for transmission and storage of generated power, whereas others stored energy wirelessly. For instance, Dagdeviren et al. used a chip-scale rechargeable battery (EnerChip CBC012; Cymbet Corporation) and a Schottky bridge rectifier (MB12S; Micro Commercial Components) co-integrated on the same flexible substrate with the iPENG to store the power directly.^[27] **Figure 27A** illustrate the co-integrated self-powered system where iPENG, rectifier, and rechargeable microbattery are co-integrated and wire connected.

On the other hand, Zheng et al. fabricated a self-powered wireless transmission system (SWTS) and successfully transmitted an electrical signal associated with the in vivo heartbeat, showing its feasibility for real-time remote cardiac monitoring (Figure 27B).^[40] A capacitor in a power management unit was charged by heartbeat-related electrical energy, transmitted through the implantable wireless transmitter, and received by the external receiving coil as electromagnetic waves. The wireless transmitted signal was subsequently recorded with an oscilloscope for further data analysis. Therefore, power can be transmitted

by both wired and wireless system, but finding a right match is required to maximize the efficiency of power transfer.

It is expected that a battery-free and fully implantable biomedical device for real-time diagnosis and treatment will materialize commercially in the near future by implanting nanogenerators in tiny medical devices.

5. Summary and Future Challenges

In this focus review, recent advances of implantable triboelectric and piezoelectric nanogenerators for biomechanical energy harvesting and powering self-driven in vivo medical devices are systematically summarized. Since the very first article on implantable nanogenerators in 2010, their applications for various medical treatments have been extended by several techniques and methods. Given the extensive advancement which has already been done, we can expect substantial development in coming days, as their infinite possibilities and applicability in implantable biomedical devices has made nanogenerators a pivotal energy-harvesting technology in recent times. It is anticipated that this technology will have a radical effect that could probably lead to a trend for replacing batteries or at least increasing the lifetime of batteries in implantable biomedical devices.

Striving toward the advancement of sustainable and flexible implantable nanogenerators and their prospects, the following experimental features essential and additional effort should be given to resolve these limitations.

- i). Optimization of material fabrication and device structures in iTENGs and iPENGs requires further investigation, considering basic theories of tribo/piezo-electricity generation to enhance the efficiency, cost effectiveness, flexibility, and sustainability for long-term in vivo application.
- ii). The encapsulation strategy needs to be more reliable and resistant to protect the device over its lifetime under in vivo environments.
- iii). Nontoxicity, biocompatibility, biodegradability of materials is essential for safe implementation of the nanogenerator inside the body, so lots of effort needs to be made in this area.
- iv). Wireless power management units with smaller system loss require to be developed for nonstop, firm and durable energy sources to in vivo bioelectronics.
- v). The interface between the implanted nanogenerator and body tissue requires to be enhanced by means of interfacial adhesion and strain relief for long-lasting coupling.
- vi). Not only small-animal experiments but also human applications and large-animal tests are essential for successful manufacture and commercialization of these IMDs.

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Figure 1. Graphical overview of this review.

Figure 2. Working principle of the iTENG.

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Figure 3. iTENG is utilized for real-time health checking purpose.

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Figure 4. Modification of surfaces of an iTENG. A a) SEM image of a nanostructure on PTFE layer. b,c) Schematic diagram and photograph of iTENG (from Ref. 40). B a,b) SEM and AFM pictures of the nano-pattern on BDP surface. c,d) Schematic diagram and photograph of iTENG (from Ref. 41). C a) Exploded-view illustration of the structure. b) Schematic drawings of the iTENG in original and bending states. c) SEM image of nanoscale feature of n-PTFE triboelectric layer on elastic Kapton substrate (from Ref. 39). D a) Schematic diagram showing an iTENG unit composed of two parts. The zoom-in illustration shows the nanostructured rubber surface. b) SEM images of the rubber layer with dry-etched nanorod structures (from Ref. 75).

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Figure 5. Miscellaneous structures of flexible iTENGs. A) Arch-shaped iTENG structure (from Ref. 3), B) Shell type iTENG structure (from Ref. 29), C,D) Core-shell structure of the flexible fabricated iTENG (from Ref. 39), E) Keel Structure of iTENG (from Ref. 40), and F) Structure of the iTENG unit with single-electrode mode (from Ref. 75).

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Figure 6. Wireless heart-rate monitoring based on an iTENG. A) Schematic illustration of the self-energized wireless transmission method based on the iTENG (iWT, implantable wireless transmitter; PMU, power management unit; WTS, wireless transmission signal). B,C) Photograph of the implantable wireless transmitter: B) schematic diagram of unfolded implantable wireless transmitter, exhibiting the multilayer structure; C) optical microscope image of an implantable wireless transmitter. D) In vivo heart-rate monitoring. E) Top: wireless transmission signal as received at different heart rates (charging time = 10 s). Bottom: wireless transmission signal as received at different charging times (HR = 60 bpm). F) Linear relationship between the heart rate and the normalized wireless transmission signal. Reproduced with permission.^[40] Copyright 2016, American Chemical Society.

Figure 7. Power production by the respiratory movement of a living rat. A) Typical voltage and B) current output of iTEG for in vivo situation. C,D) An iTEG implanted under the thoracic skin of a rat. E) Relation between the iTEG outcome and breathing vibrations.

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Figure 8. Overview of a self-energized pacemaker. A) Structure and photograph of the pacemaker. B) Circuit diagram of the model ($R_1 \approx 0\text{--}50\text{ k}\Omega$, $R_2 \approx 0\text{--}200\text{ k}\Omega$, $R_3 \approx 0\text{--}100\text{ k}\Omega$, $C_1 = 10\text{ }\mu\text{F}$, $C_2 = 0.01\text{ }\mu\text{F}$). C) Stimulation pulses at various frequencies produced by self-energized pacemaker. D) Charging curve of the capacitor bank utilizing iTENG. E) Implementation of the self-energized pacemaker for stimulating the heart of the rat. Reproduced with permission.^[29] Copyright 2014, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 9. Current generation from the diaphragmatic drive of a live rat. A) An iTENG implanted to a rat's diaphragm. B) An extended image of the device implementation. C) Current output of the device connected to the rat's diaphragm.

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Figure 10. Implant biodegradation of nanogenerator. A,B) In vivo location just after stitching and after 9 weeks. C,D) Cross-sectional and 3D photographs of in vivo BD-TENG after 9 weeks implantation exhibits the degradation amount. E,F) Image of BD-TENG prior to implantation and histological part of tissue at the implant area after 9 weeks. G–I) In vivo response of BD-TENGs. J,K) Image of in vivo area of covered BD-TENG just after insertion and three days after insertion.

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Figure 11. Electrical excitation of nerve tissues driven by BD-TENG. A) Rectified response of the device. B) Graphic representation of self-energized excitation structure. C) Photograph of the two patterned conductors. D) Bright-field microscope picture of the conductors. E) Cell orientation investigation where the cell angle is denoted by $-\cos(2\theta)$. F–H) Orientation and distribution of nerve tissues cultivated on the conductors. F,G) Nerve tissues with and without electric field excitation. H) Expanded outlook of nerve tissues driven by electric field.

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Figure 12. SPLC structure was verified to work in living creatures. A) SPLC system was affixed to a human arm. B–E) Voltage curve of the capacitor, Infrared signals, and outcome of the iTENG that was applied in vivo between the diaphragm and liver of a rat.

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Figure 13. Output of the iTEAS increased along with the blood pressure (BP). B) Linear correlation between voltage outputs and systolic BP (sBP). Blue points represent the mean values of six consecutive peaks, randomly selected every ≈ 20 s. The purple line corresponds to the linear fitting function; K , slope of the function; R^2 , adjusted R squared. C) Schematic diagram illustrating the mechanisms for monitoring the velocity of blood flow. Red arrows represent the direction of blood flow. D) Time interval (leading time, LT, shown in highlighted region) between the peaks of the two corresponding waveforms. E) The leading time decreased and the velocity of blood flow increased along with the elevation of BP. Purple points represents the mean values of three consecutive leading times randomly selected under different sBPs. Blue points represent the mean velocity of blood flow calculated according to the corresponding leading time.

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Figure 14. A) Anterior and B) posterior views of the heart schematically illustrating three selected implant sites: the left lateral wall (LLW), right lateral wall (RLW), and posterior wall (PW) of the heart. C) The peaks of output voltage fluctuated periodically and stably when the iTEAS was anchored over the LLW. Typical time intervals between two neighbouring maximal peaks were measured to be ≈ 5 s. Blue solid-line curves represent positive waveforms of the output voltage. Blue points stand for the peaks of output voltage. D) Output peaks of the device over the RLW showed good but slightly less stable cyclic fluctuations, while the output peaks varied irregularly when the iTEAS was placed beneath the PW of the heart. E) Output peaks increased from ≈ 4.8 to ≈ 6.3 V during the process of inhalation and decreased during the process of exhalation, indicating different respiratory phases. The red line indicates the trend of variation of the output amplitude.

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Figure 15. Schematics of the electricity generation of the iPENG before A) and after B) bending.

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Figure 16. A) Schematic and optical photograph of the iPENG with Chang liver tissues cultivated over it. The central part with a bright color is BZT-BCT film, whereas the dark portions situating at the top and bottom are the conductors of the iPENG (from Ref. 33). B) Photograph of the iPENG based on PMN-PT thin layer on a PET material. (from Ref. 25). C) Image of PZT MEH connected with a rectifier and rechargeable microbattery (from Ref. 27). D) SEM photograph of refined BZT-BCT nanowires (from Ref. 33). E) SEM images of the PUEH (a), Optical microscope image of the PZT diaphragm array (b), photograph of the PUEH on DIP packaging with wire bonding (c) and photograph of a bulk PZT transducer used as a transmitter in an AET system (d) (from Ref. 73).

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Figure 17. A) Vertically aligned structure of the phage nanopillars and the process of getting piezoelectricity from it (from Ref. 80). B) Graphic sketch of the manufacture method and biomedical use of a bendable PMN-PT based power harvester (from Ref. 25). C) PZT ribbons based energy harvester (a) Overall design of the device. (b) Microscopic photograph of PZT ribbons printed on a thin surface of PI. (c) Image of PZT- based energy harvester with cable for exterior joining: ACF, anisotropic conductive film (from Ref. 27). D) Representation of a phase nanopillar NG. A cyclic exterior stress was employed to the NG to obtain piezoelectricity (from Ref. 25).

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Figure 18. Energy collecting from the heartbeat and breathing of a rat utilizing a nanogenerator. A,B) A nanogenerator connected to a rat's diaphragm and its heart that pushes the nanogenerator to regularly twist and generate AC power. C) Current vs voltage curve of the nanogenerator. D) Current response of the nanogenerator for an in vivo application.

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Figure 19. Schematic and cross-sectional view of the developed PUEH integrated with a pacemaker and powered by an ultrasound head.

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Figure 20. A) Schematic and photograph of test setup for power delivery through 6 mm thick pork tissue. B) Delivered power through pork tissue when ultrasound intensity of 1 mW/cm² is applied.

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Figure 21. Analysis of iPENG biocompatibility. A) Picture of the biocompatible nanogenerator inserted in the rabbit's rear. B) The output current of the implanted device. C) The nanogenerator and the nearby cells. D) The nanogenerator and the nearby cells were cautiously detached. E–H) The H&E stained pictures of rabbit's cells: E) The rabbit skin located at next to one side of the nanogenerator corresponding to (1) and (2) in Figure 21 D. F) The rabbit muscle located at next to the other side of the nanogenerator corresponding to (3) and (4) in Figure 21D. G) The rabbit skin as a control group. H) The rabbit muscle as a control group.

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Figure 22. A) Placement of PZT energy harvesters at different position of bovine heart. B) Implant implementation of PZT energy harvesters on the diaphragm and lung. C) Image of a PZT energy harvester with and without battery, rectifier, and pacemaker connection on a bovine heart at both the chest open and closed condition.

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Figure 23. A representation of a self-powered artificial cardiac pacemaker. B) A photograph of the heart stimulation test on a live rat by PMN-PT stimulator. C,D) The ECG rate in a rat heart before the stimulation and after the stimulation.

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Figure 24. Recent Improvements in the output performances of iTENGs (from Ref. 3, 29, 39, 40 and 41).

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Figure 25. Schematic diagram showing the progress of the piezoelectric energy harvester for self-energized in vivo systems (from Ref. 25, 27, 71, 74, 84).

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Figure 26. Biocompatibility test of nanogenerator using rat smooth muscle cells. A) Live/ dead viability test showing live cells (green) with intact nucleus (blue) and one dead cell (red) as indicated by the arrow (Inset). B) Fluorescent image showing vinculin focal contact points (green), actin filaments (red), and nuclei (blue). C) SEM image of cells on PZT ribbons encapsulated by a layer of polyimide. D) Lactate dehydrogenase test shows no indications of toxicity for cells on a membrane of PZT at day 9.

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Figure 27. A) Self-powered system where an iPENG, rectifier, and rechargeable microbattery are co-integrated and wire connected (from Ref. 27). B) Self-powered wireless transmission system (iWT, implantable wireless transmitter; PMU, power management unit; WTS, wireless transmission signal) (from Ref. 40).

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Table 1. Triboelectric Series.

	Polyformaldehyde 1.3-1.4	(continued)
Positive ↑	Ethylcellulose	Polyester (Dacron)
	Polyamide 11	Polyisobutylene
	Polyamide 6-6	Polyurethane flexible sponge
	Melamine formol	Polyethylene Terephthalate
	Wool, knitted	Polyvinyl butyral
	Silk, woven	Polychlorobutadiene
	Aluminium	Natural rubber
	Paper	Polyacrylonitrile
	Cotton, woven	Acrylonitrile-vinyl chloride
	Steel	Polybisphenol carbonate
	Wood	Polychloroether
	Hard rubber	Polyvinylidene chloride (Saran)
	Nickel, copper	Polystyrene
	Sulfur	Polyethylene
	Brass, silver	Polypropylene
	Acetate, rayon	Polyimide (Kapton)
	Polymethyl methacrylate (Lucite)	Polyvinyl Chloride (PVC)
	Polyvinyl alcohol	Polydimethylsiloxane (PDMS)
	(continued)	Polytetrafluoroethylene (Teflon)
		Negative ↓

Table 2. Comparison of iTENG performances and their implementations for self-energized medical systems.

iTENG Size	Triboelectric Materials	Surface Pattern	In Vivo Output Performance			Application	Ref.
			Voltage [V]	Current [μ A]	Power Density [mW/m^2]		
25mm×10mm×1.5mm	PTFE and Al	Arbitrary nanostructure	14	5	107	Real-time wireless cardiac monitoring	40
12mm×12mm	PDMS and Al	Pyramid pattern on PDMS and arbitrary micropattern on Al	3.73	0.14	8.44	Powering of Pacemaker by breathing	29
20mm×30mm	PLGA and PCL	Arbitrary nano-structure on both materials	4	1	32.6	Nerve cell growth was oriented through powering electrodes by BD-TENG	41
15mm×10mm	PDMS and Al	PDMS with pyramid pattern and plain ITO	0.2	0.06×10^{-3}	35.4	Powering laser cure system for osteogenesis	3
30mm×20mm×1mm	PTFE and Kapton	Nano structure on PTFE and plain kapton	10	4	-	Monitoring Respiratory rate, heart rate, and blood pressure	39

Table 3. Comparison of iPENG performance and their applications for self-powered medical systems.

iPENG Size	Piezoelectric Materials	synthesis	In Vivo Output Performance			Application	Ref.
			Voltage [V]	Current [μ A]	Power Density [μ W/cm ²]		
-	ZnO nanowires (Length 100-500 μ m, diameter 100-800 nm)	Physical Vapour Deposition	0.003	0.03	-	Harvesting piezoelectric energy from the breath and heartbeat of a live rat	84
5mm×5mm	PZT diaphragm and Pt electrode	DC Magnetron Sputtering	-	-	3.75	Piezoelectric energy harvester integrated with a pacemaker	74
1cm×2cm	Mesoporous PVDF and plain Cu electrode	Electron Beam Evaporation	0.26	0.2	-	Energy from rat motion	71
-	PZT ribbons and Cr/Au electrode	Polarization	0.001	1×10^{-6}	1.2	Piezoelectric energy harvesting from motion of heart, lung, and diaphragm	27
1.7cm×1.7cm	PMN-PT thin film and Ni electrode	DC Sputtering, Grinding, CMP and UV curing.	8.2	223	-	Powering pacemaker by cardiac motion	25

Table 4. Advantages and disadvantages of iTENG and iPENG during their applications at self-powered implantable medical devices.

Type	Advantage	Disadvantage	Ref.
iTENG	<ol style="list-style-type: none"> 1. Provide enough output for developing self-powered implantable medical device. 2. Overall device fabrication is convenient and demands lower cost. 3. The efficiency of iTENG is quite high. 4. Poling of the triboelectric materials is not required. 5. Triboelectric polymers are wearable and can interface with biological system. 6. iTENG can produce continuous electricity with the motion. 	<ol style="list-style-type: none"> 1. Power output is not constant and dependent on the consistent periodic movements of the device. 2. Between two polymer layers a cavity is required to be formed. 3. Device performance can deteriorate due to unwanted misallocation of the spacers between triboelectric materials during the operation of the device. 4. Use of wire to transfer the generated electricity from iTENG to implant medical device is problematic to the patient. Wireless power management is the big challenge because of tiny power production and application. 	3, 29, 39, 40, 41
iPENG	<ol style="list-style-type: none"> 1. Offers unique capabilities in wide range of frequencies and amplitudes. 2. The overall accuracy of the performance of iPENG is quite high. 3. There is no heating effect during the operation of the device. 4. Nano-patterning of the piezoelectric materials is not required for their application in iPENG. 5. iPENG can be a sustainable electric energy source by harvesting waste energy from the body organ movement for self-powering nano-devices. 6. iPENG with ceramic type materials like PZT, ZnO, PMN-PT etc. and polymer like PVDF, trifluoroethylene etc. offers higher output and is suitable for building self-powered systems. 	<ol style="list-style-type: none"> 1. iPENG does not have power generating capability in static situation. 2. Mandatory poling of charges inside piezoelectric materials is problematic. 3. If iPENG come across bodily fluid during its placement into biological systems, the life time and output power of the device will shorten with the decay of poling effects of the piezoelectric materials. Few piezoelectric materials decay very quickly so their shelf-life is very short, not very suitable for continuous power generation. 4. Some piezoelectric materials are toxic and brittle (PZT). 5. Limited duty cycle of the device hindrance its application in electronic devices. 	25, 27, 71, 74, 84

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Recent Advances in Nanogenerator-Driven Self-Powered Implantable Biomedical Devices

M. A. Parvez Mahmud, Nazmul Huda,* Shahjadi Hisan Farjana, Mohsen Asadnia, and Candace Lang

This review highlights the recent improvements in implantable triboelectric and piezoelectric nanogenerators to drive self-powered healthcare systems. It also summarizes their applications in cardiac monitoring, pacemaker energizing, nerve-cell stimulating and orthodontic treatment by scavenging the biomechanical power within the body. Overall, this review represents realistic strategies of nanogenerators for overcoming the present difficulties as in vivo energy harvesters.

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